

Solvent Extraction and Ion Exchange

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lsei20>

An Improved Method for the Production of Ac-225/Bi-213 from Th-229 for Targeted Alpha Therapy

B. Zielinska^a, C. Apostolidis^a, F. Bruchertseifer^a & A. Morgenstern^a

^a European Commission, Joint Research Centre, Institute for Transuranium Elements, Karlsruhe, Germany

Published online: 17 Apr 2007.

To cite this article: B. Zielinska, C. Apostolidis, F. Bruchertseifer & A. Morgenstern (2007): An Improved Method for the Production of Ac-225/Bi-213 from Th-229 for Targeted Alpha Therapy, Solvent Extraction and Ion Exchange, 25:3, 339-349

To link to this article: <http://dx.doi.org/10.1080/07366290701285108>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.tandfonline.com/page/terms-and-conditions>

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

An Improved Method for the Production of Ac-225/Bi-213 from Th-229 for Targeted Alpha Therapy

B. Zielinska, C. Apostolidis, F. Bruchertseifer, and
 A. Morgenstern

European Commission, Joint Research Centre, Institute for Transuranium
 Elements, Karlsruhe, Germany

Abstract: This work describes an improved method for radium/actinium separation as part of a process for the production of Ac-225 from a Th-229 source for targeted alpha therapy of cancer. The separation method is based on the use of a newly developed extraction chromatographic resin containing the diglycolamide (DGA) class of molecules. The weight distribution ratios of Ac(III) on the extraction chromatographic resins *N,N,N',N'* tetraoctyldiglycolamide (TODGA) and *N,N,N',N'* tetrakis-2-ethylhexyldiglycolamide (TEHDGA) (both Eichrom Inc.) were determined at varying nitric and hydrochloric acid concentrations by batch experiments to optimize conditions for the separation of Ac(III) from Ra(II). Consequently, a robust and rapid procedure based on the use of TEHDGA resin was developed yielding a carrier-free, clinical-grade Ac-225 with an overall yield exceeding 98%.

Keywords: Actinium-225, Radium-225, diglycolamide, weight distribution ratio, extraction chromatography, batch method, targeted alpha therapy

INTRODUCTION

Targeted alpha therapy (TAT) is a novel and promising treatment strategy for the therapy of a variety of cancers and infectious diseases. It is based on the selective targeting of malignant cells using tumor specific carrier molecules,

Received 26 March 2006, Accepted 30 November 2006

Address correspondence to A. Morgenstern, European Commission, Joint Research Centre, Institute for Transuranium Elements, P. O. Box 2340, D-76125, Karlsruhe, Germany. Tel: +49(0) 7247-951-248; Fax: +49-(0)7247 951-99648; E-mail: alfred.morgenstern@ec.europa.eu

e.g. monoclonal antibodies or peptides, linked to alpha-emitting radionuclides. Due to the high linear energy transfer ($LET \approx 100 \text{ keV}/\mu\text{m}$) of alpha particles and their short path length in human tissue ($40\text{--}90 \mu\text{m}$) such radio-immuno-conjugates have the potential of delivering a highly cytotoxic radiation dose to the tumor cells while sparing normal body tissues. A number of pre-clinical and clinical studies have demonstrated the potential of TAT.^[1–5]

Among the α -emitting radioisotopes considered for targeted alpha therapy, ^{213}Bi ($T_{1/2} = 46 \text{ min}$) available through the decay chain of ^{225}Ac ($T_{1/2} = 10 \text{ days}$) is presently the most promising. Bi-213 is a mixed alpha/beta emitter that mainly decays to the pure alpha emitter Po-213 with a branching ratio of 98%. Due to the very short half-life of the daughter nuclide Po-213 ($T_{1/2} = 4.2 \mu\text{s}$), Bi-213 itself can be practically considered an alpha emitter. The mother nuclide ^{225}Ac can be produced through extraction from Th-229 sources and the routine process developed at the Institute for Transuranium Elements (ITU) for the separation and purification of Ac-225 from a 46 mCi Th-229 source has been reported recently.^[6] The process is based on the combination of ion exchange and extraction chromatographic methods in nitric acid media (Fig. 1). Following the separation of Ra-225/Ac-225 from the Th-229 source using Dowex 1 $\times$ 8 anion exchange resin, the separation of Ac-225 from Ra-225 was described in 4 M HNO_3 using RE (Rare Earth) extraction chromatographic resin. Although RE resin affords an effective separation of Ac(III) from Ra(II) in nitric acid media, the RE separation step has some limitations. Due to a relatively moderate retention of Ac(III) on RE resin washing steps have to be carefully controlled to avoid breakthrough and consequently the loss of Ac(III).

