Simultaneous Separation of Pa-230 and Uranium -230 Isotopes from a Proton Irradiated Thorium Matrix

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ABSTRACT: The use of radioisotopes in cancer therapy is becoming increasingly important. As a potential candidate for targeted alpha therapy (TAT), ^{230}U ($t_{1/2}$ = 20.8 d), the decay daughter of ^{230}Pa ($t_{1/2}$ = 17.4 d) is currently being investigated for cancer treatment. For radioisotopes to be used in biomedicine, they must be radiochemically pure and free from carrier interference. This can be challenging given their short half-life. Thus, radiological separation methods for harvesting isotopes for use in biomedicine must be simple, fast, and capable of obtaining the required purity levels. Herein, we demonstrate a new rapid method for the separation of ^{230}U and ^{230}Pa from a proton-irradiated ^{232}Th metal target and from coproduced fission products with high recovery and purity. A dual-column approach was used in which the first column was an anion exchange (AX) column, and the second column was a DGA column. The MP-1 anion exchange resin was used for the primary separation of the three major components (U, Pa, and Th, as well as fission products), and the DGA column was used for further purification of the separated ^{230}U. The method is simple and allows for straightforward separation of U, Pa, Th, and fission products; also, the entire process from target dissolution to shipment of ^{230}U could be completed in 3 days with an overall ^{230}U recovery yield of 96 ± 3 %. Additionally, separated ^{230}Pa fractions can be used to harvest ingrown ^{230}U after initial separation.

Keywords: Dual column, anion exchange resin, DGA resin, U-230, Pa-230

INTRODUCTION

Radiation therapy has been widely used in the treatment of cancer since its discovery [1]. The problem with many of these treatment methods is that they involve the irradiation of the general area of the cancer, thus causing harm to healthy tissues, as well. Targeted alpha therapy (TAT) is one of the most promising cancer treatments, in which high-energy alpha particles are preferentially delivered directly to cancer cells without harming the surrounding healthy tissue [2]. Its safety and efficacy have been demonstrated in multiple preclinical studies [3-4]. The linear energy transfer of alpha particles is two to three orders of magnitude greater than that of beta particles, so alpha emitters are better suited for targeting small objects such as micrometastases and single cancer cells as opposed to the beta-emitting radionuclides currently in use [5].

The isotopes of U and Th are of interest in TAT [6-12]. The isotope ^{230}U ($t_{1/2}$ = 20.8 days) can be used for TAT directly or as a generator source for its first daughter, ^{226}Th. The isotope ^{226}Th has a half-life of 30.6 min and produces four radionuclide daughters in the decay path to radioisotope ^{210}Pb ($t_{1/2}$ = 22.7 years). A unique advantage of the ^{230}U and ^{226}Th pair is that they emit multiple alpha particles as they decay. Figure 1 shows the decay scheme of ^{230}Pa with a focus on ^{230}U and ^{226}Th as potential therapeutic doses [13]. In total, this decay series produces a combined 33.5 MeV alpha dose from ^{230}U (through five alpha decays) or a combined 27.7 MeV alpha dose from ^{226}Th (through four alpha decays). Furthermore, ^{226}Th emits a 111 keV gamma ray (3.29 %) that can be used for single-photon emission computed tomography imaging [14]. If ^{226}Th is to be used for direct TAT applications, a generator concept [9-10] will be required to maintain a continuous supply of this isotope from its parent, ^{230}U. Similarly, if ^{230}U is derived from the decay of ^{230}Pa and is intended to be used as a direct TAT treatment, a ^{230}Pa/^{230}U generator must be available. Therefore, it is imperative to have a rapid and efficient method for separating Th, Pa, and U to obtain clinical grade ^{230}U. As opposed to the ^{225}Ac/^{213}Bi generator, the ^{230}U/^{226}Th generator system has some important advantages, including a longer parent half-life and daughter radionuclides with short half-lives, ranging from seconds to milliseconds [15]. This could limit the redistribution of decay products from the target site, even after dissociation from the disease-targeting vector.

