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DOI
10.1007/s10967-023-08783-x

Publication date
2023

Document Version
Final published version

Published in
Journal of Radioanalytical and Nuclear Chemistry

Citation (APA)
McLain, D. R., Brossard, T. W., De Kruijff, R., Kankanamalage, P. H. A., & Rotsch, D. A. (2023). Evaluation of two extraction chromatography resins for scandium and titanium separation for medical isotope production. *Journal of Radioanalytical and Nuclear Chemistry*, *332*(3), 553-562. https://doi.org/10.1007/s10967-023-08783-x

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Journal of Radioanalytical and Nuclear Chemistry
https://doi.org/10.1007/s10967-023-08783-x

Evaluation of two extraction chromatography resins for scandium and titanium separation for medical isotope production

Derek R. McLain[1] · **Thomas W. Brossard**[1] · **Robin De Kruijff**[1,2] · **Pavithra H. A. Kankanamalage**[1] · **David A. Rotsch**[1,3]

Received: 6 July 2022 / Accepted: 11 January 2023
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Abstract

Scandium-47 (^{47}Sc) can be used in nuclear medicine as a therapeutic-diagnostic, or "theragnostic," radioactive medical isotope for cancer detection and treatment. The ^{47}Sc isotope can be produced through the photonuclear reaction ^{48}Ti(γ,p)^{47}Sc by irradiating enriched ^{48}Ti target material. The enriched target material necessary for production is costly; $^{48}TiO_2$ costs ~ \$1550/g, and targets can be > 50 g (\$77,500) to produce medically relevant amounts of ^{47}Sc. In order to keep costs low, a highly efficient separation of scandium from bulk titanium is desired, along with efficient methods for recycling the target material. This research is focused on evaluating efficient methods for the separation of scandium from bulk quantities of titanium using commercially available diglycolamide-based and hydroxamate-based extraction chromatography resins (DGA resin and ZR resin, respectively). The sorption of ^{47}Sc and Ti on these resins were investigated at varying concentrations of HNO_3, HCl, H_2SO_4, and HF to explore how they might be used in a large-scale production/processing setting.

Keywords Extraction chromatography · Medical isotopes · ^{47}Sc · DGA resin · ZR resin · Theranostic isotope

Introduction

Scandium-47 has favorable decay characteristics for use as a therapeutic agent in nuclear medicine, with a β^- mean energy of 162 keV and a half-life of 3.349 days [1]. Further, ^{47}Sc has a gamma emission (159 keV, 68.3%) suitable for single photon emission computed tomography (SPECT) imaging, making ^{47}Sc a true theragnostic radionuclide. Scandium-47 also has two diagnostic radioisotope pairs (^{43,44}Sc) suitable for positron emission tomography (PET) imaging and to assist in therapeutic dose calculations for ^{47}Sc-based treatments. The desire for complementary imaging and therapeutic compounds for the diagnosis and treatment of disease has been demonstrated by the development and commercialization of the"matched pair" system of ^{68} Ga/^{177}Lu (NetSpot—^{68}Ga-DOTATATE; ^{68}Ga, $t_{1/2} = 67.71$ m, $I_{b+} = 88.91\%$, $E_{<b+>} = 829.5$ keV/Lutathera—^{177}Lu-DOTATATE; ^{177}Lu, $t_{1/2} = 6.647$ d, $I_{b-} = 100\%$, $E_{<b->} = 134.2$ keV). Even though ^{68}Ga and ^{177}Lu are considered theragnostic pairs, they are in fact"matched pairs" and not chemically identical. This may cause complications in the interpretation of clinical theragnostic studies when these two compounds demonstrate different biodistributions. This led to the demonstration of ^{44}Sc's superiority over the ^{68}Ga as a matched pair to ^{177}Lu complexes in vivo and provides the motivation to develop theragnostic systems with same element radioisotopes or"isotope pairs" for nuclear medicine [2].

The chemistry of Sc is much more similar to that of Lu (and the other lanthanides) than Ga, thus making radioisotopes of Sc (^{43,44}Sc) better matched pairs for ^{177}Lu than ^{68}Ga. This is of note because there are many lanthanide-based pharmaceuticals (MRI—magnetic resonance imaging contrast agents) and radiopharmaceuticals (e.g., Lutathera®) currently used in nuclear medicine [3–7]. Thus, making radioisotopes of Sc ($^{43.44}$Sc and ^{47}Sc for imaging and therapy) is very attractive as they have the potential to seamlessly slip into clinical use as true isotope pairs [8, 9].

Due to the potential the ^{43,44}Sc/^{47}Sc theragnostic system promises within the medical community, efforts to reliably produce these radioisotopes have intensified significantly over the last decade [10]. Though a clinical dose amount

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Published online: 13 February 2023

of ^{47}Sc has not been established to date, it is expected to be similar to that of ^{177}Lu currently used, which is roughly 200 mCi per dose and would require routine production runs creating on the order of 1 Ci to sustain a supply [11]. Scandium-47 can be directly produced at high specific activity via the irradiation of Ti with photons (^{48}Ti) [8, 12–14], protons (^{48}Ti) [15, 16], or neutrons (^{nat}Ti, ^{47}Ti) [17–19]; irradiation of V with protons or photons (^{nat}V) [20, 21]; and irradiation of Ca with protons (^{48}Ca) [15, 16, 22] or alpha particles (^{nat}Ca, ^{44}Ca) [23]. It is also possible to produce ^{47}Sc via the beta decay of ^{47}Ca. To do this, ^{47}Ca is generally produced via photon or proton irradiation of ^{48}Ca [24, 25], neutron irradiation of ^{46}Ca [24, 26], or fragmentation of a ^{48}Ca beam in water [27].

The ^{48}Ti(γ,p)^{47}Sc production route is attractive because it can produce high radio-purity ^{47}Sc, though the small cross-section means that large (ca. 50 g) targets of enriched $^{48}TiO_2$ would be required to produce sustainable quantities [4, 5, 8, 12]. Because highly enriched $^{48}TiO_2$ is quite costly (~ $1500/g), purification strategies with high separation factors are critical to obtain high purity product and clean target material for recycling.

A good review of the methods used to purify radioscandium was assembled by Chernysheva et al. in 2021 [10]. Of the myriad methods covered in that review, extraction chromatography is the most common with several of these utilizing the diglycolamide-based DGA Normal Resin. DGA Normal resin (Eichrom Technologies, LLC) is especially well suited to adsorb trivalent lanthanides and actinides from HNO_3 and HCl matrices, with the uptake ability of the resin for most of the periodic table well characterized [28, 29]. Pourmand et al. also showed that the presence of 0.2 M HF in varying HNO_3 had little effect on the uptake of several lanthanides [29]. These studies indicate that Ti has relatively low retention ($D_w < 100$) for all HNO_3 and HCl acid concentrations, while lanthanides and Y are very well retained ($D_w > 10^3$) for the same acids above 2 M. This indicates that Sc should also be well retained, though these studies did not include it as an analyte. More recent studies by Boron-Brenner, Roman and Bond, and Alliot et al. have shown that Sc is indeed well retained by the resin, with the highest retention occurring at HNO_3 or HCl concentrations above 2 M [30–32].