Recently a new class of extraction chromatographic resins, based on the use of diglycolamide extractants, has been developed by Horwitz et al.^[7] A

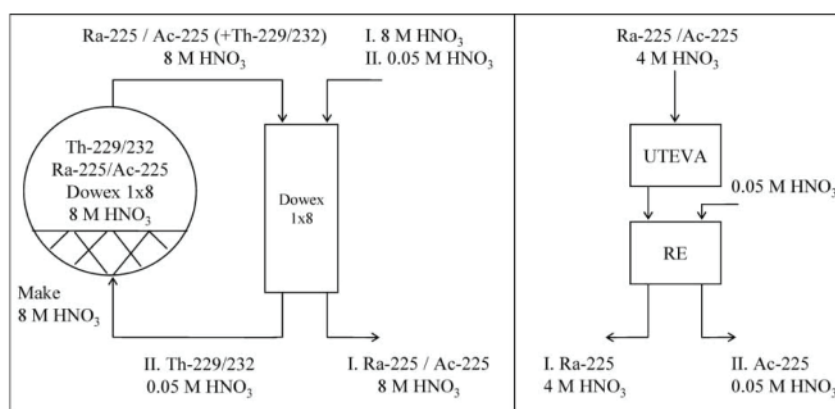


Figure 1. Anion exchange procedure using Dowex 1X8 for separation of Ra-225 and Ac-225 from a Th-229 source (left) and extraction chromatographic procedure based on UTEVA/RE resin for Ra-225/Ac-225 separation (right).

number of studies have described these extractants based on tetraalkyl-diglycolamides as unusually effective extractants of trivalent actinides and lanthanides from nitric acid. These studies are directed at the separation of long-lived minor actinides (mainly Am and Cm) and lanthanides from high level and low level waste solutions.^[8–10] Horwitz et al. have reported extensive studies of distribution coefficients for Am, lanthanides, Y, alkaline earths, and transition and post transition element cations on TODGA and TEHDGA.^[7] While it has been reported that the distribution coefficients of actinium are typically lower than those of lanthanum and cerium,^[11] our literature review failed to yield quantitative experimental data on the extraction of Ac(III) on DGA resins. In this work we have studied the weight distribution ratios of Ac(III) on TODGA and TEHDGA resins in nitric acid and hydrochloric acid, respectively. Consequently, an improved method for the separation of Ac(III) from Ra(II) could be implemented into the routine process for the production of clinical-grade Ac-225 for targeted alpha therapy.

EXPERIMENTAL

Materials

Extraction chromatographic resins commercially available from Eichrom Technologies, Inc., as DGA Resin, normal (TODGA), and DGA Resin, branched (TEHDGA) were used as purchased without further purification. Nitric and hydrochloric acid solutions were prepared from suprapur grade reagents (Merck) and deionized water obtained from a Milli-Q water purification system. ²²⁵Ra and ²²⁵Ac tracers were obtained by radiochemical separation from Th-229.

Radiometric Measurements

Gamma spectra were measured using a high resolution HpGe detector connected to a 92X spectrum master multi-channel analyzer (EG&G Ortec). For quantification of Ac-225 activity, sample aliquots were left for approx. 1 hour until a radiochemical equilibrium with the daughter nuclide Fr-221 was reached, and the gamma emission of Fr-221 (218 KeV, 11.6% emission probability) was measured.

Measurements of Weight Distribution Ratios in Batch Experiment

The uptake of Ac(III) by TODGA and TEHDGA resins from acidic solutions was measured by contacting a known volume of the solution (1 ml) spiked with an ²²⁵Ac radiotracer with a weighed amount of resin (10 mg, 50–100 μ m particle size). All experiments were performed at room

temperature ($21 \pm 2^\circ\text{C}$). The mixing of the resin and the aqueous phase was performed using a vortex mixer to keep the resin suspended in the aqueous phase. For all batch experiments the solutions were equilibrated for 4h, subsequently filtered through a membrane filter with $0.45\text{-}\mu\text{m}$ pore size to remove any resin particles, and analyzed for Ac-225 concentration. The values of D_w were calculated according to the equation:

