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Very high specific activity $^{66/68}$Ga from zinc targets for PET

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Abstract

This work describes the production of very high specific activity $^{66/68}$Ga from ^{nat}Zn(p,n) and ^{66}Zn(p,n) using proton irradiations between 7 and 16 MeV, with emphasis on ^{66}Ga for use with common bifunctional chelates. Principle radiometallic impurities are ^{65}Zn from (p,x) and ^{67}Ga from (p,n). Separation of radiogallium from target material is accomplished with cation exchange chromatography in hydrochloric acid solution. Efficient recycling of Zn target material is possible using electrodeposition of Zn from its chloride form, but these measures are not necessary to achieve high specific activity or near-quantitiative radiolabeling yields from natural targets. Inductively coupled plasma mass spectroscopy (ICP-MS) measures less than 2 ppb non-radioactive gallium in the final product, and the reactivity of ^{66}Ga with common bifunctional chelates, decay corrected to the end of irradiation, is 740 GBq/μmol (20 Ci/μmol) using natural zinc as a target material. Recycling enriched ^{66}Zn targets increased the reactivity of ^{66}Ga with common bifunctional chelates.

Keywords

^{66}Ga; ^{68}Ga; Zn electrodeposition; PETtrace; Eclipse; cation exchange

Introduction

The radionuclide ^{66}Ga ($t_{1/2}$ = 9.3 hrs, 56.5% β^+, 43.5% EC (Severin et al., 2010)) is a useful surrogate for both ^{67}Ga and ^{68}Ga. The former is used in single photon computed tomography (SPECT); the latter is commercially available in ^{68}Ge/^{68}Ga generator systems. Positron emission tomography (PET) image quality exceeds that of SPECT systems, even with high energy positrons emitted by ^{66}Ga (E_0 = 4.15 MeV). Modern preclinical PET scanners capably cope with both fast positrons and prompt gamma emissions characteristic of many nonstandard radionuclides (Laforest et al., 2002). ^{66}Ga's longer half-life makes it a more practical radiolabel of proteins, peptides, and antibodies, whose slower *in vivo* kinetics are poorly matched by 68 min ^{68}Ga (Ugur et al., 2002). Labeling chemistry with radiogallium is well studied because of the popularity of ^{68}Ga from ^{68}Ge/^{68}Ga generators (Hnatowich, 1975; Velikyan, 2009).

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Several methods for the production of no-carrier-added ^{66}Ga are reported. Lewis *et al.* irradiated natural and enriched Zn targets with 7 μA of 14.5 and 9.8 MeV protons, with separation accomplished by cation exchange chromatography and solvent extraction (Lewis *et al.*, 2002). However, their use of enriched material was limited to purchased target foils, making target recycling impossible, and final specific activities were < 5 GBq/μmol, more than a factor of 2000 below theoretical limits and significantly less than those achieved for other radiometals of interest to PET (Avila-Rodriguez *et al.*, 2007). Lewis *et al.*'s best results were achieved with extraction from isopropyl ether, which is challenging to automate and has been reported elsewhere (Rowshanfarzad *et al.*, 2004). Selective precipitation and filtration has been used to separate ^{66}Ga and ^{67}Ga from zinc targets as well, but zinc and copper remained in final products in ppm levels (Sadeghi and Mokhtari, 2010). Thermal chromatographic distillation and acid etching have been used to rapidly separate up to 60% of radiogallium from zinc targets, but without reported use of the product in labeling chemistry (Tolmachev and Lundqvist, 1996). Electroplated zinc targets resistant to irradiation currents up to 50 μA are present in the literature (e.g., (Neirinckx, 1976). However, specific activities and enriched isotope recovery efficiencies are unreported by these studies, or commonly, copper plating substrates necessitate additional separation prior to replating (Kakavand *et al.*, 2010; Naik *et al.*, 2002; Rowshanfarzad *et al.*, 2004; Sattari *et al.*, 2006). After irradiation of zinc targets, electrodeposition from their radioactive, dissolved solutions has also been used to speed separation, post-irradiation but again, the reactivity and elemental composition of the final product in solution are unreported (Neirinckx, 1976).

