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Separation of cyclotron-produced ^{44}Sc from a natural calcium target using a dipentyl pentylphosphonate functionalized extraction resin

H.F. Valdovinos [a,*], R. Hernandez [a], T.E. Barnhart [a], S. Graves [a], W. Cai [a,b,c], R.J. Nickles [a]

[a] Medical Physics Department, University of Wisconsin–Madison, Madison, WI, USA
[b] Department of Radiology, University of Wisconsin–Madison, WI, USA
[c] University of Wisconsin Carbone Cancer Center, Madison, WI, USA

HIGHLIGHTS

- Cyclotron-produced ^{44}Sc is loaded into 50 mg of UTEVA resin after dissolution of 300 mg of ^{nat}Ca target in concentrated HCl.
- 80 ± 4% of the activity at end of bombardment (EoB) is eluted using 400 μL of deionized water in < 20 min after EoB.
- The separation factor of the bulk calcium is 1.2×10^4.
- ^{44}Sc has reactivities or effective specific activities with DOTA and DTPA of 18.1 ± 6.7 and 49 ± 37 GBq/μmol, respectively.
- Metal impurities in the isolated ^{44}Sc are: Ca (2.1 mM), Fe (93 μM), Zn (72 μM), Ni (29 μM), Al (6.4 μM) and Mn (2.0 μM).

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ABSTRACT

Significant interest in ^{44}Sc as a radioactive synthon to label small molecules for positron emission tomography (PET) imaging has been recently observed. Despite the efforts of several research groups, the ideal ^{44}Sc production and separation method remains elusive. Herein, we propose a novel separation method to obtain ^{44}Sc from the proton irradiation of calcium targets based on extraction chromatography, which promises to greatly simplify current production methodologies. Using the commercially available Uranium and Tetravalent Actinides (UTEVA) extraction resin we were able to rapidly (< 20 min) recover > 80% of the activity generated at end of bombardment (EoB) in small ~1 M HCl fractions (400 μL). The chemical purity of the ^{44}Sc eluates was evaluated through chelation with DOTA and DTPA, and by trace metal analysis using microwave induced plasma atomic emission spectrometry. The distribution coefficients (K_d) of Sc(III) and Ca(II) in UTEVA were determined in HCl medium in a range of concentrations from zero to 12.1 M. The ^{44}Sc obtained with our method proved to be suitable for the direct labeling of small biomolecules for PET imaging, with excellent specific activities and radiochemical purity.

1. Introduction

Due to its favorable nuclear properties and amenable chemistry, ^{44}Sc ($t_{1/2}$ = 3.927 h, 94.3% β^+, E_{max} = 1474 keV)[1] has been recently recognized as a radiometal holding great potential for PET applications. In spite of this, only a handful of small molecules have been radiolabeled with ^{44}Sc, and even less tested in a preclinical setting (Hernandez et al., 2014; Koumarianou et al., 2012; Koumarianou et al., 2011; Muller et al., 2013; Pruszynski et al., 2012). This is a result of the non-optimal current production and separation methods, which have limited the broad availability of this isotope. Currently, ^{44}Sc can be produced from a ^{44}Ti/^{44}Sc generator (Filosofov et al., 2010) and from biomedical cyclotrons via the ^{44}Ca(p,n)^{44}Sc route (Hoehr et al., 2014; Krajewski et al., 2013; Muller et al., 2013; Severin et al., 2012a; Severin et al., 2012b). However, several issues plague these methodologies. For instance, the difficult production of the parent isotope (^{44}Ti) together with the required extensive post-elution purification of the ^{44}Sc eluate, limit the applicability of generator-based ^{44}Sc (Pruszynski et al., 2010). On the other hand, cyclotron production provides a more efficient method to produce significantly larger ^{44}Sc activities. Nevertheless, a simple yet efficient separation method to isolate ^{44}Sc from the irradiated calcium target remains inexistent. In this study, we describe a novel separation

* Corresponding author.
E-mail address: hvaldovinos@wisc.edu (H.F. Valdovinos).

[1] All nuclear physics data in this report come from UC Berkeley's *Table of the Isotopes* and were accessed via http://ie.lbl.gov/education/isotopes.htm.

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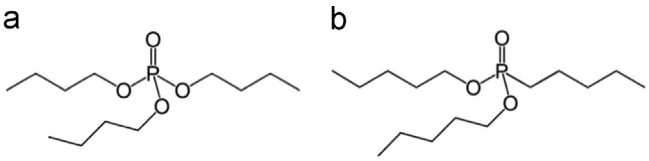

Fig. 1. (a) Tri-n-butylphosphate (TBP) and (b) Dipentyl pentylphosphonate (DP[PP]), the active extractant in the UTEVA resin.

method to obtain ^{44}Sc from irradiated natural calcium targets using extraction chromatography.

Tri-n-butylphosphate (TBP), shown in Fig. 1a, is one of the most common organophosphorus extractants, for which extensive data on distribution coefficients of most metals is available (Braun and Ghersini, 1975). Based on this data the separation of Sc(III) from bulk calcium can be effectively achieved in a TBP–HCl extraction system, since Sc(III) and Ca(II) have more than 1000-fold difference in distribution coefficients when the concentration of the acid is $\geq$9 M. Hence, given the striking structural similarities between TBP and dipentyl pentylphosphonate (DP[PP]), shown in Fig. 1b, we hypothesized that separation of radioactive scandium from calcium could be achieved using UTEVA, a commercially available resin functionalized with DP[PP].

