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Production of copper-64 and gallium-68 with a medical cyclotron using liquid targets

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This work describes the production of two clinically relevant metal radioisotopes ^{64}Cu and ^{68}Ga with a medical cyclotron by the irradiation of liquid targets. New results are presented for the implementation of this methodology in a fully automated system, using commercially available equipment. Liquid target solutions containing enriched ^{64}Ni and ^{68}Zn were loaded, bombarded and transferred to synthesis modules where a purified solution containing the desired radiometal is obtained and can then be used to further radiolabeling within only one hour after End-Of-Bombardment (EOB). Typical production runs using enriched material lead to the production of 5 GBq and 6 GBq (0.14 MBq/(μAh $\cdot$ mg) and 1.5 MBq/(μAh $\cdot$ mg)) of ^{64}Cu and ^{68}Ga; although the technique can be used to obtain up to 25 GBq and 40 GBq, respectively, by simply scaling up the amount of the enriched material. Purified solutions containing ^{64}Cu and ^{68}Ga were obtained within 30 min after EOB and used to produce ^{64}Cu-ATSM and ^{68}Ga–DOTA–NOC, respectively, with quality parameters suitable for human use.

Keywords: Cyclotron; radiometals; liquid target; ^{64}Cu; ^{68}Ga.

1. Introduction

Although Positron Emission Tomography (PET) has traditionally been using isotopes of elements that are highly prevalent in biological systems (^{11}C, ^{13}N, ^{15}O),

in recent years there is an increasing interest in non-conventional emitters, particularly metals, in a response to their expanding use in both molecular imaging and therapeutic applications.[1] Several studies have thus investigated the potential use of a wide range of radiometals discussing their basic physicochemical properties such as half-life, range, decay properties as well as dosimetric considerations.[2,3] Furthermore, it is also fundamental to investigate and optimize the possible production techniques using common commercially available cyclotrons and synthesis modules to ensure that all clinical and research applications are fulfilled.

This work reviews the main aspects involved in the use of the so-called solution ("liquid") targets for radiometal production with significant benefits when compared to the conventional ("solid") production processes in terms of reliability, purification and labeling time, and significant reduction or even elimination of the pre- and post-irradiation target preparation and handling issues. This approach is exemplified with two practical examples, ^{64}Cu and ^{68}Ga, both playing major roles in clinical practice as well as in the discovery and development of new targeted probes.[4,5] A brief review of the possible production routes is presented for these particular radionuclides in order to complete and compare with the proposed solution emphasizing the improvements and gains obtained; including significant cost reduction and the opportunity to perform consecutive synthesis.

2. Copper-64

Over the past decades, many authors have recognized the importance of the various radioisotopes of copper as they offer a wide portfolio of nuclear decay properties, from distinct decay types to an extended half-life range.[1,4,6,7] Among these, ^{64}Cu stands out since it experiences all three β^-, electron capture and positron decays with a 12.7 h half-life, making it appropriate for both imaging and targeted-therapy applications. As a result, the possible production routes for ^{64}Cu have been widely studied and used over the past decades. Although ^{64}Cu can be produced in nuclear reactors[5,8,9] it is most commonly obtained though charged particle nuclear reactions using cyclotrons to irradiate solid targets, as shown in Table 1. The ^{64}Ni$(p,n)^{64}$Cu nuclear reaction is the preferred route because it results in a higher production yield and can be used with medical cyclotrons (typically delivering up to 20 MeV protons). On the other hand, deuterons with large energy (i.e. superior to 20 MeV) and/or intensity are scarce. This explains why the $^{\text{nat}}$Zn$(d,x)^{64}$Cu reaction is not more widely used regardless of the noteworthy advantage of avoiding the use of expensive enriched material.

Despite such well-established production processes, very few facilities are currently producing ^{64}Cu.[3] Several authors have pointed out the non-negligible and time-consuming practical difficulties arising from the use of the solid targets. Indeed, several authors detailed the electroplating technique necessary to prepare the solid target to irradiate, stating processes lasting from 6 h to 48 h.[10–13] Under these conditions, particular care has to be taken regarding the quality of the

Table 1. Distinct production processes leading to the production of ^{64}Cu.

Nuclear reaction	Projectile energy (MeV)	^{64}Cu production yield (MBq/μAh)	Reference
^{nat}Zn(d, x)	13	7	17
	$13 \rightarrow 7$	1.7	16
	16	5.3	18
	19	30.9	19, 20
	15	14.8	21
	45	209	22
^{66}Zn$(p, 2pn)$	$70 \rightarrow 35$	777	23
^{66}Zn(d, α)	$13 \rightarrow 7$	6.6	16
^{64}Zn$(d, 2p)$	19.5	31	24
	19.5	36	25
^{68}Zn$(p, \alpha n)$	26.5	36.4	26
	$30 \rightarrow 20$	37.4	27
	$35 \rightarrow 20$	65	16
	$25 \rightarrow 10$	67	23
	$37 \rightarrow 20$	185	
^{64}Ni$(d, x)^{64}$Cu	19	389	28
^{64}Ni$(p, n)^{64}$Cu	15.5	85–185	13
	12	236	29
	20	7	17
	11.4	5.9 at saturation	11
	12	22–111	12
	14.5	190	3
	18	104	10, 14
	15	7.4	15

electrodeposited layer as it greatly affects the production yield.[10,14–16] Additionally, problems can occur during irradiation that lead to the loss of the enriched material. For instance, MacCarthy *et al.* have experienced evaporation and consequent loss of the expensive ^{64}Ni target layer during irradiation.[13] Besides, one should also take into account the complex procedure of recovering and recycling the expensive enriched material since only few authors have successfully implemented recovery processes with yields above 90%.[12,13]

3. Gallium-68

^{68}Ga-based radiopharmaceuticals have attracted increasing interest in recent years due to their ever expanding clinical application.[30,31] This is fostered by the emerging interest in theranostic applications in oncology where a diagnostic scan is made using a gallium-based molecule that is later labeled with a therapeutic radionuclide such as ^{90}Y or ^{177}Lu for treatment.[31,32] The demand for the ^{68}Ga radionuclide has therefore been increasing for both clinical studies and research applications and it is

essential to identify all possible sources to fulfill it. ^{68}Ga can be produced directly by induced nuclear reactions, but it is more commonly provided using ^{68}Ge/^{68}Ga generators. Generators are convenient because the long half-life of the parent nuclide ^{68}Ge (270.82 days) guarantees the supply of ^{68}Ga for several months but are limited by the amount of activity they can produce, the minimum interval between elutions and the possibility of ^{68}Ge breakthrough from the column.