Though many reports on cyclotron production of $^{66/67}$Ga exist, the effective potential of cyclotron-produced ^{66}Ga for preclinical studies of ^{66}Ga-labeled agents requiring tracer concentrations of the radiometal is poorly reported; perhaps, partially for this reason, PET imaging with ^{66}Ga is scarce. Separations reported in the literature insufficiently separate contaminant Fe(III), which exhibits nearly identical coordination chemistry to that of gallium complexes (Velikyan, 2009).

This work is an attempt to construct an economical, facile method for low energy cyclotron production of ^{68}Ga or ^{66}Ga from ^{nat}Zn or ^{66}Zn, depending on the needs of the user, in high yields and reactivities for common bifunctional chelates. We consider a measure of reactivity, defined as the mass of chelate required to achieve near-quantitative radiolabeling yields under specified reaction conditions, to be among the most important measures of radiometals' efficacy as PET synthons. High reactivity minimizes the mass of ligand necessary to achieve injectable radiolabeling yields and eliminates contaminant metals' confounding effects on chemistry and the pharmacokinetics of the labeled compound.

Materials

Optima grade HCl was purchased from Fisher Scientific. ^{nat}Zn foils (0.25 mm thick) and $^{nat}ZnCl_2$ (both 99.999%) were purchased from Sigma Aldrich. Puratronic ammonium sulfate was purchased from VWR. Isotopically enriched ^{66}Zn (98.58%) was purchased from Isoflex (San Francisco). The enriched zinc contained 0.76% ^{64}Zn, 0.6% ^{67}Zn, 0.055% ^{68}Zn, and 0.005% ^{70}Zn. Cation exchange resin (AG50W-X4, 100–200 mesh) was purchased from Biorad.

Methods

Zinc was electrodeposited from solutions comprised of 250–300 mg $ZnCl_2$ in 2.5 ml 0.05 N HCl onto 0.5 mm thick gold or silver discs. A 0.1 mm diameter platinum wire anode was used to apply 4 – 9 V DC (30 – 60 mA) across 1 cm of plating solution and a ballast resistor

of 100 Ω, with optimal deposition occurring at 6 V. Four hours after voltage was applied, 100 μl 0.1 N HCl was added to the solution to maintain acidity. In experiments to determine plating efficiency, reactivity, and isotope separation/recovery yields, 20 hours of plating deposited 91 ± 3% (n=6) onto an area of ~ 0.8 cm^2, approximately matched to proton beam dimensions. Target thickness could be experimentally varied by altering the duration of the plating procedure; targets of different thickness were used to measure experimental target yields. Electrodeposited mass was determined by weighing a clean, vacuum-oven baked gold backing disc immediately before and after the plating process. Targets were irradiated with up to 40 μA of protons of various energies on a GE PETtrace or Siemens Eclipse HP cyclotron. Aluminum degraders lowered these accelerators' nominal beam energies (16 and 11 MeV) to 13 and 7 MeV, respectively. Targets withstood these currents for irradiations of up to 4 hours without losing mass. When producing ^{66}Ga, irradiated targets of ^{nat}Zn were left on the cyclotron overnight (13 – 16 hrs) so that short-lived products could decay, and 2.5 ml 10 N HCl dissolved the targets after removal. The solution was transferred to a column containing 7 g strong cation exchange resin preconditioned with 10 N HCl, as reported previously (Lewis *et al.*, 2002). The column was washed with 20 ml of 10 N HCl to remove the Zn target material. An additional washing step was added to previously reported cation exchange methods, using 20 ml 7 N HCl to remove additional contaminant metal before eluting the ^{66}Ga fraction in 5–10 ml of 4 N HCl. The eluant was collected in fractions to select the most concentrated portion of the product peak. The 20 ml fraction of 10 N HCl was saved for recycling, and the 4 N HCl fraction was evaporated under inert gas flow or in a rotoevaporator. ^{66}Ga was recovered in 50–100 μl 0.1 N HCl for labeling use. The zinc target stock was recovered from combined 10 N HCl column wash and residual electroplating solution by evaporation with a single addition and evaporation of 0.05 N HCl.

