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Chromatographic separation of the theranostic radionuclide ^{111}Ag from a proton irradiated thorium matrix

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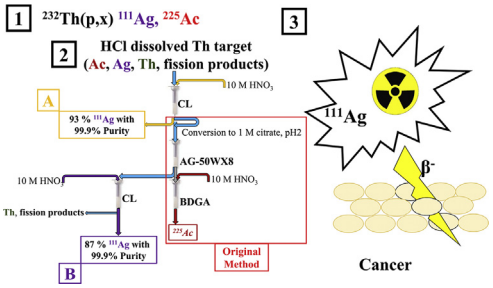
HIGHLIGHTS

- Chromatographic recovery of medical isotope ^{111}Ag from proton irradiated thorium targets.
- First-time measured equilibrium distribution coefficients for silver and ruthenium on CL resin.
- ^{232}Th (p, fission) cross-section data for the formation of ^{111}Ag and ^{110m}Ag.

GRAPHICAL ABSTRACT



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ABSTRACT

Column chromatographic methods have been developed to separate no-carrier-added ^{111}Ag from proton irradiated thorium targets and associated fission products as an ancillary process to an existing ^{225}Ac separation design. Herein we report the separation of ^{111}Ag both prior and subsequent to ^{225}Ac recovery using CL resin, a solvent impregnated resin (SIR) that carries an organic solution of alkyl phosphine sulfides ($R_3P = S$) and alkyl phosphine oxides ($R_3P = O$). The recovery yield of ^{111}Ag was 93 ± 9% with a radiochemical purity of 99.9% (prior) and 87 ± 9% with a radiochemical purity of 99.9% (subsequent to) ^{225}Ac recovery. Both processes were successfully performed with insignificant impacts on ^{225}Ac yields or quality. Measured equilibrium distribution coefficients for silver and ruthenium (a residual contaminant) on CL resin in hydrochloric and nitric acid media are reported, to the best of our knowledge, for the first time. Additionally, measured cross sections for the production of ^{111}Ag and ^{110m}Ag for the ^{232}Th(p,f)^{110m,111}Ag reactions are reported within.

1. Introduction

Silver-111 ($t_{1/2}$ 7.47 d, β_{max} = 1.04 MeV) is a β^- emitting isotope of interest for targeted radiotherapy [1–4]. The decay of ^{111}Ag also results in the emission of low energy gamma rays (245 (1.24%) and 342 (6.7%) keV), which allows for simultaneous imaging via single photon emission computed tomography (SPECT). This combination

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of imaging and therapy in one isotope allows simultaneous therapy and *in vivo* monitoring of the dose delivered [5].

Targeted radiotherapy is an emerging field of nuclear medicine where properties of radionuclidic decay are exploited to treat cancer and other diseases [6,7]. Therapeutic radionuclides emit ionizing particles such as alpha particles, beta particles, or auger electrons. Attaching these radioisotopes to a targeting moiety, such as an antibody or peptide, can effectively treat the cancer or diseased cells in the vicinity of the decay and provide minimal damage to surrounding healthy tissue [6–8]. Energy deposition as a function of particle path length traversed in tissue is called linear energy transfer (LET). Beta emitting radioisotopes have a range in tissue from one to tens of millimeters, depending on energy, and are best suited for medium to large tumors sizes [8].

The use of silver-111 for nuclear medicine purposes has been explored previously for limited applications ranging from fundamental R&D to (pre)clinical investigations. Prior works include the therapeutic management of arthritis with ^{111}Ag-labelled hydroxyapatite [1], and the use of ^{111}Ag as a radiotracer to determine the biodistribution and stability of silver-based antimicrobials [2,3]. Moreover, the longer half-life of ^{111}Ag corresponds well with the biological half-lives of antibodies, making this isotope interesting for use in radioimmunotherapy [9,10].

The incumbent ^{111}Ag production method uses thermal neutron irradiation of natural palladium targets to make the intermediate nuclide ^{111}Pd by ^{110}Pd(n,γ)^{111}Pd. Short-lived ^{111}Pd ($t_{1/2}$ 23.4 min) then decays to ^{111}Ag [11,12]. Deuteron reactions have also been investigated, i.e. ^{110}Pd(d,n)^{111}Ag [13], but these routes are limited by small ^{110}Pd neutron capture cross-section and the unavoidable co-production of ^{110m}Ag when irradiating with deuterons, respectively. For ^{111}Ag to be useful in a clinical setting, a consistent supply of tens of GBq (Ci) quantities would be necessary as typical radiotherapeutic doses range from 3700-7400 MBq(100-200 mCi)/patient [6,14].