$$D_w = \frac{(A_i - A_{eq}) V}{A_{eq} m} \quad (1)$$

where A_i and A_{eq} denote the actinium concentration of the initial solution and at equilibrium, respectively, V is the volume (ml) of the solution, and m (g) is the mass of the resin. The weight distribution ratios D_w measured on TODGA and TEHDGA resin can be converted to the number of free column volumes to peak maximum, k' (the resin capacity factor) as described in.^[7] Taking into account the volumes of the stationary phase (extractant) and the mobile phase for slurry packed columns on DGA resins, k' is calculated by multiplying D_w with 0.57 (TODGA) and 0.58 (TEHDGA), respectively, according to the equation:

$$k' = D_w^* 0.57 (\text{for TODGA}) \quad (2)$$

Column Separations of Ac-225 from Ra-225

Column chromatographic experiments were performed with wet-packed columns of the DGA resins. The resins were left overnight in 0.1 M HNO_3

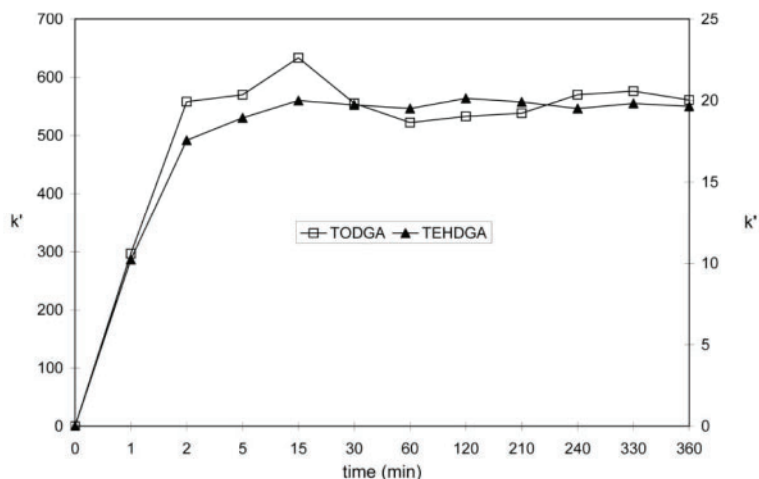


Figure 2. k' for Ac(III) vs. equilibration time on TODGA (left Y-axis) and TEHDGA resin (right Y-axis) (both $50\text{--}100\text{ }\mu\text{m}$ particle size) in 0.5 M HNO_3 at $21 \pm 2^\circ\text{C}$.

for pre-equilibration. The wet resins were packed into plastic columns (Bio-Rad), making up bed volumes of 1.0 ml and were then preconditioned with 5 bed volumes of the desired load solution (4 M HNO_3).

RESULTS AND DISCUSSION

Measurement of Distribution Coefficients

The results of the kinetic study for the extraction of actinium(III) on TODGA and TEHDGA resin from 0.5 M HNO_3 are shown in Fig. 2. For both resins an equilibrium was reached rapidly within less than 15 minutes. Equilibration times at higher acid concentrations did not differ significantly (data not shown).

Figures 3 and 4 show the uptake of Ac(III) on TODGA and TEHDGA resins from HNO_3 and HCl solutions in comparison with literature data for Ce.^[7] The k' values for Ac(III) for both DGA resins are summarized in Table 1. Uncertainties are given as standard deviations of 3 measurements. As expected for neutral extractants, the uptake of Ac(III) by TODGA and TEHDGA is lower from HCl than from HNO_3 . In the nitric acid media the maximum k' value on the TODGA resin was determined as $2,22 \times 10^3 \pm 79$ (2 M HNO_3), while in hydrochloric acid k' did not exceed