To check product chemical purity, non-radioactive samples of dissolved targets and the various elution fractions were analyzed by inductively coupled mass spectroscopy (ICP-MS) at the University of Wisconsin Hygiene Labs and the Institute of Geology at the Universidad Autonoma in San Luis Potosi. Zinc content was also checked with produced ^{65}Zn from irradiations above 13 MeV using a 60 cm^3 high purity germanium detector (HPGe) and gamma spectroscopy (FWHM = 2.7 keV @ 1333 keV) to identify ^{65}Zn's characteristic 1115.5 keV gamma (I_γ = 50.0%). $^{66/67/68}$Ga yields were quantified using the same detector and characteristic 1039 keV (^{66}Ga, I_γ = 37.0%), 300 keV (^{67}Ga, I_γ = 16.6%), and 1077 keV (^{68}Ga, I_γ = 3.2%) emissions. Detector energy and efficiency calibrations were performed with ^{137}Cs, ^{60}Co, and ^{152}Eu sources (Oak Ridge National Lab), and data was collected using Maestro (Ortec) counting software. Errors from counting statistics (3–5%), peak fitting (2–3%) and background subtractions (2–4%) were taken as reported by the software and, combined in quadrature, resulted in an error of 4–6%. Beam current was taken as reported by cyclotron control software, with an error of 5%, and error in the measured thickness and uniformity of thick targets was conservatively estimated at 10% given the lack of thorough characterization of target morphology. The total uncertainty in reported yields (12–15%) was calculated by combining these contributing errors in quadrature. A Capintec CRC 25-R dose calibrator was used to assay $^{66/68}$Ga for chemistry yields using manufacturer-supplied calibration numbers.

In order to more fully evaluate the utility of produced $^{66/68}$Ga for incorporation into common bifunctional chelates in the presence of contaminants not removed by our process, the reactivity of the $^{66/68}$Ga was measured by titration with the macrocycles 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (Yoo *et al.*, 2005) and 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) (Li *et al.*, 2007). Briefly, 50 μl aliquots of diluted $^{66/68}$Ga stock solution (in 0.1 N HCl) were added to vessels containing 200 μl of 0.25 M ammonium acetate buffer solution. Increasing concentrations of DOTA or NOTA solution (10^{-7}–10^{-5} M in 50 μl) were added to the vessels, which were then vortexed and

incubated for 30 min (80°C for DOTA, 25°C for NOTA). The percentage of the radionuclide chelated in each sample was monitored by thin layer chromatography using silica gel plates developed with 1:1 MeOH:10% NH_4OAc (w/v). Evaluation of the TLC plates was performed by autoradiography on a Packard Cyclone phosphor-storage plate.

Results and Discussion

In radioisotope production for PET imaging, long-lived radioactive byproducts must be minimized. The excitation functions for the production of ^{65}Zn, ^{66}Ga, ^{67}Ga, and ^{68}Ga (summarized in Figure 1 below) are well described (Al-Saleh et al., 2007; Blaser et al., 1951; Hille et al., 1972; Howe, 1958; Levkovskij, 1991; Nortier et al., 1991; Szelecsenyi et al., 1998; Takacs et al., 2005; Tarkanyi et al., 2005). Other isotopes with shorter half-lives, such as ^{64}Ga and ^{70}Ga, decay rapidly enough to be of small concern for this work. Production of ^{65}Zn by ^{66}Zn(p,2n) and β-decay of short-lived ^{65}Ga is open above 14 MeV, as shown in Figure 1 below, and (p,p+n) is theoretically open near 11 MeV, with a measured cross section value of 25 mb at 13.8 MeV (Levkovskij, 1991) (see also Table 1 below). In addition to expected large activities of $^{64/68}$Ga from 48.9 and 18.6% $^{64/68}$Zn, respectively, the (p,n) reaction on 4.1% ^{67}Zn in natural targets produces significant quantities of ^{67}Ga with a threshold below 3 MeV and a maximum near 10 MeV. ^{68}Zn(p,2n) also produces significant ^{67}Ga and peaks near 20 MeV. The optimal incident proton energy suggested by the literature is therefore near 13 MeV; use of enriched ^{66}Zn targets provides an additional means of controlling radioisotopic purity.

