J. Chem. Chem. Eng. 9 (2015) 462-467
doi: 10.17265/1934-7375/2015.07.006

Evaluation of Materials for the Separation of Germanium from Gallium, Zinc and Cobalt

Jonathan Fitzsimmons* and Leonard Mausner

Medical Isotope Research & Production Program, Collider-Accelerator Department, Brookhaven National Laboratory, NY 11973, USA

Abstract: In the past ^{68}Ge (Germanium-68) was purified with toxic organic solvents in liquid-liquid extractions making the product unacceptable by the FDA (food and drug Administration) for human use. The authors report initial studies utilizing three or four columns consisting of sequences of AG1, AG50, Chelex 100 and/or Sephadex G25 resins. Five purification methods were examined and a separation consisting of the sequence: AG1-Chelex100-Sephedex G25 provided 87% recovery of germanium. Fractionation of the elution resulted in high germanium concentrations.

Key words: ^{68}Ga, ^{68}Ge, Sephadex G25, radiochemical separation.

1. Introduction

PET (positron emission tomography) with peptides radiolabeled with ^{68}Ga (Gallium-68) is emerging as a suitable method for the diagnosis of disease and evaluating treatments [1, 2]. ^{68}Ga has a short half-life ($T_{1/2}$ = 68.1 min) and is formed from the electron capture of ^{68}Ge (Germanium-68) which has a longer half-life ($T_{1/2}$ = 271 days). This isotope pair has been used in PET calibration sources as well as the development and marketing of the germanium/gallium medical isotope generator. During production of ^{68}Ge the following isotopes are coproduced: ^{65}Zn (Zinc-65), $T_{1/2}$ = 244 days and trace quantities of radioactive cobalt. To isolate ^{68}Ge from the Gallium target material a two-step process is used which involves leaching ^{68}Ge from natural gallium. Followed by liquid/liquid solvent extractions performed with various concentrations of HCl and toluene or carbon tetrachloride [3]. The toxic organics are class 1 and 2 solvents according to the FDA (food and drug Administration) and should be avoided when preparing a drug substance [4, 5].

Ideally the purification of Ge should use aqueous chemistry to remove all the Zn and Co, but leave part per million levels or less of natural Ga. In the solvent extraction approach ^{68}Ge recovery yields are 85% with greater than 99% radiopurity with average activity concentrations of 92.96 mCi/mL [6]. The separation should produce ^{68}Ge with greater than 80% recovery and the final product needs to be in 0.1 M HCl with a radiochemical concentration greater than 50 mCi/mL. Volume reduction of the Ge/HCl solution to meet the activity concentration requirement is not practical as Ge and Ga tetrachloride are both extremely volatile, and would result in loss of product and a contamination issue [7, 8]. These requirements for the ^{68}Ge product make purification of Gefrom gallium metal challenging.

The studies herein evaluate the retention of Ge, Ga, Co and Zn on Chelex 100 and Sephadex G25 from alkaline solution. This knowledge was used to investigate five different separation approaches to separate Ge utilizing multiple resin sequences. These initial studies focus on a separation that utilizes the leaching step followed by column chromatography.

2. Materials and Methods

2.1 Materials

All solutions were prepared with 18 MΩ Millipore water, pH adjustments were checked with pH strips

---

[*] **Corresponding author:** Jonathan Fitzsimmons, Ph.D., research field: radiochemistry.

(EMD chemicals). Coarse, fine and medium mesh Sephadex G25 was purchased from Phamcea, and Econo-Pac columns, analytical grade AG1X8, AG50, and Chelex 100 resins were purchased from BIO-RAD. ICP-MS (inductively coupled plasma-mass spectrometry) standards for Ga, Ge, Co, Zn, a 19 element mixed standard were purchased from SPEX CertiPrep (Metuchen, NJ) and were used to prepare a set of ICP calibration and QC (quality control) standards. Gallium metal and other chemical were purchased from Sigma Aldrich. All other materials were purchased from Fisher Scientific.

