Application of ion exchange and extraction chromatography to the separation of actinium from proton-irradiated thorium metal for analytical purposes

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ABSTRACT

Actinium-225 ($t_{1/2} = 9.92$ d) is an α -emitting radionuclide with nuclear properties well-suited for use in targeted alpha therapy (TAT), a powerful treatment method for malignant tumors. Actinium-225 can be also be utilized as a generator for ^{213}Bi ($t_{1/2}$ 45.6 min), which is another valuable candidate for TAT.

Actinium-225 can be produced via proton irradiation of thorium metal; however, long-lived ^{227}Ac ($t_{1/2} = 21.8$ a, 99% β^- , 1% α) is co-produced during this process and will impact the quality of the final product. Thus, accurate assays are needed to determine the $^{225}\text{Ac}/^{227}\text{Ac}$ ratio, which is dependent on beam energy, irradiation time and target design. Accurate actinium assays, in turn, require efficient separation of actinium isotopes from both the Th matrix and highly radioactive activation by-products, especially radiolanthanides formed from proton-induced fission. In this

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study, we introduce a novel, selective chromatographic technique for the recovery and purification of actinium isotopes from irradiated Th matrices. A two-step sequence of cation exchange and extraction chromatography was implemented. Radiolanthanides were quantitatively removed from Ac, and no non-Ac radionuclidic impurities were detected in the final Ac fraction. An ^{225}Ac spike added prior to separation was recovered at $\geq 98\%$, and Ac decontamination from Th was found to be $\geq 10^6$. The purified actinium fraction allowed for highly accurate ^{227}Ac determination at analytical scales, i.e., at ^{227}Ac activities of 1-100 kBq (27 nCi -2.7 μCi).

1. Introduction

1.1. Actinium-225 in nuclear medicine

Nuclear medicine has great utility for both diagnostic and therapeutic applications [1-3]. Attachment of diagnostic or therapeutic radionuclides to selective biomolecules (peptides, antibody fragments and intact antibodies) allows for the delivery of imaging or therapeutic doses to *in-vivo* target sites (tumors or other tissues). Targeted alpha therapy (TAT) is a fast growing area which utilizes α -emitting radionuclides for the selective delivery of cell killing α -radiation doses to the tumor location [4,5]. The low penetration range (50-90 μm) and high linear energy transfer of α -particles (tens to hundreds of keV/ μm) enables maximum cancer cell destruction with minimal damage to surrounding healthy tissue. An α -emitting radionuclide has to meet several important criteria in order to be useful for TAT purposes: (1) the nuclide should have a physical half-life matching the biological kinetics of the targeting ligand; (2) the nuclide should have high α -decay ratio; (3) the effective half-life, i.e., half-life resulting from both physical half-life and biological elimination half-time, should correspond to the time required for the therapy

course; (4) the decay chain of the radionuclide should not include long-lived intermediates that may cause radiation damage to healthy tissues, (5) the nuclide should form *in vivo* stable complexes or compounds with biomolecules and finally, (6) the nuclide should be regularly available and affordable. Table 1 lists several radionuclides potentially suitable for targeted α -therapy.

Table 1.

Actinium-225 ($t_{1/2} = 9.92$ d) has significant potential as a TAT radionuclide owing to its favorable half-life and a decay cascade that includes multiple short-lived α -emitters [7,8]. It can be utilized directly for therapy when conjugated to biological targeting vectors or as a generator parent for daughter nuclide ^{213}Bi ($t_{1/2} = 45.6$ min), which, in turn, can be chelated or complexed for *in vivo* use. Currently, the main source of ^{225}Ac is the generator parent ^{229}Th ($t_{1/2} = 7340$ a), which was previously obtained from reactor-bred ^{233}U material [9]. The current global supply of decay-generated ^{225}Ac is limited to ≤ 63 GBq (1.7 Ci) per year [10]. The current demand for ^{225}Ac already exceeds the amount that can be generated from the global feedstock of ^{229}Th . Alternative methods to produce ^{225}Ac have therefore been evaluated by different groups including Los Alamos National Laboratory (LANL) in recent years [11, 12, 13]. One of the most promising routes involves activation of ^{232}Th with medium to high-energy (>70 MeV) protons via $^{232}\text{Th}(\text{p},\text{x})$ nuclear pathways.

Data acquired at LANL demonstrate that a 10-day, 250 μA , 100 MeV proton irradiation of thorium results in a production of 73.2 GBq (1.98 Ci) of ^{225}Ac [12]. This amount exceeds the yearly accumulation of ^{225}Ac from ^{229}Th presently available to the global research community.