Electrodeposition of zinc targets of varying thickness affords an additional opportunity to optimize yields and radionuclidic purity. The low threshold of the ^{67}Zn(p,n)^{67}Ga reaction means that thin targets with proton exit energies near 6 MeV offer a reasonable compromise between ^{66}Ga yield and ^{67}Ga avoidance. As Figure 2 shows, the relationship between ^{66}Ga yield and target thickness, especially when target material cost is of concern, points the cyclotron operator towards the thinnest target which can meet production demands on a given day.

If enriched isotope is used, the cost of targets (~$1/mg ^{66}Zn, ~$3/mg ^{68}Zn) and the potential to cyclically remove transition metal contaminants suggest a recycling method with limited losses. Though highly soluble zinc salts have been reported as targets, subsequent separations with C18 media are not well characterized and the highly corrosive solutions give many cyclotron facilities cause for trepidation (Jensen and Clark, 2010). Instead, the preferred method remains electrodeposition of metal targets, which offers the prospect of high current irradiations and convenient storage.

The principle factors affecting the reactivity of final $^{66/68}$Ga solutions for DOTA and NOTA are the purity of the feedstock material, the use of electrodeposition to prepare targets, the recycling of target material, and the quality of the chemical separation of gallium from other metals. The measured reactivity of produced $^{66/68}$Ga for DOTA or NOTA using 0.25 mm ^{nat}Zn foil targets does not exceed 370 MBq/μmol at end of bombardment (EoB). This is due to high Fe contamination (~50 ppm) present in the purchased product and the higher mass of target material used/needed for irradiation. However, purchased 99.999% $^{nat}ZnCl_2$ contains no such contamination, and measured reactivities for DOTA/NOTA using targets electroplated from this feedstock increase by a factor of ~$10^{2–3}$ over those from irradiated foils. For plated targets of both ^{nat}Zn and ^{66}Zn, reactivities of 160–370 GBq/μmol for DOTA or NOTA, decay corrected to EoB, are routinely achieved and have been as high as 740 GBq/μmol depending on plating results and irradiation conditions. In order to achieve these results using enriched ^{66}Zn, which also contains ppm quantities of iron at purchase, recycling must be employed, removing contaminant metals with iterative electroplating and

chromatographic purification of the product gallium. For both $^{nat}ZnCl_2$ and recycled ^{66}Zn targets, non-decay-corrected reactivities are approximately 70–200 GBq/μmol, and the products have been used to produce radiotracers for PET imaging (Avila-Rodriguez *et al.*, 2011).

When using electroplated targets of $^{nat}ZnCl_2$ or recycled ^{66}Zn targets, ICP-MS detects less than 2 ppb stable gallium present in the 4 N HCl final solution regardless of whether the intermediate 7 N HCl wash is employed, strongly suggesting that other contaminant radiometals are of greatest concern to reactivity measurements. ICP-MS finds approximately 50 ppm iron in the original solution of dissolved ^{nat}Zn foil, but only 10 ppm iron in a dissolved, electroplated target from the same foils. In the absence of the 7 N HCl wash of the resin, comparison of ICP-MS data for $^{nat}ZnCl_2$ targets from before and after plating and chemical separation gives a separation factor of 10^{-5} for zinc and 10^{-3} for iron. With the 7 N HCl wash, the separation factors for zinc and iron were improved to 10^{-6} and 10^{-4}, respectively. These results were in good agreement (within 2%) with ^{65}Zn activity quantified by HPGe γ-spectroscopy. In the same experiments, vanadium and aluminum, presumably from the cyclotron target holder, were measured by ICP-MS to exist in approximately 20 ppb quantities in the final product. A typical elution profile using cation exchange resin is shown below in Figures 3 and 4. Separation quality improves with re-use of the cation exchange resin. Typical reactivities for DOTA after packing a fresh column of resin are approximately 370 MBq/μmol; this value improves to the numbers reported above within 10 runs or with additional acid washing of the column.

