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Cyclotron production of ^{68}Ga via proton-induced reaction on ^{68}Zn target

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Abstract. ^{68}Ga is an important positron-emitting radionuclide for positron emission tomography. In this work ^{68}Ga was produced via the ^{68}Zn(p,n)^{68}Ga nuclear reaction. ^{68}Zn electrodeposition on a copper substrate was carried out by alkaline cyanide baths. ^{68}Zn target was irradiated with a 15 MeV proton beam and a 150 μA current. The production yield achieved was 136 mCi/μA·h (5.032 GBq/μA·h). ^{68}Ga was separated from zinc and copper by a combination of cation exchange chromatography and liquid-liquid extraction methods.

Key words: production • gallium-68 • zinc-68 • PET • cyclotron

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Introduction

Positron emission tomography (PET) is a non-invasive medical imaging technology that can generate high-resolution images of physiologic functions with clinical application for oncology, cardiology and neurology [19]. ^{68}Ga ($T_{1/2}$ = 68 min) decays by β^+ (89%) and therefore is suitable for PET imaging. ^{68}Ga-based imaging agents to study pulmonary, myocardial and cerebral perfusion as well as renal and hepatobiliary function, to detect blood-brain barrier defect, to image tumor, brain, and bone have been investigated [2, 7, 12]. ^{68}Ga is employed for transmission measurements for encoding calibration and normalization of detector efficiencies of PET scanners [1]. ^{68}Ga-DOTATOC is a somatostatin analogue for highly sensitive and specific PET imaging of neuroendocrine tumors [3, 11, 18].

Several methods for ^{68}Ga production have been developed using cyclotrons. The ^{68}Zn(p,n)^{68}Ga reaction is suitable for medium to low-energy cyclotrons (Table 1).

Solid targetry system on this accelerator is made up of pure copper backings onto which target material is electrodeposited. An alkaline cyanide bath was chosen as electrolyte solution.

Cation exchangers are more useful with gallium than anion exchangers [4, 6, 14]. Hence, cation exchange resin (Bio-Rad AG 50W) was used in this work.

Table 1. Nuclear reactions for the production of ^{68}Ga using TALYS code

Nuclear reaction	E_{thr} (MeV)	Natural abundance (%)	Maximum cross-section (mb)	Proton energy (MeV)	Q-value (MeV)
^{68}Zn(p,n)^{68}Ga	3.76	18.8	632	13	–3.70
^{68}Zn(d,2n)^{68}Ga	6.10	18.8	728	15	–5.92
^{70}Zn(p,3n)^{68}Ga	19.70	0.6	365	31	–19.40
^{65}Cu(α,n)^{68}Ga	6.18	30.83	601	15	–5.82

Material and methods

Target preparation

Enriched zinc (97% purity) used as the target material was prepared at the Isotopes Research Group, and irradiation was carried out with an external proton beam of a cyclotron (IBA-Cyclone 30) at the Agriculture, Medicine and Industrial Research School (AMIRS).

The optimum conditions of the electroplating bath were obtained with a volume of about 450 ml containing 2.7 g·l^{-1} ZnO, 7.1 g·l^{-1} KCN, 11.1 g·l^{-1} KOH, pH = 13–14, at 40°C, while the current density was adjusted to 8.55 mA·cm^{-2} with an 89% current efficiency.

Non-reactive plating vessels are hollow Perspex cylinders (diameter 6 cm, height 20 cm) fitted with an axial Pt anode wire mounted at the bottom by a tube-end fitting with a perforated septum. Four symmetrical windows (22.36 or 11.69 cm^2) on the vertical side wall allow up to four copper targets backing positioning. Each slot is sealed by an O-ring fitted-window. The slot geometrical shape determines the actual target electrodeposition area. Windows liquid-tight sealing is realized by stainless steel mechanical pestles mounted on a PVC ring surrounding plating vessel and by pressing the copper backing against O-ring seal. An external PVC ring is fitted with four supporting pins to hold a motor-stirrer combination in position. The stirrer is a hollow perforated POM (polyoxymethylene) cylinder mounted on the axis of a DC motor and surrounding the platinum anode. The stirrer rotation speed is set at 600 rpm; during the process, its rotating direction is reversed after each 8 s to improve deposit homogeneity. To keep the desired temperature at a preset level, a heater (a series of six isolated 1 Ω/1 W resistors, through which an appropriate DC-current is forced (1.1A – 40°C up to 1.8A – 60°C) is circularly mounted at the bottom of the vessel. An insulated sensor, introduced through the stirrer support-plate, monitors the plating bath bulk temperature. As electrolysis to depletion requires a long-time (up to 24 h) plating, evaporation of plating solution occurs. To maintain a constant liquid volume, 450 ml, a conductivity glass/graphite sensor monitors the solution level and actuates a peristaltic pump at required rate, supplying distilled water to compensate evaporation losses. The home-made electronics rack-mounted includes a motor/stirrer control, an adjustable DC voltage generator card and four V/I converters coupled to current boosters.

