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Fused Zinc Target for the Production of Gallium Radioisotopes

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Abstract: Gallium-68 is a popular radioisotope for positron emission tomography. To make gallium-68 more accessible, we developed a new solid target for medical cyclotrons. Fused zinc targets promise a new, efficient, and reliable technique without the downsides of other commonly used time-consuming methods for solid target fabrication, such as electroplating and sputtering. We manufactured targets by fusing small pressed zinc pellets into a recess in aluminum backings. Using a simple hotplate, the fusing could be accomplished in less than two minutes. Subsequently, the targets were cooled, polished, and used successfully for test irradiations at E_p = 12.8 MeV and up to 20 μA proton current.

Keywords: PET; medical isotopes; Ga-68; solid target

1. Introduction

As positron emission tomography (PET) is becoming more accessible, the use of radiotracers labeled with positron-emitting radiometals has steadily increased. Isotopes such as ^{44}Sc, ^{68}Ga, ^{64}Cu, ^{86}Y and ^{89}Zr offer a wide range of half-lives, and chemical and imaging characteristics, thus greatly advancing the development of new radiopharmaceuticals. In recent years, ^{68}Ga, in particular, has gained much interest in oncological imaging, where it is used in combination with analogous therapeutic radiotracers labelled with ^{90}Y, ^{177}Lu or ^{225}Ac [1].

^{68}Ga is commonly eluted from ^{68}Ge/^{68}Ga generators. It can also be produced on small medical cyclotrons via the ^{68}Zn(p,n)^{68}Ga reaction (see Figure 1 for relevant cross sections) in quantities that exceed those available from current generators [2–6]. While other nuclear reactions are also feasible [7], the irradiation of ^{68}Zn with protons is most convenient and offers high production yield.

Several types of targets, such as foils and coatings, have been described; however, the commercial availability of isotopically enriched foils is rather limited. Zinc can also be sputter coated or electroplated on various substrates. Both processes are time consuming and require specialized equipment and expertise.

Metallic zinc targets necessitate a solid target station on the cyclotron. The target plate may be placed and retrieved manually or via a dedicated transfer system. Manual removal results in radiation exposure to the operator due to radiation fields from the target and activated components in its vicinity. Once the irradiated plate has been moved to the processing hotcell, the target material needs to be dissolved and the gallium radioisotope purified.

A particularly attractive way of extracting gallium radioisotopes from zinc foils is the thermal diffusion method described by Tolmachev and Lundqvist [8]. In their experiments, irradiated foils were heated to approximately 400 °C for an extended period, which caused the gallium isotopes to migrate to the surface of the foil, from which they could be removed by etching with diluted acid.

Reportedly, more than 60% of the produced radioactivity could be separated from the zinc matrix in 15 min, with minimal loss of target material.

Here, we set out to develop an efficient, fast target preparation method to facilitate the production of gallium radioisotopes for research and development of radiopharmaceuticals. Furthermore, we attempted to apply the thermal diffusion method to our fused targets. Finally, we demonstrated the radiochemical purification of gallium radioisotopes from zinc based on the method by Engle et al. [7].

(**a**) (**b**)

Figure 1. Target plate preparation. (**a**) A Ø35 mm × 1 mm aluminum backing plate with a Ø10 mm × 0.3 mm recess for the target material, and the pellet formed from zinc (150–300 mg) before fusing; (**b**) Zinc pellet fused to the backing plate before polishing.

2. Materials and Methods

The target backing was manufactured from 1100 grade aluminum (AL1100, McMaster-Carr) because of its good heat transfer properties, low cost and low activation in the target area of a medical cyclotron. A quantity of 150–300 mg of irregularly shaped natural zinc shavings (99.9%, Sigma-Aldrich) were pressed into flat 10-mm-diameter pellets using a hydraulic press at ~12,500 MPa. A density of 94% of bulk zinc material was achieved. Targets were prepared by fusing the pressed pellet to the aluminum backing (35 mm diameter × 1 mm thickness) by heating the aluminum backing to 450–500 °C on a hotplate (Corning), then placing the pellet into the 0.3 mm deep recess. The fusing process was allowed to proceed for 20–30 s. The target was then removed from the hotplate and quickly cooled by placing it on a cold metal surface. The entire process took about 2 min. After cooling, the targets were manually polished with sandpaper of grades 400, 600, 800 and 1000 (Norton Abrasives), rinsed with methanol and dried.