Within the ongoing investigation of accelerator production of ^{225}Ac via $^{232}\text{Th}(\text{p},\text{x})$, an efficient and rapid chemical separation and purification methodology is sought for the following reasons: (1) to validate projected actinium isotope yields, (2) to measure $^{227}\text{Ac}/^{225}\text{Ac}$ isotopic ratios and (3) to determine the amounts of non-actinium isotopic impurities. Results will enable additional research efforts and guide the future implementation of reliable production.

1.2 Actinium recovery from thorium

While a number of actinium/thorium separation methods have been reported in the literature, the selective chemical recovery of ^{225}Ac from irradiated Th targets poses some challenges. Researchers at Oak Ridge National Laboratory (ORNL) have routinely performed isolation of ^{225}Ac from ^{229}Th using a cascade of anion exchange columns with HCl and HNO_3 eluates, followed by ^{225}Ac purification via cation exchange/ HNO_3 systems [9]. Sani et al. [15] employed co-precipitation with barium and extraction with cupferron to isolate Ra and Ac from bulk thorium amounts. Other reported methods have applied liquid-liquid extraction with tributyl phosphate (TBP) to remove the major thorium mass with subsequent purification of ^{225}Ac via extraction chromatography [16] or cation exchange chromatography [11, 14]. Filosofov et al. [17] used a combination of anion and cation exchange columns to separate Ac and fission products from Th matrices and Ac/Th from each other. The bulk Th amount was first sorbed on an anion exchanger column in nitric acid media. Then, a second anion exchange column was utilized to separate no-carrier-added radionuclides from each other. Chelation methods have been developed as well; such methods create anionic complexes of Th while Ac is retained in cationic form, which was studied with citrate [18] and other reagents [19, 20] as chelators. Reported

methods either use liquid-liquid extraction steps involving organic solvents and toxic extractants, or they do not account for efficient fission product removal.

Validation of accelerator production yields requires a fast and simple method to isolate actinium from the thorium matrix as well as lanthanide impurities [21]. The present study introduces a novel procedure for the isolation of Ac from irradiated Th targets. This method has been developed to enable convenient Ac isolation and $^{225,227}\text{Ac}$ assay for quality assurance purposes, as well as to confirm our previous studies on yields of $^{225/227}\text{Ac}$ derived from thin foil studies and other co-produced no-carrier added radionuclides.

2. Experimental

2.1 Materials and methods

Thorium metal targets were manufactured at the Los Alamos National Laboratory (LANL). Small pieces of Th metal (purity >99% as determined via X-ray fluorescence spectroscopy) were obtained from LANL's internal inventory. The raw material was arc melted and rolled into sheets with mean thickness of 0.50 ± 0.02 mm for the use as proton beam targets.

2.1.1 Chemicals

All chemicals were used without further purification. Nitric acid and hydrochloric acid, both Optima grade, were purchased from Fisher Scientific (Pittsburgh, PA, USA). Citric acid (99.9%) was obtained from Sigma Aldrich (St Louis, MO, US), and deionized water (≥ 18 M Ω cm) was prepared on site with a Millipore water purification system. Cation exchange resin AG 50WX8, 200-400 mesh, was obtained from Biorad (Hercules, CA, USA). DGA resin (N,N,N',N'-tetra-n-octyldiglycolamide), 100-150 μm , was purchased from Eichrom Inc, (Lisle, IL, USA).

Ammoniumhexafluorosilicate, $(\text{NH}_4)_2\text{SiF}_6$ 98%, was obtained from Acros Organics (Fisher Scientific, Pittsburgh, PA, USA).

2.1.2 α -particle spectroscopy

Samples for α -ray spectroscopy were prepared by pipetting small analyte aliquots (volume $200 \pm 5 \mu\text{L}$) onto stainless steel discs (20 mm diameter x 1 mm thick), which were allowed to dry in air. The discs were subsequently heated to 900-1050°C (orange candescence) using a Bunsen burner. The α -ray spectroscopy counting was performed on Ortec Octete+ alpha spectrometers. Ortec Alpha Vision analytical software was used to control the spectrometer, to acquire and analyze the data. The sample was loaded into the detector chamber at “Shelf 5”, approximately 1 cm away from the detector face. The large distance between sample and detector resulted in a reduced efficiency, but gave improved peak resolution. The sample geometry matched the primary calibration standard geometry of 20 mm diameter active area. A count time of 1000 minutes yielded peak areas of approximately 11,000 counts for ^{225}Ac , ^{221}Fr , and ^{217}At , and 10,000 counts of ^{213}Po , each with estimated statistical uncertainties of approximately 1%.