2.2 Single Column Studies

2.2.1 Sephadex Procedure

A solution contining 100 μg of Ga, Zn and Ge was prepared from the ICP standards and the solution was adjusted to pH 13.0 with 10 M NaOH. Then the solution was loaded onto a Sephadex G25 (fine or coarse) column, and the column was rinsed with 2-5 bed volumes of 0.1 M NaOH, then 1-2 bed volumes of water. The Ge was eluted with 0.1 M HCl and the elutions were fractionated. The separation was repeated with a solution containing Ga, Ga and Co.

2.2.2 Chelex 100

A solution containing 100 μg of Ga, Zn, Co and Ge was prepared from the ICP standards and the solution was adjusted to pH 14.0 with 10 M NaOH. The solution was loaded onto a Chelex 100 column, and the column was rinsed with 2-5 bed volumes of 1.0 M NaOH, then 1-2 bed volumes of water. The retained metals were eluted with 0.1 M HCl and the elutions were fractionated.

2.3 Multi-Column Separations

2.3.1 Gallium Stock Solution

A 0.14 g/mL gallium stock solution in 4 M HCl was prepared [9].

2.3.2 Working Metal Solution

To a beaker was added 0.5 mL of 1,000 μg/mL of Zn and Co ICP standards and the beaker was heated to dryness. To the beaker was added 3-7.143 mL of the gallium solution (0.5-1 grams) and 1 mL of 604 μg/mL Germanium in 0.05 M HCl. The solution was diluted to 20 mL with 4 M HCl. This solution represents the leached amount of Ga, Ge Zn and CO from an irradiated gallium target and was prepared and used for methods 1-5.

2.3.3 Separation Studies

A flow chart and column conditions that summarize the different separation methods are illustrated in Fig. 1 and Table 1. AG1X8, Chelex 100 and medium Sephadex resins were prepared in Econo-Pac columns, and the AG50 column was prepared in poly-prep column. Briefly, in methods 1-5 twenty mL's of the metal solution was diluted to 1.6 M HCl and an AG1 column was used to remove Zn. Next 10 M NaOH was added to the solution to neutralize the acid and generate a solution at a pH of 14, which was checked by pH paper. The sequence of columns used in methods 1-5 was: Method 1: [AG1, (NaCl spike), Sephadex G25, AG50]. After the AG 1 column NaCl was added to the basic metal solution to generate a 1 M NaCl, the pH adjusted to 14.0 and the solution stirred until dissolved. Method 2: [AG1, Chelex 100, Sephadex G25]. Method 3: [AG1, (NaCl spike) Chelex 100, Sephadex G25]. Method 2 was used with the exception that the eluted solution from the AG1 column was added to NaOH and NaCl to make a 1 M NaOH and 1 M NaCl solution prior to adding the solution to the Chelex 100 column. Method 4: [AG1, Chelex 100, (NaCl spike) Sephadex G25]. Method 2 was used with the exception that the eluted solution from the Chelex 100 column was added to NaCl to make a 1 M NaCl solution prior to adding the solution to the Sephadex G25 column. Method 5: [AG1, Chelex 100 (NaCl spike) Sephadex G25, AG50]. Method 4 was used with the exception that the HCl eluted from the Sephadex G-25 column was passed through an AG 50 column.