Another, more recently developed, extraction chromatography resin that has shown potential for separating Ti and Sc is ZR resin (Triskem International) [9, 33]. As the name implies, this resin was developed to adsorb Zr ions from solution. It also does an excellent job of retaining Ti under all HNO_3 and HCl acid concentrations. Initial characterization of this resin also showed minimal retention of Sc under moderate- to high-concentrations of these same acids (max D_w is 1 at ≥ 0.5 M acid) [33]. The primary drawback to this resin is that Ti is difficult to remove once it has been adsorbed. Despite this difficulty, reasonable recovery of Ti (≥ 78%) has been achieved with citric acid, oxalic acid, and a mixture of $HCl + H_2O_2$, though in all cases only µg amounts of Ti needed to be recovered from the resin [9, 34].

Generally, the most reliable methods for dissolving Ti targets have utilized HF, mixtures of HCl + HF, or mixtures of $H_2SO_4 + (NH_4)_2SO_4$ [8, 17, 18, 35–37]. Unfortunately, neither of the extraction chromatography resins described above have been characterized for Ti or Sc adsorption in H_2SO_4 or in systems that contain significant amounts of HF. This research looks to fill those gaps in knowledge for DGA resin and to determine if ZR resin could be an additional separation medium that could be used in the purification of ^{47}Sc produced from Ti targets.

Experimental

Materials

The extraction chromatography resins utilized in this work were DGA Normal resin and ZR resin. DGA Normal resin is comprised of inert polymer beads loaded with N,N,N′,N′-tetra-*n*-octyldiglycolamide, and was obtained from Eichrom Technologies (Lisle, IL, USA) [28]. ZR resin is similar but uses a hydroxamate compound to achieve ion retention and was obtained from TrisKem International (Bruz, France) [38]. Though the specific structure of the extractant has not been shared by TrisKem, similar Ti retention has been achieved in HCl using resin loaded with n-methylhydroxamate which suggests this could be the extractant [39]. Both DGA Normal and ZR resins were used as received in all experiments. All batch studies were carried out using 50–100 µm particle size resin. Radioactive scandium (^{46,47,48}Sc) was produced by irradiating natural titanium targets at the Low Energy Accelerator Facility at Argonne National Laboratory and purified using an established procedure prior to use in batch studies [8, 40]. Nitric, hydrochloric, sulfuric, and hydrofluoric acid (HNO_3, HCl, H_2SO_4, and HF, respectively) solutions were prepared using ultra-high purity Optima Grade reagents from Fisher Scientific (Hampton, NH). All solutions were prepared with deionized water from a Thermo Scientific™ Barnstead™ MicroPure™ water purification system. Where stable elements were required in standards and spike solutions, these were prepared using certified elemental standards of titanium, scandium, and gallium obtained from Agilent Technologies (Santa Clara, CA, USA).

Procedure

Following purification of the radio-scandium as described previously [8], the solution was added to a known amount of titanium spectroscopic standard solution and split into equal portions; one for each batch study performed. These solutions were then evaporated to dryness and reconstituted in an appropriate acid matrix to be used in spiking the batch study samples. After adding the acid matrix to the dried Sc/Ti residue, the vials were closed and gently swirled periodically over the course of an hour to allow for complete dissolution. The acid matrix solutions were comprised of 0.01 M or 1 M solutions of HNO_3, HCl, or H_2SO_4. For the mixed acid batch studies, the spike solution was reconstituted in a 5 M solution of the appropriate primary acid (HCl, HNO_3, or H_2SO_4) and added to already-mixed solutions that were used to precondition the resin. Unless otherwise noted, spike solutions contained roughly 200 ppm Ti and 50 µCi/mL ^{47}Sc.

Batch studies were used to assess the separation power of the chromatography resins with respect to Ti and Sc and were similar to those carried out previously [41]. The weight distribution value for the two elements was determined by measuring the concentration (or activity concentration) before and after contact with a known amount of resin in a known volume of solution. The weight distribution ratios (D_w) for the two elements in each batch study were calculated using Eq. (1), as derived in Chiarizia et al. [42] In Eq. (1), A_0 and A_s are the concentrations of metal ion in the aqueous phase before and after equilibration, respectively, measured in either parts per million (ppm) or activity (cpm/mL), w is the mass of resin in grams, and V is the volume of aqueous phase in mL.

$$D_w = \frac{A_0 - A_s}{A_s} \times \frac{V}{w} \tag{1}$$

Batch studies were performed by weighing out approximately 25 mg of resin into a 2 mL microcentrifuge tube and adding 1.4 mL of the appropriate acid matrix for preconditioning. The tube was then capped and secured on an orbital mixer for 30 min at 10 revolutions per minute to mix the resin and solution thoroughly. Following this, 0.1 mL of the appropriate prepared spike solution was added to the mixture. The sample was returned to the orbital mixer for an additional 30 min to ensure equilibration. Upon mixing completion, the sample was passed through a 0.45 µm PTFE syringe filter to separate the aqueous phase from the resin, after which an aliquot was taken for analysis by gamma spectroscopy. Stable Ti was determined by taking an additional aliquot from the aqueous phase, adding a Ga internal standard, and diluting it to 15 mL with 2% HNO_3 for analysis via inductively coupled plasma mass spectrometry (ICP-MS). Each concentration of acid in each batch study was investigated in triplicate. Unless otherwise noted, error bars on all figures indicate $\pm 2\sigma$ standard deviation on triplicate measurements.

In addition to determining weight distribution ratios, the time to equilibrium and resin capacity for Ti were determined for ZR resin using batch studies. To determine the time to equilibrium, the amount of time the resin was contacted with the spike solution was varied while the resin mass and acid matrix were kept constant. Similarly, to estimate the Ti capacity for the resin, Ti concentration was varied while the acid concentration and mass of resin remained constant. To check this capacity value in a real-world format, gravity flow columns were slurry packed with ~ 0.1 g of ZR resin and loaded with 4 mL of a solution of 0.05 M Ti in 1 M acid (HNO_3, HCl, or H_2SO_4), well in excess of the preliminary Ti capacity determined with the batch study in HNO_3. The column was then rinsed with 5 bed volumes of the same acid without Ti to ensure all of the metal was removed from interstitial space on the column. The resin capacity was then determined from the amount of Ti depleted from the solution that was passed through the column.