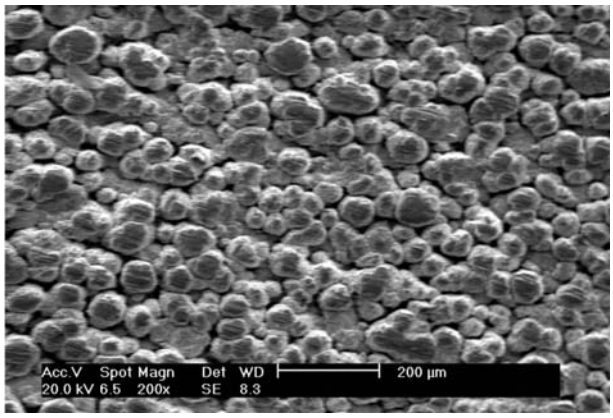

Fig. 1. SEM of a zinc deposit on the Cu backing grown at a current density of 8.55 mA·cm^{-2} from 2.7 g·l^{-1} ZnO, 7.1 g·l^{-1} KCN, 11.1 g·l^{-1} KOH, pH = 13–14, pH = 12, 40°C, 52 µm thickness.

The deposits were examined for morphology by a scanning electron microscopy (SEM) technique (using a JEOL model JSM 6400 at an accelerating voltage of 20 kV). Neither crack nor peeling off was observed on irradiated zinc target (Fig. 1).

Production

According to TALYS-1.0 code and experimental data, to take full benefit of the related excitation function and to minimize undesired radionuclide impurities formation, the incident proton energy should be 15 MeV [8, 9, 15, 16]. The physical thickness of the zinc layer is chosen in such a way that for a given beam/target angle geometry the particle exit energy should be 5 MeV. According to SRIM code [20], the thickness has to be 520 µm for a 90° geometry. It is advisable to minimize zinc deposit thickness to perform irradiations on a 6° target geometry. In such a case a 52 µm (0.037 g·cm^{-2}) deposit is recommended. This target was electroplated for 3.56 h.

To produce ^{68}Ga, the ^{68}Zn target was bombarded with 15 MeV protons. The irradiation parameters are summarized in Table 2. Identification and assay of gamma-ray emitting radionuclides was carried out using a high-purity germanium (HPGe) detector and γ-ray spectrometry (Canberra™ model GC1020-7500SL).

Table 2. Irradiation parameters of ^{68}Ga production

Run	Irradiation time (h)	Beam current (µA)	^{68}Zn weight (mg)	^{68}Zn thickness (µm)	Proton energy (MeV)
1	0.25	150	434	52	15

Table 3. ^{68}Ga production yield for proton-induced reactions in zinc target

Reaction	Beam energy (MeV)	^{68}Ga yield at EOB (GBq/μAh)	Reference
^{68}Zn(p,n)^{68}Ga	15	6.32	[15]
^{68}Zn(p,n)^{68}Ga	15	5.032	This work
^{nat}Zn(p,n)^{68}Ga	15	~ 1	[1]

Table 4. Production yields of main isotopes for run #1

Isotope	^{68}Zn(p,n)^{68}Ga	^{68}Zn(p,2n)^{67}Ga	^{nat}Cu(p,*x*)^{65}Zn
Half-life	1.1 h	2.26 d	244.4 d
Yield at EOB (GB/μAh)	5.032	3.94E-5	ND

ND: not detected.