2.1.3 γ -ray spectroscopy

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 53.5 mm; Be window thickness 0.5 mm; outer dead-layer thickness 0.3 μm . Radionuclide decay data were taken from Reference [6]. 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 , ^{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 time was kept below 10%.

2.1.4 Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES)

Analyses of final Ac fractions for the content of other elements were performed via ICP-AES (inductively coupled plasma atomic emission spectroscopy) using a Shimadzu ICPE-9000 instrument equipped with a 2 cm x 2 cm CCD detector calibrated on the day of use. Calibration solutions were prepared from certified stocks for thorium. All other elements were determined using a qualitative measurement method based on calibrating the response of the instrument to known concentrations of two reference elements, namely Al and Ba. Analyses were performed in triplicate and based on a 30 s sample exposure time. Output data were managed and analyzed using the ICPE solutions software version 1.01 (Shimadzu Corp. 2005).

2.2 Proton irradiations

A 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 (92 MeV incident energy) of the IPF target assembly (Fig. 1). IPF targetry and 4 π water cooling were identical to the design as described previously [22, 23].

The target was irradiated in a proton beam of 150 μA beam current for 1 hour and for a second hour at 230 μA . The target was then transported to the LANL Hot Cell Facility where it was removed from the Inconel shell. A small section of the target (0.533 g) was allowed to decay for 60 days until it could be safely handled in a radiological fume hood. The total mass of the Th metal target was 10.40 ± 0.02 g. The analytical aliquot used in this work had a mass of 0.533 ± 0.005 g.

Figure 1.

2.3 Chemical separation

2.3.1 Non-Ac radionuclide tracking via γ -ray-spectroscopy

The separation chemistry was monitored via γ -ray detection of element representative radionuclides. Calculated activities were determined starting from a series of experiments that have previously been reported [11, 12, 21]. The nuclear excitation functions measured in these experiments were obtained by irradiating stacks of thin Th foils; the calculated activities extrapolate these excitation functions to the thicker Th disc irradiated for this work. A defined amount of ^{225}Ac activity $A_0 = 18.5 \pm 0.4$ kBq (0.50 ± 0.01 μCi), derived from a ^{229}Th generator, was added to the dissolved Th target for the purpose of obtaining a chemical recovery yield y according to $y = A_{\text{sep}}/A_0$ with A_{sep} representing the Ac activity as recovered upon completion of the separation process.

2.3.2 ^{227}Ac tracking via ^{225}Ac spike and ^{225}Ac decay daughter γ -ray-spectroscopy

Table 2.

The irradiated thorium target was processed starting 60 days after the end of bombardment. Because of the current lack of dedicated, α -hot-cell capability at LANL, targets were held for a 60 day period to allow for sufficient decay such that the target materials could be handled in a radiological fume hood. As a result of the extended hold time, the only Ac radioisotope still present in the matrix to a significant extent was long-lived ^{227}Ac ($t_{1/2} = 21.773$ a), which is the longest-lived isotope of the element. Actinium-227 is co-produced with desired ^{225}Ac during proton irradiation of Th targets. As it has no significantly abundant γ -line (Table 2.), tracking its decay daughters, e.g. ^{227}Th , is the only feasible method to assay ^{227}Ac content in the sample. Due to the relatively low level of ^{227}Ac activity compared to the high background caused by fission products, this isotope could not be detected until it was chemically isolated. The decay scheme of ^{227}Ac is shown in Fig. 2 (right).

In order to track Ac during chemical separation, Actinium-225 (Fig. 2 left) was added as a tracer (“spike”; matrix HNO_3 $c=0.1 \text{ mol}\cdot\text{dm}^{-3}$; $v=0.1 \text{ cm}^3$; $A_0 = 18.5 \pm 0.4 \text{ kBq}$ ($0.50 \pm 0.01 \mu\text{Ci}$), for recovery yield determination. It can be tracked directly via γ -ray spectroscopy. Indirectly, the isotope can be detected via its decay products, e. g. ^{213}Bi ($t_{1/2} = 45.59 \text{ min}$) and ^{221}Fr ($t_{1/2} = 4.9 \text{ min}$). To ensure decay equilibrium, samples were held for daughter in-growth and measured 24 hours after separation.

2.3.3 Thorium-232 matrix and thorium-227 tracer

Thorium-227 ($t_{1/2} = 18.72\text{d}$), formed during the target irradiation via $^{232}\text{Th}(p,6n)^{227}\text{Pa} \rightarrow ^{227}\text{Th}$, $^{232}\text{Th}(p,p5n)^{227}\text{Th}$, and $^{232}\text{Th}(p,\alpha 2n)^{227}\text{Ac}$ reactions, was used as a tracer

for the bulk Th mass. The amount of ^{227}Th grown in from ^{227}Ac during the separation procedure was negligibly small.