Measurement

Elemental concentrations of Ti and Ga were measured with a NexION 2000 Inductively Coupled Plasma Mass Spectrometer (ICP-MS) (PerkinElmer, Shelton, CT). This system was equipped with a PerkinElmer S-10 autosampler and a discrete dynode electron multiplier detector. A PFA Barrel spray chamber and a Type C PFA ST3 nebulizer formed the sample introduction-system. All ICP-MS samples and calibration standards were prepared by mass and ratio-based data reduction and calibration formulas were employed to reduce systematic error, as recommended by Salit et.al. [43–45]

Radio-scandium activities were measured using a WIZARD^2 2480 automatic gamma counter equipped with a 3-inch well-type NaI(Tl) detector with a 75 mm solid lead shield for background reduction obtained from PerkinElmer, Inc (Waltham, MA). Samples were counted in 13 mm diameter culture tubes, and used the 159 keV gamma emission line from ^{47}Sc for quantitation.

Results and discussion

ZR resin

Because Ti had been shown to have a high retention factor in HCl and HNO_3 by the manufacturer and others, the kinetics of the resin were investigated to see if it could be used as a purification clean-up step [46, 47]. Because of the excellent retention of Ti in HNO_3, this matrix was used when investigating the kinetics of the resin. Figure 1 shows the results of the kinetics study, which indicate that equilibrium Ti uptake is reached within the first 5 min of contact with

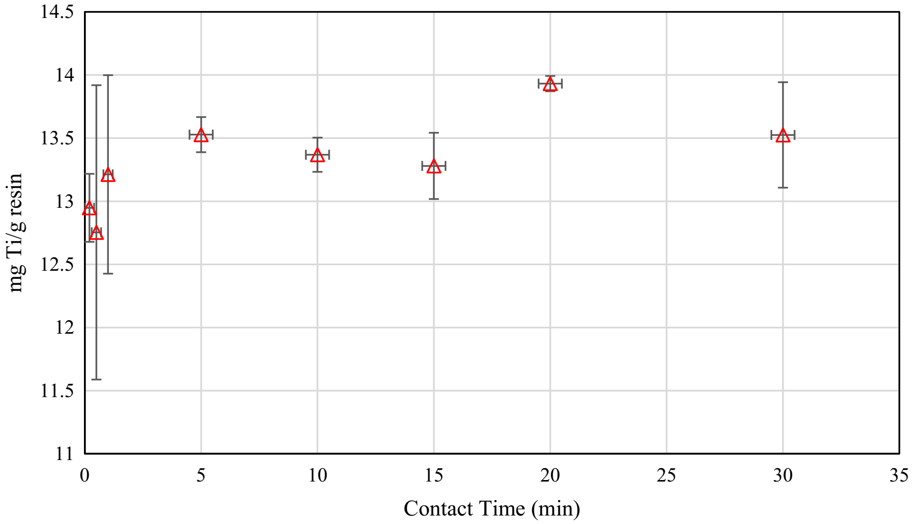


Fig. 1 Average Ti extracted at varying contact times with ZR resin in 1 M HNO_3. Error bars correspond to the 95% confidence interval based on duplicate measurements

the resin. This is similar to other commercially available extraction chromatography resins and was assumed to be representative of HCl and H_2SO_4 systems as well [28, 42]. Given this information, 15-min contact times were used for all subsequent batch studies with this resin.

Following the kinetics study, a batch study was performed to determine which H_2SO_4 concentration was most favorable for the extraction of Ti. The results of this study are found in Fig. 2, and indicate that Ti retention is high over all H_2SO_4 concentrations, similar to the results previously published for the HCl and HNO_3 matrices [33]. Though HF is generally a much faster method of Ti metal or TiO_2 dissolution than methods that use mixtures of HCl + HF, or mixtures of $H_2SO_4 + (NH_4)_2SO_4$, separation in a pure HF matrix was not pursued due to the strong Ti-complexing ability of the fluoride anion. The possibility of a quick and easy dissolution did, however, justify the investigation of just how dilute HF might have to be in another acid to still allow for separation of the two analytes. The results of this investigation are illustrated in Fig. 3, which contains a plot of the fractional D_w values for Ti retention at varying concentrations of HF in 1 M solutions of HNO_3, HCl, or H_2SO_4. In the plot, the vertical axis was calculated by dividing the measured D_w by the weight distribution of Ti with no HF in solution (D_{w0}). The D_{w0} value for H_2SO_4 was established at ~ 250 and was ~ 10,000 in HCl and HNO_3.

Unfortunately, as Fig. 3 illustrates, the retention of Ti drops off quickly in the presence of HF. Though the retention values for Ti do start quite high without the presence of HF, the separation factor for Ti/Sc drops to the limit of quantitation for this method by the time the concentration of HF has reached 0.1 M. This phenomenon is similar to what O'Hara et al.observed for Zr on a synthesized hydroxamate resin, though that work found the drop off at much lower

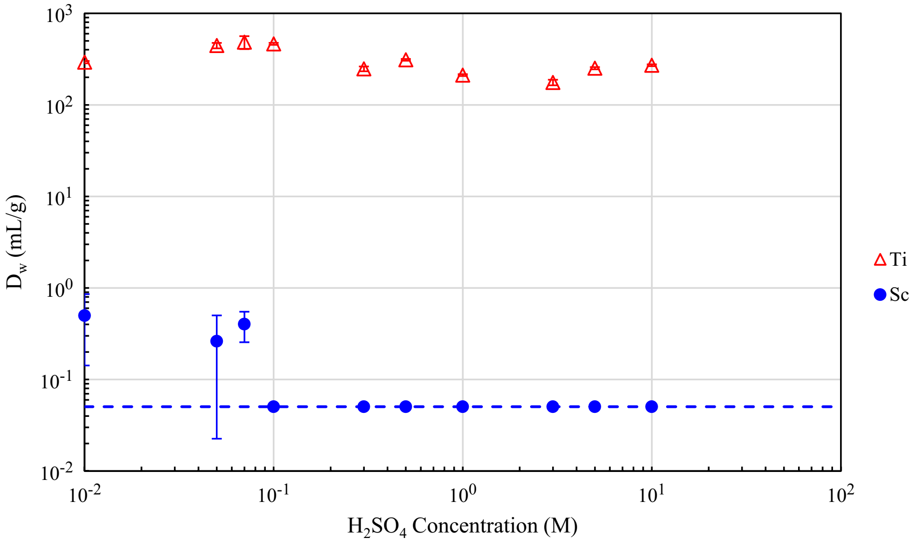


Fig. 2 Batch study data for Ti and Sc in varying H_2SO_4 concentrations. minimum measurable D_w value for Sc is denoted by the dashed line