3.1. *Production of ^{68}Ge*

The production of ^{68}Ge via nuclear reaction has originated several detailed studies in the last decades in which the potential nuclear reaction routes were presented, discussed and compared.[33–36] ^{68}Ge can be obtained as a spallation product or can be produced via the ^{nat}Ge$(p,x)^{68}$Ge or ^{nat}Zn$(\alpha,x)^{68}$Ge nuclear reactions.[37] However, the preferential nuclear reaction consists in proton bombardment of natural Gallium (60.1% ^{69}Ga and 39.9% ^{71}Ga) targets, making use of the ^{69}Ga$(p,2n)$, and eventually ^{71}Ga$(p,4n)$, nuclear reactions; since it requires lower energies to provide significantly higher yields,[34] it avoids the use of the enriched material and mainly because facilities with α-particles beams and/or high energy protons are scarce. Table 2 presents experimental production yields obtained from several authors using the solid target technique and for the distinct nuclear reactions mentioned.

Table 2. Distinct production processes leading to the production of ^{68}Ge.

Nuclear reaction	Target material	Projectile energy (MeV)	^{68}Ge production yield (μCi/μAh)	Reference
^{nat}Ge(p,pxn)	Ge metal	64 → 28	48	34
^{nat}Zn(α,xn)	Zn metal	40 → 20	1–1.5	38
		100 →	3.2	39
^{nat}Ga(p,xn)	Ga_4Ni	19.5 →	9.2	40
	Ga_2O_3	55 → 13	45	33
	Ga-Ni	21 →	10	41
	Ga-Ni	28 → 18 27 → 17	31	36
	Ga-Ni Ga encapsulated in Nb	16 →	1.2	42
	Ga_2O	34 → 2	15.1	43
	Ga encapsulated in Nb	25 →	27	43

In contrast to the ease of use of the ^{68}Ge-generator, the production of ^{68}Ge is complex and time-consuming. The ^{69}Ga$(p,2n)^{68}$Ge reaction presents a high threshold, at around 12 MeV, and since large activities of tens of GBq per batch are required and because of the long half-life of ^{68}Ge, inappropriately long irradiations lasting several days with high beam currents are inevitable. For instance,

Meinken *et al.* make use of irradiations of 30–45 thousands of μAh obtained during four weeks to produce around 15–18 GBq of ^{68}Ge, while Fassbender *et al.* claim to produce around 16 GBq of ^{68}Ge by accumulating 37,000 μAh of 36 MeV protons.[45–47] The development of optimized Ga targets with efficient cooling is thus understandably another critical complex production process in order to dissipate the high powers generated during such bombardments. For instance, targets irradiated with currents up to 300 μA and reaching 250°C were used.[36–41] On the other hand, other authors explained the complex process of preparing the solid target, from preparation of the backing support lasting more than 60 h,[36] complex target electrodeposition,[48] thermal resistance tests,[36,40,43] large and long post-irradiation cooling time up to one month to allow radio-impurities with shorter half-lives to decay to post-irradiation ^{68}Ge activity losses during processing.[40,43] In addition, gallium is not an appropriate material since it is corrosive to most metals and due to its insufficient thermal transmission and low melting point of 39°C. Consequently, the development and characterization of effective targets has been the subject of studies by several authors in order to overcome such a critical feature. As illustrated in Table 2, several distinct Ga targets have been considered; ranging from Ga_2O_3, Ga_xNi_y (both with melting point higher than 400°C) to Ga encapsulated in niobium since this latter does not react with Ga below 400°C,[40,42,44] among others. For instance, Ga_2O_3 has been simultaneously preferred by some authors over Ga-based alloys to avoid complicating the process by the addition of other components, while also discarded by others.[40,43] As a result of such complex considerations, only few facilities supply ^{68}Ge on a regular basis.

In addition to all the referred difficulties to produce the parent nuclide ^{68}Ge, the use of the ^{68}Ge/^{68}Ga generator is inevitably accompanied by the constant risk of the possible breakthrough of ^{68}Ge in the eluate. Even if ^{68}Ge is present in trace amounts, with reported concentrations around $2–5 \times 10^{-3}$%,[35,49] its existence is of particular relevance due to its long half-life of 270.82 days. It is consequently fundamental to control the level of the impurity in both the eluate and the labeled ^{68}Ga-based radiopharmaceuticals especially since this sensitive parameter is known to increase as the generator ages.[50] The European Pharmacopeia, for example, requires the value to be below 0.001%. However, since ^{68}Ge decays exclusively by electron capture and is thus indirectly detected by the emission of its daughter nuclide ^{68}Ga; this task can only be performed when the eluted ^{68}Ga is no longer present, i.e. long after the time-frame of utilization of both the eluted solution and the final radiopharmaceutical. Several alternative techniques have been developed in order to quantify the presence of the sensitive ^{68}Ge but only few permit its determination before the administration of the ^{68}Ga-based radiopharmaceutical produced.[51–53] Besides, one has to refer that another quality control consists of determining the trace amounts of the several possible elements present in the eluate,[50,54] in a process similar to the procedure used to assess the quality of the cyclotron-produced radiopharmaceuticals.

3.2. *Production of* ^{68}*Ga*

As generators are expensive and deliver limited activities of ^{68}Ga per elution, the latter can also be produced directly. Among several possible nuclear reactions,[55,56] the irradiation of Zn by protons is the preferred nuclear reaction as it leads to a larger production yield and uses protons, the simplest of all cyclotron projectiles.[55] Since several radioisotopes of gallium with longer half-lives are also produced when irradiating natural Zn, it is mandatory to bombard enriched ^{68}Zn. However, the irradiation of ^{68}Zn by protons also leads to the production of the undesired long-lived ^{67}Ga radioisotopic impurity through the ^{68}Zn$(p, 2n)^{67}$Ga reaction for protons with energy higher than 12.0 MeV,[55] forcing us to choose the beam energy wisely to achieve high radionuclidic purities suitable for human use.