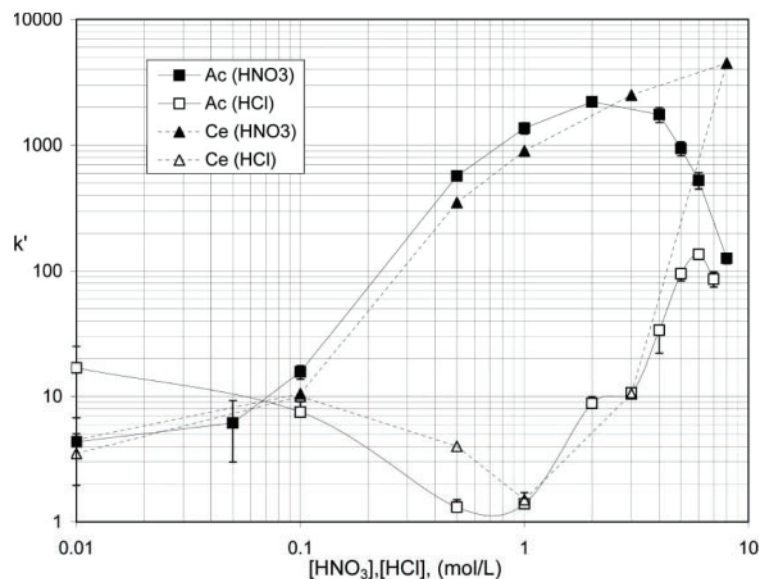


Figure 3. k' for Ac(III) on TODGA resin (50–100 μm particle size) vs. HNO_3 and HCl concentration at $21 \pm 2^\circ\text{C}$, 4 h equilibration time, compared with k' values for Ce(III) from.^[7]

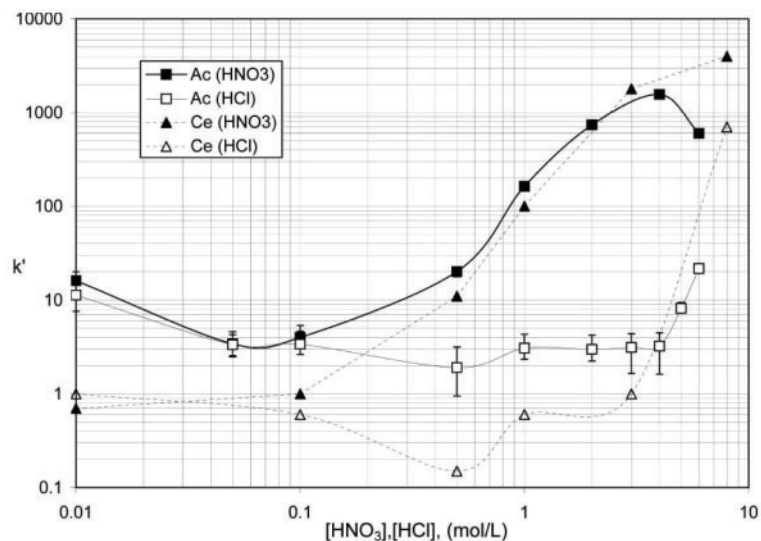


Figure 4. k' for Ac(III) on TEHDGA resin (50–100 μm particle size) vs. HNO_3 and HCl concentration at $21 \pm 2^\circ\text{C}$, 4 h equilibration time, compared with k' values for Ce(III) from.^[7]

136 ± 13 (6 M HCl). For the TEHDGA resin a similar trend in the uptake of Ac(III) as a function of acidity can be observed; however, k' values are lower for TEHDGA than for TODGA over the whole range of acidities studied. The maximum k' values for Ac(III) on TEHDGA were found to be $1,57\text{e}3 \pm 1,5\text{e}2$ (4 M HNO_3) and $21,7 \pm 1,3$ (6 M HCl). In nitric acid media, the decrease of k' with decreasing acidity is more pronounced for TEHDGA, indicating the potential for more efficient stripping of Ac from TEHDGA using dilute acid. The reproducibility of data was found to decrease at acidities < 1 M. This may be due to poor wetting of the resin materials at these acid concentrations although solutions were equilibrated overnight.

Horwitz et al.^[7] report that the extraction behavior of Ac often follows that of Ce, but the uptake is typically a factor of two to three lower. However, for both the TODGA and TEHDGA resin our data show that k' values for Ac and Ce are in the same order of magnitude in dilute to half-concentrated acids, except in the TEHDGA/ HCl system, where the k' values for Ac are even higher than for Ce. The differences in the behavior of Ac and Ce are more pronounced on both resins at higher acid molarities. While k' values for Ac go through a maximum at 2 M HNO_3 on TODGA resin and at 4 M HNO_3 on TEHDGA, the extraction of Ce increases further with increasing acidities. A similar trend can be observed at higher hydrochloric acid concentrations, where k' values for Ce are orders of magnitude higher than those for Ac.

