Simplified targetry and separation chemistry for ^{68}Ge production

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Introduction

Ge-68 ($t_{1/2}$= 270.8 d, 100% EC) is an important radionuclide for two reasons: 1) once in equilibrium with its daughter nuclide ^{68}Ga ($t_{1/2}$= 68 min, 89% β^+, 3% 1077 keV γ), it can be used as a positron source for attenuation correction and calibration of PET/MRI scanners; and 2) it can be employed as a generator of ^{68}Ga for radiopharmaceutical preparation.

Ge-68 is produced using natural gallium (60.1% ^{69}Ga, 39.9% ^{71}Ga) as target material for proton bombardment at energies >11.5 MeV, the threshold energy for ^{69}Ga(p,2n)^{68}Ge . Gallium targetry, however, is challenging due to its low melting point (39°C) and corrosivity towards most metals. Niobium, however, does not react with liquid gallium at a temperature < 400 °C [1], and this is why large-scale production of ^{68}Ge is carried out by irradiating water-cooled targets made of gallium encapsulated in niobium containers [2, 3], albeit niobium's low thermal conductivity, that is about a quarter of that of aluminum, 54 vs 235 W/mK at room temperature. Hence, gallium-based compounds with higher melting points and no corrosivity, such as Ga_2O_3 (mp = 1900°C) [4, 5] or Ni_xGa_y alloys (mp > 800°C) [6, 7], have been used as target compounds. The latter one being preferred for targetry applications due to its electric and thermal conductivity properties.

The separation chemistry technique employed by large-scale production facilities is liquid-liquid extraction using CCl_4 [3, 5], a solvent classified as Q3C class 1 by the USA Food and Drug Administration (FDA), not recommended for drug manufacturing due to unacceptable toxicity. Hence, alternative radiochemical separation methods that employ nontoxic reagents but maintain high separation yields are needed.

In this work, two simple methods for Ni_xGa_y alloy preparation are presented as well as a simple germanium separation procedure, with a separation efficiency of 75% in 2 mL of diluted HNO_3, using a commercially available extraction resin.

Material and Methods

Ni_xGa_y alloy targets were prepared by two methods: A) electrodeposition and B) by mixing molten gallium with nickel. The details for each method are as follows:

A) The electrolytic solution is made by dissolving Ga_2O_3 (99.9%, Aldrich) and $NiSO_4$•$6H_2O$ (99%, Sigma-Aldrich), in a 3:2 mass ratio, in (27%) H_2SO_4 (Fisher, >99.99% trace metal grade), adjusting the pH to 1.5 using concentrated NH_4OH (Sigma-Aldrich, >99.99% trace metal grade). This solution is then transferred into either a 18 or 50 mL electrolytic cell in which the cathode is a gold disk (0.61 mm thick, 1.9 cm diameter) mounted on an aluminum plate. The electroplated area is 1.3 cm^2. A platinum wire is used as the anode, with the tip bent into a spiral shape in order to have a more homogeneous electric field. A DC power supply (EXTECH 382200) provides the voltage. The applied current was 39 ± 9 mA/cm^2 (n = 12) with the platinum anode at 1 cm from the gold surface.

One of the electroplated targets was heated at 400 °C for 15 min in an argon atmosphere to verify that the melting point of the alloy was indeed higher than this temperature.

B) Gallium pellets (99.99999%, ~650 mg/pellet, Alfa Aesar) were mixed together with Ni powder (99.9%, Strem Chemicals) in a 4:1 Ga:Ni molar ratio inside a test tube (1 cm I.D.), which was then positioned on top of a crucible at the center of an induction furnace (EIA Power Cube 45/900, average reactive power = 45 kVAR). The two metals fused together after ~2 min with the furnace set to 45% maximum power. The metal mixture was left in the inductor under this power setting for > 15 min to let the alloy homogenize or anneal, as it is claimed that the induced currents have a stirring action over the alloy material [6]. After this, the alloy pellet was left to gradually cool down by lowering the power of the inductor in 5% steps every one minute until the inductor was turned off. The resulting alloy pellet was then rolled to a foil using a jeweler's mill pressed between Nb foils to avoid contamination.

As with the electroplated alloy, a fused alloy was heated to 400 °C for ~15 min in an argon atmosphere. In this case, however, the foil was placed on top of a silver disk in order to verify that it is not corrosive in contact with this metal, and thus to know whether it can be irradiated if directly placed on top of this excellent heat

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conductor having water-jet cooling applied on the opposite side.