Producing ^{68}Ga by using the solid target technique presents the unique advantage of enabling the irradiation of electrodeposited ^{68}Zn target layers with large beam currents, up to 200 μA, as confirmed by several authors as long as proper improved cooling system is provided. Such technique can be used to produce yields of about 5–6 GBq/μAh of ^{68}Ga, as reported by several authors.[57–60]

However, such large activities of ^{68}Ga are achieved at the expense of several important technical difficulties. Indeed, the production of solid targets requires long and complex electrodeposition processes taking from a few hours up to 20 h,[57,61] in a process that additionally requires significant optimization studies and even additional quality control prior irradiation in order to guarantee that it is suitable for production and to avoid product contamination from the backing layer.[48,59] Moreover, beyond the inconvenience of the inevitable activation of the backing material upon which the layer of the enriched material is deposited, the post-irradiation handling and transport of the solid target are particularly important issues since the target cannot be allowed to cool down due to the much shorter half-life of ^{68}Ga when compared to its radioisotopic impurities ^{66}Ga and ^{67}Ga. Furthermore, not only such solid targets require large amount of expensive enriched material (hundreds of mg of ^{68}Zn are necessary) but such a long and complicated process is also synonymous of an inevitable and non-negligible loss of the enriched material, as confirmed by Stoll *et al.* and also quantified to be about 15% by Kakavand *et al.*[59,62]

4. ^{64}Cu and ^{68}Ga produced by bombarding liquid targets

In order to avoid the described practical difficulties associated with the irradiation of solid targets, an alternative production technique has been suggested,[63] by irradiating a liquid target containing a solution based on the enriched target material. Distinct possible liquid target solutions have been tested;[63,64] in a process that benefits from the high yields provided by the same nuclear reactions used in the solid target technique while simultaneously avoiding the limitations inherent to the use of such targets.

This work describes the development of an improved production technique based on the latter method, from the cyclotron irradiation of a liquid target to the puri-

fied solution containing the desired radioisotope, suitable for radiopharmaceutical labeling for human use; for the particularly relevant radioisotopes ^{64}Cu and ^{68}Ga. This method was implemented in a fully automated system employing commercially available equipment produced by the company IBA (Louvain-la-Neuve, Belgium). An IBA Cyclone 18/9® cyclotron delivering 18 MeV protons was used to bombard the IBA Nirta Ga® and IBA Nirta Cu® niobium liquid target systems especially developed for the production of ^{68}Ga and ^{64}Cu, respectively to automatically load, irradiate and transfer the target solutions while enabling consecutive productions. As Induced Plasma Mass Spectrometry (ICP-MS) studies previously confirmed the chemical inertness of niobium during the process, pure niobium was also chosen as the material for the target window in order to avoid eventual additional metallic impurities. Enriched ^{64}Cu and ^{68}Zn were purchased from CMR (Centre of Molecular Research, Russia). The liquid target solutions were prepared by dissolving the enriched material in a nitrate solution which was then diluted in a nitric acid solution. Several concentrations of both nitric acid and enriched material were tested in order to reach a good compromise between the dissolution of convenient amounts of enriched material and the stability of the solution (from non-precipitation, non-limitating viscosity, long-time stability and behavior during irradiation to avoid pressure build up).

The activity measurements were performed using γ-spectroscopy with a High Purity Germanium detector (HPGe), model GEM30P4-76 from ORTEC (ORTEC, Tennessee, US), calibrated with a ^{152}Eu radioactive source and placed in a low-background shielding. γ-spectra were acquired using point-source like samples, keeping a dead-time inferior to 4% and using the software package GammaVision (ORTEC Inc.) to determine the photopeak areas. We estimated the error in the determination of the activity of the samples to be about 10%, mainly due to the uncertainty from the absolute efficiency calibration curve.

4.1. *Copper-64 from the irradiation of liquid targets*

4.1.1. *Liquid target irradiation*

An IBA Nirta Cu® niobium liquid target was mounted with a target window composed of two foils, namely, a 35 μm thick Havar window followed by a 35 μm thick niobium window in contact with the liquid target solution. Such a configuration combines the proven mechanical resistance of Havar during irradiation to the benefits of the chemical inertness of niobium.

Calculations were conducted to determine the production yields of the possible nuclear reactions occurring from the interaction of the resulting 16.9 MeV protons beam impinging on the ^{64}Ni-based liquid target. An illustrative example of the set of results is presented in Table 3 for a particular ^{64}Ni concentration; and where the inevitable production of ^{13}N from the ^{16}O$(p,\alpha)^{13}$N reaction from the water of the target solution was not considered, since the purification process guarantees the exclusion of ^{13}N from the final product. We should point out here that the release

Table 3. Proton-induced nuclear reactions occurring in ^{64}Ni-enriched nickel and theoretical productions yields for a typical irradiation of 16.9 MeV protons impinging on a liquid target solution containing 200 mg of ^{64}Ni.