Herein, we report the successful production and facile UTEVA-based separation of ^{44}Sc from proton irradiated natural calcium targets with excellent yield and chemical purity, in a chemical form amenable for radiolabeling. Additionally, we determined the distribution coefficients of Sc(III) and Ca(II) between UTEVA and HCl to confirm the optimal conditions for their separation. We compare this novel and simple separation method with those from (Krajewski et al., 2013; Muller et al., 2013; Severin et al., 2012a, 2012b), which are based on the difference in binding affinity of scandium and calcium to the chelating resin Chelex 100, the difference in their distribution coefficients in the extraction resin *N,N,N′,N′*-tetra-*n*-octyldiglycolamide (DGA), their difference in solubility, and their difference in distribution coefficients in a hydroxamate-functionalized resin, respectively.

Finally, we believe that the implementation of our simple purification method promise to greatly simplify the cyclotron production of radioactive scandium using metallic calcium targets and allow for its readily automation.

2. Materials and methods

Optima grade HCl comes from Aristar Ultra, VWR, West Chester, PA. Natural calcium (^{nat}Ca, 99.99%) in dendritic chunks comes from Sigma-Aldrich, St. Louis MO. UTEVA (100–150 μm) resin comes from Eichrom, Lisle IL. The cyclic chelating ligand1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) was purchased from Macrocyclics, Dallas TX. The acyclic chelating ligand diethylenetriamine pentaacetic acid (DTPA) was purchased from Acros Organics, Geel, Belgium. Sodium acetate (NaOAc) was purchased from Fisher Scientific, Pittsburg PA. Both chelating ligands and NaOAc were dissolved in 18 MΩ-cm deionized (DI) water and mixed with Chelex 100 from Sigma-Aldrich for trace metal purification. Scandium foil (99.9%) was purchased from Alfa Aesar, Ward Hill MA. A 50 ppm multi-element standard for calibration and Agilent's 4200 Microwave Plasma Atomic Emission Spectroscopy (MP-AES) system come from Agilent Technologies, Santa Clara CA.

2.1. Cyclotron targetry and irradiations

The target system is very similar to that described in (Severin et al., 2012a). Briefly, 312 ± 19 mg (n=11) of ^{nat}Ca were pressed with a hydraulic press at >400 kg/cm^2 into an annular ring of 1.26 cm^2, 2.2 mm deep made of aluminum. A 0.56 mm thick silver disk in direct contact with the pressed calcium separated it from water-jet cooling applied on the backside. A 25 μm molybdenum foil was placed over the irradiated face of the target to protect the cyclotron from vaporized calcium. Irradiations were performed on the UW-Madison PETtrace cyclotron using 16 MeV protons for 1 h with an average current of 25 μA.

2.2. Target yields, separation yields and radionuclidic contaminants

^{44}Sc activities for separation yield quantification were measured with a Capintec CRC-15 (Capintec, Ramsey NJ) dose calibrator using the calibration setting 938 suggested by the manufacturer. However, the actual activity from ^{44}Sc and other radionuclidic impurities was measured from the gamma intensities of 50 μL samples placed at distances with known efficiency calibration from a 60 cm^3 high purity germanium (HPGe) detector (Canberra C1519) (FWHM=2.7 keV @1333 keV). Gamma-ray spectrum analysis software package, Maestro-32 MCA Emulator (Ortec, Oak Ridge TN), was used to collect and analyze the gamma-ray spectra. The gamma lines used to determine yields are listed in Table 1. The dead time was always kept below 10% and the acquisition time was set so that the statistical uncertainty from the number of counts per peak was kept below 1%, except for the 373 keV peak from ^{43}Sc, for which the statistical uncertainty was 3%. From the accurate activity value of ^{44}Sc it was confirmed that the Capintec measurement was within 10% of the HPGe result, thus this reading was used for the quantification of the separation yields.

Theoretical activity yields at saturation for ^{43}Sc, ^{44}Sc and ^{44m}Sc at EoB were calculated using the cross-section data from (Levkovskij, 1991). However, this cross-section data was reduced by 20%, due to incorrect assessment of the excitation functions of the monitor reactions in the original publication (Takacs et al., 2002). The stopping power of protons in calcium was obtained from the SRIM software (Ziegler et al., 2013).

2.3. Radiochemical separation

The ~300 mg calcium target was pushed out of the target holder cavity into a 50 mL centrifuge tube, to which 5 to 15 mL of concentrated HCl were added to dissolve the target and maintain the H^+ concentration >9 M. This solution was then transferred manually to one of the three syringes that act as reservoirs connected to an automated module, similar to the one described in (Siikanen et al., 2012), which contains programmable dual pinch valves that control the access to the reservoirs. The module also includes two radiation detectors made in-house by encapsulating PIN photodiodes (HTV S8746-01, Hamamatsu Photonics, Japan) coupled with a CsI scintillator crystal. One detector monitors de activity in the syringe with the target solution and the other one the activity in the chromatography column. Before the activity was transferred onto the module, new syringes were connected and then filled with several milliliter of DI water to flush the tubing and remove metal impurities left from previous separations. Then, one of the reservoirs was filled with 5 mL of 10 M HCl for the washing step and another one with 400 μL of deionized water for the ^{44}Sc release step. A peristaltic pump with a flow rate of

Table 1
Gamma emissions from the scandium radioisotopes used for determining yields.

Nuclide	Gamma energies (keV)	Branching ratio
^{43}Sc	373	0.23
^{44}Sc	1157	0.999
^{44m}Sc	271	0.867
^{47}Sc	159	0.683
^{48}Sc	983.5	1.00