Currently, Los Alamos National Laboratory (LANL), Brookhaven National Laboratory (BNL) and Oak Ridge National Laboratory (ORNL) are investigating the production and purification of ^{225}Ac ($t_{1/2}$ = 9.92d) [15,16], another radionuclide of interest for therapeutic applications, by proton induced spallation reactions on thorium targets [17]. During this process, many additional radionuclides of interest are generated, including isotopes of Pa [18] and Ra [19] and proton-induced fission products like ^{103}Ru and ^{111}Ag. Amounts of radionuclides generated via charged particle induced nuclear reactions are typically within picogram to nanogram ranges, which poses the challenge of chemically separating nearly massless quantities of product from a large amount of target matrix. Such circumstances often relate radionuclide recovery and purification problems to the discipline of analytical chemistry.

With respect to the recovery of several radionuclides from the same target and, more specifically, for isolating radiochemically pure ^{111}Ag alongside ^{225}Ac and possible other useful radionuclides from proton irradiated thorium, there are two main hurdles: 1) the separation of ^{111}Ag from an isotope mixture containing many additional fission products contained in the bulk thorium mass and 2) the minimization of additional impact on the already streamlined ^{225}Ac isolation and purification process. To overcome these hurdles, column chromatographic methods are resorted to.

CL resin is a solvent impregnated resin (SIR) manufactured by Triskem that carries an organic solution of alkyl phosphine sulfides (R_3P = S) and alkyl phosphine oxides (R_3P = O). This resin was primarily designed for the separation of chloride and iodide ions from aqueous solutions after preloading the resin with silver ions [20]. The preloaded silver is complexed to the sulfur bearing moiety first. This immobilized silver complex then, in turn, strongly binds to halide ions, which are consequently extracted from aqueous media. Selective liquid-liquid extraction of silver and noble/heavy metals from nitric acid media into solutions of thiophosphates or alkyl phosphine sulfides has been reported [21–25], and results predispose immobilized phosphine based complexants to the efficient sorption of silver from aqueous media. The novelty of macroporous resins impregnated with these extractants thus lies in the combination of Ag selectivity with the ease of operation of column chromatography. Although similar alkyl phosphine based systems for nobel/heavy metal immobilization have been reported previously [26,27], the SIR based sorption selectivity for silver ions has not been established as yet.

In our study, we investigated the resin's affinity for silver as a means to adsorb no-carrier-added radiosilver ^{111}Ag, i.e., minute amounts of Ag in terms of mass, from the isotope mixture in the aqueous thorium target dissolution solution. The resin's affinity to ruthenium was also tested as ^{103}Ru was a common residual contaminant in the recovery of ^{111}Ag based on some of our initial studies. Equilibrium distribution coefficients for the sorption of thorium (IV), actinium (III), ruthenium (VI) and silver (I), the most likely and stable oxidation states of these elements encountered in aqueous systems, have been measured and are reported in our study. Initial results suggested that a separation of silver from the bulk thorium mass with a high decontamination factor could be feasible. Hence, a separation strategy has been developed to provide ^{111}Ag in high radiochemical yield and radionuclidic purity. The production and separation of ^{111}Ag as an ancillary process to the production of ^{225}Ac using this new method are discussed.

Nuclear excitation functions, i.e., nuclear reaction cross sections as a function of proton energy, reflect the probability at which a desired nuclear reaction occurs. Carefully measured excitation functions provide the radionuclide production scientist with an invaluable tool to estimate both product yield and expected levels of unwanted byproducts. Target thicknesses, particle energies and separation chemistry design are developed according to excitation function based estimates. Hence, to provide a link between the analytical data of this work and the application to radionuclide production science, the excitation functions for the proton induced formation of ^{111}Ag and ^{110m}Ag (249.8 d) through the reactions ^{232}Th(p,f)^{110m,111}Ag, at incident proton energies below 200 MeV, are reported as well. Excitation functions were calculated by the analysis of data collected from previous thin foil measurements [28]. These cross section results predict theoretical thick target yields of up to 540 GBq (14.6 Ci) of ^{111}Ag to be formed in a 100 g thorium target (thickness 8.6 mm) after exposure to 49.9 mAh of integrated proton beam current, which are the projected target irradiation conditions for full scale production of ^{225}Ac at the Isotope Production Facility at LANL.