Table 1. K' values of AC(III) on TODGA and TEHDGA resins (both 50–100 μm particle size) in nitric and hydrochloric acid at $21 \pm 2^\circ\text{C}$. Uncertainties are given as standard deviations of 3 measurements

TODGA				TEHDGA			
$[\text{HNO}_3]$ (mol/l)	K'	$[\text{HCL}]$ (mol/l)	K'	$[\text{HNO}_3]$ (mol/l)	K'	$[\text{HCL}]$ (mol/l)	K'
0,01	$4,34 \pm 2,4$	0,01	$16,8 \pm 8,2$	0,01	$16,1 \pm 3,9$	0,01	$11,3 \pm 3,7$
0,05	$6,13 \pm 3,1$	0,1	$7,49 \pm 1,6$	0,05	$3,41 \pm 0,8$	0,05	$3,35 \pm 0,9$
0,1	$15,6 \pm 1,9$	0,5	$1,31 \pm 0,2$	0,1	$4,00 \pm 1,4$	0,1	$3,38 \pm 0,4$
0,5	569 ± 39	1	$1,40 \pm 0,3$	0,5	$20,1 \pm 2,4$	0,5	$1,90 \pm 0,9$
1	$1,37\text{e}3 \pm 1,4\text{e}2$	2	$8,80 \pm 1,2$	1	163 ± 16	1	$3,06 \pm 0,7$
2	$2,22\text{e}3 \pm 79$	3	$10,7 \pm 0,9$	2	740 ± 72	2	$2,98 \pm 0,7$
4	$1,75\text{e}3 \pm 2,4\text{e}2$	4	$33,8 \pm 2,4$	4	$157\text{e}3 \pm 1,5\text{e}2$	3	$3,13 \pm 1,5$
5	$943 \pm 1,2\text{e}2$	5	$95,1 \pm 2,5$	6	600 ± 56	4	$3,23 \pm 1,6$
6	525 ± 78	6	136 ± 13			5	$8,16 \pm 0,3$
8	126 ± 12	8	$86,4 \pm 12$			6	$21,7 \pm 1,3$

Development of Improved Ra/Ac Separation using TEHDGA

A typical chromatogram of the previously reported method for the Ra/Ac separation based on the use of RE resin is shown in Fig. 5. The radium/actinium eluate from the prior anion exchange step used to remove Th-229 (Fig. 1) is loaded on a UTEVA/RE column cascade in 4 M HNO₃. The UTEVA resin retains residual traces of thorium while the radium and the actinium are not extracted on UTEVA. Ra(II) is also not retained on the RE resin and can be washed through the column using 4 M HNO₃. Although Ac(III) is extracted on the RE resin, an increasing breakthrough can be observed after washing with approx. 15 bed volumes. This can be problematic in particular when the Ra/Ac load solution from the prior anion exchange separation step contains high amounts of organic impurities from the radiolytic degradation of the organic anion exchange material and extensive washing is required. The quantitative elution of Ac(III) from Re resin requires up to 10 bed volumes of 0.05 M HNO₃. Consequently, an evaporation and concentration step is required before the final Ac(III) product can be loaded on an Ac-225/Bi-213 generator from 4 M HNO₃ as described in.^[6]

Following the measurements of Ac(III) uptake on TODGA and TEHDGA, both resins were tested for robust and effective radium/actinium separation. The chromatograms obtained on both resins are shown in Figs. 6 and 7. As described in,^[7] Ra(II) is not retained on either resin. Both resins

