

Production of high specific activity ^{68}Ge at Brookhaven National Laboratory

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Germanium-68 is produced at the Brookhaven Linac Isotope Producer (BLIP) by irradiating $^{\text{nat}}\text{Ga}$ targets with ~ 45 MeV protons. Typical irradiation yields are 17.4 GBq (470 mCi) from a 4 week irradiation (0.52 MBq/ μAh). Germanium-68 is recovered from the target by extraction into 4N HCl and 30% H_2O_2 . Further purification is achieved by extraction into carbon tetrachloride and back-extraction into H_2O . Recovery yields are greater than 85%, with greater than 99% radiopurity, and activity concentrations are greater than 3.15 GBq/ml (85 mCi/ml). The final pH of the product solution, which is 0.03M diethylenetriaminepentaacetate (DTPA), can now be adjusted to user specifications.

Introduction

Germanium-68 is widely used to calibrate PET systems. It is long-lived ($T_{1/2} = 271$ d), decaying by electron capture to ^{68}Ga ($T_{1/2} = 68.1$ min) which then decays by positron emission (90.5%).¹ This pair is also used as a generator system for research with gallium radiopharmaceuticals.^{2,3} Germanium-68 has been produced for many years at Brookhaven National Laboratory (BNL) using the BLIP.⁴ Product solutions were provided to the user community in 0.1–0.5N HCl with activity concentrations of ~ 0.37 GBq/ml (10 mCi/ml). New applications for this isotope require product solutions with solution $2 \leq \text{pH} \leq 4$ and much higher activity concentrations, > 3.15 GBq/ml (85 mCi/ml). These new requirements present several challenges to the separation procedure. Germanium tetrachloride is extremely volatile, making any volume reduction from dilute HCl to meet the activity concentration specification difficult. Another difficulty involves adjusting the pH of the final solution while minimizing total volume. We report here on developments to improve the procedure to meet these new requirements. A distillation method was investigated to recover ^{68}Ge directly from the target into a small volume of distillate. Another approach was studied whereby ^{68}Ge was converted to a nonvolatile complex with DTPA before final volume reduction by evaporation. Results of these studies will be discussed.

Experimental

Production

Germanium-68 is produced by irradiating $^{\text{nat}}\text{Ga}$ targets (60% ^{69}Ga , 40% ^{71}Ga , 99.99% purity, 120 g) with 45 ± 8 MeV protons at the BLIP. The target is placed at the back of the target array and acts as a beam stop. The incident proton energy on target varies, depending on the identity and thickness of upstream

targets in the array. Excitation functions for the various reactions occurring within this target are shown in Fig. 1.⁴ The predominant reaction is $^{69}\text{Ga}(p,2n)^{68}\text{Ge}$ with $\sigma = 470$ mb at 19 MeV. Although this energy is always reached within the target, it is not always possible to encompass the higher energy peak of the excitation function in the target. Targets consist of gallium metal encapsulated in niobium: 7.62 cm diameter, 0.762 cm thick, with 0.051 cm windows electron beam welded to the “can”. Niobium is used since gallium is very corrosive and attacks other metals and alloys such as stainless steel. Targets typically accumulate 33,000–45,000 $\mu\text{A}\cdot\text{h}$ of beam during a four-week irradiation, to produce 14.8 GBq–18.5 GBq (400–500 mCi) of ^{68}Ge at end of bombardment (EOB). The primary long-lived contaminant is ^{65}Zn ($T_{1/2} = 244$ d), whose excitation function peaks at $E_p \sim 25$ MeV.⁵ The impurity ratio is ~ 1.1 $^{68}\text{Ge}/^{65}\text{Zn}$ at EOB.

Chemistry

All reagents used were ACS reagent grade or superior. Germanium content as well as other metals were assayed using an inductively coupled plasma optical emission spectrometry (ICP-OES). Radiopurity was determined by gamma-spectroscopy using a high purity germanium (HPGe) detector system calibrated with National Institute of Standards (NIST) traceable standards.

Results and discussion

After irradiation, the target is not processed for approximately two weeks to allow decay of short-lived isotopes such as ^{69}Ge and ^{67}Ga . The niobium can is then opened by cutting off one of the windows. Opening the target probably releases some fraction of the total ^{68}Ge activity, presumably in the form of germane, GeH_4 , produced during the irradiation. A typical irradiation would deposit greater than 33,000 $\mu\text{A}\cdot\text{h}$, or 1.3 mmoles

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of hydrogen ion in the target. Therefore, the hydrogen source is most likely the proton beam itself since the target acts as a beam stop.