Nickel nuclide (% in natural Ni)	Abundance in the enriched of ^{64}Ni (%)	Nuclear reaction	Decay					Theoretical yield (MBq μA_{sat})	Cross-section references	Activity@EOB(MBq) for a 5 h long irradiation with 100 μA on target
			Half-life	β^- (MeV)	β^+ (MeV)	EC (%)	γ-rays (keV)			
^{58}Ni 68.01%	2.71	^{58}Ni$(p, 2p)^{57}$Co	272 days			100%	122.1 (85.6%) 136.4 (10.4%)	0.778	66, 67	8.93E-02
		^{58}Ni$(p, \alpha)^{55}$Co	17.5 h		1.513 (81%)	19%	477.2 (20.2%) 511 (154%) 931.3 (75.0%) 1408.4 (16.88%)	0.209	67, 68	8.10
		^{58}Ni$(p, pn)^{57}$Ni	35.6 h		0.863 (43.4%)	56.6%	127 (16%) 511 (86.8%) 1377.6 (81.2%) 1757.6 (6.1%) 1919.6 (12.5%)	0.078	66, 67, 69	1.557
^{60}Ni 29.22%	1.62	^{60}Ni$(p, n)^{60}$Cu	23.7 min		92.6%	7.4%	511 (185.2%) 826.1 (21.7%) 1332.5 (88.0%) 1791.6 (45.4%)	1.409	67, 69, 70	304.7
		^{66}Ni$(p, \alpha)^{57}$Co	272 days			100%	122.1 (85.6%) 136.4 (10.4%)	0.306	67–69	3.52E-02
^{61}Ni 1.14%	0.14	^{61}Ni$(p, n)^{61}$Cu	3.33 h		2.237 (61.5%)	38.5%	283 (12.0%) 511 (123%) 656 (10.4%)	0.164	29, 69, 70	22.90
		^{61}Ni$(p, \alpha)^{58}$Co	70.9 days		0.475 (14.9%)	85.1%	511 (29.9%) 810.8 (99.4%)	0.0204	69, 71	8.97E-03
^{62}Ni 3.63%	0.53	^{62}Ni$(p, n)^{62}$Cu	9.67 min		2.92 (98%)	2%	511 (196%) 875.7 (0.15%) 1172.9 (0.34%)	1.160	66, 69, 72	250.7
^{64}Ni 0.93%	95.0	^{64}Ni$(p, n)^{64}$Cu	12.7 h	0.579 (38.5%)	65.3% (17.52%)	43.5%	511 (35.04%) 1346 (0.48%)	157.2	11, 29, 73	8116.5
		^{64}Ni$(p, \alpha)^{61}$Co	1.65 h	1322 (100%)			67.4 (85%) 841.2 (0.79%) 908.6 (3.6%)	3.80	67, 74	721.6

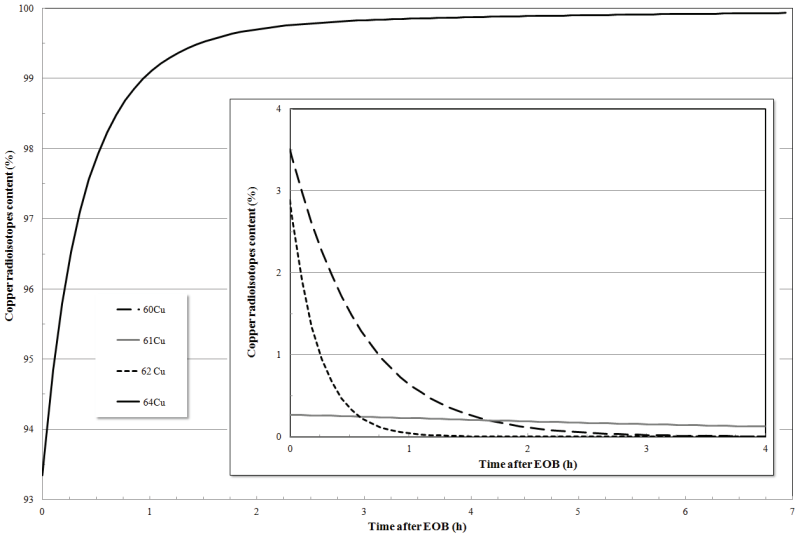

Fig. 1. Theoretical predictions of the purity of the ^{64}Cu produced, as a function of time after EOB, after a typical 5 h long irradiation. The inset graph focuses on the importance of the low fractions of ^{60}Cu, ^{61}Cu and ^{62}Cu also as a function of time after EOB.

of the radioactive gas arising from the production of ^{13}N forces us to consider this process to be essentially a ^{13}N production in terms of radiation protection. The cross-section values used for these calculations are the experimental results from the EXFOR database.[65] For each nuclear reaction considered, the respective excitation function is a polynomial function fit of the experimental data from several authors, as listed in Table 3.

Figure 1 shows that the purity of the ^{64}Cu produced improves with time as ^{64}Cu is the radioisotope of copper produced with longer half-life when compared to its radioisotropic impurities ^{60}Cu, ^{61}Cu and ^{62}Cu. It should also be pointed out that, as shown in Fig. 2, the purity of the ^{64}Cu produced also improves as the irradiation time increases since the production of the other radioisotopes of copper reach saturation long before ^{64}Cu does. As a result, longer irradiations are preferred. It should also be pointed out that the relative importance of the shorter radioisotropic impurities ^{60}Cu, ^{61}Cu and ^{62}Cu is greatly influenced by the remaining percentage of each nickel isotope present in the enriched ^{64}Cu used.

For our particular production demands, a typical irradiation consists of the bombardment of the IBA Nirta Cu® niobium liquid target containing a liquid solution with 100 mg of ^{64}Ni during 5 h, resulting in the production of about 5 GBq of ^{64}Cu at EOB, as detailed in Table 4. As explained earlier, we estimated the uncertainty in the activity measured to be about 10% while theoretical predictions are expected to present an error of about 20%, mainly due to the uncertainty in the proton beam energy and from the experimental error in the cross-sections used to determine the excitation function curves necessary to perform the calculations.

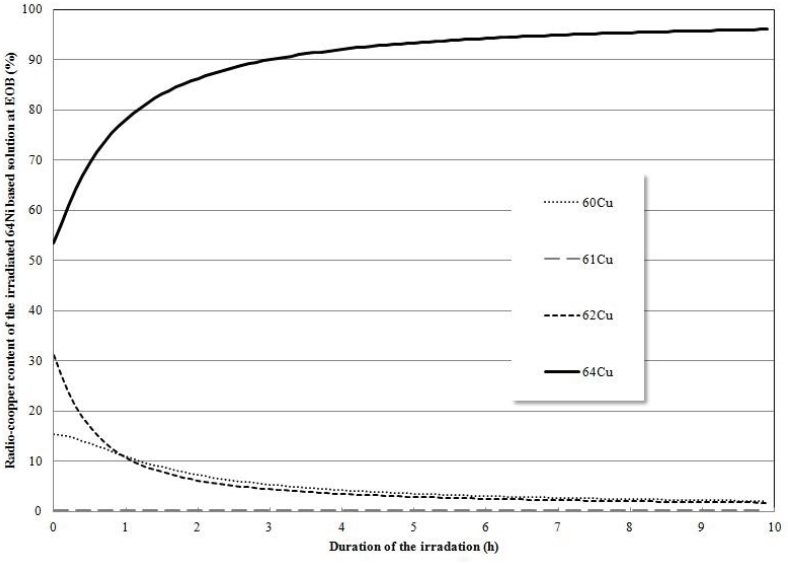

Fig. 2. Theoretical predictions of the purity of the ^{64}Cu produced at EOB, as a function of duration of the irradiation.