Figure 2.

2.3.4 *Th metal target dissolution*

A small portion (533 ± 5 mg out of 10.40 ± 0.02 g) of the irradiated Th metal target was placed in a Teflon beaker. HCl ($12 \text{ mol}\cdot\text{dm}^{-3}$, 20 cm^3) and $(\text{NH}_4)_2\text{SiF}_6$ solution (2 cm^3 , $0.05 \text{ mol}\cdot\text{dm}^{-3}$) were added as well as the ^{225}Ac spike in HCl ($0.1 \text{ mol}\cdot\text{dm}^{-3}$, 0.5 cm^3) as described above. After complete dissolution (approximately 30 minutes), the solution was filtered through a small plastic frit and evaporated to dryness on a hot plate with the surface temperature maintained below 150°C . The evaporated residue was re-dissolved in 22 cm^3 of $15.4 \text{ mol}\cdot\text{cm}^{-3}$ HNO_3 for the oxidation of Ce isotopes from Ce (III) to Ce(IV). The mixture was then evaporated again under the conditions as described above. The remaining residue was then reconstituted in $0.5 \text{ mol}\cdot\text{dm}^{-3}$ of citric acid solution, and the solution was adjusted to pH 2 with concentrated aqueous ammonia solution. The final solution volume was 75 cm^3 .

2.3.5 *Cation exchange chromatography*

Cation exchanger resin (AG 50X8, 200-400 mesh, H^+ , 1.5 cm^3 ; column dimensions $1.0 \times 3.1 \text{ cm}$) was placed in a Bio-Rad plastic column (10 cm^3 capacity) and converted to the NH_4^+ form with saturated NH_4Cl solution (20 cm^3). The exchanger column was then preconditioned with $0.5 \text{ mol}\cdot\text{dm}^{-3}$ citric acid (pH 2) (20 cm^3). The target solution (75 cm^3) was loaded on the cation exchanger column. The effluent was collected and analyzed via γ -ray spectroscopy (f1) .

The column was washed with ammonium citrate ($0.5 \text{ mol} \cdot \text{dm}^{-3}$, pH 2, 20 cm^3 , fraction 2), and eluted successively with HNO_3 ($1 \text{ mol} \cdot \text{dm}^{-3}$, 5 cm^3 , fraction 3), and HNO_3 ($6 \text{ mol} \cdot \text{dm}^{-3}$, 20 cm^3 , fraction 4). Eluted fractions were analyzed via γ -ray spectroscopy.

2.3.6 *N,N,N',N'*-tetrakis-2-éthylhexyldiglycolamide(DGA) extraction chromatography

DGA, branched resin (1.0 mL, column dimensions 1 x 2.1 cm) was placed in a Bio-Rad plastic column (10 cm^3 capacity) and preconditioned with water (10 cm^3) and HNO_3 ($6 \text{ mol} \cdot \text{dm}^{-3}$, 5 cm^3). Fraction 4 from the previous elution was directly loaded onto the DGA column. The column was washed with HNO_3 ($4 \text{ mol} \cdot \text{dm}^{-3}$, 2 x 5 cm^3 , fractions 6 and 7) to elute radium isotopes. Then, the column was eluted with HNO_3 ($10 \text{ mol} \cdot \text{dm}^{-3}$, 15 cm^3 , fraction 8) to elute actinium, and finally with HCl ($0.1 \text{ mol} \cdot \text{dm}^{-3}$, 10 mL, fraction 9) to elute lanthanides.

2.3.7 $^{225,227}\text{Ac}$ final fraction assessment

To confirm the efficiency of the separation methodology, several Ac analyses were carried out with the final Ac eluate. Fractions containing $^{225,227}\text{Ac}/^{213}\text{Bi}$ were evaporated to dryness and taken up in HNO_3 ($2 \text{ mol} \cdot \text{dm}^{-3}$, 5 cm^3). Samples were subjected to α -ray spectroscopy, γ -ray spectroscopy and ICP-AES analysis. The content of the ^{225}Ac spike and ^{227}Ac in the final eluate was measured immediately after separation and after 70 days to allow for ^{225}Ac spike decay. Additional previous measurements [21] were used for comparison of measured cross sections and thick target yields of ^{227}Ac .