Separation of ^{68}Ge from gallium target

The target can is heated gently to liquefy the gallium (m.p. = 29.76 °C) after which the gallium is poured into a beaker. A solution of 6 ml of 4N HCl and 2 ml of 30% H_2O_2 is added to the beaker, gently stirred, and ^{68}Ge is extracted from the gallium in the form of the tetrachloride, GeCl_4 . Gallium does not appreciably

dissolve. Several extractions are required to achieve quantitative recovery (Table 1). Zinc-65 is co-extracted, as is a trace amount of the gallium target (mg quantities).

Separation of ^{68}Ge from residual stable gallium and ^{65}Zn

The separation of ^{68}Ge from ^{65}Zn and gallium is based on the extraction of the germanium tetrachloride from 9–12N HCl into organic solvents such as toluene, carbon tetrachloride, and benzene.⁶

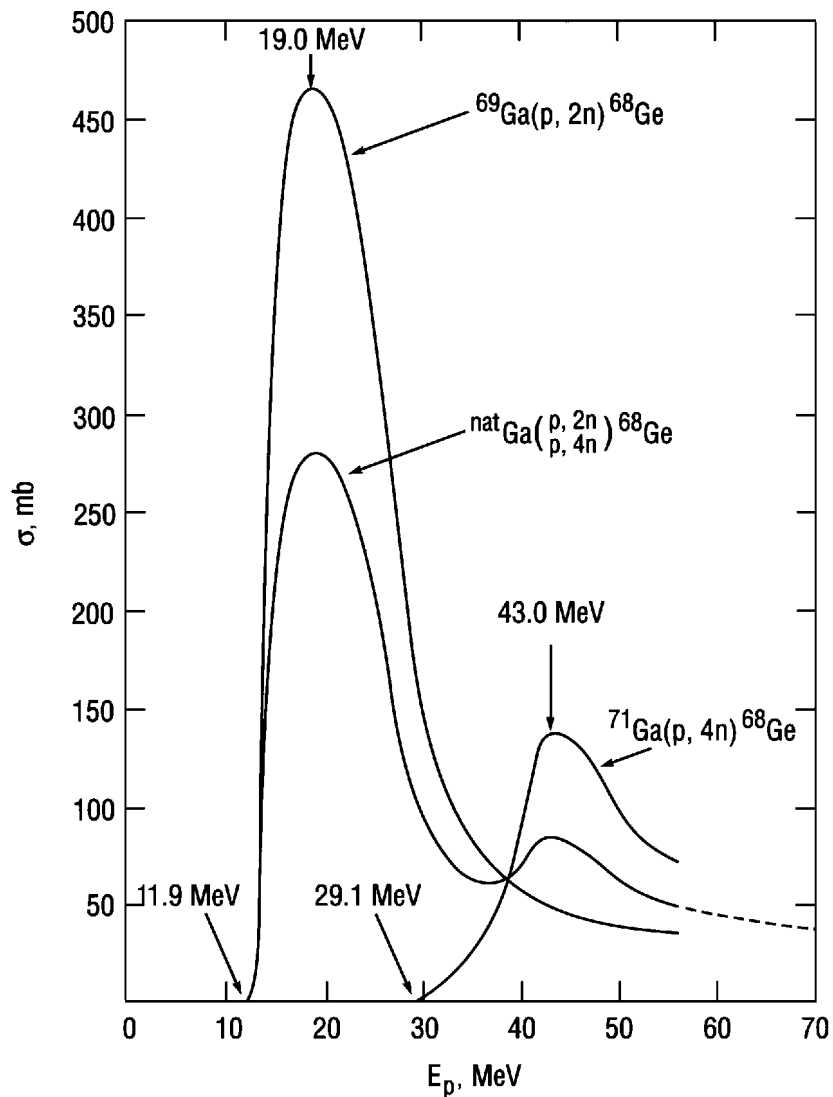


Fig. 1. Excitation functions for ^{68}Ge production from proton irradiated gallium targets as a function of incident proton energy⁴