The isotope ^{230}U can be produced either directly or indirectly. Direct pathways include proton or deuteron irradiation of ^{231}Pa via reactions (a) ^{231}Pa (p, 2n) ^{230}U and (b) ^{231}Pa (d, 3n) ^{230}U. However, the target material, ^{231}Pa ($t_{1/2}$ = 3.3 × 10^4 years), is a decay product of ^{235}U and must be isolated from aged U samples, which will be difficult because of the limited availability of raw materials [9-16]. Indirectly, ^{230}U can be made through proton- or deuteron-induced reactions on Th nuclei via reactions (a) ^{232}Th (p, 3n) ^{230}Pa → ^{230}U and (b) ^{232}Th (d, 4n) ^{230}Pa → ^{230}U, which produces ^{230}Pa ($t_{1/2}$ = 17.4 days), which then decays into ^{230}U with a branching ratio of 7.8 % [11, 16]. Major advantages of the indirect production route are the easy availability of Th metal and the high product yield compared with the reactions with deuterons. Also, by ingrowing ^{230}U from ^{230}Pa decay, carrier-free ^{230}U can be isolated without additional U impurities (e.g., ^{235}U, ^{238}U).

Numerous separation approaches have been developed and investigated for the separation of U and Pa from bulk Th and from coproduced fission products. These methods include solvent extraction [17-19], solid phase extraction or chromatographic separation [20-24], and anion exchange separation [25-27]. For example, Dybczynski et al., used a cation exchange resin for the separation of U and Pa from Th in 10 M HNO_3, followed by the elution of the Pa(V) with 3–4 M HNO_3 [28]. Radchenko [11] demonstrated Pa(V) separation on an AX column in high HCl concentrations (>8 M HCl). The Pa(V) retains on an AX column, whereas the Th elutes in high HCl concentrations. The adsorbed Pa(V) was then eluted from the column with 3 M HCl or a mixture of HCl and HF. A further purification of Pa(V) was performed using UTEVA (diamyl amylphosphonate) or transuranium (TRU) chromatography columns. Mastren et al., [21] proposed two-step processes for the separation of Pa(V) from the bulk of the Th and fission products [21]. In the first step, Pa(V) was separated from bulk impurities using CL resin or a custom-made diglycolthioamide resin, followed by further purification using Eichrom (DGA) resin.

A reverse ^{230}U/^{226}Th generator approach [14] was also developed using a DGA column in which ^{230}U/^{226}Th parent-daughter solutions were loaded onto the DGA column in > 6 M HCl, followed by elution of the parent ^{230}U first with 0.1 M HNO_3 and then the daughter ^{226}Th with a 0.1 M citrate buffer at pH 5. A small amount of ^{230}U parent contamination (~0.2%) was reported in the ^{226}Th fraction, which may pose a problem for clinical trials. Recently, Ermolaev et al., demonstrated a similar concept using a two-column generator approach (TEVA + DGA or TEVA + UTEVA) to obtain high-purity ^{226}Th in a solution suitable for further labeling [29]. A two-

column approach provides higher-purity ^{226}Th than a single-column approach, with ^{230}U parent contamination of 0.01% in the ^{226}Th fraction. An advantage of this approach is the delivery of ^{226}Th in a citrate buffer at pH 5, which can be directly used for biomedical chelation.

Most of the separation methods described in the preceding paragraph require strong acids and prolonged separation times, making them unsuitable for chelation and radiopharmaceutical application. To make the ^{230}U/^{226}Th eluent suitable for chelation reactions, it must either be evaporated, or the pH adjusted to neutralize excess acids, which is time-consuming. Considering the short half-life of ^{230}U/^{226}Th, time efficiency is a major concern throughout the entire process, from obtaining ^{230}U/^{226}Th to the final radiopharmaceutical administration. Alternatively, ^{230}U/^{226}Th can be eluted in a form that is suitable for direct labeling with the chelates. This ability would reduce the chelation time and result in a radiolabeled compound with minimal loss of activity. The growing interest in ^{230}U/^{226}Th for medical applications has motivated the development of a system that is more efficient for separating Pa, Th, and U. Within this context, this study attempted to develop a new separation procedure for obtaining high purity ^{230}U that could be rapid, efficient, require fewer steps, and generate less radioactive waste.