2.4 Analysis

Stable metals analysis of the final HCl elutions was

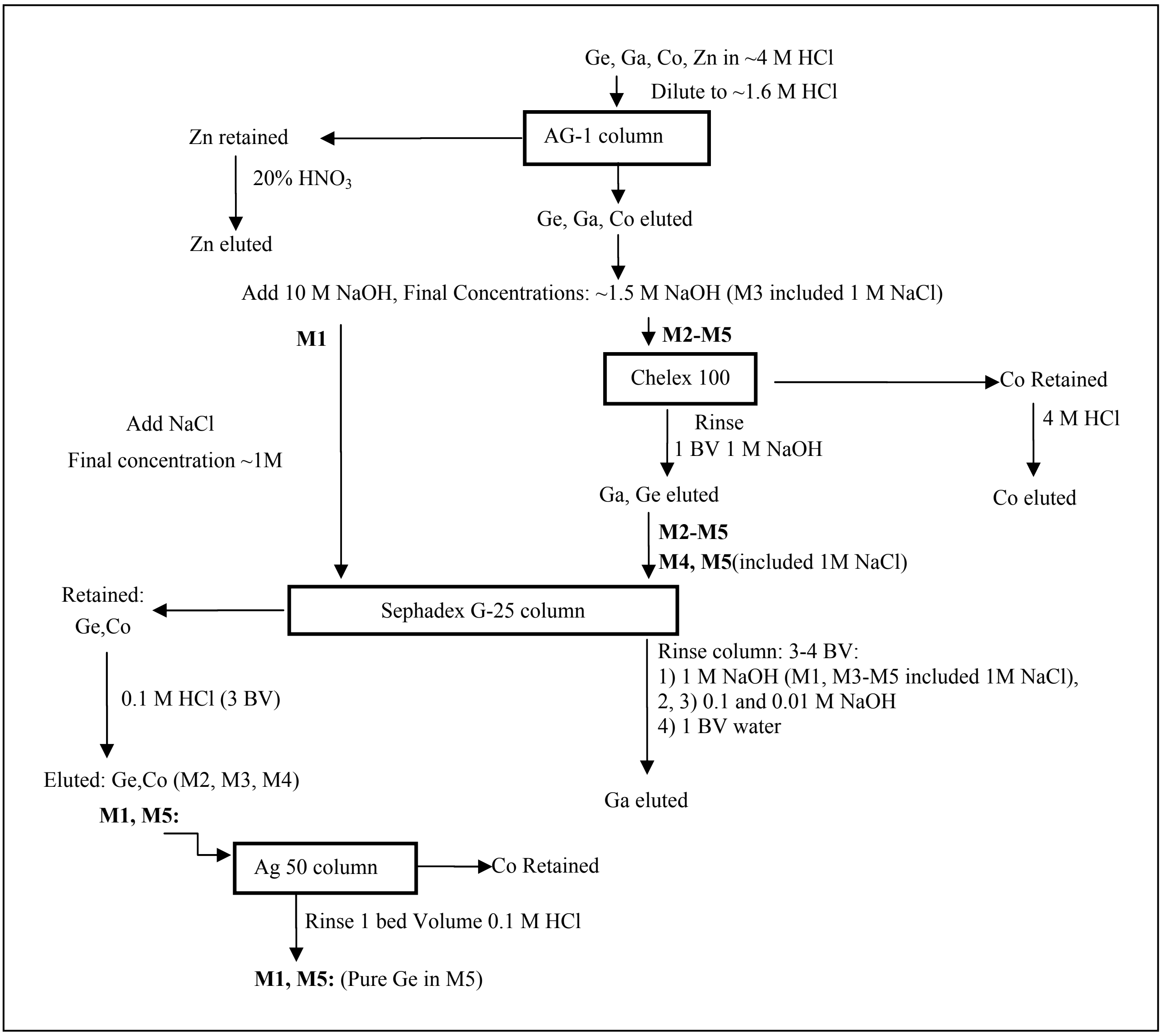

Fig. 1 Flow chart for separation methods 1-5. MX = method x. BV = bed volumes.

Table 1 Properties of different columns used in the different methods. a = time needed to elute the load solution.