2. Materials and methods

2.1. Reagents

All reagents used were trace metal grade unless specified elsewhere. Aqueous solutions were prepared with 18 MΩ water (Millipore). For nuclear reaction cross section measurements, natural thorium foils of 99.7% purity were obtained from Goodfellow Corporation (Oakdale, PA, USA). The foils were of 2.5 × 2.5 mm approximate dimensions, with mass thicknesses ranging from 60.5 to 70.5 mg cm^{-2} [28]. Aluminum foils of 99.9% purity and similar dimensions with 65 mg cm^{-2} thickness were used as beam current monitors based on the ^{27}Al(p,x)^{22}Na nuclear reaction and the respective excitation functions reported by Steyn et al. [29]. Foils were enclosed in a single layer of adhesive-backed 25 μm thick Kapton tape. Thorium metal targets were manufactured at the Los Alamos National Laboratory (LANL). For larger-scale experiments,

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small pieces of thorium metal (purity >99% as determined via X-ray fluorescence spectroscopy) were obtained from LANL's internal inventory. The raw material was rolled into sheets with a mean thickness of 0.50 ± 0.02 mm for the use as proton beam targets. Chloride (CL) resin (50-100 μg) was obtained from TrisKem International (Bruz, France), AG MP1 and AG 50W-X8 resins were obtained from Bio-Rad Laboratories (Hercules, CA, USA). Normal DGA and BDGA resins (50-100 μg) were obtained from Eichrom Technologies (Lisle, IL, USA). All separation studies reported within were performed in triplicate.

2.2. High purity germanium (HPGe) detector analyses

2.2.1. Gamma-ray spectroscopy for cross section measurements

Proton induced fission cross sections for the formation of ^{111}Ag and ^{110m}Ag were determined utilizing nondestructive gamma ray spectroscopy of irradiated foils to quantify the activity of each radionuclide of interest [28,30]. The foils were prepared for gamma ray spectroscopy several hours after end of bombardment (EOB), to allow short-lived isotopes to decay. The thorium foils were counted on an ORTEC GEM10P4-70 detector with a relative efficiency of 10% at 1333 keV and a measured FWHM of 1.99 keV at 1333 keV, while the aluminum foils were counted on a Princeton Gamma-tech lithium-drifted germanium Ge(Li) detector with a relative efficiency of 13.7%. Both detectors were well shielded and calibrated using NIST-traceable gamma calibration sources. The thorium foils were counted more than 35 times over a period of several months, and the decay curves of all isotopes of interest were closely followed to ensure proper identification and to evaluate any possible interferences. The aluminum foils were counted approximately 12 times within the first week after EOB to monitor the ^{24}Na decay curve, followed by a minimum of three 8 h counts several weeks later to quantify the ^{22}Na activity at EOB.

Uncertainties in linear regressions fitted parameters were computed from covariance matrices as the standard deviation in the activity extrapolated to the end of bombardment. This value was combined according to the Gaussian law of error propagation with estimated contributing uncertainties from detector calibration and geometry reproducibility (5.9% combined), target foil dimensions (0.1%), and proton flux (6-18%). Multiple photopeaks were used (up to a maximum of four) when possible, and so additional uncertainty as the standard deviation of these complimentary measurements was combined with the uncertainties described above, again according to the Gaussian law of error propagation.

2.2.2. Gamma-ray spectroscopy for separation chemistry experiments

All yields and purities from separation experiments were determined via gamma-ray spectroscopy using a High Purity Germanium detector (HPGe). Gamma-ray spectroscopy was conducted using an EG&G Ortec Model GMX-35200-S HPGe detector system in combination with a Canberra Model 35-Plus multichannel analyzer. Detector diameter was 50.0 mm, detector length was 53.5 mm, Be window thickness was 0.5 mm, and outer dead-layer thickness was 0.3 μm. Detector response function determination and evaluation were performed using standards of radionuclide mixtures containing ^{241}Am, ^{109}Cd, ^{57}Co, ^{139}Ce, ^{203}Hg, ^{113}Sn, ^{137}Cs, ^{88}Y, and ^{60}Co, traceable to the National Institute of Standards and Technology (NIST) and supplied by Eckert & Ziegler (Atlanta, GA, USA). The detector was a p-type Al-windowed HPGe detector with a measured FWHM at 1333 keV of approximately 2.2 keV and a relative efficiency of about 10%. Relative total source activity uncertainties ranged from 2.6% to 3.3%. Counting dead times were kept below 10%.

2.3. Irradiations for cross section measurements

Thin thorium foils were irradiated in two separate experiments at the Los Alamos Neutron Science Center (LANSCE) at LANL using incident proton energies of 100 and 200 MeV as described previously [28]. In each experiment, the original beam energy was degraded to approximately half of its original value using aluminum degraders. Beam current was monitored using thin aluminum foils and the ^{27}Al(p,x)^{22}Na reaction. The beam profile was assessed following the experiment by the activation of thin stainless steel plates whose dimensions significantly exceeded those used for the thorium foils. The steel plates were exposed to Gafchromic® film following the end of irradiation in order to map the beam profile, which was determined to have been quantitatively incident on the desired targets in both experiments.