Table 4 also shows that the experimental results are in agreement, or even surpass, the predictions calculated based on the excitations functions selected. Beyond the previously mentioned sources of uncertainty, the uncertainty in the foils thicknesses has also to be taken into account as the manufacturer claims it to be ±15%, representing thus an additional and significant uncertainty in the beam energy impinging on the liquid target. On the other hand, the large amount of production routinely implemented, with wide range of ^{64}Cu activities requested, shows that the experimental production yield is consistently around 0.14 MBq/(μAh·mg); proving that the presented technique enables the production of up to 20–25 GBq of ^{64}Cu if necessary (by simply increasing the irradiation time and/or the concentration of ^{64}Ni). Although the production yield is, as expected, lower than the experimental values reported with the solid target technique,[13,29] this liquid target-based technique presents considerable practical improvements while simultaneously enabling

Table 4. Activities produced after a typical 5 h long irradiation of target solution containing 90 mg of ^{64}Ni.

	Activity@EOB (MBq) (±10%)	Theoretical predictions (MBq) (±20%)
^{60}Cu	101.7	96.0
^{61}Co	220.3	231.9
^{64}Cu	4610.0	2719.0
^{55}Co	3.45	2.72
^{57}Ni	1.16	0.53

consecutive synthesis. Besides, the amount of the expensively enriched ^{64}Ni to be used in the liquid target as well the irradiation time are systematically calculated to fulfill the requirements of each production while optimizing the production costs.

4.1.2. *Purification*

After irradiation of the target solution, ^{64}Cu was separated from ^{64}Ni and prepared in a small volume of $^{64}CuCl_2$ purified solution by the combination of two methods,[75,76] in an automated Synthera® Extension module (IBA, Louvain-la-Neuve, Belgium). The first step was the separation of ^{64}Cu from ^{64}Ni using a high selective Cu resin (TrisKem International). Firstly, the irradiated solution was loaded onto a cartridge with the resin preconditioned with 10 ml of water. The column was washed with 10 ml of 1 mM HNO_3 to remove traces of Ni target material in the resin. After, the column was then dried with inert gas and eluted with 7 ml of 8 M HCl transferring the ^{64}Cu onto a strong anion exchange (SAX) resin, preconditioned with 10 ml of water followed by 10 ml of 8 M HCl. In a second step, the SAX column was dried with inert gas before being eluted with 2 ml of 0.1 M HCl in order to achieve a final $^{64}CuCl_2$ solution ready to be used in a labeling process. The final Cu fraction obtained showed an excellent chemical purity with a decay corrected yield of $77.9 \pm 4.1\%$.

After the purification process, the recovered ^{64}Ni solution can be reprocessed to be reused. More than 80% of the enriched material can be typically recovered. This process is simple and reliable and can reduce the costs of ^{64}Cu production.

4.1.3. *Labeling*

Briefly, the $^{64}CuCl_2$ solution obtained in the purification step (about 2 ml) was added to a reaction vial preloaded with 4 ml of 3 M sodium acetate buffer and 0.1 ml of H_2-ATSM (4 μg) in anhydrous DMSO. The reaction mixture was bubbled with inert gas during the reaction time (10 min) at room temperature (25°C). After reaction, the mixture was transferred onto a tC18 Sep-Pak light column preconditioned with 5 ml of EtOH followed by 5 ml of water. The column was washed with 5 ml of water and dried with inert gas. The ^{64}Cu-ATSM was eluted from the column with 1 ml of EtOH followed by 9 ml of saline solution.

The final product was analysed by radio-HPLC showing 100% radiochemical purity, as shown in Fig. 3.

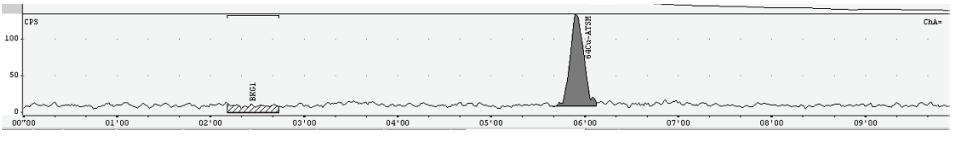

Fig. 3. Analytical HPLC of a final solution of ^{64}Cu-ATSM.

Table 5. Proton-induced nuclear reactions occurring in ^{68}Zn-enriched zinc and theoretical productions yields for a typical irradiation with 14.2 MeV protons impinging on 3 ml of target solution with a 200 mg of ^{68}Zn.