EXPERIMENTAL SECTION

Chemical and Reagents. All reagents used were trace metal–grade unless specified. Aqueous solutions were prepared with 18 MΩ deionized water (Milli-Q Gradient A10 system). The Th metal targets were manufactured at Los Alamos National Laboratory. The HNO_3 (69–70% American Chemical Society Grade) and HCl (37%, trace metals–grade) were received from BDH Chemicals and RICCA Chemical Company, respectively. The H_2O_2 (30%) was purchased from Fisher Scientific. The HF (40%) was purchased from EMD Millipore.

The Bio-Rad MP-1 resin (100–200 mesh) was purchased from Bio-Rad Laboratories. The MP-1 is a strongly basic anion exchanger with quaternary ammonium functional groups attached to the styrene divinylbenzene copolymer lattice. The MP-1 resin was stirred with water or low HCl to create a slurry and then loaded onto a 2 mL cartridge. DGA resin-normal (*N*,*N*,*N*′,*N*′-tetra-*n*-octyldiglycolamide, 100–150 μm) was obtained from Eichrom Technologies Inc. (Lisle, Illinois, USA). The DGA columns were prepared by loading dry resin directly into 2

mL cartridges and wetting them with 2M HNO_3 and deionized water. Sample loading, washing, and elution operations were done using syringes.

The work reported here was carried out at the Radiochemical Engineering Development Center at the US Department of Energy's Oak Ridge National Laboratory (ORNL). A negative-pressure glove box was used for both the preliminary tests and the actual separation of ^{230}U from irradiated ^{232}Th targets.

Safety considerations. Solutions containing HF and HCl are potentially dangerous and appropriate personal protective equipment should be used when using these acids. Similarly, use of radioactive materials is potentially hazardous and appropriate ALARA principals should be considered prior to conducting experiments using radioactive materials.

Apparatuses. A variety of radiometric methods were employed in this study. A Gross-Alpha Protean MPC 2000 gas flow proportional counter was used for gross alpha counting. A Canberra Alpha Spectrometer Model 7401 was used for alpha spectrometry, and high-purity Ge detectors were used for gamma spectrometry (ORTEC and Canberra). The alpha and gamma spectra were processed using Canberra Genie2K acquisition and analysis software. When analyzing spectra, a reference table integrated into the software calculates interferences between gamma lines. The mass spectrometry analysis was carried out with a Thermo Scientific iCAP Q inductively coupled plasma mass spectrometer. All analytical results were provided by the Nuclear Analytical Chemistry and Isotopes Laboratory. Uncertainties associated with these measurements are ±10 %.

Irradiation of ^{232}Th (natural Th) Metal Target. The Scanditronix MC50 cyclotron at the University of Washington was used to irradiate a Th metal target. A target holder containing a 12 × 12 mm square plate with 0.5 mm thickness was placed in an Al holder. Afterward, the target was mounted on a target station and irradiated with a proton beam with an average intensity of 30 MeV and a beam current of 22 μA·h. The irradiated target was then cooled by water flowing past the back of the target assembly. Targets were removed from target stations after cooling and sent to ORNL for chemical processing. The irradiated target is expected to contain about

1.17E+06 Bq of ^{230}U and 2.92E+07 Bq of ^{230}Pa. A detailed description of the target fabrication can be found elsewhere [9, 12, 15, 16].

Dissolution of Irradiated ^{232}Th (natural Th) **Metal Foil.** The irradiated ^{232}Th target (~0.9 g) was placed in a 20 mL glass vial. The glass vial containing the ^{232}Th metal (natural Th) foil was then placed inside a glass beaker (The beaker was used to hold the vial upright and prevent it from tilting or spilling). The beaker containing the vial is placed on a hot plate and heated at ~110-120°C with concentrated HCl first and then subsequently with concentrated HCl spiked with trace amount of HF (conc. HCl spiked with trace amount of HF means concentrated HCl solution containing up to 50 µL of 1M HF). The concentrated HCl spiked with HF is a common dissolution technique for Th metal. The dissolution of Th metal foil in concentrated HCl produces a dark black solution with dense puffs of vapor and vigorous bubbling. As the solution is heated with concentrated HCl spiked with HF traces, the dark black solution gradually becomes transparent. The solution was then brought to near dryness and reconstituted in 2–3 mL of 10 M HCl + 0.003 M HF (actual HF concentration was 0.00266 M HF) for column separation. During the slow drying down, a porous, gel-like foam may form, which dissolves in 10 M HCl spiked with HF. There may occasionally be residual white foam floating in the HCl–HF solution. A few drops of 30% H_2O_2 can be used to dissolve the white foam. Figure S1 illustrates progression of the Th metal target dissolution inside a glove box.