3 Results

3.1 Target dissolution

The addition of HCl to the Th metal initiated a rapid, vigorous reaction with the formation of a black solid, which could be mostly dissolved after the addition of a catalytic amount of $(\text{NH}_4)_2\text{SiF}_6$ solution [19]. Visible black solids (presumably thorium oxide, characterization studies are underway) remained upon reaction completion. Solids could be removed via filtration; the filter residue contained less than 1% of radionuclide activities (0.9% of ^{103}Ru and 0.8% of ^{95}Zr activity). The dissolution took approximately 20 minutes.

3.2 Cation exchange chromatography

Per ^{227}Th assay, cation exchange effluent f1 (75 cm³ volume, see Figure 3) contained more than $98 \pm 5\%$ of the Th mass along with $98 \pm 5\%$ of the total activities of fission nuclides ^{103}Ru ($t_{1/2} = 39.25$ d) and ^{95}Zr ($t_{1/2} = 64.03$ d), which were the main source of γ -ray dose rates prior to separation. Thorium was quantitatively removed from the cation exchanger by additional washes with citric acid (0.5 mol·dm⁻³, 20 cm³, f2). After washing with citric acid, neither ^{227}Th nor ^{95}Zr were detected on the exchanger column; these washes also did not contain any detectable $^{225,227}\text{Ac}$. Elution with 1 mol·dm⁻³ HNO₃ (f3) resulted in the further removal of residual of ^{103}Ru and ^{223}Ra ($t_{1/2} = 11.43$ d).

Radiolanthanides were represented by the cerium isotope ^{141}Ce , and no other lanthanide isotopes were detected 60 days after end of bombardment (EOB). Unique to Ce among the lanthanides is its occurrence in both tri- or tetravalent oxidation states. Cerium (III) was partially oxidized to Ce (IV) via treatment with nitric acid, which allowed for elution in the first two fractions, accompanying Th (IV). Cerium (III), on the other hand, eluted alongside Ac(III) in fraction f4 (6 mol·dm⁻³ HNO₃ matrix, 20 cm³ volume). The major portion of the ^{223}Ra activity

was present in fractions f1 ($\geq 85\%$) and f2 ($\geq 5\%$), while fraction f3 contained less than 1% of total ^{223}Ra activity.

Fraction f4 included $>99\%$ of the $^{225/227}\text{Ac}$ activity, while neither Th radionuclides nor ^{103}Ru nor ^{95}Zr could be detected. Major radionuclidic impurities accompanying Ac in fraction f4 were ^{223}Ra (with its decay products), ^{141}Ce ($t_{1/2}$ 32.5 d) and ^{140}Ba ($t_{1/2}$ 12.75 d).

Figure 3.

3.3 Extraction chromatography (DGA resin)

Fraction f4 (after cation exchange) was subjected to further purification via DGA resin extraction chromatography. The solution was directly loaded onto the DGA column without any reconstitution or preconditioning, and the DGA effluent becomes fraction f5 ($6\text{ mol}\cdot\text{dm}^{-3}\text{ HNO}_3$ matrix, 20 cm^3 volume, fraction f5 in Figure 4). Under these conditions, $\geq 90\%$ of ^{223}Ra and $\geq 80\%$ of ^{140}Ba eluted from the DGA column, while ^{225}Ac and ^{141}Ce were quantitatively retained on the resin. Residual ^{223}Ra and ^{140}Ba were further removed with HNO_3 ($4\text{ mol}\cdot\text{dm}^{-3}$, 5 cm^3 , fraction f6), as previously described [24]. Additional rinse (f7) showed no activity. More than 99% of the retained Ac was subsequently eluted with HNO_3 ($10\text{ mol}\cdot\text{dm}^{-3}$, 15 cm^3 , fraction f8), resulting in a recovery of $\geq 98\%$ of the original ^{225}Ac spike that was added after Th dissolution. Cerium-141 was retained on the extraction chromatography column. According to Ref [25], under the conditions that retain Ce(III) on the column ($\log K_d = 3.4$ for HNO_3 , $10\text{ mol}\cdot\text{dm}^{-3}$), La(III) should behave similarly ($\log K_d = 3.4$ for HNO_3 , $10\text{ mol}\cdot\text{dm}^{-3}$) while heavier lanthanides(III) should be sorbed even more strongly ($\log K_d > 4.0$ for HNO_3 , $10\text{ mol}\cdot\text{dm}^{-3}$). In a final step, ^{141}Ce could be eluted with HCl ($0.1\text{ mol}\cdot\text{dm}^{-3}$, 10 cm^3 , fraction f9).

The actinium fraction f8 was evaporated to dryness and reconstituted with HNO₃ (0.1 mol·dm⁻³, 5 cm³) for the evaluation of product radionuclidic and radiochemical purity.

Figure 4.