In this proof-of-principle study we used natural zinc with its isotopic composition shown in Table 1. The prevalent cross sections for the production of gallium radioisotopes (Table 1), scaled by the abundance of the starting zinc isotopes, are shown in Figure 2. The long-lived gallium isotope ^{66}Ga ($T_{1/2}$ = 9.49 h) was used to study the diffusion of radioactive gallium in the target matrix as well as the radiochemical purification.

Table 1. Natural abundance of zinc isotopes [9] and produced gallium isotopes. Half-lives from [10].

Zn isotopes	**^{64}Zn**	**^{66}Zn**	**^{67}Zn**	**^{68}Zn**	**^{70}Zn**
Abundance	48.63%	27.90%	4.10%	18.75%	0.62%
Ga isotope	**^{64}Ga**	**^{66}Ga**	**^{67}Ga**	**^{68}Ga**	**^{70}Ga**
Half life	2.627 min	9.49 h	3.2617 d	67.71 min	21.14 min
Production	^{64}Zn(p,n)^{64}Ga ^{66}Zn(p,3n)^{64}Ga	^{66}Zn(p,n)^{66}Ga ^{67}Zn(p,2n)^{66}Ga ^{68}Zn(p,3n)^{66}Ga	^{67}Zn(p,n)^{67}Ga ^{68}Zn(p,2n)^{67}Ga	^{68}Zn(p,n)^{68}Ga ^{70}Zn(p,3n)^{68}Ga	^{70}Zn(p,n)^{70}Ga

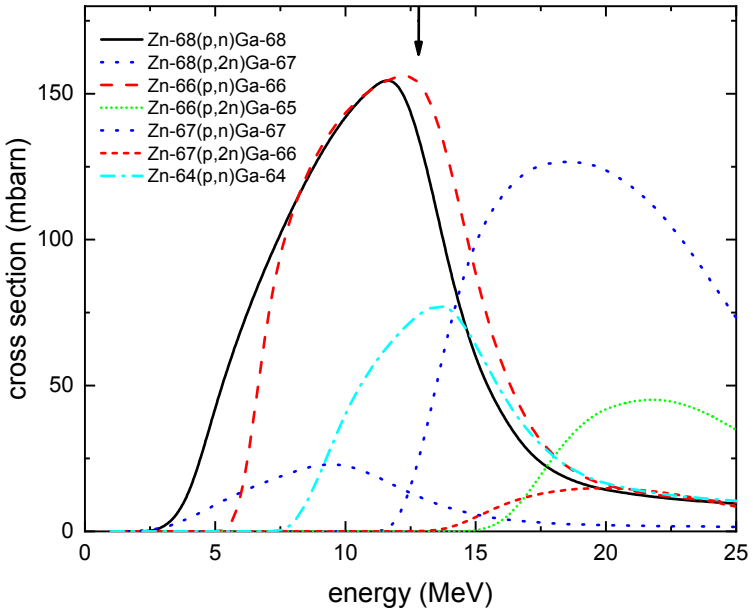


Figure 2. Main cross sections for the production of gallium isotopes from zinc, with the zinc isotopes scaled for natural abundance (see Table 1). The entrance energy of the proton beam in our production is marked with an arrow. Data from [11].