Table 1. Germanium-68 extraction yields from gallium metal

Extraction	^{68}Ge recovered, %
First	~52
Second	~33
Third	~9
Fourth	~4
Fifth	~2

In the past, germanium was extracted into toluene since toluene, unlike carbon tetrachloride, is less dense than water. Therefore, further reduction in volatility losses could be achieved by adding chilled toluene to the funnel before adjusting the acidity of the aqueous phase to $>9\text{N}$ HCl. The less dense toluene would form a layer covering the aqueous phase, preventing loss of the volatile ^{68}Ge species. Then conc. HCl (12N) was added to bring the overall normality to 10N HCl. The volume of the organic phase was typically 20% of the volume of the aqueous phase, i.e., 55 ml toluene extracted with 275 ml aqueous phase. The contents were stirred for 5 minutes, the phases were allowed to settle, and the aqueous phase, containing ^{65}Zn and gallium, was easily removed from the bottom of the extraction vessel. The toluene phase was washed with an equal volume of 10N HCl and the aqueous wash was removed. Less than 0.1% of the total ^{68}Ge recovered was detected in the aqueous phase or washes.

Final product preparation

The final product was prepared as follows. Germanium-68 was back-extracted twice from the organic phase into small volumes of 0.1N HCl, the volume of which was determined from the activity concentration requirement as specified by the user, which in the past ranged from 0.37 to 2.22 GBq/ml (10–60 mCi/ml). Recovery of ^{68}Ge varies with the volume of aqueous phase used in the back extraction, ranging from a high of 99% when the aqueous phase is 30% of the organic phase (i.e., 15 ml 0.1N HCl to 55 ml toluene), to 55%, when the aqueous phase is 5% of the organic phase volume (i.e., 3 ml 0.1N HCl to 55 ml toluene). Losses are attributed to difficulty in manipulating these small volumes under remote conditions. The two aqueous phases from the back extractions were combined to create the final product. The specific activity of this product was typically $\sim 58\text{ MBq}$ (1.57 mCi) per μg of stable germanium with a gallium separation factor of $3.4 \cdot 10^5$. Other stable metal impurities were typically 37 ppm Zn, <1 ppm Cu, Pb, Co, Cr, Cd, Ni, Fe, Mn, and Al, and <7 ppm Nb. Radiopurity was greater than 99%.

New applications of ^{68}Ge presented challenges to this separation scheme. One new requirement is higher

activity concentration and, therefore, even smaller product volume than previously supplied. An activity concentration in the range 3.15–3.70 GBq (85–100 mCi) of ^{68}Ge per ml requires the total product to be contained in less than 4 ml, given total production yields of less than 18.5 GBq (500 mCi) at EOB that can be achieved at BLIP. Volume reduction from 0.1–0.5N HCl to achieve these higher activity concentrations is extremely difficult. Reducing the volume of dilute HCl solutions increases acidity since HCl forms an azeotrope in H_2O of $\sim 20\%$ HCl. At this concentration, $\sim 6\text{N}$ HCl, ^{68}Ge is volatile, leading to unacceptable losses. However, back-extracting into smaller aqueous volumes results in much lower product recovery due to handling losses as discussed above.

Another new requirement is an increase in pH of the product solution. In the past, ^{68}Ge was supplied in 0.1–0.5N HCl solutions. However, recent applications require a pH range of 2–4. An attempt to raise pH by back-extracting from toluene into H_2O instead of 0.1N HCl was unsuccessful. While ^{68}Ge quantitatively extracted, the final acidity, measured using titration, was determined to be 1.5N HCl. The increased acidity is due to the small solubility of 10N HCl in toluene itself. The solubility of H_2O in toluene is 0.03% at 25°C ⁷ and the solubility of HCl might be considered comparable or higher. The solvent was changed from toluene to carbon tetrachloride, in which H_2O is less soluble (0.008%).⁷ However, the final pH of the back-extractant was still $\ll 2$, requiring further adjustment.