3.4 Product yields and radionuclidic purity

3.4.1 Radioisotope yields determined prior to chemical separation

Table 3 lists decay properties, measured and calculated activities that could be obtained via γ -spectrometric assay of the dissolved Th target prior to chemical separation.

Table 3

3.4.2 Radioisotope yields and purity subsequent to chemical separation

3.4.2.1 Stable and quasi-stable isotopes via ICP-AES

The concentration of quasi-stable ²³²Th in the final aliquot f9 (10 cm³ volume) was below the detection limit ($\leq 70 \mu\text{g}/\text{dm}^3$) of the instrument, which corresponded to a decontamination factor of $\geq 10^6$, defined as the quotient of contaminant level prior over the level subsequent to purification. The major chemical impurity was identified as Fe (III) (360 $\mu\text{g}/\text{cm}^3$), which could be a result of chemical impurities introduced during the separation procedure or a significant stable contaminant present in the irradiated ²³²Th target material.

3.4.2.2 ^{225,227}Ac assays

Actinium isotopes in the final product sample f9 were measured 24 h after separation and 70 days later to allow for ^{225}Ac decay and in-growth of ^{227}Ac daughter ^{227}Th . An activity of 70 ± 7.4 kBq (1.9 ± 0.2 μCi) of ^{227}Ac was measured via γ -ray spectroscopy, which is within experimental uncertainty and in good agreement with the thick target yield predicted on the basis of reaction cross sections, i.e., 82 kBq [12]. With respect to an Ac chemical recovery yield of 98 ± 5 %, this amounts to 87 ± 9 % of the theoretical ^{227}Ac formation yield. Alpha particle spectroscopy did not show any other radionuclides besides $^{227/225}\text{Ac}$ and their decay products.

No non-Ac radionuclidic impurities were detected in the final sample f9 other than $^{225,227}\text{Ac}$ decay products (Fig. 5) 24 hours after separation.

Figure 5.

Likewise, alpha-ray spectroscopy did not reveal any α -ray emitting radionuclides other than $^{225/227}\text{Ac}$ and their decay products (Figures 6 and 7) in the final Ac fraction f9.

Figure 6.

Figure 7.

4 Discussion

The irradiation of Th targets with protons generates a complex mixture of radionuclides. We developed a robust and fast separation methodology to allow efficient extraction of Ac isotopes from this mixture on an analytical scale for quality assurance assay purposes and to compare/confirm previous data on production yield of $^{225/227}\text{Ac}$ and other nca radionuclides in proton irradiated Th target.

Table 4.

Table 4 gives a broad overview of published methods aimed at the isolation of Ac from thorium matrices. It is very difficult to directly compare these methods due in part to differences associated with how the Ac isotopes were produced. Furthermore, the various studies presented have much different objectives and end-product characterization methodologies. However, we present this data for reference as well as to place our process method in context for subsequent discussion.

A schematic of the chemical separation methodology is depicted in Fig. 8.

Figure 8.

Our approach uses two solid-liquid chromatographic steps. In the first step, Ac is separated from the dissolved Th matrix solution and purified from the majority of activation by-products via cation exchange chromatography. This first step also reduces apparatus dimensions

from a gram- to sub-mg scale owing to the extraction of quasi massless Ac isotopes and other non-carrier added radionuclides from a large amount of Th mass. Cerium, the only detected lanthanide, partly follows Th (as Ce(IV)) and partly accompanies Ac(III) (as Ce(III)) to the second step. During this second step, Ac is finally separated and purified from residual dipositive elements and (tripositive) radiolanthanides, as represented by a Ce(III) radioisotope, via DGA resin extraction chromatography.

For the first (cation chromatography) sorption step, a strongly acidic cation exchanger/-citric acid chelation system was chosen. Citric acid at pH 2 forms anionic complexes with most tetrapositive (4+) cations, while tripositive (3+) cations remain in a positively charged state [18]. Under these conditions, Ac(III) is quantitatively retained on the cation exchanger, while Th(IV) citrate elutes. Furthermore, most anionic transition metal species, like ^{103}Ru and ^{95}Zr , elute alongside Th(IV). Removal of these elements, which contribute to overall dose, enables a rapid progress towards a purified solution free of the majority of fission products and γ -emitting radionuclides.

The recovered activity of ^{227}Ac (70 ± 7.4 kBq) from this new separation process correlates well with the predicted activity of 82 kBq. Other radionuclides (e.g. ^{103}Ru , ^{95}Zr , ^{141}Ce) were also measured in this work, and the results were also found to be in good agreement with predicted values.