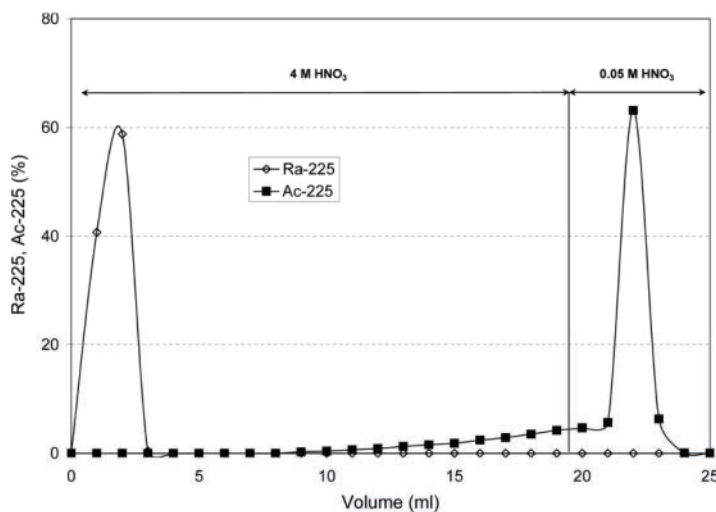


Figure 5. Typical chromatogram for the separation of Ra-225/Ac-225 on RE-resin (total column volume 1 ml). After loading Ra-225/Ac-225 in 2 ml 4 M HNO₃, the column is washed with 4 M HNO₃ to remove Ra(II) and other impurities. Washing steps have to be carefully controlled to avoid breakthrough of Ac(III). Ac(III) is stripped using 0.05 M HNO₃.

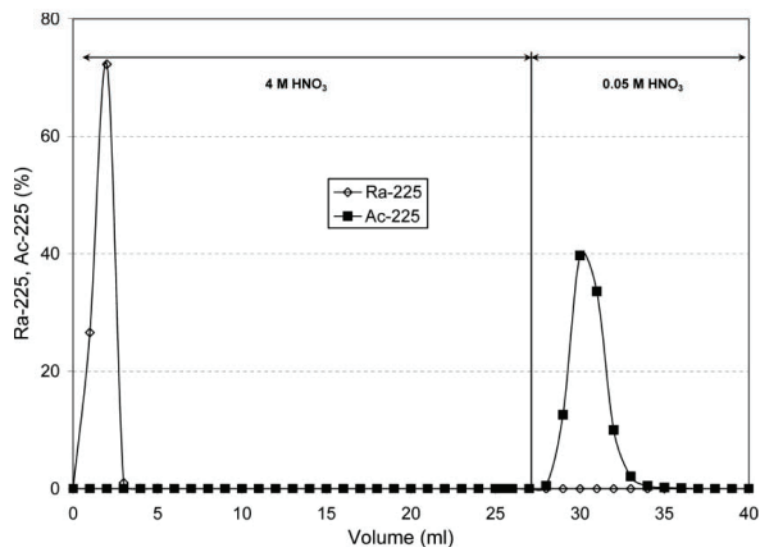


Figure 6. Typical chromatogram for the separation of Ra-225/Ac-225 on TODGA resin (total column volume 1 ml). After loading Ra-225/Ac-225 in 2 ml 4 M HNO₃, the column is washed with 4 M HNO₃ to remove Ra(II) and other impurities. Ac(III) is stripped in 5 bed volumes 0.05 M HNO₃.

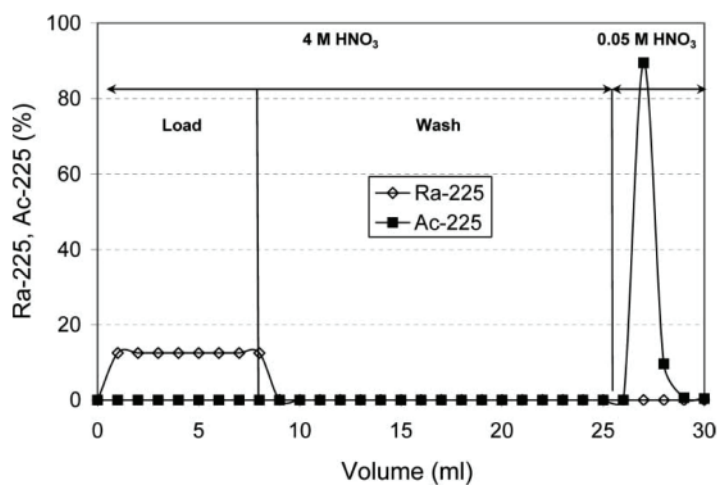


Figure 7. Typical chromatogram for the separation of Ra-225/Ac-225 on TEHDGA resin (total column volume 1 ml). After loading Ra-225/Ac-225 in 8 ml 4 M HNO₃, the column is washed with 4 M HNO₃ to remove Ra(II) and other impurities. Ac(III) is stripped in 2 bed volumes 0.05 M HNO₃.