^{65}Zn is below the limits of gamma spectroscopy detection in the dissolved product of 13 MeV thick target irradiations of any target used. Measured yields of ^{66}Ga, ^{67}Ga, and ^{68}Ga, the only gallium radioisotopes present 10 hours after the end of bombardment (EoB), establish that without limits on ^{67}Ga contamination shorter irradiations maximize the ratio of ^{66}Ga to ^{67}Ga.

Table 1 below summarizes the activity ratios for irradiation conditions chosen for the production of $^{66/68}Ga$. For preclinical studies, the 300 keV gamma emission and longer-lived ^{67}Ga from ^{nat}Zn targets may relax the timing of biodistribution experiments involving resection in animal subjects. It is also possible to produce radionuclidically clean ^{68}Ga at EoB using low energy (7 MeV) irradiations for immediate use. In this work, ^{68}Ga had a measured thick target yield of 200 ± 30 MBq/μA from ^{nat}Zn, extrapolated to the end of saturated bombardment (EoSB; Fig. 5). The 18.5% isotopic abundance of the primary target, ^{68}Zn, and a lower threshold energy than the reactions which produce ^{66}Ga (see Table 1 below) make this production route a viable choice using natural targets. However, ^{68}Ga productions for any clinical purpose would require irradiation of enriched ^{68}Zn, because the value of this production lies in the initially large ratio of ^{68}Ga to contaminating, longer-lived ^{67}Ga and ^{66}Ga.

Irradiations with higher beam energies produce higher relative amounts of ^{66}Ga and ^{67}Ga, and are hence more suitable to the production of the longer-lived ^{66}Ga. Irradiating ^{nat}Zn targets at 13 MeV, measured EoSB thick target yields for ^{66}Ga, ^{67}Ga, and ^{68}Ga were 1150 ± 130, 260 ± 40, and 1550 ± 170 MBq/μA, respectively, while a 160 mg/cm^2 target yielded 880 ± 100 MBq/μA of ^{66}Ga at 11 MeV. Irradiating a 130 mg/cm^2 ^{66}Zn target produced EoSB ^{66}Ga and ^{67}Ga yields of 2800 ± 310 and 70 ± 10 MBq/μA, respectively; a 152 mg/cm^2 ^{66}Zn target produced EoSB yields of 3810 ± 460 and 110 ± 20 MBq/μA. In both cases, ^{67}Ga represented less than 0.1% of activity produced for hour-long irradiations.

Conclusions

^{66}Ga has been produced in very high specific activities (<2 ppb stable gallium) from ^{nat}Zn and ^{66}Zn targets. Reactivities for common bifunctional chelates of 740 GBq/μmol, or 6% of carrier free specific activity (12.2 TBq/μmol) have been achieved. Radionuclidic purity of the product is >95% between 2 and 5 half-lives of ^{66}Ga following irradiation and exceeds 99.9% when the ^{66}Zn target is used. ^{68}Ga can also be produced with high radioisotopic purity using this method, using either targets of ^{nat}Zn or ^{68}Zn. The separation is simple and the principal cost incurred, even using enriched targets, results from the use of ultra-pure reagents.

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Highlights

- Cyclotron-produced $^{66/68}$Ga with AG50W separation has high S.A. (<2 ppb cold Ga).
- Product $_{66/68}$Ga has a reactivity for NOTA of >700 GBq/μmol (20 Ci/μmol).
- ^{nat}Zn and ^{66}Zn targets are economical and produce similar radiochemical purities.

