Rapid Communication

The thermal release of scandium from titanium metal – a simple way to produce pure [44]Sc for PET application

By D. Wittwer[1,2,*], R. Dressler[2], R. Eichler[1,2], H. W. Gäggeler[1,2], D. Piguet[2], A. Serov[1,2], A. Türler[1,2] and A. Vögele[2]

[1] Department of Chemistry and Biochemistry, University of Bern, 3012 Bern, Switzerland
[2] Laboratory of Radiochemistry and Environmental Chemistry, Paul Scherrer Institute, 5232 Villigen, Switzerland

Summary. The radionuclide-generator based access to radiopharmaceutical isotopes represents a valuable alternative to directly produced isotopes at particle accelerators or nuclear reactors. The [44]Ti based generator is of increasing interest for the delivery of PET-radiopharmaceutical isotopes used for imaging. The product of this generator [44]Sc represents with its 3.97 h half-life and 94.3% positron branching [1] a very promising candidate for labeling PET radiopharmaceuticals. The long half-life of 58.9 ± 0.3 y [2] of the [44]Ti assures a constant and long lasting production of the daughter nuclide.

Here we present a gas phase separation method of scandium from titanium *via* thermal release in vacuum. Titanium foils were irradiated with [40]Ar to produce scandium in multi-nucleon transfer reactions. Another production reaction used was the irradiation of titanium by neutrons from the SINQ neutron source at the Paul Scherrer Institute (PSI).

The titanium metal foils containing [44m]Sc and [46]Sc were heated up for time periods of 15 and 60 min to temperatures between 900 and 1500 °C in vacuum. Thus, release properties of scandium from titanium under these conditions were studied. The released scandium was collected on tantalum foils and could be rinsed of with concentrated nitric acid resulting in carrier free scandium nitrate solutions. From the experimental results optimum release conditions are suggested.

1. Introduction

Despite the increasing number of cyclotron installations at medical centers, the delivery of radionuclides by generator systems is still considered the most convenient way to provide isotopes to medical installations located away from nuclear reactors or accelerators. Beside the most common [99]Mo/^{99m}Tc generator, several radionuclide generator systems such as the [82]Sr/[82]Rb [3] or the [68]Ge/[68]Ga [4] proved their excellent applicability. The [44]Ti/[44]Sc system gains importance, since trivalent metals are frequently discussed for labeling of radiopharmaceuticals. The ideal half-life of the [44]Sc ($T_{1/2} = 3.97$ h) permits the use of this isotope for moni-

toring slow biological processes. The big positron emission branch from [44]Sc of 94.3% [1] allows for smaller doses to be used for labeling. Moreover, the [44]Ti with a half-life of 58.9 ± 0.3 y [2] yields an almost constant [44]Sc activity over several decades.

An efficient procedure must be elaborated to gain the daughter activity with high yields and purity. The obtained product must be in a certain chemical state to be easily available for further processing, while the parent nuclide should remain completely in the radionuclide generator. Simple handling in terms of security as well as chemical and mechanical stability of the radionuclide generator systems are further important points.

Usually, [44]Ti is produced in the [45]Sc$(p, 2n)$[44]Ti reaction with a production cross-section of 63.8 mb at 20 MeV proton incidence energy (see *e.g.* TENDL-2009 library [5]). The drawback of this production method is the need for long-term irradiations with high intensity cyclotron beams due to the long half-life of the mother nucleus. An alternative way to produce the desired isotope is the irradiation of elemental titanium by neutrons following the reaction path [nat]Ti(n, xn)[44]Ti with a peak production cross-section of 24.0 ± 5.3 mb at 35.9 MeV kinetic neutron energy [5]. Even though having a lower production cross section this method is an alternative production way because larger target amounts can be irradiated for longer times. Other ways involve spallation reactions with high energy particles using for example vanadium or iron as a target. Major drawbacks of the last methods are the large activities of by-products after the required long term irradiation. Therefore, efficient chemical separation procedures of [44]Ti from other products need to be developed. Several attempts were undertaken to design [44]Ti/[44]Sc generators [6–12]. First clinical studies were performed using this kind of radionuclide generator system [13, 14]. These methods comprise liquid separation using ion exchange, liquid extraction or distillation of thionyl chloride adducts. We reevaluate here a method proposed by Alekseev *et al.* [15] to separate scandium from titanium by thermal release in vacuum. This method has the advantage of being a one step procedure that does not produce any liquid waste.