Two approaches were investigated to solve the challenges of increasing both activity concentration and pH in the final product solution. One method was based on a distillation procedure used to recover ^{68}Ge from irradiated molybdenum targets at Los Alamos National Laboratory.⁸ Separating germanium as its volatile tetrachloride by distillation from 6–12N HCl is a classic purification method.⁹ The advantage to using this approach is that the ^{68}Ge could be distilled directly from the gallium target into a small volume of 0.01N HCl or H_2O , in one step, eliminating the multiple extractions presently used. In order to test this approach, 200 μg stable germanium was added to a 6N HCl solution and heated to 110°C to achieve distillation. Germanium recoveries were almost quantitative. An oxidizing environment is required since the distillation was unsuccessful using Ar to sweep the distillate but was successful using air. However, in the presence of gallium metal, germanium did not distil to any great extent with distillation yields less than 15%. This was attributed to the fact that gallium was dissolving in HCl to some small extent during the distillation as H_2 was observed to evolve on the metal surface. This reducing environment was sufficient to inhibit the germanium distillation.

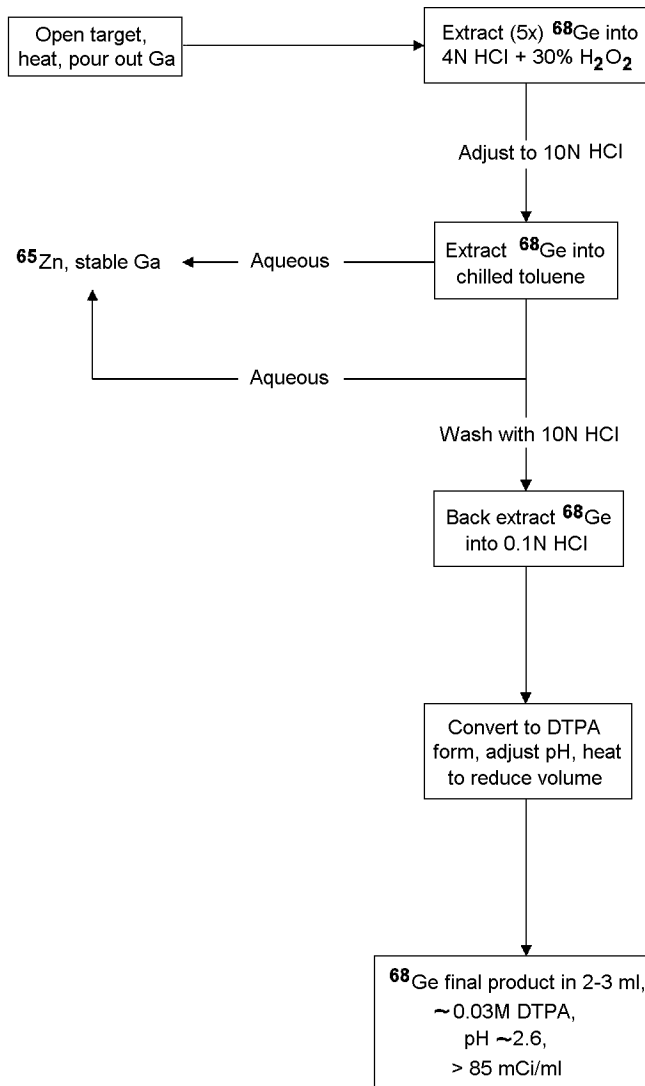


Fig. 2. Flowchart of $^{68}\text{Ge}/\text{Ga}$ separation procedure incorporating chelation with DTPA

Another approach was then investigated which involved converting ^{68}Ge from its volatile chloride to a non-volatile complex, Ge-DTPA, before final reduction of volume by heating. To test this hypothesis, a known activity of ^{68}Ge was added to 10 ml of 0.1N HCl. To this solution, 30 mg DTPA (7.5 ml 0.01M DTPA, pH 4) were added and the final pH was adjusted by titration to pH 3 with NaOH. This typically involved adding several ml of 1N NaOH. This solution was evaporated to 2.5 ml to achieve the desired activity concentration. The final pH was measured to be 2.57 with $[\text{DTPA}] = 0.029\text{M}$. Further evaporation was not possible since NaCl salt would have precipitated (present from the neutralization). Loss of ^{68}Ge was negligible.

Product solutions of this composition were given to an outside user for evaluation in source preparation and the results compared favorably to ^{68}Ge in the tetrachloride form. Incorporating these new steps into the previous scheme gives an overall ^{68}Ge recovery of 87%. The final separation procedure incorporating volume reduction with DTPA is shown in Fig. 2.

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