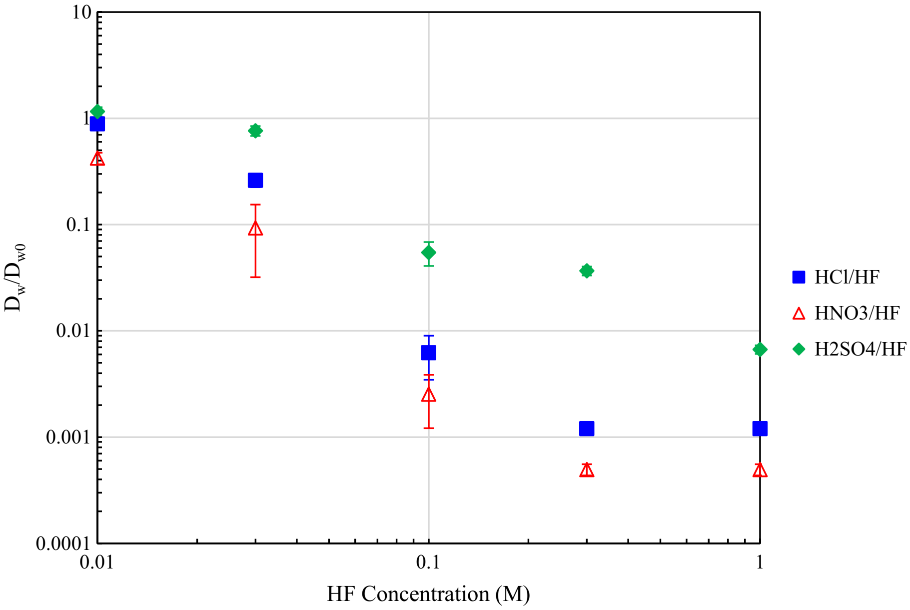


Fig. 3 Fractional D_w values for Ti at varying HF concentrations, with the primary acid (HCl, HNO_3, or H_2SO_4) concentration set at 1 M

concentrations of fluoride in solution [48]. It is likely these differences reflect the use of tracer levels of Zr in the previous study and ppm levels of Ti in this study. Because of the significant drop in Ti retention in its presence, it was attempted to remove HF via evaporation after dissolution, but the Ti crashed out of solution well before the fluoride content was low enough to perform an effective separation. Based on these observations, nearly 20 L of solution would be required to keep the HF concentration low enough to perform the separation while simultaneously keeping enough HF to stabilize the Ti in solution and makes the use of such solutions for Ti/Sc separations unattractive.

To understand if the ZR resin could be used to clean up multiple processed targets before replacement, capacity studies were undertaken. The initial batch study for establishing an approximate resin capacity was done in 1 M HNO_3 and indicated that the resin could hold 21 ± 2 mg Ti/g resin (Fig. 4). Given that the manufacturer indicated the capacity of the resin for Zr was 40 mg/g resin, this would suggest that the resin has roughly the same capacity for Ti on an atom/g resin basis [47]. Following this, an additional trial was executed using the column method described above with 1 M HNO_3 as the matrix to confirm the resin capacity established by the batch study. This method was also applied to 1 M HCl and 1 M H_2SO_4 matrices, and all three trials produced resin capacity values within 5% of that found via the batch contact method. Further, the column capacity trials showed good agreement with each other. The average of the three column capacity trials was 21 ± 3 mg Ti/g resin ($k = 2$), which is shown in Fig. 5 along with the individual determined values.

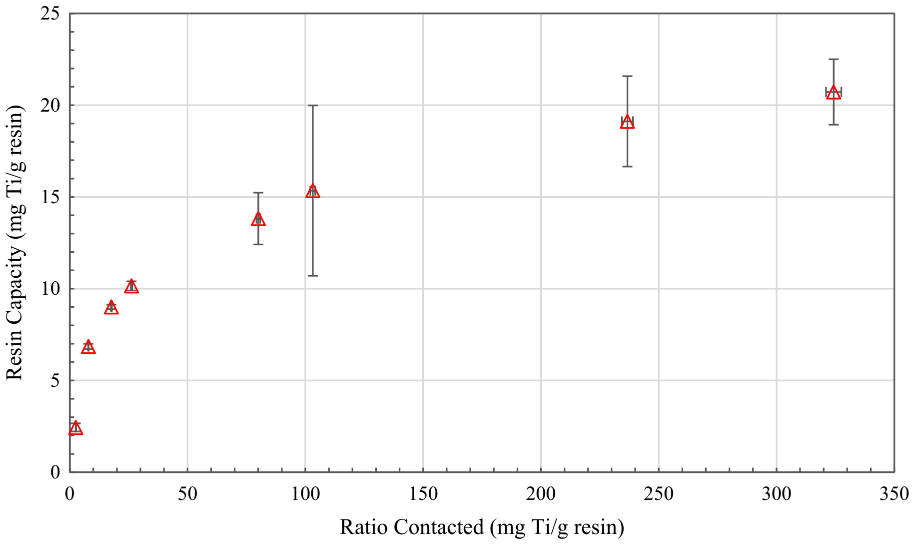


Fig. 4 Average capacity of the resin for retaining Ti in 1 M HNO_3

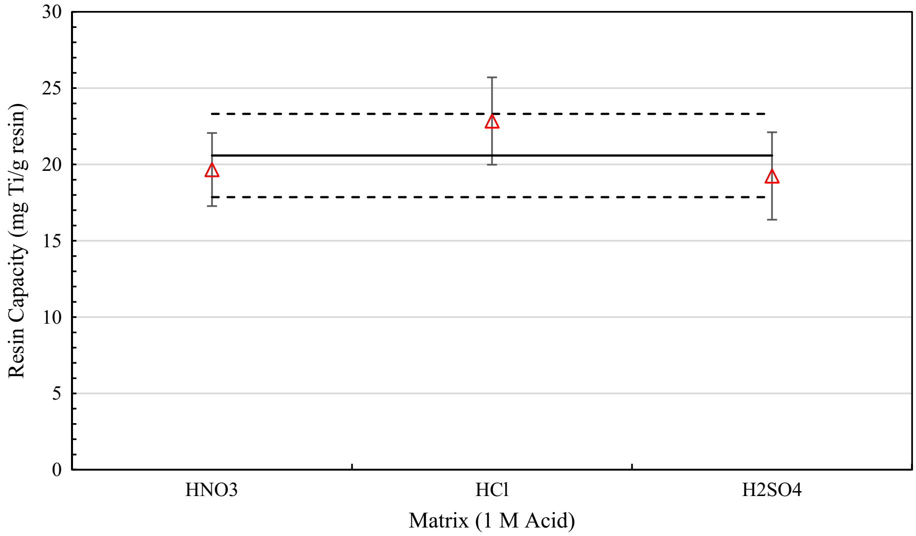


Fig. 5 Results from the column resin capacity experiments. Solid line and dashed lines indicate the average value across acids and the expanded uncertainty associated with the measurements, respectively. Error bars on individual measurements were estimated using GUM Workbench ($k=2$)