Zinc nuclide (abundance in ^{nat}Zn)	Abundance (%)	Nuclear reaction	Decay					Theoretical yield (MBq/μA$_{sat}$)	Cross-section references	Activity@EOB (MBq) for a 1 h long irradiation with 50 μA
			Half-life	β^- (MeV)	β^+ (MeV)	EC (%)	γ-rays (keV)			
^{64}Zn 48.6%	0.01	^{64}Zn$(p,\alpha)^{61}$Cu	3.33 h		1.215 (61.5%)	38.5	283 (12.0%) 511 (123%) 656 (10.4%)	4.15E-03	67, 77	0.039
		^{64}Zn$(p,pn)^{63}$Zn	32.4 s				669.6 (8%)			
		^{64}Zn$(p,\gamma)^{65}$Ga	15.2 min				115.09 (54%) 751.8 (8.1%)	4.44E-05	78, 79	2.08E-03
		^{64}Zn$(p,n)^{64}$Ga	2.63 min				807.8 (14.54%) 991.6 (46%)			
^{66}Zn 27.9%	0.01	^{66}Zn$(p,n)^{66}$Ga	9.49 h		4.153 (56.0%)	44	511 (114%) 833 (5.9%) 1039 (37%) 2190 (5.3%) 2751 (22.7%)	0.037	60, 67, 80	0.130
		^{66}Zn$(p,2n)^{65}$Ga	15.2 min					0	67	0
		^{66}Zn$(p,pn)^{65}$Zn	244.0 days		0.33 (1.42%)	98.6	1115 (50.23%)	3.95E-04	60, 67, 81	2.34E-06
^{67}Zn 4.1%	0.3	^{67}Zn$(p,n)^{67}$Ga	3.26 days			100	93.3 (70.6%) 184.6 (21.3%) 300.2 (16.67%)	1.222	60, 82	0.539
		^{67}Zn$(p,\alpha)^{64}$Cu	12.7 h	0.579 (38.5%)	0.653 (17.52%)	43.5	511 (35.04%) 1346 (0.475%)	5.68E-02	67	0.151
		^{67}Zn$(p,2n)^{66}$Ga	9.49 h		4.153 (56%)	44	511 (114%) 833 (5.9%) 1039 (37%) 2190 (5.3%) 2751 (22.7%)	9.31E-03	60, 67, 81	0.0328
^{68}Zn 18.8%	99.5	^{68}Zn$(p,n)^{68}$Ga	67.8 min		1.899 (88.9%)	11.1	511 (178%) 1077 (3.24%) 1883 (0.142%)	599.0	60, 67, 80	13732.9
		^{68}Zn$(p,2n)^{67}$Ga	3.26 days			100	93.3 (70.6%) 184.6 (21.3%) 300.2 (16.67%)	23.2	60, 82	10.23
		^{68}Zn$(p,n\alpha)^{64}$Cu	12.7 h	0.579 (38.5%)	0.653 (17.52%)	43.5	511 (35.04%) 1346 (0.475%)	2.31	16	6.12
^{70}Zn 0.6%	0.18	^{70}Zn$(p,\alpha)^{67}$Cu	2.58 days	0.577 (100%)			184.6 (48.7%)	9.39E-03	67, 83	5.24E-03
		^{70}Zn$(p,n)^{70}$Ga	21.14 min	1.656 (99.6%)		0.41	176 (0.29%) 1039 (0.65%)		84	
		^{70}Zn$(p,pn)^{69}$Zn	56.4 min	0.906 (100%)			319 (0.0012%)	2.72E-03	67	0.071

4.2. *Gallium-68 from the irradiation of liquid targets*

4.2.1. *Liquid target irradiation*

Calculations were conducted in order to determine the production yields of the possible nuclear reactions resulting from the proton-irradiation of the enriched zinc contained in the IBA Nirta Ga® niobium target used. An illustrative example of the set of results is shown in Table 5 for a particular configuration of beam energy (i.e. a particular target window thickness) and ^{68}Zn concentration. The procedure adopted was similar to the ^{64}Cu case as we considered experimental cross-section values from the EXFOR database to fit the excitation function of interest and performed the calculations,[65] as indicated in Table 5.

As it can be seen in Table 5, the proton-irradiation of the nitric acid target solution containing the ^{68}Zn also leads to the production of the other radioisotopes of gallium. Particular attention has to be paid to those with longer half-life than ^{68}Ga, namely ^{66}Ga and ^{67}Ga, since these are isotopic impurities that will end in the final purified solution of ^{68}Ga. One has to point out that, while other production yields are greatly reduced by the use of highly enriched ^{68}Zn, significant production of ^{67}Ga remains since it occurs on ^{68}Zn, through the competitive $^{68}\mathrm{Zn}(p, 2n)^{67}\mathrm{Ga}$ reaction. As the cyclotron delivers a fixed energy proton beam of 18 MeV, it is necessary to degrade the energy of the beam in order to minimize the production of the long-lived impurity ^{67}Ga, whose reaction threshold is 12.0 MeV as it can be observed in Fig. 4. Figure 4 also shows the thick target production yields for ^{68}Ga and the relevant radioisotopic impurities ^{66}Ga and ^{67}Ga as a function of the incident beam energy, for particular target conditions, in order to determine the beam energy (i.e. the thickness of the target window) to use depending on the final product purity required. Irradiations were conducted with different target windows, corresponding to distinct proton beam energies on target; as detailed in Table 6 where the corresponding production yields for ^{66}Ga, ^{67}Ga and ^{68}Ga are also presented.

As the purified solution containing the ^{68}Ga will also contain the radioisotopic impurities with longer half-lives ^{66}Ga and ^{67}Ga, the purity of the final product will deteriorate over time. Figure 5 shows the attenuation of the purity of the final solution as a function of time, for the distinct beam energies resulting from the use of the several target windows considered. Besides the considerations to reduce the incident beam energy in order to minimize the presence of ^{67}Ga, it is also important to use an enriched ^{68}Zn with minimized amount of ^{66}Zn because the $^{66}\mathrm{Zn}(p, n)^{66}\mathrm{Ga}$ reaction presents relevant cross-sections in the region of interest.

A large number of irradiations were conducted with solutions of different concentrations and distinct target volumes, with various target pressures up to 35 bar and/or with target window of different thicknesses, in order to verify the consistency of the experimental data obtained and to study the various irradiation conditions and their impact on the process, to prevent expected experimental difficulties as indicated by Hoehr *et al.*[85] As described in Ref. 86, significantly faster degrada-