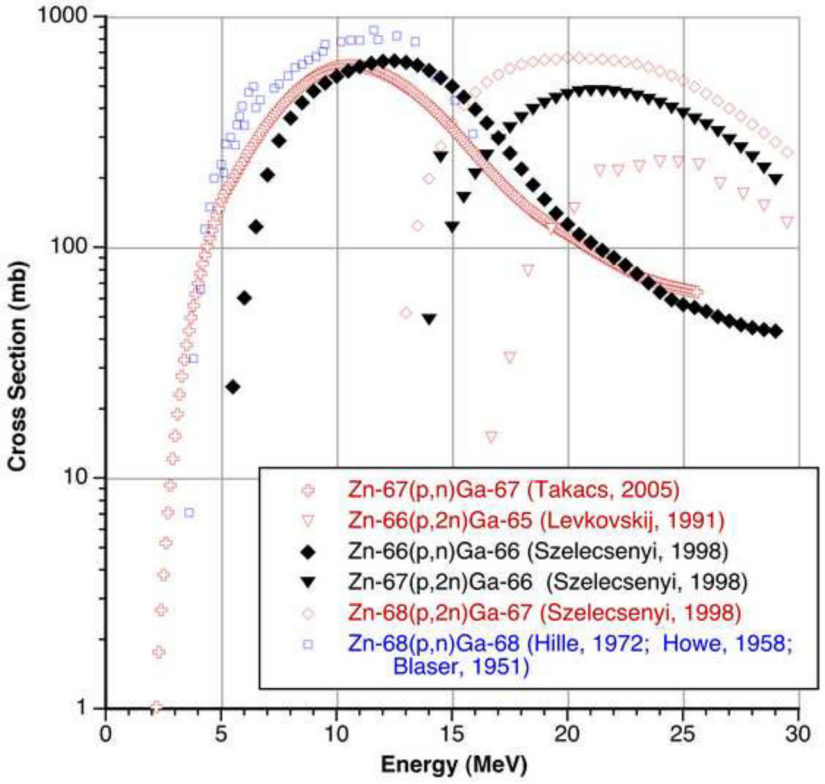

Figure 1.
Published excitation functions for ^{67}Zn(p,n)^{67}Ga, ^{66}Zn(p,2n)^{65}Ga, ^{68}Z(p, 2n)^{67}Ga, ^{66}Zn(p,n)^{66}Ga, ^{67}Zn(p,2n)^{66}Ga, and ^{68}Zn(p,n)^{68}Ga

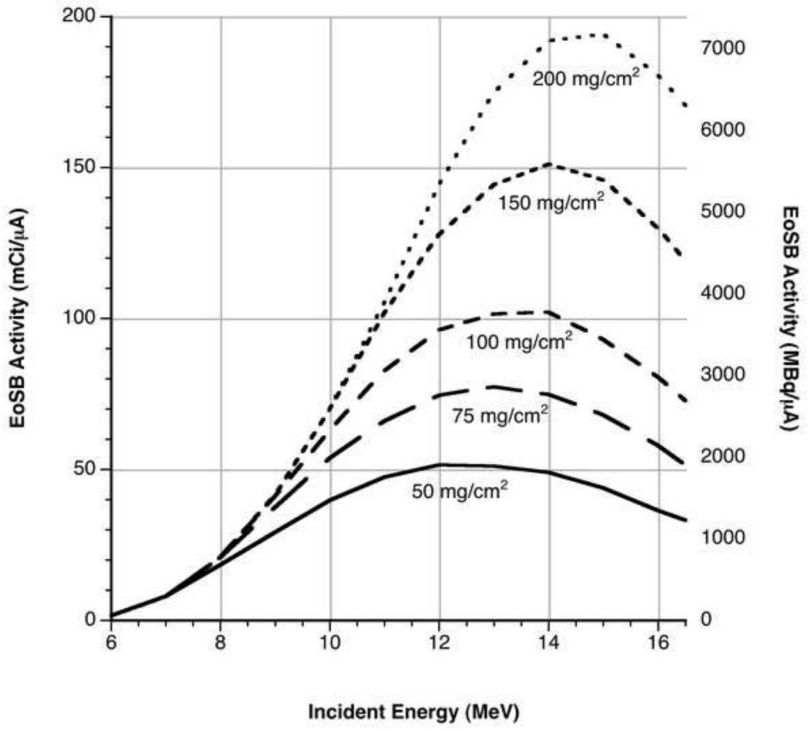

Figure 2.
Calculated integral yield of ^{66}Ga at the end of saturated bombardment using data from Szelecsenyi *et al.* (1998).

