

A Chromatographic Method to Separate Sc(III) from Zn(II) Ions: A Step in the Purification of Sc⁴⁴ – An Isotope of Medical Interest.

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ABSTRACT

CERN MEDICIS produces radioactive isotopes by recovering the 1,4 GeV proton beam from ISOLDE before it reaches the beam dump using different types of targets behind the ISOLDE targets[1]. In the end, the isotopes are implanted on a zinc-coated gold foil. Therefore, the radioisotope of interest needs to be separated from the zinc coating on which it is implanted. The goal of this project was to develop an ion-exchange chromatography method to separate scandium (III) ions from zinc (II) ions. Four different resins were tested as stationary phases and several concentrations of nitric acid were used as solvents, rinsing and eluting agents. Preliminary assays showed a reduction in zinc concentration from 348,7 ppm to 0,6 ppm using 70 mg of the DGA resin while maintaining a concentration of ~5,0 ppm of scandium ions in the eluate according to ICP-MS analysis. During the studentship, other short tasks were done. For example, basic laboratory equipment was procured for the lab, a literature review on ²²⁵Ra/²²⁵Ac purification was written and two scientific visits were completed: one to the Nuclear Medicine Service at CHUV Hospital (Lausanne) and one to the cyclotron facility at Bern University Hospital (Bern).

INTRODUCTION

CERN MEDICIS produces radioactive isotopes by recovering the 1,4 GeV proton beam from ISOLDE before it reaches the beam dump using different types of targets behind the ISOLDE targets. After irradiation, the sample is transported back into the extension area by a rail conveyor system. The target is placed in a shielded decay and monitoring area until the dose rate at 1 m is below 1Sv/h. When that dose rate is reached, the isotopes are extracted as a beam and mass-separated and finally implanted on a metallic foil. Therefore, the radioisotope of interest needs to be separated from the metal in which it is implanted [1].

In the production of medical isotopes, separation based on ion exchange chromatography technique is commonly used. This technique is based on the interaction between charged solute molecules and oppositely charged moieties covalently linked to a chromatography matrix. Optimal separation conditions are met when only the ions of interest strongly bind to the resin and contaminants flow directly through the column. The advantages of this technique rely on its reproducibility, selectivity and easy automation[2].

⁴⁴Sc decays by the emission of low-energy positrons ($E_{\beta^+} = 632$ keV, $I = 94,3\%$) with a half-life ($T_{1/2} = 3.97$ h) longer than most positron emitters. Moreover, Sc(III) behaves chemically similarly to therapeutic radiometals (e.g. ⁹⁰Y and ¹⁷⁷Lu) so the complexation with a DOTA-chelator results in

the same coordination sphere and similar stability constants. That is why ^{44}Sc has been proposed as an alternative for pre-therapeutic imaging and monitoring the response to radionuclide therapy[3].

^{44}Sc is produced from calcium targets or obtained through a $^{44}\text{Ti}/^{44}\text{Sc}$ generator in other facilities. However, at MEDICIS, it is produced using a Ti target, and after the mass-separation process, the scandium ions are implanted on a zinc-coated gold foil. Most recently published articles in radiochemistry propose a two-step purification of Sc(III) isotopes. First, a DGA (N,N,N',N' - tetra-n-octyldiglicolamide) or UTEVA extraction resin (composed of diamyl amylphosphonate) is used to minimize potential metal impurities coming from the target holder. Then, a second column containing DOWEX 50Wx2 or SCX cartridges is used to concentrate the Sc(III) ion. The goal of this project was to test four different resin - including both DGA and UTEVA resins- to separate Sc(III) from Zn(II) ions[3-4].

EQUIPMENT PROCURED FOR THE LABORATORY

Currently, there are no radiochemistry procedures being done at MEDICIS. There is, however, a small lab (Thermolab, 3-1/033) where cold experiments are carried out in order to optimize the separation parameters and allow the radiochemists to perform the procedures with more confidence and precision. As part of the studentship, the items listed in Table 1 were procured using CERN' s electronic document handling (EDH) system.