Stoichiometrically converting 0.9 g of Th metal into $ThCl_4$ would require <2 mL of concentrated HCl. In reality, 6 – 8 mL of concentrated HCl spiked with HF were required to dissolve the Th metal target foil. Caution should be exercised when adding HF to the solution. During these experiments, researchers observed that trace amounts of HF cannot accelerate Th dissolution, but excessive amounts of HF (>1 mL of 1 M HF) precipitate Th as ThF_4. Usually, the dissolution of Th metal foil takes a day to complete.

RESULTS AND DISCUSSION

Primary Separation of ^{230}U, ^{230}Pa, Bulk of ^{232}Th, and Fission Products. A HNO_3 medium is commonly used for actinide separation. However, it would require multiple drying cycles with concentrated HNO_3 to convert the Th target dissolution solution from 10 M HCl + 0.003 M HF

to HNO_3. Because this process is time-consuming, we decided to perform the separation of ^{230}U, ^{230}Pa, ^{232}Th, and the fission products in HCl media spiked with HF instead, which is crucial given the short half-life of ^{230}U. As indicated by the literature search, five different resins have been evaluated for their ability to separate U from other radionuclides in HCl solutions. Among the resins evaluated, Eichrom TRU, UTEVA, and TK400 (octanol impregnated onto an inert support) were unable to extract Th from high HCl solutions. By contrast, TEVA and AX resins retain U and Pa, while allowing Th to pass through in high HCl solutions.

Supporting information Table S1 summarizes the distribution coefficients (K_d) of Th, Pa, and U on TEVA, TRU, UTEVA, and TK400 resins taken from references [9, 30-36]. The Pa, which is predominantly pentavalent in aqueous solutions, is well-retained by TK400 resin at high concentrations of HCl (>7 M), but U(VI) and Th(IV) are poorly retained at any HCl concentration ($K_d < 5$). The TEVA and AX resins, on the other hand, demonstrated quantitative retention of Pa(V) and U(VI) at high HCl concentrations but could not retain Th(IV) in high-concentration HCl solutions ($K_d < 1$). The retention behavior of TRU is very similar to that of TEVA, except that Th(IV) is also quantitatively retained at high HCl concentrations. The UTEVA retains Pa(V) strongly at high HCl concentrations ($K_d = 10^4$) while showing moderate affinities for both U(VI) and Th(IV). UTEVA was not chosen in this case because it cannot remove Th(IV) from U(VI) in bulk. In order to design a separation process that is simple, rapid, and uses a fewer number of column steps, bulk separation of impurities is a crucial first step.

The comparison of the behaviors of these resins indicates that AX resin has the potential to selectively and sequentially elute Th(IV) and Pa(V) in high HCl solutions with varying concentrations of HF. Radchenko et al.,[11] also demonstrated quantitative elution of Th(IV) in high HCl solutions from the AX resin and our preliminary experiments showed that Pa(V) can be eluted from the AX resin with high HCl (10M HCl) and high HF (>1M). Furthermore, AX resin is also more radiation-resistant, which is advantageous when working with dissolved, irradiated targets with a high radiation dose. Therefore, AX resin (in this case, MP-1) was selected as the primary column to separate U from Pa, Th, and fission products.

A number of experiments were conducted using ^{234}U and ^{233}Pa prior to the actual separation of the dissolved irradiated ^{232}Th target to determine the optimal conditions for