Resin	Mass (g)	BV (mL)	Retained	Eluted
AG1X8	1.5	3	Zn	Ga, Ge, Co
Chelex 100	3.5	5	Co	Ga, Ga
Sephadex G25	0.8	4	Ge, Co	Ga
AG50	0.5	1	Co	Ge

performed using Optima 2000 ICP-OES (inductively coupled plasma-optical emission spectroscopy) unit (Perkin Elmer) with plasma operated at 1,300 W and samples were prepared in 2% nitric acid. A standard curve was prepared from a 19 element standard containing Cu, Pb, Zn, Co, Cr, Cd, Ni, Fe, Mn, Al, Ga, Ge, Sr, Be, Mg, Rb, Ca, Ba, and Nb at concentrations from 0.05-10 ppm. For the single column studies the amount of Co, Ga, Ge, and Zn was determined in the eluted load solution, NaOH rinses, water rinse and the HCl. In each method ICP-OES samples were prepared from diluted samples of: the eluted water (1 bed volume) and the fractionated (6 × 2 mL) 0.1 M HCl elutions. In the five methods the mass of each metal was determined in each 2 mL HCl fraction, the masses summed for the HCl fractions, and the concentration determined for the entire HCl elution (12 mL).

3. Results and Discussion

The evaluation of Sephadex G25 resin for Ge purification was based on research where Ge was purified from rocks [10]. Attempts to perform the separation with a Sephadex column at pH values below 13.0, as described in the literature, resulted in the slow formation of a white insoluble solid that stopped column flow. ICP-OES analysis of the insoluble species indicated the presence of both gallium and germanium. At values above pH 10 Ga speciation diagrams indicate Ga is present in the form of $Ga(OH)_4^-$ and insoluble $Ga(OH)_3$ which was the cause of the insoluble Ga [11]. Ge speciation diagrams indicate Ge is present in the form of the soluble species $GeO(OH)_3^-$ and $GeO2(OH)_2^{2-}$ [9]. As a consequence of insoluble metal hydroxides at pH values between 10 and 13, high concentration of hydroxide was needed to form complexes of soluble metal hydroxides and the separations were performed at pH 14.

3.1 Single Column Studies

Table 2 summarizes the single column studies with Sephadex G25 and Chelex 100. Briefly, in the Sephadex G25 studies the amount of Ga in the elutedload and rinse solution was 98% and the HCl elutions contained: 91.5% of the Ge, 13% of Zn and > 95% of Co. Single column studies with Sephadex indicated Ge and Co behave similar with very high retention on the resin; in contrast, Ga has minimal retention on Sephadex. Only 80% of Zn was removed utilizing the Sephadex. Clearly the approach with Sephadex would require more than one column and Chelex 100 was analyzed for its ability to remove Co and Zn. In a single column study the Chelex 100 retained 91% of the Co and 18% of the Zn while > 95% of the Ge and Ga were eluted in the load and rinse steps. Separation attempts with Bio Rad 501 resin with Ga/Ge/Co/Zn in 0.1 M HCl resulted in mixed results with 43-70% of the metals being eluted, and in a similar separation with 1 M NaOH > 95% of Ga, Ge, and Co were eluted in the load and washings along with 76% of Zn. A one or two column method with NaOH/NaCl approach will not separate Co and Zn from Ge. From these initial studies a three column purification approach was evaluated where Zn was removed first by an AG1 column [12], and Co is removed by either Chelex 100 and/or AG50, and a Sephadex G25 column is used for the separation of Ga from Ge.

3.2 Multicolum Studies

Table 2 illustrates the differences of the methods and compares the characteristics of the final product (12 mL of the 0.1 M HCl elutions) of methods 1-5 to the current organic extraction method [6]. The

Table 3 The percent Ga, Ge, Zn, and Co recovered in the rinse steps and the HCl elutions in single column studies.

	Percent			
	Ga	Ge	Zn	Co
Sephadex G25				
Eluted in load, NaOH rinses	98	6.2	70	0.4
Water	0.0	0.0	8.0	0.0
Eluted in HCl	2.3	92	14	99
Chelex 100				
Load and NaOH rinse	99	97	81	8.6
Water rinse	0.2	0.5	1.5	0.1
0.1 M HCl	0.3	2.8	18	91

Table 3 Summary of the five methods and properties of the final product for the tested methods and the organic extraction method.