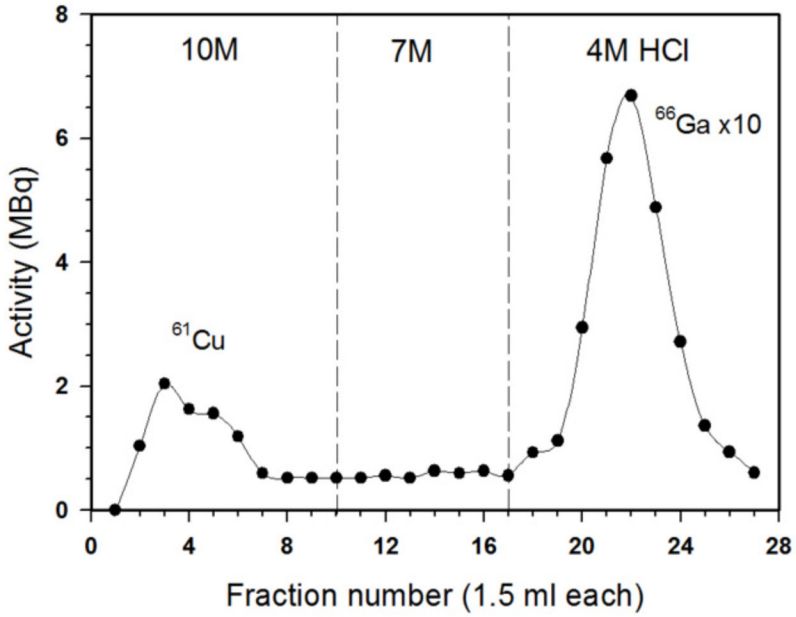

Figure 3.

Elution profile of Zn-Cu-Ga separation using cation exchange resin AG50W-X4 (7 g, 1.5 cm diameter column), 14 h after 11 MeV irradiation of ^{nat}Zn target. Zinc is co-eluted with ^{61}Cu. Activity was measured by ionization chamber and activity of fractions 17–27 was divided by 10.

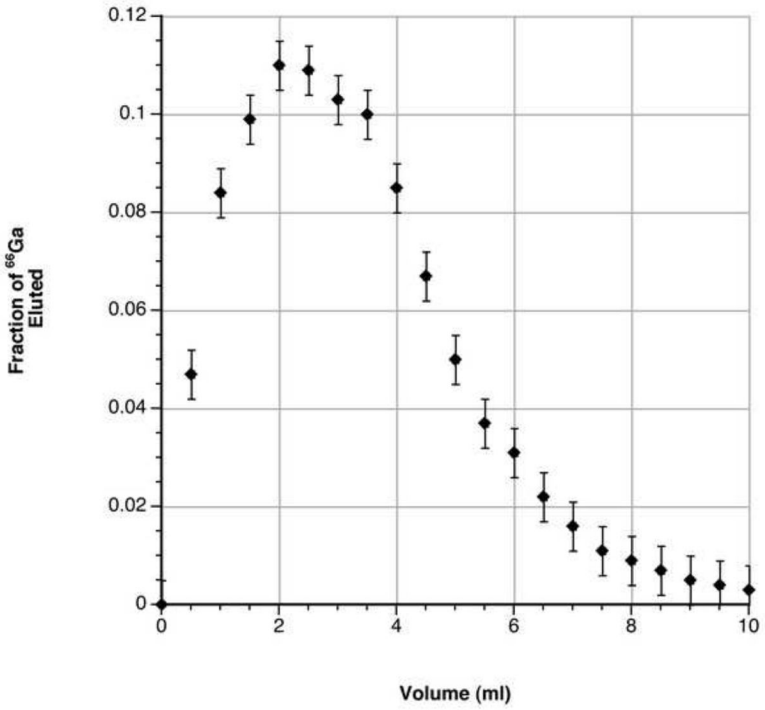

Figure 4.