removing Th as well as to understand retention characteristics of U and Pa on MP-1 resin. Because both these radionuclides are alpha emitters, their alpha peaks can be easily determined by counting their respective alpha and gamma peaks (4.77 MeV alpha peak for ^{234}U and 312 KeV gamma peak for ^{233}Pa). The concentrations of HCl and HF tested for loading and elution ranged from 9 to 10 M for HCl and 0 to 0.3 M for HF. Preliminary experiments show that (1) U(VI) retains on the AX resin in high HCl solutions, and the presence of HF enhances the retention of U on the AX resin; (2) Pa(V) retains on the AX resin in high- HCl solutions in the presence of little or no HF; and (3) Th(IV) does not retain on the AX resin in high HCl solutions with or without HF. Therefore, for this study, the MP-1 column was loaded with 10 M HCl + 0.003 M HF and was preconditioned with 10 mL of 10 M HCl + 0.003 M HF. In this condition, Pa and U are strongly retained in the MP-1 AX resin, and the majority of the Th passes through the column (~95%). This condition also allowed near-quantitative removal of the majority of the fission products ^{95}Zr, ^{137}Cs, $^{141, 144}$Ce, ^{140}Ba, and ^{140}La, as well as the partial removal of ^{95}Nb, $^{103, 106}$Ru, and ^{155}Eu. After loading, the column was rinsed with 15 mL of 10 M HCl + 0.003 M HF. After rinsing, ^{230}Pa was eluted from the column with 20 mL of 10 M HCl + 1.4 M HF (actual HF concentration was 1.413 M HF). A high concentration of HF in an HCl solution is typically used to remove ^{230}Pa from AX resins. Although ^{230}Pa and some remnant impurities were effectively removed from the column by elution with 10 M HCl + 1.4 M HF, U remained in the column, further confirming that HF facilitates U retention on the MP-1 column in high-concentration HCl solutions. A schematic of the separation is shown in Figure 2, and the actual separation processes being performed inside a glove box are shown in Figure S2.

Purification of ^{230}U from Residual Impurities. After separating ^{230}U from Pa, the bulk of Th, and fission products on an MP-1 column, further purification of the retained ^{230}U on the MP-1 column was accomplished by transferring it to a DGA column. A dual-column approach, in which the MP-1 column from the previous step was stacked on top of the DGA column (pre-conditioned with 10 mL of 10 M HNO_3), was used to recover high-purity ^{230}U. The process scheme is shown in Figure 2. A rinse of 10 mL of 10 M HNO_3 was added directly to the stacked columns (MP-1 + DGA) to ensure sorbed ^{230}U was eluted from the MP-1 column and sorbed onto the DGA column. The dual column is then further washed with 10–15 mL of 10 M HNO_3. Following washing, the DGA column was detached from the MP-1 column. The retained ^{230}U

was stripped from the DGA column with 20 mL of 0.5 M HNO_3. The purified ^{230}U fraction collected in a V-vial is shown in supporting Information Figure S3.

The K_d values for U(VI) on DGA resin are approximately 200 in 3–10 M HNO_3 solutions and 1,000 in 10 M HCl + HF (Table S2), which are high enough to retain ^{230}U eluted from the MP-1 column onto DGA despite the solution media being a mixture of HCl + HF and HNO_3. When performing chromatography or ion exchange separations, solution media changes are common. This step involves drying the solution down, bringing it up in a new media, and repeating this process several times. The process is time-consuming and accumulates impurities from multiple additions of liquid (despite being made with deionized water). As long as the retained metal ions in both media have a high K_d value, the media can be changed directly on the same resin columns. As an example, Pu(IV) has a high K_d (~10^3) in both HNO_3 and HCl at high concentrations. If Pu(IV) is retained on the MP-1 column in a high HCl solution, it can be replaced with a high HNO_3 solution by adding a high HNO_3 solution. It is also possible to transfer the retained metal ions from one resin column to another resin column by stacking them together and using the appropriate solution medium.

To achieve media change for the U, the following points must be taken into account. The K_d value of U(VI) on AX resin is high in HCl solutions but low in HNO_3 solutions, whereas the K_d value of U(VI) on DGA resin is high in both high HCl and high HNO_3 solutions but low in low HCl and low HNO_3 solutions. Therefore, the retained U(VI) from the top AX column was transferred to the bottom DGA column using the 10 M HNO_3 solution after attaching the AX column to the DGA column. A low HNO_3 concentration can then strip off the U(VI) from DGA, which is also desirable to ship the final product.

Based on the K_d values of Nb(V) and Ru(III) (Table S2), it is reasonable to anticipate that Ru(III) should be eluted from DGA during the 10 M HNO_3 rinse, and Nb(V) can also be removed if the column is sufficiently washed with 10 M HNO_3. The DGA retains hexavalent U in both HCl and HNO_3 at concentrations >2 M. However, little to no retention was observed at lower concentrations.