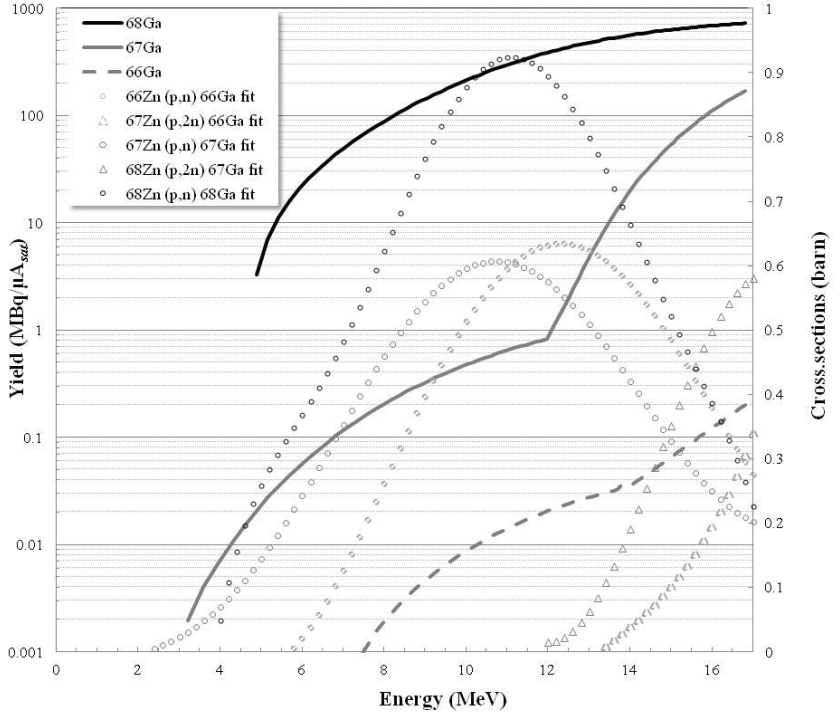

Fig. 4. Thick target yields at saturation (solid curves) for the production of ^{66}Ga, ^{67}Ga and ^{68}Ga from a typical proton-irradiation of a liquid target with 200 mg of ^{68}Zn and excitation functions (open symbols) of the nuclear reactions of interest.

Table 6. Predicted production yields of ^{66}Ga, ^{67}Ga and ^{68}Ga for the different niobium target windows used.

200 mg ^{68}Zn	Target window					
Production yields (±20%) (MBq/μA@sat.)	35 μm Havar and 35 μm Nb (16.9 MeV protons)	125 μm Nb (16.1 MeV protons)	35 μm Havar and 125 μm Nb (15.5 MeV protons)	250 μm Nb (14.2 MeV protons)	35 μm Havar and 250 μm Nb (13.6 MeV protons)	325 μm Nb (12.9 MeV protons)
^{66}Ga	0.20	0.13	0.097	0.048	0.032	0.027
^{67}Ga	169.4	113.0	81.79	24.4	10.54	3.65
^{68}Ga	729.2	717.1	690.3	599.0	545.6	484.9

tion of the target window was observed when compared to the more conventional irradiations. However, this phenomenon does not represent any inconvenience for the production of ^{68}Ga, apart from the eventual need of more frequent maintenance. This increased deterioration may be attributed to the particular conditions at the foil/solution interface when under bombardment with low pH. Moreover, additional concern in the target foil resistance arises from the use of thicker target

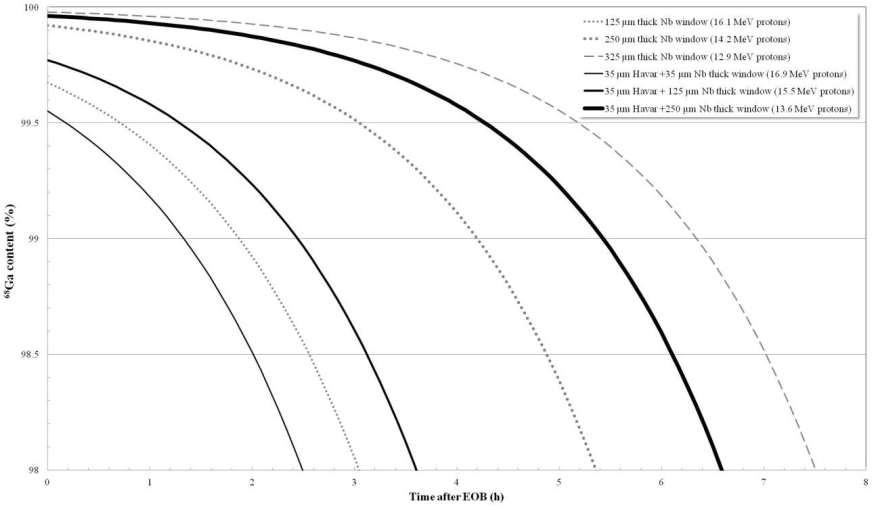

Fig. 5. Theoretical predictions of the purity of the ^{68}Ga produced, as a function of time after EOB, for several target windows.

foils to degrade the beam energy.[86] Although all the target window foils referred were successfully used routinely,[86] we also investigate the use of a target window composed by a thin Havar foil followed by a niobium foil as used for the production of ^{64}Cu, in order to provide additional mechanical strength as Havar foils have proven beam resistance.

The conducted productions of ^{68}Ga show that the activity of ^{66}Ga, ^{67}Ga and ^{68}Ga transferred corresponds consistently to about 70% of the theoretical predictions. A typical 45 min long irradiation with a solution of concentration around 30 mg/ml irradiated with 45 μA leads to the production of about 6 GBq of ^{68}Ga. Furthermore, the irradiations also confirmed that the production yield of the present technique is 1.5 MBq/(μAh $\cdot$ mg); enabling thus (i) the minimization of the amount of ^{68}Zn required and the optimization of the production conditions according to each production requirements and (ii) the production of more than 40 GBq of ^{68}Ga when required (e.g. by simply increasing the concentration of ^{68}Zn).

Table 7 presents the purity of the produced ^{68}Ga as a function of time for both the theoretical predictions and experimental data, confirming that high purity is maintained even several hours after EOB. The experimental results are quantitatively in agreement with the calculated predictions; although small discrepancies were expected due to the uncertainty in the niobium foils thicknesses (the manufacturer claimed a precision of 10%).

4.2.2. *Purification*

Purification was performed as described previously.[86,87] The irradiated target solution was loaded onto a strong cation exchange resin column to separate ^{68}Ga from

Table 7. Theoretical predictions and experimental measurements of the purity of the ^{68}Ga produced with time, for two distinct target windows composed of a 35 μm thick Havar followed by 35 μm and 250 μm thick niobium foils.