Following method B), alloys with Ga:Ni molar ratios of 1.0, 2.0, 2.9, 3.7 and 5.2 were manufactured to be used as standards for the analysis of the electroplated ones by x-ray fluorescence (XRF) spectroscopy using a ^{109}Cd excitation source (23 keV) and quantifying the characteristic x-rays peaks 9.26 keV and 7.48 keV from Ga and Ni, respectively, using a low energy high purity germanium (HPGe) detector (Canberra GL0110P).

Target irradiations were performed on a GE PETtrace with 16 and 15.2 MeV protons on the electroplated and fused targets, respectively. The electroplated alloys were mounted on a custom-made solid target irradiation system with direct water-jet cooling applied to the backside of the gold disk, a schematic of which is shown in Figure 1. The alloy foils were placed on top of in a 1.2 cm diameter, 406 µm deep pocket made of niobium, to avoid corrosion, and sealed against a 51 µm Nb foil using a teflon O-ring, as shown in Figure 2. These Nb-encapsulated alloys were placed on the same solid target irradiation system used with the electroplated alloys, also having water-jet cooling applied on the backside, as shown in Figure 3. Only one thick $NiGa_4$ foil (409.5 mg/cm^2 = 635 µm) and one thick electroplated $NiGa_3$ alloy (245.3 mg/cm^2 = 375 µm) have been irradiated for ^{68}Ge production.

The irradiations were carried out over several days, increasing the proton current by 5 µA each day, the initial current being 15 and 20 µA for the fused and electroplated targets, respectively. The integrity of the targets was verified between irradiations by visual inspection to determine if higher currents were feasible.

Ge separation was achieved based on the difference in distribution coefficients between Ge, Ga, Zn, Cu, Ni and Co at different HNO_3 molarities in DGA resin (branched 50-100 µm, Triskem International) [9]. The irradiated NiGa alloys were left to decay for 2 weeks in order to significantly reduce the co-produced radionuclidic impurities ^{69}Ge ($t_{1/2}$ = 39.05 h) and ^{55}Co ($t_{1/2}$ = 17.53 h) from ^{69}Ga(p,n) and ^{58}Ni(p,α), respectively, and then dissolved in 6 mL of concentrated HNO_3 (Ultra grade, VWR). The solution was then passed through 200 mg of DGA resin packed in a 5 mm diameter column (SPE 1.5 mL reservoir, Grace Davison Discovery Sciences) at a constant flow rate of 1.1 mL/min using a peristaltic pump (Welco). The packed resin is previously rinsed with 1 mL of deionized water and then equilibrated with 1 mL of concentrated HNO_3. The "trap and release" sequence, which is summarized in Figure 4, was as follows:

1. Load the target solution with an HNO_3 concentration > 8 M to trap ^{68}Ge.
2. Wash the column with 5 mL of concentrated HNO_3.
3. Elute ^{68}Ge in fractions of 200 µL of deionized water.

A separation profile for Ge, Ga and Co was obtained by collecting 0.2 – 1.0 mL fractions throughout the separation process, which were analyzed by gamma ray spectroscopy using an HPGe detector (Canberra C1519).

The radionuclidic purity of the isolated ^{68}Ge was determined by gamma ray spectroscopy on a sample composed of the first five 200 µL fractions (1 mL). This sample with ~2.95 MBq (79.6 µCi) of ^{68}Ge was placed at 1 m from the face of the HPGe detector, having a deadtime < 10%, where an efficiency calibration with ^{137}Cs and ^{60}Co NIST-traceable standards (Amersham) had been performed. The gamma lines used to quantify the yields and radionuclidic impurities were: 1077 keV (^{68}Ge/^{68}Ga), 122 keV (^{57}Co) and 1115 keV (^{65}Zn).

An electroplated alloy (82.7 mg/cm^2 thick) was processed in a "cold run", that is, without irradiation, for trace metal analysis using Agilent's microwave plasma atomic emission spectroscopy (MP-AES) system. The separation factors (SF) for each of the main metal impurities was calculated by dividing the total mass of each in the target dissolution over the mass in the 2 mL eluate that contains the separated ^{68}Ge.

Results and Conclusion

Table 1 summarizes the electroplating results. Using the 50 mL cell, a deposited layer that is 245.3 mg/cm^2 (375 µm) was obtained after two electroplating runs over the same disk, each run being 6 days long. Figure 5 shows the typical macroscopic and microscopic appearance of the electroplated NiGa alloys, demonstrating the homogeneity and smoothness of the deposit.