5 Conclusion

An efficient, elegant and convenient chromatographic separation method was developed for the recovery of actinium isotopes from irradiated thorium material. Actinium-227 is co-produced in these irradiations with the desired medical isotope ^{225}Ac ($t_{1/2} = 9.92$ d). Although present at comparatively low levels (ratio $^{227}\text{Ac}/^{225}\text{Ac} \sim 0.1$ % at the end of proton bombardment), ^{227}Ac is

considered an unwanted by-product as it increases internal patient dose. As higher levels of ^{227}Ac impact the quality of ^{225}Ac and may limit clinical use, it is essential to have accurate quantification of both isotopes. The two-step stationary liquid phase sorption procedure developed here uses chelation/cation exchange and extraction chromatography in sequence, and it was primarily developed for recovery and determination of long-lived ^{227}Ac ($t_{1/2} = 21.8$ a) for target design validation, nuclear reaction thick yield confirmation and quality assurance purposes.

The introduced separation method also allows for the quantification of fission product nuclides, especially radiolanthanides. Compared to other reported recovery and separation methods, the new method has the advantage of fewer sorption/extraction steps, smaller apparatus dimensions and a higher Ac recovery yield.

The first step in the procedure entails the conversion of Th(IV) to an anionic species and the extraction of di- and tripositive elements via cation exchange chromatography. In the second step, cationic Ac(III) is separated from di- and tripositive elements (Ba, Ra and fission product lanthanides) via DGA extraction chromatography. The measured Ac recovery yield amounted to $98 \pm 5\%$, and Ac fission product de-contamination factors of $\geq 10^6$ could be obtained. Notably, chemically similar behaving radiocerium (^{141}Ce) could be quantitatively removed from the relatively small amount of ^{227}Ac activity that had been successfully recovered. The developed separation method was successfully demonstrated on an analytical scale.

Future research will focus on challenging this process with targets with much smaller hold times in order to fully address the separation of a variety of lanthanide isotopes as well as larger Th target masses anticipated with scaled-up production. This ongoing effort represents a

multifaceted, integrated effort between the Los Alamos, Brookhaven and Oak Ridge National Laboratories focused on the investigation of accelerator-produced ^{225}Ac for TAT purposes.

Ongoing work at Los Alamos includes investigation into the sorption behavior of other lanthanides under similar conditions, especially ^{140}La , ^{147}Nd , $^{148\text{m}}\text{Pm}$, as well as the testing of these conditions with irradiated thorium material closer to the end of bombardment. Preliminary results suggest sorption behavior as predicted in section 3.3 also for non-Ce lanthanides. Future investigations will focus on the isolation of other important medical isotopes (e.g. Ra isotopes and $^{230}\text{Pa}/^{230}\text{U}/^{226}\text{Th}$) from this matrix, as they are co-produced by proton irradiation of thorium. Radium isotopes may be sorbed during the cation exchanger step at higher matrix pH along with Ac and lanthanides.

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531 **Figure Captions**

532 Figure 1. View of the Th target encapsulated in Inconel subsequent to LANL-IPF proton
533 irradiation. Note the pattern on the target window resulting from the interaction with IPF's
534 rastered proton beam.

535 Figure 2. Decay schemes of ^{225}Ac (left) and ^{227}Ac (right) [6].

536 Figure 3. Chelation/ cation exchange chromatographic elution profile for nuclear reaction
537 products originating from proton-activated thorium.

538 Figure 4. DGA extraction chromatographic elution profile for nuclear reaction products
539 originating from proton activated thorium.

540 Figure 5. γ -ray spectrum of the final ^{225}Ac fraction 24 hours after separation. Actinium-227 is
541 present and can be identified via Ac-227 decay chain daughter isotope γ -rays, e.g. ^{227}Th ..
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543 Figure 6. Alpha-spectrum of the final Ac fraction 24 hours after separation dominated by ^{225}Ac
544 decay products.

545 Figure 7. Alpha-spectrum of the final Ac fraction 70 days after separation now dominated by
546 ^{227}Ac decay products.