show excellent retention of Ac(III) from 4 M HNO₃ even after extensive washing. However, as expected from the differences of the k' values in dilute nitric acid, the stripping of Ac(III) using 0.05 M HNO₃ was found to be more effective from the TEHDGA resin than from the TODGA resin. Five bed volumes of 0.05 M HNO₃ were required to strip >98% of Ac(III) from the TODGA resin, similar to the results reported in^[7] using 0.1 M HCl. However, >99% of Ac(III) could be stripped from the TEHDGA resin in only 2 bed volumes. Following acidification to 4 M HNO₃, the Ac(III) eluate from the TEHDGA resin can therefore be directly loaded onto an Ac-225/Bi-213 radionuclide generator (maximum loading volume 3 ml^[6]), making an additional concentration step obsolete and saving the time and the radiation dose for the operators. The use of a corrosive hydrochloric acid for stripping of Ac(III) as described in^[7] can be avoided, allowing the implementation of the separation method in a glove-box environment designed for the production of clinical grade Ac(III).

CONCLUSIONS

The extraction chromatographic resin TEHDGA offers a new possibility for rapid, robust, and effective separation of actinium from radium. The resin shows a strong retention of Ac(III) from half-concentrated nitric acid and efficient stripping of Ac(III) in dilute nitric acid. It is particularly useful for the rapid separation of high activity levels of the alpha emitter Ac-225 from Ra-225 for application in targeted therapy of cancer and infectious diseases. Consequently, the use of TEHDGA was implemented into the routine procedure used at ITU for the production of Ac-225/Bi-213 radionuclide generators.

REFERENCES

1. Jurcic, J.G.; Larson, S.M.; Sgouros, G.; et al. Targeted alpha particle immunotherapy for myeloid leukaemia. *Blood* **2002**, *100* (4), 1233–1239.
2. Allen, B.J.; Raja, C.; Rizvi, S.; et al. Intralesional targeted alpha therapy for metastatic melanoma. *Cancer Biol. Ther.* **2005**, *4* (12), 1318–1324.
3. Bloechel, S.; Beck, R.; Seidl, C.; et al. Fractionated locoregional low-dose radio-immunotherapy improves survival in a mouse model of diffuse type gastric cancer using a ²¹³Bi-conjugated monoclonal antibody. *Clin. Cancer Res.* **2005**, *11*, 7070–7074.
4. Dadachova, E.; Patel, M.; Toussi, S.; et al. Targeted killing of virally infected cells by radiolabeled antibodies to viral proteins. *PLoS Med* **2006**, *3* (10), e427. DOI: 10.1371/journal.pmed.0030427.
5. Kneifel, S.; Cordier, D.; Good, S.; et al. Local targeting of malignant gliomas by the diffusible peptidic vector DOTAGA-substance P. *Clin Cancer Res.* **2006**, *12*, 3843–50.

6. Apostolidis, C.; Molinet, R.; Rasmussen, G.; Morgenstern, A. Production of Ac-225 from Th-229 for targeted α therapy. *Anal. Chem.* **2005**, 77 (19), 6288–6291.
7. Horwitz, E.P.; McAlister, D.R.; Bond, A.H.; Barrans, R.E.; Jr. Novel extraction of chromatographic resins based on tetraalkyldiglycolamides: characterization and potential applications. *Solv. Extr. Ion Exch.* **2005**, 23, 319–344.
8. Hoshi, H.; Wei, Y.-Z.; Kumagai, M.; Asakura, T.; Morita, Y. Group separation of trivalent minor actinides and lanthanides by TODGA extraction chromatography for radioactive waste management. *J. Alloys Compd.* **2004**, 374, 451–455.
9. Nave, S.; Modolo, G.; Madic, C.; Testard, F. Aggregation properties of *N,N,N',N'*-tetraoctyl-3-oxapentanediamide (TODGA) in n-dodecane. *Solv. Extr. Ion Exch.* **2004**, 22 (4), 527–551.
10. Ansari, S.A.; Pathak, P.N.; Manchanda, V.; et al. *N,N,N',N'*-tetraoctyl diglycolamide (TODGA): a promising extractant for actinide-partitioning from high-level waste (HLW). *Solv. Extr. Ion Exch.* **2005**, 23, 463–479.
11. Eberle, S.H. Liquid-liquid extraction from aqueous solution. In *Gmelin Handbook of Inorganic Chemistry, Ac, Suppl, vol. 1*; Kugler, H.K. and Keller, C. (eds); Springer Verlag: Berlin, 1981, 239–264.