The same trend is observed with Pa(V), making DGA resin ineffective in separating Pa(V) and U(VI). Thus, this study's strategy was to separate U(VI) from Pa(V), the bulk of ^{232}Th, and

fission products with an MP-1 column, followed by a dual column (MP-1 + DGA) to further improve its chemical and radiochemical purity by removing residual impurities.

Figure 3 illustrates the ^{230}U, ^{230}Pa, and radioactive impurities separation profiles during the combined column runs (single MP-1, dual MP-1 + DGA, and single DGA), and supporting information Table S3 provides the percentage distribution of each isotope among the fractions. As estimated by the mass balance, the proposed separation method could recover 99.3% of ^{230}U. Alpha analysis of the separated ^{230}U fraction showed minor amounts of ^{230}Pa (0.024%), ^{95}Nb (0.726%), and ^{103}Ru (0.217%) as impurities, indicating room for future improvement. Several improvements can be made, such as washing the detached DGA column with more 10 M HNO_3 to remove residual Nb(V) and Ru(III) or washing of dual column with additional 10 M HCl + 1.41 M HF to remove the remaining ^{230}Pa from the DGA column prior to eluting ^{230}U. Despite its limitations, the proposed method has the advantage of being rapid and able to separate U, Pa, Th, and fission products with ease. Moreover, the whole process from target dissolution to shipment of ^{230}U could be completed in 3 days, which is advantageous given the short half-life of ^{230}U (20 days). Additionally, ^{230}U separation from a Th target is much faster than ^{225}Ac separation from an irradiated ^{232}Th target that the Tri-Lab Project currently uses [37]. The isotope ^{225}Ac is one of the most significant medical isotopes currently undergoing clinical trials. This radioisotope has been shown to be effective against metastasized cancer through TAT. As shown in supporting Information Figure S4, the Tri-Lab effort to isolate ^{225}Ac entails six columns and four evaporation steps, and it takes almost 20 days from target dissolution to shipment of ^{225}Ac, which is twice as long as the half-life of ^{225}Ac (10 days).

CONCLUSION

A new rapid separation scheme for the extraction of ^{230}U from proton-irradiated Th targets has been presented in this study. A dual-column approach using an AX column and a DGA column was used to separate and purify ^{230}U. The simple method not only allows for straightforward separation of U, Pa, Th, and fission products but also produces radiochemically pure ^{230}U with a recovery yield of 96 ± 3 %. Overall, the process from the dissolution of the target to shipment of the ^{230}U could be completed within 3 days, which is advantageous given the short half-life of ^{230}U. Furthermore, after initial separation, separated ^{230}Pa fractions can be used to harvest ingrown ^{230}U. Rapid and robust radiochemical separation is an important for the

development of medical isotopes. This new method will aid in the purification, availability, and distribution of life-saving isotopes to the medical community for further development. A dual-column approach and this research in particular will enable producers to manufacture alpha-emitting radioisotopes faster, easier, and more cost-effectively.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/

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Declaration of Conflict of Interest

The authors wish to confirm that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

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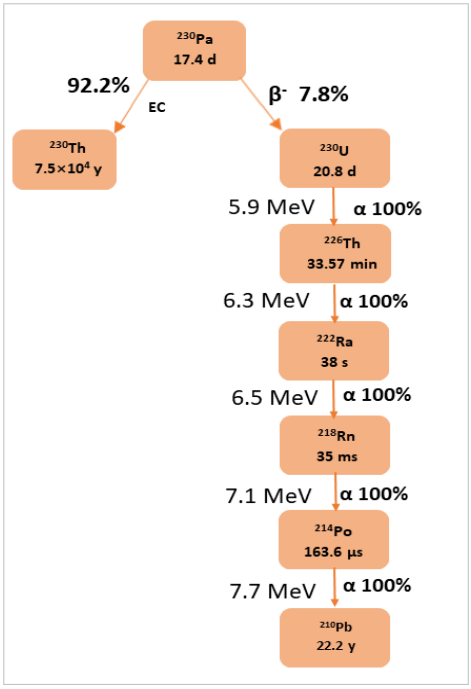

Figure. 1 Decay scheme of ^{230}Pa, ^{230}U and ^{226}Th from reference [13].