2.4. Radionuclide production irradiations

A 10 g thorium metal target was irradiated at the Isotope Production Facility (IPF), Los Alamos National Laboratory (LANL, NM, USA). The target was encapsulated in Inconel cladding and placed into the high energy "A" slot (nominal 92 MeV incident energy) of the IPF target assembly. IPF targetry and 4π water cooling were identical to the design as described previously [31,32]. The target was irradiated in a 230 μA of 89.6 MeV protons for 22.5 h.

2.5. Distribution coefficients for chloride (CL) resin

Equilibrium distribution coefficients were determined for silver, thorium, and ruthenium using the batch mode. Each condition was run in triplicate. Approximately 50 mg of chloride resin (CL resin) were added to pre-weighed and tared 2 mL centrifuge tubes. One milliliter of liquid phase (HCl or HNO_3 of variable concentrations ranging from 0.1-12 M) along with a 5 μL aliquot containing 5 kBq of ^{111}Ag, 15 kBq of ^{227}Th, 6 kBq of ^{225}Ac, or 15 kBq of ^{103}Ru in 0.1 M HCl were added to each tube and weighed. The mixtures were vortexed and allowed to equilibrate for 24 h on a rocker at ambient temperature. The mixtures were filtered with 4 mm nonsterile hydrophilic polytetrafluoroethylene (PTFE) syringe filters (EMD Millipore, Billerica, MA) and the characteristic γ-ray lines of ^{111}Ag, ^{227}Th, or ^{103}Ru in the filtrate were measured with a high purity germanium (HPGe) detector. The total activity in the aqueous phase was calculated from this aliquot; the activity adsorbed on the resin was determined by subtraction of total aqueous activity from the total original activity added. Distribution coefficients were calculated using Equation (1), where A_i is the initial activity, A_{eq} is the equilibrium activity in the aqueous phase, V is the volume of the equilibrium liquid phase (mL) and m is the mass of the resin (mg). Considering the detection limit as dictated by signal-to-noise ratio, detector efficiency and reasonable counting time, the maximum distribution coefficient that could be measured under the experimental circumstances described above was ~10^4 mL mg^{-1}.

$$K_d = \frac{C_{eq1}}{C_{eq2}} = \frac{A_i - A_{eq}}{A_{eq}} \cdot \frac{V}{m} \quad (1)$$

2.6. Separation of ^{111}Ag

Currently, the LANL/ORNL/BNL developed process for actinium separation includes an anion, cation, and branched DGA (N,N,N′,N′-tetrakis-2-ethylhexyldiglycolamide) column in series [15–19]. Two processes were developed to separate ^{111}Ag from the irradiated thorium target; one with a column inserted prior to the anion

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column, and a second one with a column inserted post cation column (Fig. 3). Both processes are described below.

2.6.1. Process 1: pre ^{225}Ac anion column

A LANL irradiated thorium target was shipped to Oak Ridge National Laboratory (ORNL) for recovery of ^{225}Ac. The irradiated 10 g target was dissolved in 200 mL 10 M HCl and 0.1 mL of 2 M HF with heating (80-90 °C) for approximately 2 h. A 0.1 mL aliquot of the dissolved target was diluted to 5.1 mL with 0.1 M HNO_3, and a 50 μL aliquot of this solution was further diluted to 5.0 mL with 10 M HCl. The solution was then passed through a column (0.8 cm inner diameter) containing 1 mL of CL resin (Triskem, 50-100 μg) preconditioned with 10 M HCl. The eluent was then passed through an anion column and continued through the normal ^{225}Ac separation process (described below). The CL column was then contacted with 3 mL 10 M HCl (wash) followed by 5 mL 10 M HNO_3 (for Ag elution). Each fraction was analyzed with an HPGe detector following the characteristic γ-lines of the various isotopes present.

2.6.2. Process 2: post ^{225}Ac cation exchange column

Alternatively, a post cation column recovery of Ag was attempted. For this, the above dissolved thorium target was first passed through 15 mL of AG MP1 resin (100-200 mesh, chloride form), which is typically employed in actinium purification. The eluate from the column plus a 15 mL wash with 10 M HCl was evaporated to near dryness and converted into 750 mL of 1 M citric acid/citrate matrix of pH 2 by readjustment with concentrated ammonium hydroxide solution. This solution was then passed through a cation exchange column containing 15 mL of AG50W-X8 (100-200 mesh) for actinium sorption. This was followed by two column washes with 5 bed volumes 1 M citrate pH 2. The effluent from this cation column was retained for ^{111}Ag recovery, and small aliquots of this solution were used for further experimentation: 1 mL portions of the citrate eluent were diluted to 50 mL with citrate pH 2 and then passed through a column with 1 mL chloride resin. The CL resin was then washed with an additional 5 mL of citric acid pH 2 followed by 5 mL of 10 M HCl. Finally, 5 mL of 10 M HNO_3 was added to the CL resin to elute the ^{111}Ag. Each step was analyzed using a high purity germanium detector following the characteristic γ-lines of the various radioisotopes present and to determine the final purity of the ^{111}Ag fraction.