Method	1	2	3	4	5	Organic extraction
Conditions						
Column 1	AG 1	AG 1	AG 1	AG 1	AG 1	-
Solution modification	1 M NaCl	-	1 M NaCl	-	-	-
Column 2	Sephadex G25	Chelex 100	Chelex 100	Chelex 100	Chelex 100	-
Solution modification	-	-	-	1 M NaCl	1 M NaCl	-
Column 3	AG 50	Sephadex G25	Sephadex G25	Sephadex G25	Sephadex G25	-
Column 4	-	-	-	-	AG 50	-
Results						
% recovery of Ge	45.6	87.8	82.5	43.2	41.5	~85
% Ge in BVs 1&2[a]	96.1	99.4	97.2	93.2	96.7	
Mass Ge (µg)	275.5	530.3	498.3	260.9	250.6	80-525
Conc. Ga (ppm)	0.13	15	1.7	1.6	0.1	41.1
Mass Ga (µg)	1.5	183	20	19	1.4	80-525
% Ga remain	0.0002	0.0244	0.0027	0.0025	0.0002	---
Conc. Zn (ppm)	ND	ND	ND	ND	ND	Up to 10.2
Conc. Co (ppm)	0.13	0.24	3.13	0.062	ND	ND
Mass Co (µg)	1.6	2.9	37.6	0.75	0	ND
% Co Remain	0.32	0.58	7.52	0.15	0	ND

ND: not detectable. ICP-OES LLOQ (lower limit of quantification): 0.1 ppm (Zn), and 0.005 ppm (Co). In methods 1-5 the final volume of Ge in the 0.1 M HCl was 12 mL. The % recovery or remaining is calculated from the sum off all HCl fractions. a = % Ge in BVs 1 & 2 was calculated based on the total Ge eluted in the HCl fractions.

following properties were compared: % Ge recovered, concentration of Ga and Co, and the mass (µg) of Ge, Ga, Co and Zn. Ge recovery: In methods 2 and 3 the percent Ge recovered was 87 and 82% as compared to 40-45% for methods 1, 4 and 5. Fractionation of HCl: The final concentration of Ge needs to be high in order to meet activity concentration requirements. The percent of eluted Ge in the HCl fractions was greater than 96% in bed volumes 1 & 2 for methods 1-3, and 5, and was 93% for method 4. This indicates a narrow band of Ge on the Sephadex G25 column that is rapidly eluted from the column with 0.1 M HCl. It is worth noting that the high concentrations of Ge in bed volumes 1 & 2 would translate into high radioactivity concentrations, and concentration step of the final product would not be needed. This is extremely important because germanium chloride is volatile making it difficult to concentrate the product safely. Alternatively, eluting with 0.1 M nitric acid could be problematic, as a white solid was observed when the solution was evaporated. Evaporating high specific activity ^{68}Ge in nitric acid solution could lead to irrecoverable losses to the glassware [7]. Ga remaining: The organic extraction method produced Ga concentration in the final product from 30-50 ppm. In methods 1-5 the final product (Ge in 12 mL of the eluted HCl) would have a Ga concentration of 15 ppm for method 2, and 1.6-1.7 ppm for methods 3 and 4, and 0.11-0.13 ppm for methods 1 and 5. The AG50 column used in methods 1 and 5 reduced the mass of Ga in the product by a factor of 10 over methods 3 and 4 which did not use the column. Influence of NaCl: Methods 1, 3-5 used Sephadex with NaCl and the concentration of Ga was reduced when compared to method 2 which did not use NaCl. Method 2 does not use NaCl in either Sephadex or Chelex 100 steps and has a 10 fold higher concentration of Ga than similar methods 3 & 4 that use NaCl. A study varying the concentration of NaCl from 0.1-1.5 indicated no correlation between NaCl concentration and Ge and Co concentration in the final product. However, a linear correlation was present between the concentration of Ga in the final product and the concentration of NaCl used in the separation (y = 2.3x + 0.6, R^2 = 0.88). Although this is an interesting finding the final concentration of Ga in the HCl fractions of all the methods was below the concentrations obtained by the organic extraction method. Method 3 looks the most promising for removal of Ga and recovery of Ge, on the other hand the amount of Co in the final product is much higher than the other methods. Zn remaining: The amount of Zn in the HCl fractions for methods 1-5 was below the functional limit of detection (1 ppm) for the ICP-OES, so the first step in the separation has to be the dilution of the sample to 1.5 M HCl and removal of Zn with an AG 1 column. Co remaining: The percentage of Co remaining out of the initial 500 μg was: 0.32% (method 1), 0.58% (method 2), 7.5% (method 3), and 0.15% (method 4). The concentration of Co remaining after method 5 was below the LLOQ for the ICP-OES.