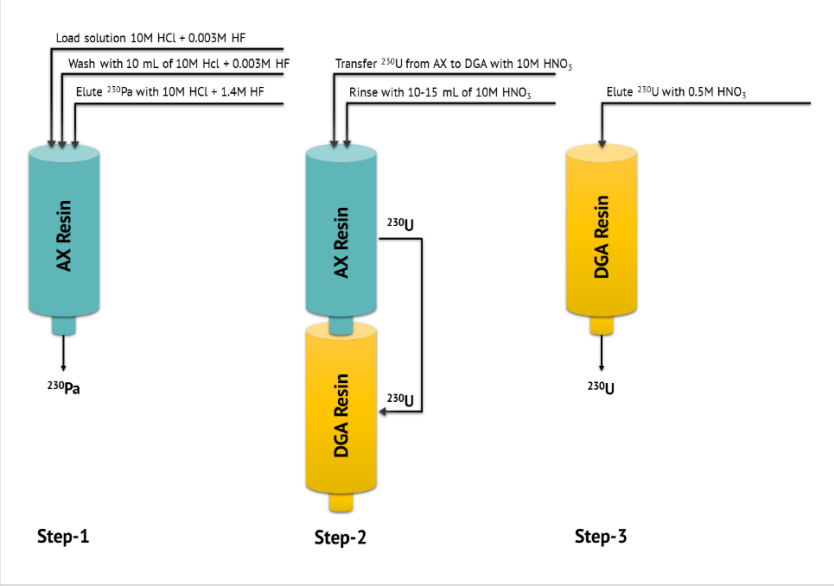

Figure 2. Schematic of dual-column approach for the separation of ^{230}U, ^{230}Pa, ^{232}Th, and fission products.

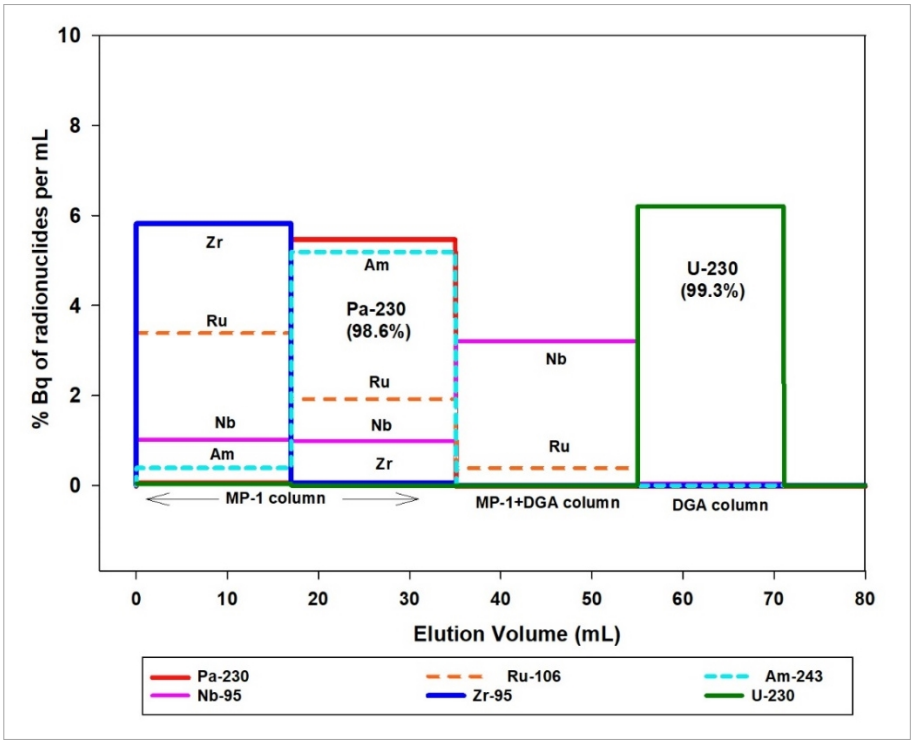

Figure 3. Separation profile of ^{230}Pa, ^{230}U, and fission products from dissolved ^{232}Th target using a single MP-1 column, dual MP-1 + DGA columns, and a single DGA column (the non-rad ^{232}Th and the other fission products that were removed completely during 10 M HCl + 0.003 M HF stage were not plotted).