Table 1. Equipment procured for the radiochemistry laboratory.

EQUIPMENT	MODEL/ SPECIFICATIONS	SUPPLIER
1. Peristaltic pump	Ismatec REGLO Digital 4CHNL 8RLR 115/230 ISM834C	Cole Parmer
2. Peristaltic pump tubing	3-STP PVC SOLVA 1.30 MM 12 PK SC0294	Cole Parmer
3. pH meter	Hanna Instruments HI98103 15 mm x 40 mm x 55 mm Electrode S7	Fisher Scientific
4. pH determination strips	GE Healthcare pH 1-12	Fisher Scientific
5. 3 mL Syringes	Thermo Scientific 1X100 Luer Slip Plastic	Fisher Scientific
6. Analytical balance	Fisher Brand 210 g/0,1 mg internal calibration	Fisher Scientific
7. Micropipette kit	10, 100 and 1000 μL micropipette Fisherbrand	Fisher Scientific
8. DGA resin	DGA Resin, Branched, 50-100 μm (10 grams bottle)	Triskem International
9. Columns	Empty columns 2 ml kit (100 pack)	Triskem International
10. Column funnels	Extension funnels 25ml	Triskem International
11. Column tips	Columns Tip closures (x 100)	Triskem International
12. 2 way valves	Flow valve (pack of 12) polycarbonate	Triskem International
13. Glass wool	8 μm	Fisher Scientific
14. Zinc determination strips	QUANTOFIX Zinc 0-100 mg/L	Macherey-Nagel

SCANDIUM (III)– ZINC (II) SEPARATION

MATERIALS

Artificial target solution

An aqueous mixture of 5 ppm of Sc(III) and 350 ppm of Zn(II) ions in HNO₃ 8 M was used as a starting target solution.

Concentrated acids are usually used to dissolve rapidly and quantitatively metallic targets. The use of nitric acid is due to the observations made by Alliot and collaborators [5]. In their studies of the DGA resin, they demonstrated that Zn(II), Fe(III) and Sc(III) ions exhibit strong and similar behaviour in HCl medium, thus it is not an appropriate solvent to separate these elements. Additional experiments showed that Sc(III) was strongly absorbed over a wide HNO₃ concentration range, while Zn(II) and Fe(III) remained in the aqueous solution. A concentration of 8 M HNO₃ was considered appropriate since similar concentrations have been reported for the conditioning of the resins used.

Resins

70 mg of the following resins were tested for the separation of Sc(III) from Zn(II):

Resin	Size	Supplier
DGA (resin A)	50–100 µm	Triskem International, France
UTEVA (resin B)	100–150 µm	Eichrom, Lisle IL, United States
TRU - B (resin C)	100–150 µm	Triskem International, France
DN- B (resin D)	100–150 µm	Triskem International, France

ASSAY #1

The protocol used in this assay was adapted from previous separation protocols performed at MEDICIS and from scandium separation methods reported in the literature [2–6]. The set-up for the assay is illustrated in Figure 1. The goal of this first assay was to identify which resin or resins were more efficient for the separation of scandium from zinc ions.

All of the resins were hydrated with DM water and introduced into the 2 mL columns. Afterwards, they were conditioned with 4 mL HNO₃ 8 M. The artificial target solution was loaded to the column and the average flow rate was measured to be 0,3 mL/min. The feedthrough fraction was collected in a flask labelled as “feedthrough” .

The columns were rinsed with 5 mL of HNO₃ 2 M. These fractions were collected in a flask labelled as “waste” . 2 mL of DM water was tested as eluting agent for all of the resins. These fractions were collected in a flask labelled as “elution” .

ICP-MS (inductively-coupled mass spectrometry) analysis were performed to each of the collected samples in order to determine the concentration of zinc and scandium ions. The results of the analysis are presented in Table 2.