DGA resin

The results of the batch studies for Ti and Sc extraction with hydrochloric acid, nitric acid, and sulfuric acid are found in Figs. 6, 7, and 8, respectively. In each system, scandium is poorly retained by the resin at low acid concentrations, but highly retained at high acid concentrations. In the HCl and HNO_3 systems, the D_w values for Sc reached > 300 000 mL/g (maximum measurable for this batch study) in high acid, while the D_w values for Ti remained low (< 20 mL/g) across all acid concentrations. The data for Ti agrees well with what Pourmand and Dauphas found during their comprehensive examination of DGA in 2010 [29]. Previous investigations of Sc uptake on DGA resin in HCl and HNO_3 show similar trends, though the absolute D_w values differ slightly [30–32]. The trends observed here also closely match those of *Y* (a close chemical analog to Sc, for which there is ample data), which bolsters the credibility of our findings [28, 29]. In the H_2SO_4 system, the D_w value for Sc begins below the minimum detectable value in 0.01 M H_2SO_4 and then climbs to a peak of approximately 38,000 mL/g in 5 M H_2SO_4 before falling back to 400 mL/g in 12 M H_2SO_4. The D_w values for Ti in H_2SO_4 remained below 13 mL/g for all concentrations of H_2SO_4.

In each acid, the optimal separation occurs at a concentration between 3 and 7 M. It is preferable to keep the acid concentration on the lower end of this range to suppress Ti retention as much as possible.

As mentioned previously, HF is often required to completely dissolve Ti target compounds in a timely manner. To test the effects of HF that could be left in solution after digesting a target, additional batch studies were carried out in which the three acids (HNO_3, HCl, and H_2SO_4) were fixed at 5 M while the HF concentration

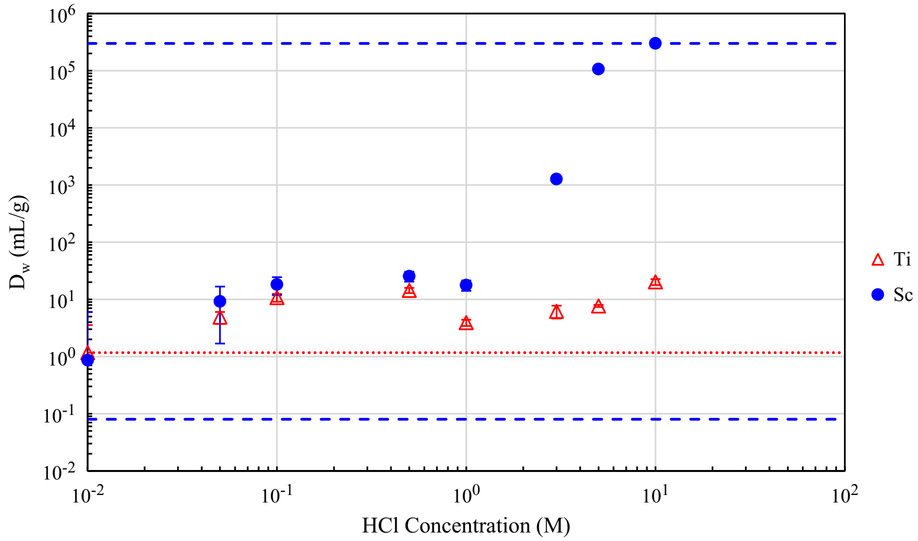


Fig. 6 Scandium and titanium batch study results for the HCl system. Minimum and maximum measurable D_w values for Sc are denoted by the dashed lines. Minimum measurable D_w value for Ti is denoted by the dotted line

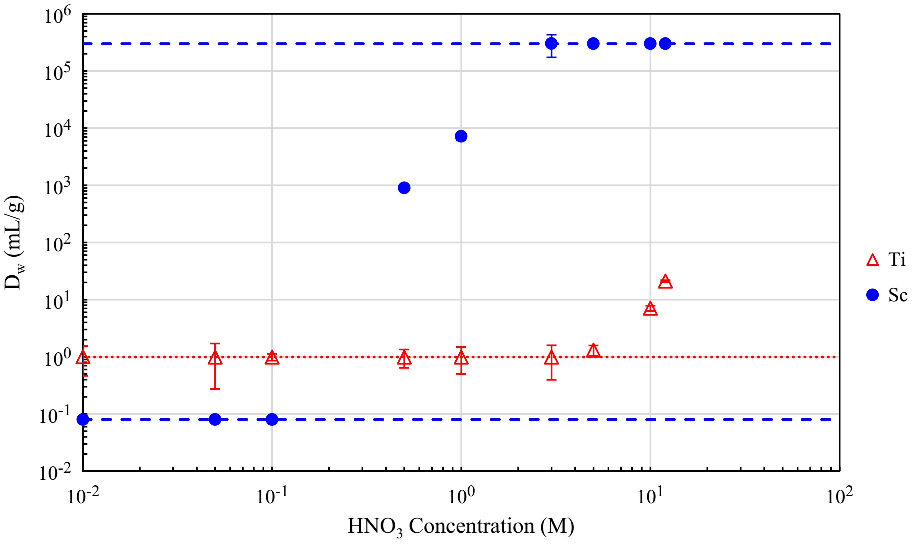


Fig. 7 Scandium and titanium batch study results for the HNO_3 system. Minimum and maximum measurable D_w values for Sc are denoted by the dashed lines. Minimum measurable D_w value for Ti is denoted by the dotted line

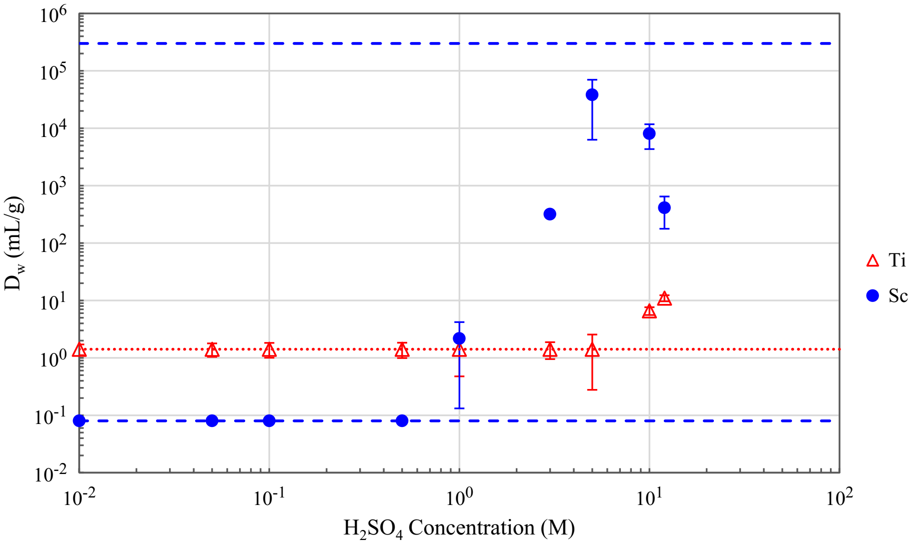


Fig. 8 Scandium and titanium batch study results for the H_2SO_4 system. Minimum and maximum measurable D_w values for Sc are denoted by the dashed lines. Minimum measurable D_w value for Ti is denoted by the dotted line