Separation technique

Ion exchange chromatography and liquid-liquid extraction methods were used for the separation of ^{68}Ga. The irradiated target was dissolved in 10 N HCl (15 ml) and the solution was passed through a cation exchange resin (Bio-Rad AG 50W, 200–400 mesh, H^+ form, Ø: 1 cm, h: 10 cm, treated with 25 ml of 9 N HCl). The column was eluted with 9 N HCl (25 ml) to remove copper and zinc ions and ^{68}Ga was absorbed on the column. Then, the ^{68}Ga cations were washed out with 4 N HCl (20 ml). The solvent extraction method was used to achieve high-purity ^{68}Ga. 10 N HCl (20 ml) was added to the eluted 4 N HCl solution in order to obtain the optimum normality to extract ^{68}Ga. Isopropyl ether was used to extract ^{68}Ga from the aqueous phase (2 times). Nitrogen bubbling was used for 10 min to mix the aqueous and organic phases. The mixed organic phases were back extracted using 0.05 N HCl (12.5 ml).

Recovery of ^{68}Zn

The gathered residue solution in the recovery bulk was heated to near dryness, and the residue was dissolved in 6 N HCl. This solution was introduced into an anion exchange chromatography column (AG 1 × 8, 100–200 mesh, Cl^- form, 25 × 1.5 cm, treated with 100 ml of 6 N HCl). Copper and zinc were eluted with 2 N HCl (50 mL) and 0.05 N HCl, respectively.

The condition of the prepared electroplating bath was exactly the same as previous baths; the acquired deposit was smooth and shiny.

Results

Various nuclear reactions for the production of ^{68}Ga have been suggested. Our available reaction was restricted to ^{68}Zn(p,n)^{68}Ga. ^{68}Zn was electroplated on a copper backing by DC-current from alkaline plating solutions. Figure 1 shows the SEM of zinc deposit on Cu backing grown under a DC current density of 8.55 mA·cm^{-2}, pH between 13–14 and 40°C. Irradiated zinc targets on the copper backing were efficiently removed with a liquid flow-through stripper cycle using 15 mL of 10 N HCl at 24°C.

The production of ^{68}Ga via proton bombardment has been reported previously and an overview of some methods is given in Table 3. The production yield of 5.032 GBq/μA·h in our case is in agreement with the value of 6.32 GBq/μA·h reported by Szelecsényi *et al*. [15] and 1 GBq/μA·h (for natural zinc) reported by Al-Saleh *et al*. [1].

The radionuclides ^{68}Ga, ^{67}Ga were detected by a high-purity Ge detector. The production yields of gallium isotopes and the main radionuclidic impurities for longer irradiation are summarized in Table 4.

Several methods have been introduced for the separation of gallium from zinc and copper [5, 10, 13, 17]. For the separation of ^{68}Ga from Zn and Cu in this research, a combination of cation exchange chromatography and liquid-liquid extraction methods was used. The whole chemical processing step took bout 1.5 h. The activity of the obtained ^{68}Ga was 5.1 Ci at the end of bombardment (EOB). Production yields of ^{68}Ga and ^{67}Ga were 5.032 GBq/μAh and 3.94 × 10^{-5} GBq/μAh, respectively. The chemical separation yield was 90%. High-purity germanium detector (HPGe) was used to detect the radioactivity of $^{68/67}$Ga (Fig. 2).

Conclusion

In summary, we have proposed a new method for producing ^{68}Ga for medical purposes from enriched zinc according to the reaction (p,n) in a medium-proton cyclotron. Electroplated zinc on a copper target was successfully tested for high-current irradiation in cyclotron production of multi/sub Curies amounts of the radionuclide ^{68}Ga. Use of 12.3 MeV proton-induced

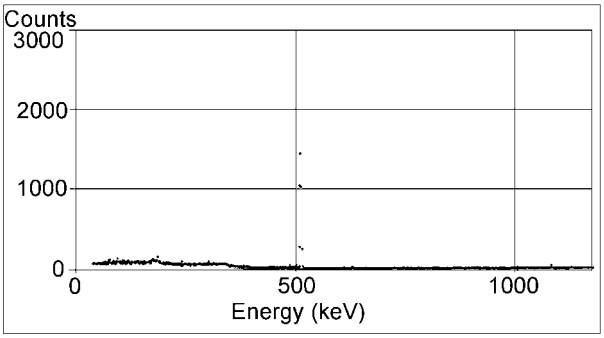

Fig. 2. HPGe spectrum of radiochemically separated ^{68}Ga.

energy is mandatory, otherwise the ^{67}Ga impurity is high. Purification of ^{68}Ga from the proton-bombarded ^{68}Zn target material has been achieved easily by the proposed method based on cation exchange chromatography and solvent-solvent extraction.

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