The electroplated target did not melt and looked intact under 10x magnification on an optical microscope after heating it at 400 °C, which indicated that this alloy was indeed going to sustain high power irradiations. Heating the fused alloy at 400 °C on top of a silver disk, on the other hand, resulted in visible spots of corrosion on the silver surface, indicating that small heterogeneities exist in the alloy, in which pure gallium had not fused with nickel. This result demonstrated that even though the fused alloys have a high melting point, they are not homoge-

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nous enough to ensure that the solid target station components will not be corroded by traces of pure gallium that could potentially come into contact with them. For this reason these alloys were encapsulated in niobium for irradiation.

From the XRF spectroscopy analysis a linear relationship with an R^2=0.967 was found between the ratio of count rates of the Ga and Ni characteristic x-rays peaks to the alloy Ga:Ni molar ratio, from which the molar ratio composition of the electroplated alloy was determined as 3:1, Ga:Ni. This result was confirmed by trace metal analysis of a dissolved target using the MP-AES system, obtaining 2.9 ± 0.2, Ga:Ni. These results indicate that the molecular formula of this alloy is $NiGa_3$.

A simulation of 16 MeV protons over $NiGa_3$ material, using the SRIM (Stopping and Range of Ions in Matter) software [8] software, indicates that a thick target for ^{68}Ge production needs to be at least 330 µm (216 mg/cm^2) thick, a thickness that has been achieved using the 50 mL cell as shown in Table 1.

Different from the fused alloys, the electroplated $NiGa_3$ targets are not corrosive against the solid target station. Therefore, niobium components with low thermal conductivity are not required. In fact, the gold substrate of the electroplated targets acts as an excellent heat conductor for water-cooling during irradiation due to gold's outstanding thermal conductivity of 320 W/mK. The irradiation parameters and results are summarized in Table 2. As can be seen, a current of 40 µA is feasible.

Table 3 shows the results from the irradiation experiment on a $NiGa_4$ alloy. After the first irradiation with a current of 20 µA for ~5 h, the target looked intact. Hence, the following day the proton current was increased to 25 µA and the target was irradiated for 3.4 h. Visual inspection of the target revealed that the niobium degrader had reacted with traces of molten gallium from the alloy, which means that the temperature at this spot was > 400 °C, the point at which gallium and niobium react [1]. The niobium degrader was replaced after this bombardment, and a maximum current of 22 µA was applied for ~3 h for a total charge of 65 µAh, after which the target looked intact. Therefore, 22 µA is the maximum current that can be applied to this target system without compromising the integrity of the degrader.

Figure 6 contains the separation profile and Figure 7 the elution profile with DGA resin. 75% of the ^{68}Ge produced at end of bombardment is eluted in 2 mL of deionized water.

The gamma spectroscopy analysis revealed that the main radionuclidic impurity in the separated fraction is ^{65}Zn ($t_{1/2}$ = 243.93 d) from ^{69}Ga(p,nα), which accounts for <0.1% of the total activity in the eluted fraction.

The results from the trace metal analysis are summarized in Table 4.

In conclusion, we have developed two simple methods for the manufacture of thick NiGa alloys. The best method for targetry applications is via electrodeposition of $NiGa_3$ on a gold disk, which we believe is a more convenient target for ^{68}Ge production compared to gallium encapsulated in niobium. The separation method based on the extraction resin DGA offers a 75% ^{68}Ge separation yield that is similar to the one from liquid-liquid extraction employed by most large-scale production facilities. We believe this is a more convenient separation method since it only requires a single "trap-and-release" step and not many extraction steps. Furthermore, this method avoids the use of toxic solvents such as CCl_4 not recommended for drug manufacturing by the FDA.

	18 mL cell	50 mL cell
Electrodeposition time per run [days]	3 ± 1	6
Deposited mass per run [mg/cm^2]	34.2 ± 4.9	123.4 ± 12.5
Maximum thickness [mg/cm^2]	83.1 ± 10.9	245.3
(Number of sequential runs)	(3)	(2)

TABLE 1. Electrodeposition results

Irradiation day	I_{max} [µA]	Q [µAh]	Yield [kBq/µAh] ^{68}Ge	^{65}Zn
1	20	50		
2	25	24		
3	30	56		
4	35	70		
5	40	60	43	1.3

TABLE 2. Irradiation parameters and yields after proton bombardment on $NiGa_3$ electroplated on gold.