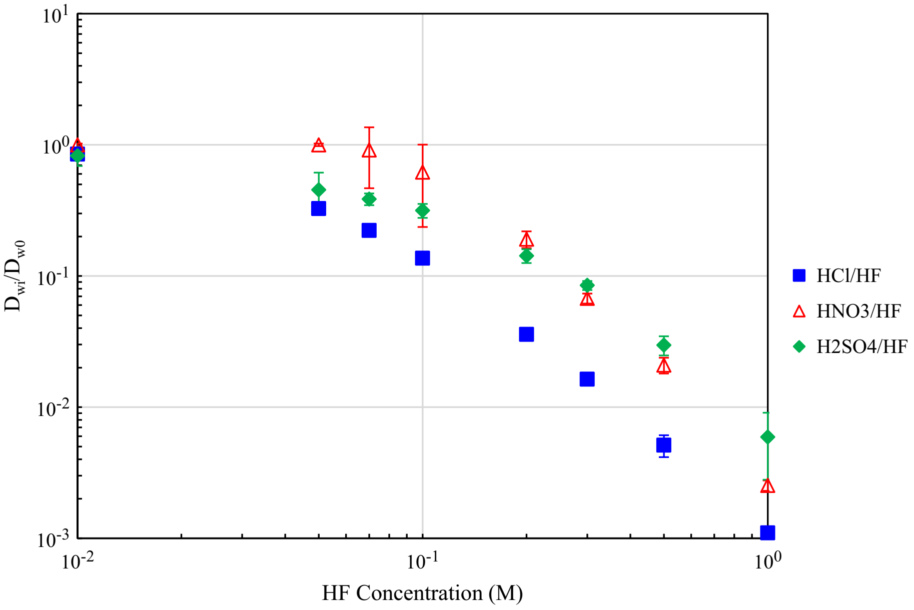
was varied from 0.01 to 1 M. The results of these batch studies, shown as fractional D_w values in Fig. 9, clearly indicate that Sc retention is suppressed as HF concentration increases. Despite this suppression, D_w values for Sc are still at or above ~ 100 mL/g for systems containing up to 0.5 M HF due to the extremely high retention factors in the 5 M single-acid matrices.

Unfortunately, much like the HF system investigated for the ZR Resin, to dilute down concentrated HF to 0.5 M with one of the three primary acids examined here for 50 g Ti targets, would result in a total volume of just over 5 L. While it is certainly possible to carry out a separation with such a large volume, the logistics of execution and dealing with the large volume of waste is likely to be prohibitive.

Conclusions

The results of the tests performed herein on ZR resin indicate that it has an excellent rate of uptake for Ti in HNO_3. Given the repeatability of experiments in the batch format, we conclude that the rate of uptake in HCl and H_2SO_4 is similar. In addition, this work showed that ZR resin can separate Ti from Sc in a wide range of H_2SO_4 concentrations. Unfortunately, the presence of ≥ 0.1 M HF was found to suppress Ti retention such that separation of the two analytes is unreasonable. While HF is the gold standard for Ti dissolution, the suppression of Ti retention at such low levels makes it unattractive in this instance.

Fig. 9 Fractional D_w values for Sc at varying HF concentrations, with the primary acid (HCl, HNO_3, or H_2SO_4) concentration set at 5 M



Tests also showed that the maximum capacity of the resin for Ti was approximately 21 mg/g resin, which corresponds to roughly 1.4 kg of resin required to retain a full target used in the production of radioscandium via the $^{48}Ti(\gamma,p)^{47}Sc$ pathway. Though this precludes ZR resin from being used in initial purification steps, it could be used as a secondary "clean-up" column to remove any Ti that breaks through the primary separation column. This work also supports the prior efforts carried out by Radchenko et al. discussing the possibility of utilizing the ZR resin as a $^{44}Ti/^{44}Sc$ generator [9].

The tests performed on DGA resin in HCl and HNO_3 agree well with previously published efforts that characterized Ti and Sc uptake in these acid matrices [29–31]. Resin performance in the H_2SO_4 system shows trends similar to the HCl system, with low Sc retention at low acid concentrations and a rapid increase starting around 1 M. These results establish that Sc can be purified from bulk Ti using DGA resin in any of these acid systems at concentrations of 3–7 M. A significant decline in Sc retention was observed in the presence of even small amounts of HF in the three primary acids. While the D_w values in the individual acids are high enough that a separation may still be possible with the suppression caused by HF, the total volume of solution after diluting to an acceptable HF concentration is still prohibitive and indicates that HF needs to be removed from solution if it is used for target dissolution.

Clearly, further work needs to be undertaken to identify a digestion method for Ti that utilizes little or no HF while still being rapid and robust enough to be used in the high radiation fields that are present during large batch processing of radioisotopes. If this can be accomplished, the results presented in this work indicate that pure ^{47}Sc can be isolated using a combination of DGA resin and ZR resin when using the large targets requried for photonuclear production.

Acknowledgements This research was supported by the U.S. Department of Energy Isotope Program, managed by the Office of Science for Isotope R&D and Production and Argonne National Laboratory under U.S. Department of Energy contract DE-AC02-06CH11357. The authors would like to thank Argonne's Yifen Tsai and the Analytical Chemistry Laboratory for collecting the ICP-MS data and Argonne's Low Energy Accelerator Facility (LEAF) for irradiating the Ti target material. The submitted manuscript has been created by UChicago Argonne, LLC, Operator of Argonne National Laboratory ("Argonne"). Argonne, a U.S. Department of Energy Office of Science laboratory, is operated under Contract No. DE-AC02-06CH11357. The U.S. Government retains for itself, and others acting on its behalf, a paid-up nonexclusive, irrevocable worldwide license in said article to reproduce, prepare derivative works, distribute copies to the public, and perform publicly and display publicly, by or on behalf of the Government. The Department of Energy will provide public access to these results of federally sponsored research in accordance with the DOE Public Access Plan. http://energy.gov/downloads/doe-public-access-plan.

Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

References

1. Burrows TW (2007) Nuclear data sheets for A = 47. Nucl Data Sheets 108:923–1056. https://doi.org/10.1016/j.nds.2007.04.002
2. Umbricht CA, Benešová M, Schmid RM, Türler A, Schibli R, van der Meulen NP, Müller C (2017) ^{44}Sc-PSMA-617 for radiotheragnostics in tandem with ^{177}Lu-PSMA-617—preclinical investigations in comparison with ^{68}Ga-PSMA-11 and ^{68}Ga-PSMA-617. EJNMMI Res 7:9. https://doi.org/10.1186/s13550-017-0257-4

3. Price EW, Orvig C (2014) Matching chelators to radiometals for radiopharmaceuticals. Chem Soc Rev 43:260–290. https://doi.org/10.1039/C3CS60304K
4. Qaim SM (2019) Theranostic radionuclides: recent advances in production methodologies. J Radioanal Nucl Chem 322:1257–1266. https://doi.org/10.1007/s10967-019-06797-y
5. Qaim SM, Scholten B, Neumaier B (2018) New developments in the production of theranostic pairs of radionuclides. J Radioanal Nucl Chem 318:1493–1509. https://doi.org/10.1007/s10967-018-6238-x
6. Wahsner J, Gale EM, Rodríguez-Rodríguez A, Caravan P (2019) Chemistry of MRI contrast agents: current challenges and new frontiers. Chem Rev 119:957–1057. https://doi.org/10.1021/acs.chemrev.8b00363
7. Wester H-J, Schottelius M (2019) PSMA-targeted radiopharmaceuticals for imaging and therapy. Semin Nucl Med 49:302–312. https://doi.org/10.1053/j.semnuclmed.2019.02.008
8. Rotsch DA, Brown MA, Nolen JA, Brossard T, Henning WF, Chemerisov SD, Gromov RG, Greene J (2018) Electron linear accelerator production and purification of scandium-47 from titanium dioxide targets. Appl Radiat Isot 131:77–82. https://doi.org/10.1016/j.apradiso.2017.11.007
9. Radchenko V, Meyer CAL, Engle JW, Naranjo CM, Unc GA, Mastren T, Brugh M, Birnbaum ER, John KD, Nortier FM, Fassbender ME (2016) Separation of ^{44}Ti from proton irradiated scandium by using solid-phase extraction chromatography and design of ^{44}Ti/^{44}Sc generator system. J Chromatogr A 1477:39–46. https://doi.org/10.1016/j.chroma.2016.11.047
10. Chernysheva M, Loveless SC, Brossard T, Becker K, Cingoranelli S, Aluicio-Sarduy E, Song J, Ellison P, Nolen J, Rotsch DA, Lapi SE, Engle JW (2021) Accelerator production of scandium radioisotopes: ^{43}Sc, ^{44}Sc, and ^{47}Sc. Curr Radiopharm 14:359–373. https://doi.org/10.2174/1874471014999210112205535
11. Lutathera Dosage (2022) Drugs.com. https://www.drugs.com/dosage/lutathera.html. Accessed 12 Dec 2022
12. Loveless CS, Radford LL, Ferran SJ, Queern SL, Shepherd MR, Lapi SE (2019) Photonuclear production, chemistry, and in vitro evaluation of the theranostic radionuclide ^{47}Sc. EJNMMI Res 9:42. https://doi.org/10.1186/s13550-019-0515-8
13. Yagi M, Kondo K (1977) Preparation of carrier-free ^{47}Sc by the ^{48}Ti (γ, p) reaction. Int J Appl Radiat Isot 28:463–468. https://doi.org/10.1016/0020-708X(77)90178-8
14. Mamtimin M, Harmon F, Starovoitova VN (2015) ^{47}Sc production from titanium targets using electron linacs. Appl Radiat Isot 102:1–4. https://doi.org/10.1016/j.apradiso.2015.04.012
15. Misiak R, Walczak R, Wąs B, Bartyzel M, Mietelski JW, Bilewicz A (2017) ^{47}Sc production development by cyclotron irradiation of ^{48}Ca. J Radioanal Nucl Chem 313:429–434. https://doi.org/10.1007/s10967-017-5321-z
16. Sitarz M, Szkliniarz K, Jastrzębski J, Choiński J, Guertin A, Haddad F, Jakubowski A, Kapinos K, Kisieliński M, Majkowska A, Nigron E, Rostampour M, Stolarz A, Trzcińska A, Walczak R, Wojtkowska J, Zipper W, Bilewicz A (2018) Production of Sc medical radioisotopes with proton and deuteron beams. Appl Radiat Isot 142:104–112. https://doi.org/10.1016/j.apradiso.2018.09.025
17. Deilami-nezhad L, Moghaddam-Banaem L, Sadeghi M, Asgari M (2016) Production and purification of Scandium-47: a potential radioisotope for cancer theranostics. Appl Radiat Isot 118:124–130. https://doi.org/10.1016/j.apradiso.2016.09.004
18. Kolsky KL, Joshi V, Mausner LF, Srivastava SC (1998) Radiochemical purification of no-carrier-added scandium-47 for radioimmunotherapy. Appl Radiat Isot 49:1541–1549. https://doi.org/10.1016/S0969-8043(98)00016-5
19. Srivastava SC (2011) Paving the way to personalized medicine: production of some theragnostic radionuclides at Brookhaven National Laboratory, vol 99, pp 635–640. https://doi.org/10.1524/ract.2011.1882
20. Pupillo G, Mou L, Boschi A, Calzaferri S, Canton L, Cisternino S, De Dominicis L, Duatti A, Fontana A, Haddad F, Martini P, Pasquali M, Skliarova H, Esposito J (2019) Production of ^{47}Sc with natural vanadium targets: results of the PASTA project. J Radioanal Nucl Chem 322:1711–1718. https://doi.org/10.1007/s10967-019-06844-8
21. Snow MS, Foley A, Ward JL, Kinlaw MT, Stoner J, Carney KP (2021) High purity ^{47}Sc production using high-energy photons and natural vanadium targets. Appl Radiat Isot 178:109934. https://doi.org/10.1016/j.apradiso.2021.109934
22. Walczak R, Sitarz M, Misiak R, Pruszynski M, Majkowska-Pilip A, Jastrzebski J, Haddad F, Bilewicz A (2020) Trends in radiopharmaceuticals (ISTR-2019). International Atomic Energy Agency, Vienna
23. Minegishi K, Nagatsu K, Fukada M, Suzuki H, Ohya T, Zhang MR (2016) Production of scandium-43 and-47 from a powdery calcium oxide target via the Ca-nat/44(alpha, x)-channel. Appl Radiat Isot 116:8–12. https://doi.org/10.1016/j.apradiso.2016.07.017
24. Müller C, Bunka M, Haller S, Köster U, Groehn V, Bernhardt P, van der Meulen N, Türler A, Schibli R (2014) Promising prospects for ^{44}Sc-/^{47}Sc-based theragnostics: application of ^{47}Sc for radionuclide tumor therapy in mice. J Nucl Med 55:1658–1664. https://doi.org/10.2967/jnumed.114.141614
25. Starovoitova VN, Cole PL, Grimm TL (2015) Accelerator-based photoproduction of promising beta-emitters ^{67}Cu and ^{47}Sc. J Radioanal Nucl Chem 305:127–132. https://doi.org/10.1007/s10967-015-4039-z
26. Pawlak D, Wojdowska W, Parus LJ, Cieszykowska I, Zoltowska M, Garnuszek P, Mikolajczak R (2019) Comparison of separation methods for ^{47}Ca/^{47}Sc radionuclide generator. Appl Radiat Isot 151:140–144. https://doi.org/10.1016/j.apradiso.2019.05.020
27. Abel EP, Domnanich K, Clause HK, Kalman C, Walker W, Shusterman JA, Greene J, Gott M, Severin GW (2020) Production, collection, and purification of ^{47}Ca for the generation of ^{47}Sc through isotope harvesting at the National Superconducting Cyclotron Laboratory. ACS Omega 5:27864–27872. https://doi.org/10.1021/acsomega.0c03020
28. Horwitz EP, McAlister DR, Bond AH, Barrans RE (2005) Novel extraction of chromatographic resins based on tetraalkyldiglycolamides: characterization and potential applications. Solvent Extr Ion Exch 23:319–344. https://doi.org/10.1081/SEI-200049898
29. Pourmand A, Dauphas N (2010) Distribution coefficients of 60 elements on TODGA resin: application to Ca, Lu, Hf, U and Th isotope geochemistry. Talanta 81:741–753. https://doi.org/10.1016/j.talanta.2010.01.008
30. Boron-Brenner LP (2018) Development of chemical separation methods using transition metals for nuclear forensic and medicinal applications. University of Nevada, Las Vegas
31. Roman AR, Bond EM (2016) A new method for separating first row transition metals and actinides from synthetic melt glass. J Radioanal Nucl Chem 307:2471–2478. https://doi.org/10.1007/s10967-016-4695-7
32. Alliot C, Kerdjoudj R, Michel N, Haddad F, Huclier-Markai S (2015) Cyclotron production of high purity ^{44m,44}Sc with deuterons from ^{44}CaCO$_3$ targets. Nucl Med Biol 42:524–529. https://doi.org/10.1016/j.nucmedbio.2015.03.002
33. Dirks C, Happel S, Bombard A (2016) On the development and characterization of an hydroxamate based extraction chromatographic resin. In: RANC 2016, Budapest, Hungary, 10–16 April 2016
34. Chaple IF, Thiele K, Thaggard G, Fernandez S, Boros E, Lapi SE (2020) Optimized methods for production and purification of