4. Conclusions

This research evaluates a basic solvent system with various resins for the purification of germanium. Five different methods were evaluated for the purification of Ge from Ga, Co and Zn. Methods 2 and 3 have the best properties for the purification of Ge and will be evaluated further with irradiated Ga targets to determine if either can be used in the production of ^{68}Ge. The high concentration of germanium in the eluted HCl fractions (bed volumes 1 and 2) of the Sephadex G25 column is ideal for the purification of ^{68}Ge.

Acknowledgments

This study was supported by funding provided by the Department of Energy, Office of Nuclear Physics, subprogram Isotope Development and Production for Research and Applications.

References

[1] Breeman, W., Jong, M. D., Blois, E. D., Bernard, B. F., Konijnenberg, M., and Krennin, E. 2005. “Radiolabelling DOTA-peptides with ^{68}Ga.” *Eur. J. Nucl. Med. Mol. Imaging* 32 (4): 478-85.

[2] Morgenstern, A., Bruchertseife, F., Apostolidis, C., Giesel, F., Mier, M., Haberkor, U., et al. 2012. “Synthesis of ^{213}Bi-DOTATOC for Peptide Receptor Alpha-therapy of GEP-NET Patients Refractory to Beta Therapy.” In *SNM’s 59th Annual Meeting:* 455.

[3] Meinkin, G. E., Kurczak, S., Mausner, L. F., Kolsky, K. L., and Srivastava, S. C. 2005. “Production of High Specific Activity ^{68}Ge at Brookhaven National Laboratory.” *J. Radioanal. Nucl. Chem*. 263 (2): 553-7.

[4] FDA Documents: Guidance for Industry Q3C Impurities: Residual Solvents 1997.

[5] FDA Guidance for Industry Q3C-Tables and lists 2003.

[6] Isotope Production Group, Brookhaven National Laboratory, Batch Records of Germanium production. Upton, NY, Number of batches = 21, from 2/2008 to 7/2011.

[7] Mirzadeh, S., and Lambrecht, R. M. 1996. “Radiochemistry of Germanium.” *J. Radioanal. Nucl. Chem*. 202 (1): 7-102.

[8] Lewis, J. 1961. *The Radiochemistry of Aluminum and Gallium*. National Academy of Sciences—National Research Council Report.

[9] Fitzsimmons, J. M., and Mausner, L. 2015. “Development of a Production Scale Purification of ^{68}Ge from Irradiated Gallium Metal.” *Radiochimica Acta* 103 (2): 117-23.

[10] Harada, A., Tarutani, T., and Yoshimura, K. 1988. “Spectrophotometric Determination of Germanium in Rocks after Selective Adsorption on Sephadex Gel.” *Analytica Chim. Acta* 209: 333-8.

[11] Wood, S. A., and Samson, I. M. 2006. “The Aqueous Geochemistry of Gallium, Germanium, Indium and Scandium.” *Ore Geology Reviews* 28 (1): 57-102.

[12] Kraus, K., and Nelson, F. 1995. *Ion Exchange Chromatography*, edited by Walton, H. F. Dowden, Hutchinson & Ross, Inc., Vol. 1, 161-70.