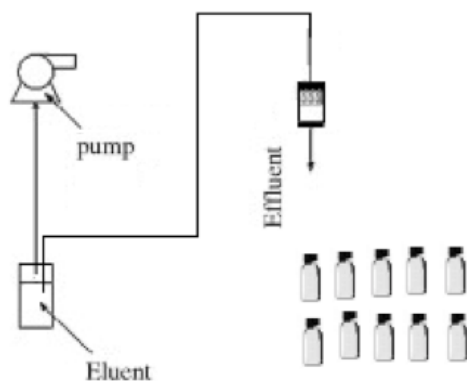


Figure 1. Diagram (left) and picture (right) of the set-up for the chromatographic assay

Table 2. ICP-MS results of the samples collected from the first separation assay (corrected by dilution factor).

Samples	⁶⁶ Zn ppm ±0,1 ppm	⁶⁸ Zn ppm ±0,1 ppm	⁴⁵ Sc ppm ±0,1 ppm
Stock solution	170,1	175,7	5,0
Feedthrough A	65,9	65,9	<0,1
Feedthrough B	66,6	66,1	0,3
Feedthrough C	97,1	96,7	1,1
Feedthrough D	94,2	145,6	2,4
Waste A	88,3	97,0	<0,1
Waste B	85,2	85,0	1,4
Waste C	26,8	36,5	3,6
Waste D	31,0	28,5	2,3
Elution A	11,5	12,0	5,1
Elution B	15,3	18,3	2,9
Elution C	30,2	35,2	0,1
Elution D	40,6	0,6	0,4
HNO ₃ 4M	0,1	0,1	<0,1
DM Water	<0,1	<0,1	<0,1

Source: Andre Dziewa, HSE-CEN.

ASSAY #2

For the second separation assay, only the DGA (resin A) and UTEVA (resin B) resins were used since the best separation results from Assay #1 were obtained with these resins. However, in this assay, two changes were made to the original protocol: (1) the separation was performed twice in order to reduce the zinc concentration in the eluate even further and (2) the nitric acid concentration for the washing procedure was changed to 5M for the UTEVA resin in order to promote a better retention of scandium ions. The results are presented in Table 3.

Table 3. ICP–MS results of the samples collected from the second separation assay (corrected by dilution factor).

Resin	Samples	⁶⁶ Zn ppm ±0,1 ppm	⁶⁸ Zn ppm ±0,1 ppm	⁴⁵ Sc ppm ±0,1 ppm
DGA resin	Stock solution	178,6	170,1	5,4
	Feed Through 1	36,8	22,2	<0,1
	Waste 1	140,9	145,7	<0,1
	Feedthrough 2	0,4	0,4	<0,1
	Waste 2	<0,1	<0,1	<0,1
	Elution	0,3	0,3	5,6
UTEVA resin	Stock solution	178,6	170,1	5,4
	Feedthrough 1	35,2	29,7	0,2
	Waste 1	126,8	126,5	1,3
	Feedthrough 2	15,0	12,5	0,1
	Waste 2	0,4	0,4	1,1
	Elution	0,3	0,3	2,8

Source: Andre Dziewa, HSE–CEN.

The results presented in Tables 2 and 3, and Figure 2 suggest that DGA resin is the best resin for the separation of scandium (III) from zinc (II) ions. The DGA resin trapped more than 90% of the total scandium ions present in the stock solution. Besides, by performing the separation assay twice the percentage of removed zinc increased from 93% to more than 99%. The efficiency of the UTEVA resin in trapping scandium ions was not improved in this second assay.

As it was mentioned in the introduction, a second column containing DOWEX 50Wx2 or SCX cartridges could be tested to further concentrate the Sc(III) ions.