2.7. Fine purification of ^{111}Ag

2.7.1. Process 1: pre ^{225}Ac anion exchange column

The ^{111}Ag activity that was separated from the bulk thorium mass prior to anion exchange column contact during the ^{225}Ac recovery process contained several radioisotope contaminants such as ^{117m}Sn, ^{95}Nb, ^{99}Mo, ^{95}Zr, ^{126}Sb, ^{131}I, and ^{103}Ru, which comprised ~21% of the total activity. To separate these contaminants from ^{111}Ag, the solution was evaporated to dryness and reconstituted in 5 mL of 10 M HCl. This solution was then passed through a column containing 1 mL normal DGA (N,N,N′,N′-tetra-*n*-octyldiglycolamide) extraction chromatographic resin, followed by a 3 mL 10 M HCl wash. The eluent and wash were then passed through another column containing 250 μL CL resin to separate ^{111}Ag from any residual ^{103}Ru impurities: Ag was retained on the resin while ^{103}Ru eluted. The resin was then washed with an additional 2 mL of 10 M HCl followed by 5 mL 10 M HNO_3 to elute ^{111}Ag.

2.7.2. Process 2: post ^{225}Ac cation exchange column

Silver-111 separated from the bulk thorium mass and contaminant isotopes after the cation column in the ^{225}Ac process contained a small (<1%) amount of ^{103}Ru impurity. To remove ^{103}Ru from the final product, the solution was evaporated to dryness and reconstituted in 5 mL 10 M HCl. This solution was then passed through a column containing ~250 μL of CL resin. The resin was then washed with 2 mL of 10 M HCl followed by 5 mL 10 M HNO_3 to elute ^{111}Ag.

3. Results and discussion

3.1. Cross section measurements

Measured excitation functions of ^{110m}Ag and ^{111}Ag are plotted in Fig. 1 along with the previously reported measurements for the same reactions found in the literature [33–35]. The cross sections obtained in this work and the corresponding uncertainties are listed in Table 1. In addition to proton induced fission, neutron induced fission does occur and may have an impact on the data. The effect of neutron induced fission is understood to be small, as the secondary neutron fluence is smaller than that of the primary beam by several orders of magnitude, and may be qualitatively understood by comparing the 97 and 92 MeV data points, which result from irradiations with nominal incident energies of 200 and 100 MeV, respectively. Because secondary neutrons' angular distribution is forward-directed, their effect increases towards the “rear”, or lower energy, portion of a target foil stack. The similarity of these two points' magnitude provides assurance that secondary neutrons effects are indeed small. Details of these measurements have been discussed previously and the reader is referred to prior words for detailed explanations of uncertainty quantification and the methods employed in model calculations [28,30,36,37]. No current model accurately represents the measured data.

3.2. Equilibrium distribution coefficients for CL resin

The equilibrium distribution coefficients for silver in hydrochloric and nitric acid media were measured and are shown in Fig. 2. The results demonstrate that at high and low hydrochloric acid conditions silver is highly adsorbed onto the CL resin. At nitric acid molarities $\leq$2 M, silver was quasi quantitatively removed from the liquid phase, and minimum equilibrium distribution coefficients of 10^4 were assumed based on detection limits (see 2.5). Thorium and actinium, however, showed no sorption for any of the hydrochloric acid conditions measured. Therefore, under these conditions, ^{111}Ag could be extracted from the bulk thorium target without impact to ^{225}Ac recovery. Additionally, equilibrium distribution coefficients were measured for ^{103}Ru, as it was a common residual contaminant. Results showed very little affinity for the resin under both nitric and hydrochloric conditions (Fig. 2). Silver can be eluted from CL Resin using nitric acid concentrations $\geq$6 M. Upon elution of ^{111}Ag using nitric acid at these concentrations the resin color changes from white to a light green color. This is likely due to oxidation of the extractant.

3.3. Separation of ^{111}Ag

The thorium target was dissolved in 10 M HCl spiked with HF. This matrix concentration corresponds to strong silver sorption onto the CL Resin. Therefore, the first separation strategy attempted was to place a column with CL resin at the beginning of the ^{225}Ac process (Fig. 3). In this process, > 94 ± 9% of the ^{111}Ag was retained on the column. The ^{225}Ac and bulk thorium mass, as expected, did not sorb, and greater than 98% eluted from the column in the flow through. This fraction was then added to the anion exchange column, and the remaining ^{225}Ac separation scheme was followed. The ^{111}Ag was eluted from the CL resin using 10 M HNO_3.