All irradiations were performed on TRIUMF's TR13, a 13 MeV self-shielded, negative hydrogen ion cyclotron [12,13]. The target plate was manually mounted in our standard solid target holder, which places the plate perpendicular to the proton beam. The target body and the back of the target plate were water cooled. The front of the target plate was cooled via helium jets impinging onto the plate and onto a 25-µm-thick aluminum foil that separates the target assembly from the cyclotron vacuum. The energy of the proton beam on the target was approximately 12.8 MeV as determined by [14]. As the target body was electrically isolated, the beam current on the target could be directly measured. The maximum beam current was limited to 20 µA due to license restrictions and radiation safety concerns.

In all experiments, a basic target holder was used [15]. The assembly was held together concentrically with four screws. In order to retrieve the irradiated plate, the system needed to be manually removed from the target selector on the cyclotron, which required disconnecting the water and helium cooling lines. The target system was then transported to a fume hood, where it was completely dismantled and the irradiated disc removed. The entire retrieval process took 8–10 min on average, with the operator having to spend approximately 5 min in close proximity to the highly radioactive targets on the selector.

In order to reduce the radiation dose to technical staff, the target was left to decay overnight (16 h). The irradiated plate was then transported to the processing fume hood in a shielded container. Yields were estimated with an ionization chamber (Capintec).

Thermal diffusion experiments were performed using a borosilicate beaker placed on a hotplate. The temperature of the target plate was measured with a thermocouple and displayed on a local readout device. A series of 13 experiments were performed to investigate the effect of various parameters on the diffusion process. Briefly, all targets were heated to a temperature near the melting point of zinc, i.e., up to ~410 °C. Diffusion was allowed to proceed for a period of 60, 120 or 180 min (n = 3, 5, 5, respectively). Targets were heated either in air (n = 10) or under argon flow (n = 3), with the zinc material facing up (n = 11) or down (n = 2).

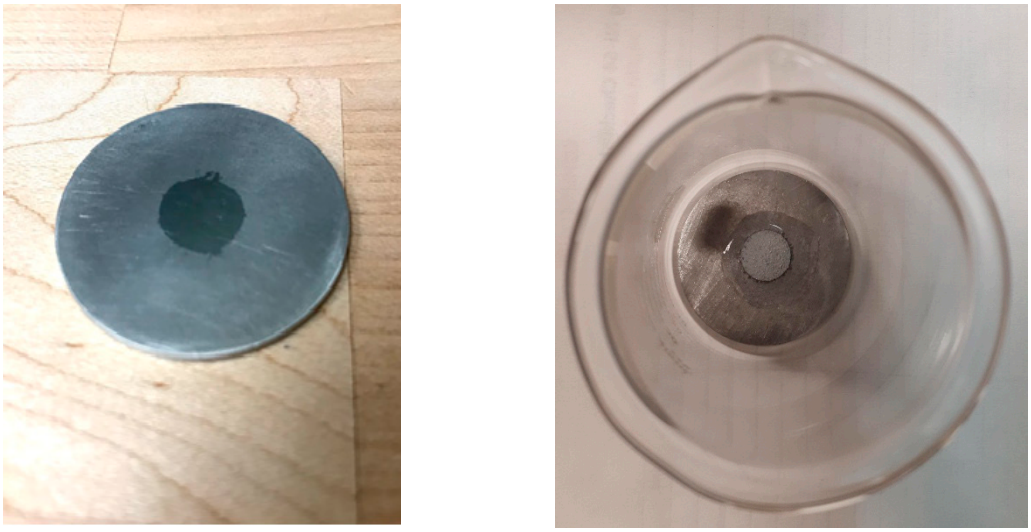
For the radiochemical purification, the target was placed into a 50-mL beaker and the zinc dissolved with 10–12N HCl (Sigma-Aldrich); lower concentrations proved to dissolve the zinc too slowly. Over 95% of the target material was dissolved in less than 10 min at room temperature, and in 2–5 min at ~50 °C. A small quantity of aluminum (milligrams) was co-dissolved in the process. In order to minimize the dissolution of aluminum, Kapton tape (U-Line) was applied in some experiments to protect the aluminum target face.