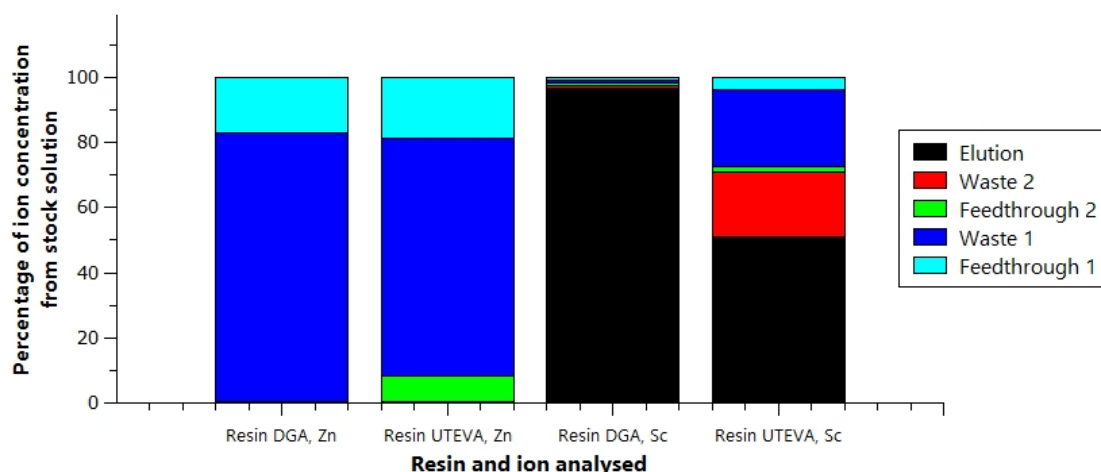


Figure 2. Stack Column Graph depicting the relative zinc and scandium ion concentrations of each fraction.

At CERN, it takes 1–2 weeks to get the results from ICP–MS analysis. It would be useful to consider a faster and cheaper method to analyse the zinc ion concentrations in samples for the development of the separation protocols. During the studentship, the use of zinc determination strips (eg. QUANTOFIX Zn strips from Macherey Nagel®) was proposed for future projects.

LITERATURE REVIEW

Alpha particle emitting radionuclides are rapidly becoming of greater interest for short range and site-specific therapy of cancers and micrometastatic disease. ^{225}Ac is an alpha particle emitting radionuclide with a 10,0 day half-life. It yields several daughter radionuclides in its decay scheme and four alpha particle emissions. Therefore, actinium could serve as an in vivo generator of alpha particle emitting radionuclides. A literature review of radium–actinium separation was conducted in order to explore the theoretical feasibility of a $^{225}\text{Ra}/^{225}\text{Ac}$ generator. A solvent extraction method using TTA (thenoyltrifluoroacetone) and TBP (tributylphosphate) seemed most promising [7–9].

SCIENTIFIC VISITS

During the internship, two visits were made: one to the Nuclear Medicine Service at CHUV Hospital (Lausanne) and one to the cyclotron facility at Bern University Hospital (Bern). During the visit to Bern, it was helpful to notice that the group used a CdZnTe detector to analyse the isotopes produced at the solid target (Figure 3).

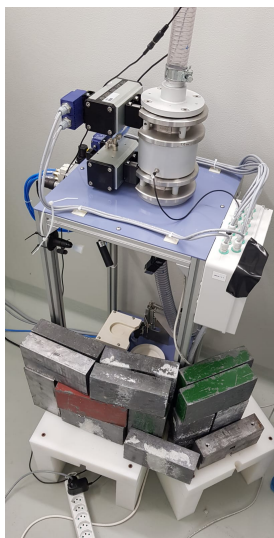


Figure 3. Shielded configuration where the solid target shuttle is received and analysed remotely with a CdZnTe detector.

CONCLUSIONS AND RECOMMENDATIONS

A chromatographic method yielding >99% efficiency in zinc removal and >90% efficiency in scandium trapping was developed using a DGA resin (50–100 μm) and different nitric acid concentrations for loading, washing and elution procedures.

A second column containing DOWEX 50Wx2 or SCX cartridges could be tested to further concentrate the Sc(III) ions. Once the entire protocol has been optimized and the target scandium and zinc ion concentrations are reached, the protocol should be discussed with the colleagues from Radiation Protection Department in order to get approval for hot experiments at MEDICIS.

At CERN, it takes 1–2 weeks to get the results from ICP–MS analysis. It would be useful to consider a faster and cheaper method to analyse the zinc ion concentrations in samples for the development of the separation protocols. During the studentship, the use of zinc determination strips (eg. QUANTOFIX Zn strips from Macherey Nagel®) was proposed for future projects.

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