547 Figure 8. Schematic of the chromatographic separation methodology introduced in this paper.

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550 **Figure 1**

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Figure 2 left

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560 **Figure 3**

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Figure 6

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582 **Figure 8**

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584 TABLES

585 Table 1: Physical properties of potential TAT (α -emitting) radionuclides [6]

Radionuclide	Half-life	α -emission ratio %	α -emission energy keV (branching ratio)
¹⁴⁹ Tb	4.118 h	16.7	4000
²¹¹ At	7.214 h	41.8	6051
		58.2 (²¹¹ Po)	7450 (²¹¹ Po)
²¹² Bi	60.55 min	35.9	6051(25.1%), 6090(9.8%)
		64.1(²¹² Po)	8784(²¹² Po)
²¹³ Bi	45.59 min	2.2	5549(0.15%)
			5896(1.94%)
			97.8(²¹³ Po) 8537(²¹³ Po)
²²³ Ra	11.43 d	100	5607(25.2%)
			5716(51.6%)
²²⁴ Ra	3.6319 d	100	5449(5.1%)
			5685(94.9%)
²²⁵ Ac	9.92 d	100	5793(18.1%)
			5830(50.7%)

^{226}Th	30.57 min	100	6234(22.8%) 6337(75.5%)
^{227}Th	18.68 d	100	5757(20.4%) 5978(23.5%) 6038(24.2%)
^{230}U	20.8 d	100	5818(32.0%) 5888(67.4%)
^{255}Fm	20.07 h	100	6963(5.0%) 7022(93.4%)

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590 Table 2. Gamma-ray lines and abundances for the tracking of ^{225}Ac and ^{227}Ac via the
591 emissions of their decay daughters [6].

Radionuclides	$t_{1/2}$	Energy (keV)	Abundance (%)
^{225}Ac	9.9 d	99.8	1.0
^{221}Fr (^{225}Ac daughter)	4.9 min	218.1	11.4
^{213}Bi (^{225}Ac daughter)	45.59 min	440.5	25.9
^{227}Th (^{227}Ac daughter)	18.72 d	236.0	12.9
^{223}Ra (^{227}Ac daughter)	11.43 d	269.5	13.9

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596 Table 3: Decay properties and estimated production yields of non-Ac radioisotopes considered
 597 and measured in this work (normalized to the whole 10.4 g target). Calculated activities were
 598 obtained as described in section 2.3.1.

Radionuclide	$t_{1/2}$ (d)	Calculated activity at 60 days after EOB (MBq)	Measured activity 60 d after EOB (MBq)	Activity at EOB (MBq)	Production yield (kBq/ μ Ah)
^{103}Ru	39.25	55.3	56.0	161.0	423.7
^{95}Zr	64.03	43.6	42.2	80.8	212.6
^{141}Ce	32.51	25.3	27.2	97.7	257.1
^{140}Ba	12.75	6.2	7.0	182.6	480.5
^{227}Th	18.68	34.8	36.7	338.5	890.7

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603 Table 4. Overview of methods for isolation of Ac from thorium matrixes

Reference	Separation method	Number of separation steps	Ac recovery %	Source of Ac	Th mass	Other impurities n.c.a	Th decontamination factor, other impurities
This work	1.ion exchange 2.solid phase extraction	2	98	$^{232}\text{Th}(\text{p},\text{x})^{225,227}\text{Ac}$	0.5 g (^{232}Th)	Fission products (60 days after EOB)	10^6 (ICP), no other impurities detected ($\gamma+\alpha$ spectroscopy)
Zhuikov et. al. [11]	1.liquid liquid extraction 2.solid phase extraction	2	90	$^{232}\text{Th}(\text{p},\text{x})^{225,227}\text{Ac}$	<1g (^{232}Th)	Fission products	not reported, other radionuclides < 0.1%
Filosofov et al. [17]	ion exchange	3	not reported	$^{232}\text{Th}(\text{p},\text{x})^{225,227}\text{Ac}$	1.2 g (^{232}Th)	Fission products	Not given, ^{140}La , ^{144}Ce , ^{88}Y ($\leq 1\%$)
Boll et al. [9]	ion exchange	4	80	$^{229}\text{Th} \rightarrow ^{225}\text{Ac}$	^{229}Th	^{225}Ra	$4 \cdot 10^{-5} \%$, $\leq 0.6 \%$ of ^{225}Ra
Zielenska et al. [23]	1.ion exchange 2.solid phase extraction	2	99	$^{229}\text{Th} \rightarrow ^{225}\text{Ac}$	^{229}Th	^{225}Ra	not reported
Tsoupko-Sitnikov et al. [18]	ion exchange	1	100	$^{229}\text{Th} \rightarrow ^{225}\text{Ac}$	(5mg) ^{229}Th	^{225}Ra	not detected
Sani et al. [15]	precipitation	1	37-57	$^{232}\text{Th} \rightarrow ^{228}\text{Ac}$	(5 g) ^{232}Th	^{232}Th decay products	purity $\geq 99.5\%$
Chen et al. [20]	ion exchange	1	Not reported	$^{232}\text{Th} \rightarrow ^{228}\text{Ac}$	(5 g) ^{232}Th	^{232}Th decay products	not reported

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