Gallium radioisotopes were purified as reported in [7] by ion exchange chromatography on AG50W-X8 cation exchange resin. The gallium was eluted in 4N hydrochloric acid.

3. Results and Discussion

3.1. Irradiation

Figure 3a shows a fused target after a 15-min irradiation with 12.8 MeV protons and 20 μA beam current. There was no indication of overheating, discoloration or loss of target material. All targets remained intact, with the fused zinc pellet firmly attached to the backing. Further experiments at higher beam currents and with longer irradiation times will be conducted once an improved target system that allows remote handling of the irradiated disc becomes available [15].



(**a**) (**b**)

Figure 3. (**a**) Target plate after irradiation. The streaks of zinc on the aluminum plate are caused by the polishing. (**b**) Target plate being dissolved inside a beaker.

The ^{66}Ga yield from a 15-min irradiation with 10-μA beam current decay corrected to the end-of-bombardment (EOB) was 400 MBq. Taking the experimental results from [16] and scaling the ^{68}Ga activity from the ^{66}Ga activity, we estimate the EOB activity of ^{68}Ga from our fused target to amount to approximately 3.1 GBq.

3.2. Thermal Diffusion Experiments

In summary, none of our diffusion experiments yielded results comparable to those published in [8]. In all cases, the recovery of ^{66}Ga from the zinc pellet remained below 10% of the total ^{66}Ga radioactivity produced, which is six to eight times less than the yields reported by Tolmachev et al. [8]. We did not notice any effect of varying process parameters or the orientation of the target plate during the heating cycle or whether the experiment took place in an argon atmosphere or in air. The particular reason for this discrepancy remains unknown. It was speculated that our particular heating apparatus (hot plate/beaker) may have been less than adequate, as the experiments reported in the literature were conducted in a sealed tube furnace under tight temperature control and in high purity argon. Moreover, [8] describes the thermal diffusion of radiogallium in thin, rolled zinc foils. Fused zinc targets may have a different matrix structure or contain a small quantity of zinc oxide that could potentially impede the migration of gallium through the matrix.

3.3. Radiochemical Purification

The radiochemical purification of gallium isotopes from zinc is well established, and several procedures to isolate high specific activity $^{66/68}$Ga have been proposed. We chose to demonstrate the general feasibility of extracting ^{66}Ga from fused zinc targets using the cation exchange method by Engle and co-workers due to its efficiency and convenience.

After irradiation and cooldown, the zinc material was dissolved in an excess of 10N hydrochloric acid (HCl) and passed through a 2-mL column of AG50W-X8 cation exchange resin conditioned with 10N HCl. The column was rinsed with two column volumes each of 10N HCl and 7N HCl. ^{66}Ga was then eluted with 4N HCl. Approximately 90% of the produced ^{66}Ga was recovered in the product solution. The entire separation procedure took approximately 30 min.

4. Conclusions

We reported on a simple zinc target manufacturing for the production of gallium isotopes. The target plate fabrication took about 2 min using a simple hotplate. Due to the manual operation of our solid target system, the proof-of-principle was conducted on the longer lived ^{66}Ga to reduce radiation exposure to the cyclotron team and the chemist processing the target. The target was irradiated up to 20 μA at a beam energy on target of 12.8 MeV. No negative effect on the target plate was observed. Heating the irradiated target plate to diffuse the produced ^{66}Ga to the surface was unsuccessful, maybe due to the heating on a hot plate instead of a more sophisticated tube furnace. After dissolution of the target plate, 400 MBq was measured (decay-corrected). This relates to an estimated activity of 3.1 GBq for ^{68}Ga at EOB (natural Zn) or 16.7 GBq (99.5% ^{68}Zn).

Fused targets require little preparation of the target backing, minimal manufacturing time, few materials and tools, thus reducing overall manufacturing cost. Furthermore, the simplistic nature of the method opens up the possibility of large-scale target production. Future experiments will be required to confirm the integrity of fused targets at higher beam currents and extended irradiation periods.

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