Titanium-45. Appl Radiat Isot 166:109398. https://doi.org/10.1016/j.apradiso.2020.109398

35. Bokhari TH, Mushtaq A, Khan IU (2010) Separation of no-carrier-added radioactive scandium from neutron irradiated titanium. J Radioanal Nucl Chem 283:389–393. https://doi.org/10.1007/s10967-009-0370-6
36. Pietrelli L, Mausner LF, Kolsky KL (1992) Separation of carrier-free ^{47}Sc from titanium targets. J Radioanal Nucl Chem 157:335–345. https://doi.org/10.1007/BF02047448
37. Mausner LF, Kolsky KL, Joshi V, Srivastava SC (1998) Radionuclide development at BNL for nuclear medicine therapy. Appl Radiat Isot 49:285–294. https://doi.org/10.1016/S0969-8043(97)00040-7
38. Holland JP, Sheh Y, Lewis JS (2009) Standardized methods for the production of high specific-activity zirconium-89. Nucl Med Biol 36:729–739. https://doi.org/10.1016/j.nucmedbio.2009.05.007
39. Gajecki L, Marino CM, Cutler CS, Sanders VA (2023) Evaluation of hydroxamate-based resins towards a more clinically viable ^{44}Ti/^{44}Sc radionuclide generator. Appl Radiat Isot 192:110588. https://doi.org/10.1016/j.apradiso.2022.110588
40. Brown MA, Rotsch DA, Nolen JA (2019) Process for the separation and purification of scandium medical isotopes. United States Patent US010344355B2, 9 July 2019
41. McLain DR, Liu C, Sudowe R (2018) Using Sr resin with mixed acid matrices. J Radioanal Nucl Chem 316:485–490. https://doi.org/10.1007/s10967-018-5778-4
42. Horwitz EP, Dietz ML, Chiarizia R, Diamond H, Essling AM, Graczyk D (1992) Separation and preconcentration of uranium from acidic media by extraction chromatography. Anal Chim Acta 266:25–37. https://doi.org/10.1016/0003-2670(92)85276-C
43. Salit ML, Turk GC (1998) A drift correction procedure. Anal Chem 70:3184–3190. https://doi.org/10.1021/ac980095b
44. Salit ML, Turk GC, Lindstrom AP, Butler TA, Beck CM, Norman B (2001) Single-element solution comparisons with a high-performance inductively coupled plasma optical emission spectrometric method. Anal Chem 73:4821–4829. https://doi.org/10.1021/ac0155097
45. Salit ML, Vocke RD, Kelly WR (2000) An ICP-OES method with 0.2 expanded uncertainties for the characterization of $LiAlO_2$. Anal Chem 72:3504–3511. https://doi.org/10.1021/ac0000877
46. Radchenko V, Engle JW, Medvedev DG, Maassen JM, Naranjo CM, Unc GA, Meyer CAL, Mastren T, Brugh M, Mausner L, Cutler CS, Birnbaum ER, John KD, Nortier FM, Fassbender ME (2017) Proton-induced production and radiochemical isolation of ^{44}Ti from scandium metal targets for ^{44}Ti/^{44}Sc generator development. Nucl Med Biol 50:25–32. https://doi.org/10.1016/j.nucmedbio.2017.03.006
47. Happel S (2021) An overview over some new extraction chromatographic resins and their application in radiopharmacy. TrisKem International, Bruz
48. O’Hara MJ, Murray NJ, Carter JC, Kellogg CM, Link JM (2018) Tandem column isolation of zirconium-89 from cyclotron bombarded yttrium targets using an automated fluidic platform: anion exchange to hydroxamate resin columns. J Chromatogr A 1567:37–46. https://doi.org/10.1016/j.chroma.2018.06.035@@@

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