The final eluted fraction contained ~94% of the initial ^{111}Ag activity with a radionuclidic purity of 79%. The contaminants present

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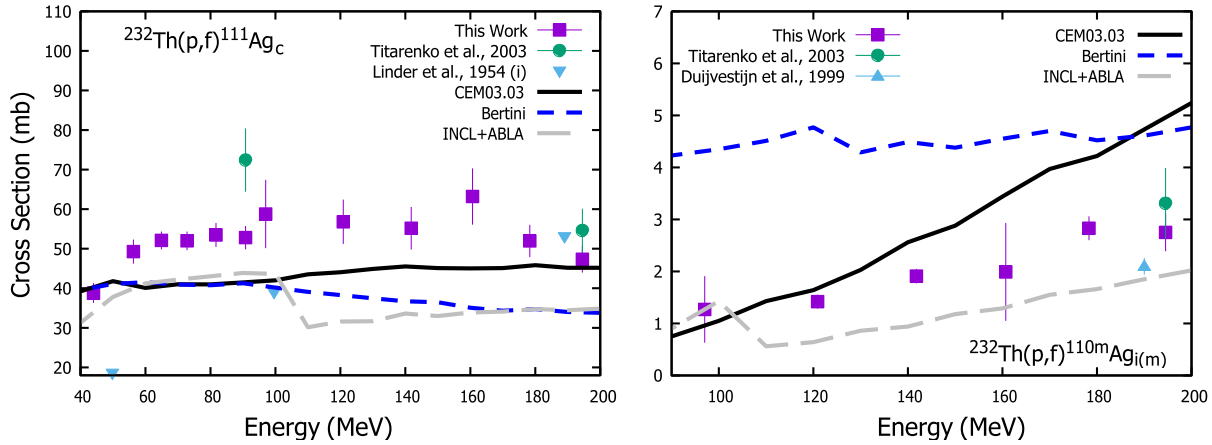

Fig. 1. Qualitative comparison of MCNP6 event generator predicted excitation functions with measured excitation functions for the formation of (A) ^{111}Ag and (B) ^{110m}Ag for proton energies less than 200 MeV [33–35].

Table 1
Measured excitation functions for the ^{232}Th(p,f)^{111}Ag and ^{232}Th(p,f)^{110m}Ag reactions.

Nominal energy (MeV)	^{232}Th(p,f)^{111}Ag (mb)	Uncertainty (mb)	^{232}Th(p,f)^{110m}Ag (mb)	Uncertainty (mb)
194.5	47.33	3.36	11.25	1.06
178.3	51.96	4.07	2.75	0.36
160.7	63.20	7.11	2.83	0.23
141.8	55.17	5.38	1.99	0.94
120.9	56.80	5.60	1.91	0.14
97	58.76	8.63	1.42	0.13
90.8	52.80	2.94	1.27	0.64
81.7	53.47	3.03	–	–
72.8	51.99	2.34	–	–
64.9	52.10	2.24	–	–
56.3	49.27	3.05	–	–
44	38.81	2.51	–	–

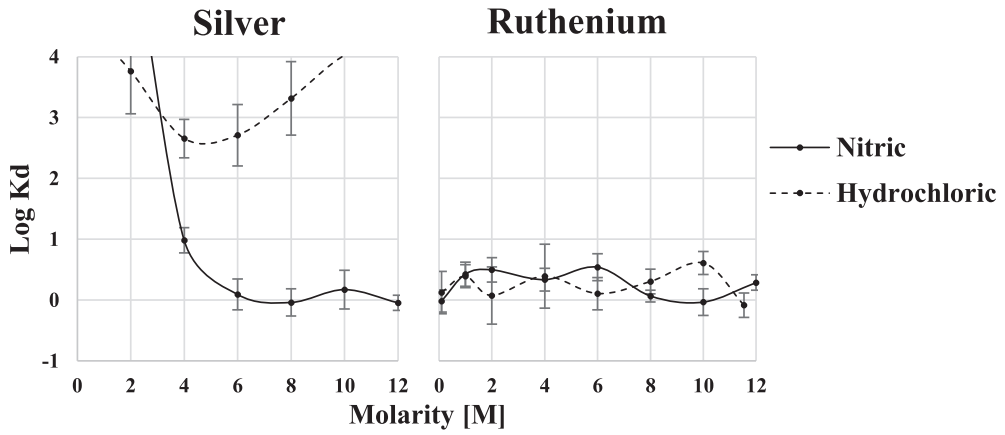

Fig. 2. CL Resin distribution coefficients (log [K_d/mL·mg^{-1}]) for silver and ruthenium in HCl and HNO_3 media. K_d's for silver in ≤2 M HNO_3 and <2 M HCl exceed 10^4 mL mg^{-1}.