Irradiation day	I_{max} [µA]	Q [µAh]	Yield [kBq/µAh] ^{68}Ge	^{65}Zn
1	20	100		
2	25	85		
3	22	65	44	1.8

TABLE 3. Irradiation parameters and yields after proton bombardment on a $NiGa_4$ foil encapsulated in Nb.

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	Ga	Fe	Zn	Ni	Co	Cu
ppm	41	19	5.0	3.1	0.23	0.23
mM	0.59	0.76	0.077	0.053	0.004	0.0040
µg	82	80	10.1	6.2	0.5	0.46
SF	770	570	10	2900	990	1200

TABLE 4. Metal impurities in the 2 mL ^{68}Ge eluate.

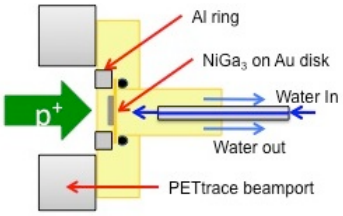


FIGURE 1. Schematic of the electroplated NiGa targets mounted on the solid target station of our GE PETtrace cyclotron.

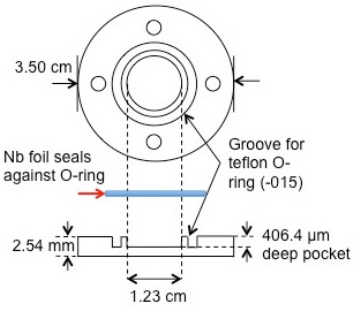


FIGURE 2. Drawing of the Nb pocket for encapsulating the fused NiGa foils.

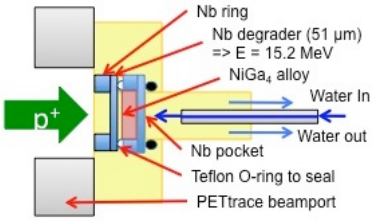


FIGURE 3. Schematic of the fused alloy targets mounted on the cyclotron's solid target station.

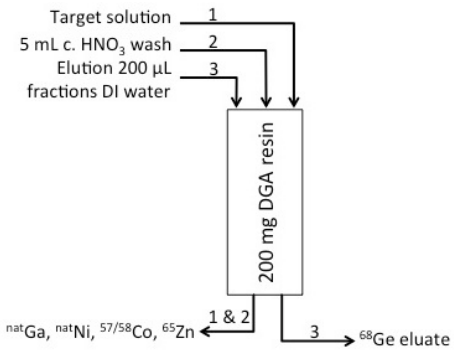
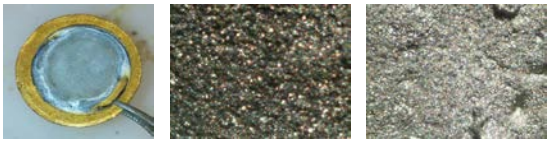


FIGURE 4. ^{68}Ge separation scheme.



(a) (b) (c)

FIGURE 5. (a) Macroscopic appearance of NiGa electroplated over a gold disk and microscopic appearance from an optical microscope using (b) 4x and (c) 10x magnification.

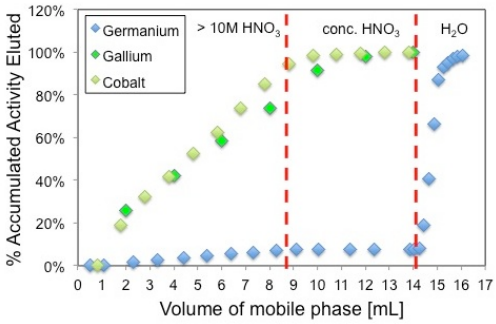


FIGURE 6. Separation profile of Ge, Ga and Co in DGA resin

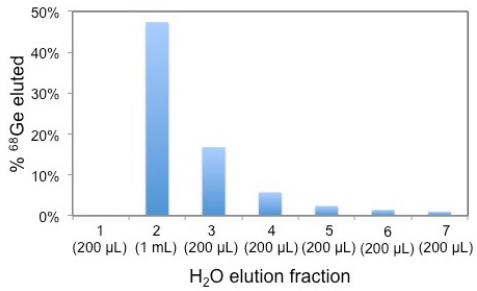


FIGURE 7. Elution profile of ^{68}Ge trapped in DGA.

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