Detailed elution profile of ^{66}Ga in 500 μl aliquots of 4 N HCl from AG50W cation exchange resin. Error bars are the standard deviation of three consecutive measurements. Reactivity measurements are made using fractions 4 – 8 to minimize tailing metal impurities from the 7 N HCl column wash.

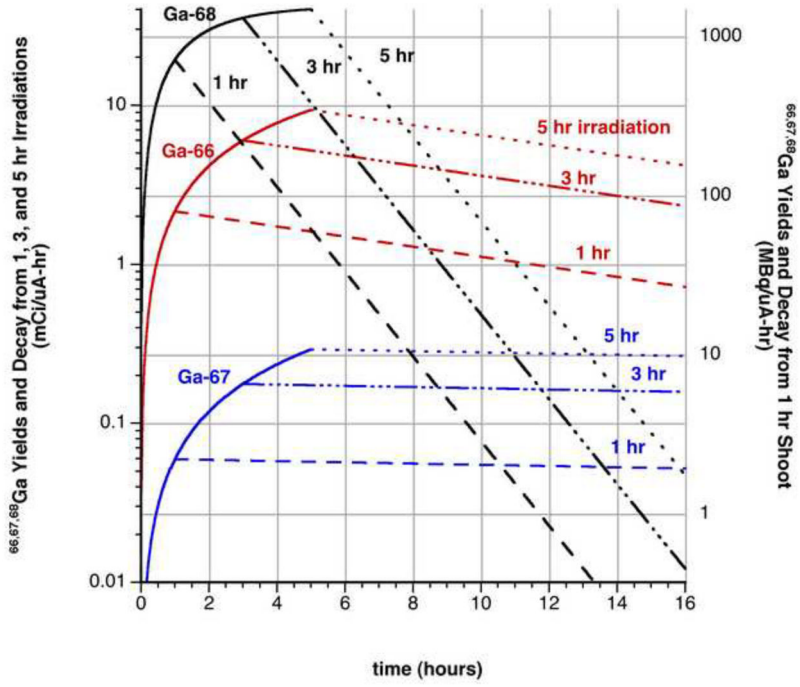

Figure 5.
Calculated extrapolation from measured thick target EoB production yields and decay of ^{66}Ga, ^{67}Ga, and ^{68}Ga for 1, 3, and 5 hr proton irradiations of ^{nat}Zn at 13 MeV.

Table 1

Radioisotope product ratios of ^{68}Ga, ^{67}Ga, and ^{66}Ga from 1 hour irradiations at various energies.

Product	½	Reaction(s)	Q value (MeV)	Ratio of Product to ^{68}Ga at EoB for 7 MeV	Ratio of Product to ^{66}Ga 14 h after EoB at 11 MeV*	Ratio of Product to ^{66}Ga 16 h after EoB at 13 MeV	Ratio of Product to ^{66}Ga 16 h after 16 MeV EoB
^{64}Ga	2.6 m	^{64}Zn(p,n)	−7.95	--	--	--	--
^{65}Zn	243.7 d	66Zn(p,2n+β); ^{66}Zn(p,pn)	−15.10; −11.06	--	--	--	$9.5x10^{-4}$
^{66}Ga	9.5 h	^{66}Zn(p,n); ^{67}Zn(p,2n)	−5.96; −13.01	$1.5x10^{-2}$	1.0	1.0	1.0
^{67}Ga	3.3 d	^{67}Zn(p,n); ^{68}Zn(p,2n)	−1.78; −13.01	$3.8x10^{-3}$	$6.7x10^{-2}$	$7.0x10^{-2}$	$1.9x10^{-1}$
^{68}Ga	68 m	^{68}Zn(p,n)	−3.70	1.0	$6.0x10^{-3}$	$3.3x10^{-3}$	$5.1x10^{-4}$
^{70}Ga	21.1 m	^{70}Zn(p,n)	−1.44	--	--	--	--

*Thin target (11 → 6 MeV)