in the final fraction, and their relative percentage compared to the total activity, were ^{117m}Sn (6%), ^{95}Nb (6%), ^{99}Mo (3%), ^{95}Zr (2%), ^{126}Sb (2%), ^{131}I (1%), and ^{103}Ru (1%), which made up the remaining 21% of the activity. The majority of these contaminants could be removed with a secondary purification column filled with 1 mL DGA resin. At 10 M HCl tin, niobium, molybdenum, zirconium, and antimony are highly adsorbed onto the resin, while silver and ruthenium are not [38]. The remaining ^{103}Ru impurity was then removed to limits below detection by running the 10 M HCl flow through and wash through a column containing 250 μL of CL resin. With this method, 93 ± 9% of the silver can be recovered with a radiochemical purity of >99.9%. The addition of a column upstream to the ^{225}Ac purification process had very little effect on routine ^{225}Ac recovery.

Placing the CL column downstream of the ^{225}Ac purification process (post cation column) shown in Fig. 3 resulted in a recovery of 89 ± 9% of ^{111}Ag with a radiochemical purity of ~99%. The

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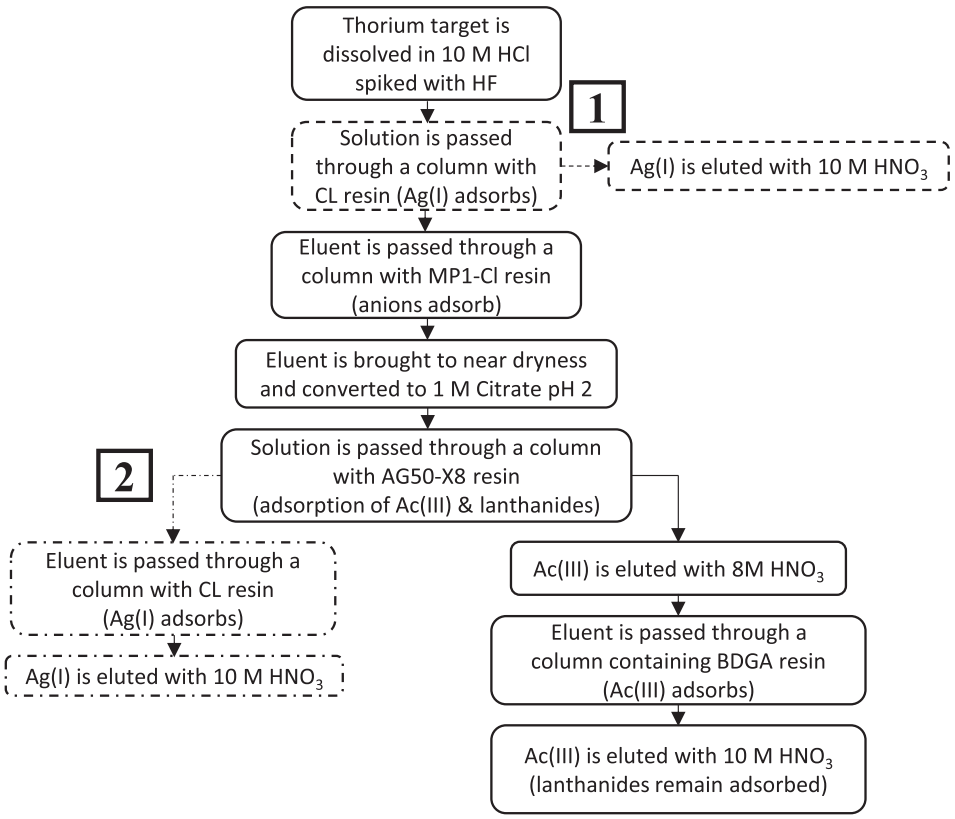

Fig. 3. Schematic showing alternate strategies for the integration of ^{111}Ag separation into the ^{225}Ac separation strategy. Solid line: Original ^{225}Ac separation profile [15] 1: ^{111}Ag separation prior to anion exchange column; 2: ^{111}Ag separation post cation exchange column.

impurity present in the eluent was ^{103}Ru (~1%). The separation factor for ruthenium using this method was ~1900. Therefore, ^{103}Ru was removed to limits below detection by drying down the silver eluent, reconstituting in 10 M HCl and passing through a second smaller CL column. The total recovery yield using this method was 87 ± 9% and resulted in a product with a radiochemical purity of >99.9%. Fig. 4 is a sample HPGe spectra of the final ^{111}Ag product (separated using the downstream process) analyzed approximately four weeks after end of bombardment. All gamma peaks were assigned to either ^{111}Ag or ^{110m}Ag.