		^{68}Ga		^{67}Ga		^{66}Ga	
		Theo.	Exp.	Theo.	Exp.	Theo.	Exp.
35 μm Havar and 35 μm niobium	@EOB	99.55	99.51	0.44	0.48	0.004	0.009
	1 h after EOB	99.18	99.11	0.81	0.88	0.007	0.015
	1 h after EOB	98.51	98.38	1.48	1.59	0.012	0.026
	1 h after EOB	97.3	97.07	2.68	2.88	0.021	0.045
	1 h after EOB	95.16	94.77	4.80	5.16	0.036	0.075
	1 h after EOB	91.47	90.81	8.46	9.06	0.059	0.124
35 μm Havar and 250 μm niobium	@EOB	99.96	99.95	0.037	0.042	0.0009	0.0037
	1 h after EOB	99.93	99.92	0.068	0.078	0.0015	0.0064
	1 h after EOB	99.87	99.85	0.124	0.142	0.0027	0.011
	1 h after EOB	99.77	99.72	0.227	0.260	0.0046	0.019
	1 h after EOB	99.58	99.49	0.416	0.475	0.0078	0.032
	1 h after EOB	99.23	99.08	0.76	0.87	0.013	0.056

^{68}Zn and other impurities. The target solution was mixed and dissolved in water 10 times (3 ml target volume) and loaded to a cation exchange resin (SCX; DOWEX 50W-X8, 200–400 mesh, H+ form, pre-treated with 10 ml of 3 M HCl followed by 10 ml of water). The column was washed with 5 ml of water to remove isotopes such as ^{11}C, ^{13}N and ^{18}F. The column was then eluted with 30 ml of 0.5 M HBr in 80% acetone to remove the zinc ions,[87] followed by 5 ml of water to remove any traces of HBr and acetone. Subsequently, ^{68}Ga cations were eluted with 3 M HCl (6 ml), mixed with concentrated HCl (to increase molarity) and passed through an anion exchange column (SAX; Biorad 1X8, 100 mesh; Ø: 1 cm; h: 2 cm, treated with 10 ml of water, 10 ml of 8 M HCl and dried with air). ^{68}Ga was retained in the column and a flow of inert gas was applied to dry the column and remove any traces of HCl. Finally, ^{68}Ga was eluted from the column with 0.1 M HCl to a final product vial in the form of $^{68}GaCl_3$.

All the solutions were analyzed with atomic absorption spectroscopy (AAS) for the quantitative determination of possible metal contaminants such as iron and copper.

4.2.3. *Labeling*

The ^{68}Ga solution obtained in purification step was loaded onto a cation exchange column to be concentrated as described by Zhernosekov *et al.*[89] Briefly, the ^{68}Ga solution was loaded to a SCX cartridge preconditioned with 1 ml of 4 M HCl followed by 10 ml of water. The cartridge was then purged with inert gas to remove any traces of HCl. The ^{68}Ga was eluted from the SCX cartridge with 1 ml of acetone (98%)/HCl 0.02 M directly into a reaction vial pre-loaded with 50 μg of DOTA-NOC peptide dissolved in 1 ml of 0.5 M HEPES buffer (pH = 3.9) and allowed

to react during 10 min at 105°C. After the reaction, the crude mixture was cooled and diluted with 5 ml of sterile water before being loaded into a C18 SPE cartridge for the quantitative adsorption of the peptide onto the column. The cartridge was washed with 5 ml of sterile water and the ^{68}Ga-labeled peptide was eluted from the cartridge with 1 ml of ethanol:saline (3:1) followed by 9 ml of saline solution to obtain the purified ^{68}Ga-labeled peptide. The product was then sterilized by filtration through a 0.22 μm membrane filter and transferred to the final vial.

5. Conclusions

This work describes the development of an improved technique to produce radioisotopes through the irradiation of liquid targets, exemplifying the process by emphasizing the particular relevant productions of ^{64}Cu and ^{68}Ga. The set-up developed is a fully automated system commercially available, including the cyclotron, targets and synthesis modules from IBA. ^{64}Cu and ^{68}Ga are produced through the proton irradiation of ^{64}Ni and ^{68}Zn-based solutions, respectively, loaded into IBA Nirta Ga® and IBA Nirta Cu® niobium liquid target systems with an IBA Cyclone 18/9 cyclotron. ^{64}Cu and ^{68}Ga are then separated, purified and incorporated in a final injectable labeled radiopharmaceutical solution using the Synthera® synthesis modules (Synthera® Extension and Synthera®).

The technique enables the production of purified solutions suitable for labeling radiopharmaceuticals for human use with final activities large enough to make possible the distribution to other PET centres. The production yields are about 0.14 MBq/(μAh · mg) and 1.5 MBq/(μAh · mg) for ^{64}Cu and ^{68}Ga, respectively, leading to the production of about 5 GBq and 6 GBq of ^{64}Cu and ^{68}Ga with typical irradiations. However, it is possible to produce batches of 25 GBq and 40 GBq of ^{64}Cu and ^{68}Ga, respectively, if necessary by maximizing the concentration of the liquid target solution. Since the amount of the expensive enriched material can be chosen and optimized to suit the requirements of each production, a very substantial cost reduction is achieved when compared to the solid target technique.

The purification of the irradiated solution and the following synthesis leading to the production of the labeled radiopharmaceuticals suitable for human use are performed in only one hour after EOB; which is a significant improvement with respect to the inevitable delicate and time-consuming post-irradiation processing associated with the solid target technique. This improvement is even more important for the case of ^{68}Ga since it allows us to maintain the high purity of the product several hours after EOB. Similarly, the time-consuming and delicate preparations inevitably occurring for each irradiation in the solid target technique are eliminated when using the present technique, since a unique preparation of the enriched target solution is enough to satisfy tens of productions.

For the particular case of the production of ^{68}Ga, one has to point out two additional major advantages arising from the use of the technique presented when compared to the use of the ^{68}Ge/^{68}Ga generator. On one hand, consecutive synthesis can be performed unlike what happens when using a ^{68}Ge/^{68}Ga generator

for which the down-time between the elutions is non-negligible and inevitable, thus representing a major inconvenience in the daily production schedule of ^{68}Ga-based radiopharmaceuticals. On the other hand, apart from referred the radioisotropic impurities, the purified solution does not contain additional long-life radio-impurities; as it occurs with ^{68}Ge/^{68}Ga generators for which the constant risk of ^{68}Ge breakthrough is a main concern.

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