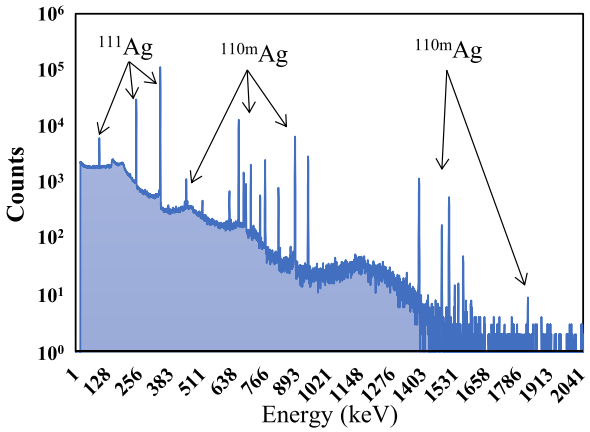

Fig. 4. HPGe spectra of final ^{111}Ag product (downstream method) four weeks after bombardment. All peaks were identified and assigned to ^{111}Ag or ^{110m}Ag.

While extraction of the ^{111}Ag upstream of the ^{225}Ac process resulted in minimal effect on ^{225}Ac recovery yields, this method has some drawbacks. First, adding a column upstream requires longer processing times for ^{225}Ac. The gravity flow rate for 1 mL of CL resin is 10 mL hr^{-1}. This would result in an additional day of processing (based on volumes used for a 10 g target) and further decay of the final ^{225}Ac product resulting in lower overall yields. Additionally, this method results in the extraction of several other fission products that then have to be purified from the ^{111}Ag to obtain a radiochemically pure product.

Extracting ^{111}Ag subsequent to ^{225}Ac recovery does not have any effect on ^{225}Ac yield or purity. Essentially, the effluent ("waste") from the cation exchange step is processed in further parallel to ^{225}Ac and is passed through the CL resin for silver recovery. Silver-111 obtained by this method also has the advantage of carrying very little additional contamination, which can be further minimized by a very simple secondary purification process. The downside to this method is that several days would be required for the large volumes of citrate solution to pass through the CL column. Large volumes of citrate are required to separate thorium from actinium. At pH 2, citric acid forms a strong complex with thorium without complexing actinium. This allows ^{225}Ac to bind to the cation column while the thorium passes through the column effectively separating ^{225}Ac from the mass thorium. To complex a 10 g thorium target, 750 mL of citric acid is required. The scale up to 100 g targets would require a very large volume of citrate (7.5 L). This drawback could be minimized, however, by researching different column geometries to allow for faster flow rates or by employing a thorium de-bulking step (through precipitation or liquid-liquid extraction) to decrease the amount of thorium in solution and therefore minimize the volume of citrate.

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The final ^{111}Ag product contains the isotopic impurity ^{110m}Ag (249.8 d). Predicted yields of ^{111}Ag in tandem with anticipated full scale ^{225}Ac production, according to measured cross sections, are 518 GBq (14 Ci) from LANL irradiated targets, 90 MeV incident proton energy, 200 μA intensity, and 370 GBq (10 Ci) from BNL irradiated targets, 190 MeV energy and 160 μA intensity. The contribution of ^{110m}Ag to the total silver activity at EOB would be ~0.1% and ~0.7% respectively. For ^{111}Ag produced by this method to be used clinically, preclinical studies examining the additional dose received by the ^{110m}Ag impurity would be necessary.

4. Conclusions

A novel method for the extraction of ^{111}Ag from proton irradiated thorium matrices has been presented in our study and demonstrated on an analytical scale. To the best of our knowledge, this is the first published use of CL resin for silver trace recovery and purification purposes. Cross sections for the formation of ^{111}Ag and ^{110m}Ag from proton irradiation of thorium targets have also been reported. Silver-111 was obtained with high radiochemical yield and purity. The introduced ^{111}Ag recovery method can be seamlessly integrated into the existing ^{225}Ac recovery design with little to no impact on ^{225}Ac yield or purity when using the method post ^{225}Ac separation. Apart from radiosilver recovery for radionuclide production purposes, the introduced method can be used in analytical chemistry applications for the selective separation and preconcentration of (stable) trace Ag as part of a sample preparation procedure. Future work will focus on the scale up of ^{111}Ag recovery from the analytical scale to >10g target masses along with assessing the clinical efficacy of ^{111}Ag obtained with this method given the ^{110m}Ag impurity.

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