*Author for correspondence (E-mail: david.wittwer@psi.ch).

2. Materials and methods

2.1 Production of scandium in a titanium matrix *via* transfer reaction

A titanium foil (Goodfellow, 5 μm, > 99.99% purity) was irradiated with an argon beam ($^{40}Ar^{11+}$, 220 MeV, 200 nA$_{el}$) from the Philips cyclotron at Paul Scherrer Institut, Villigen, Switzerland. Multi-nucleon transfer from the titanium to the beam particles formed the desired scandium isotopes $^{43-49}Sc$ within the target.

2.2 Production of scandium in a titanium matrix *via* neutron irradiation

A titanium foil (0.5 g, similar foil as in Sect. 2.1) was irradiated with neutrons using the Production Neutron Acitvation (PNA) installation at the spallation neutron source SINQ at Paul Scherrer Institut, Switzerland. The SINQ provides also fast neutrons at a rate of about 3×10^{11} n/cm^2/s around the maximum of the excitation function of the $^{46}Ti(n, 3n)^{44}Ti$ reaction [5]. Additionally to ^{44}Ti various scandium isotopes were produced ($^{nat}Ti(n, pxn)^{43-49}Sc$), which also remain embedded in the titanium metal lattice [16].

2.3 Release by heating

To prove that the main activity of the scandium isotopes is located inside the titanium matrix the irradiated samples were immersed for 5 min in HNO$_3$ (65%) trying to dissolve all adsorbed and not implanted activities. Afterwards, the samples were washed with water and ethanol and dried. No considerable loss of scandium activity was observed. Subsequently, the titanium foil was cut into small pieces. Each piece was measured to determine the scandium content using an HPGe-γ-detector, with 2.13 keV resolution at 1.33 MeV in conjunction with an acquisition and analysis system based on standard nuclear electronics and data acquisition system (Canberra's Genie2k$^{®}$). The activities of the whole irradiated samples were typically some

100 kBq. Afterwards the metal foil was placed into a one side closed tubular tantalum crucible, see Fig. 1. The tantalum crucible was held in place by a corundum tube within the copper coil of the induction furnace (Ameritherm Inc., NovaStar$^{®}$ 3LW). The tantalum crucible was placed with the open end towards a tantalum foil which was attached on a water cooled mounting about 0.5 cm from the opening of the crucible to catch efficiently the effusing scandium activity. The closed end of the crucible pointed towards the window of the vacuum vessel. The temperature of the crucible was permanently monitored through this window *via* an infrared thermometer (Optoelektronik, Portable Radiation Thermometer, IR-AH3SU). The vessel was evacuated to a pressure of 3×10^{-4} mbar. The crucible containing the irradiated titanium samples was heated up to a defined temperature between 900 and 1420 °C and kept at this temperature for a certain time between 15 and 60 min. Afterwards, the heating was switched off and the crucible was cooled down for 15 min. The extracted titanium foil was measured again on the HPGe-γ-detector to determine the remaining scandium. This data was used to determine the relative release yield. The tantalum foil, which collected the evaporated products, was also measured on the detector to control the separation factor. Finally, this tantalum foil was washed with HCl (36%) to recover the released scandium isotopes.

3. Results and discussion

The separation of scandium from a titanium matrix by thermal release appears possible. Quantitative yields are achievable without any problems above a certain temperature. Fig. 2 shows for example the release plot of ^{46}Sc for different heating times. At temperatures around 1200 °C and heating times of 60 min an almost complete release was observed. This means no scandium activity was found in the titanium foil after the heating process above the background of the
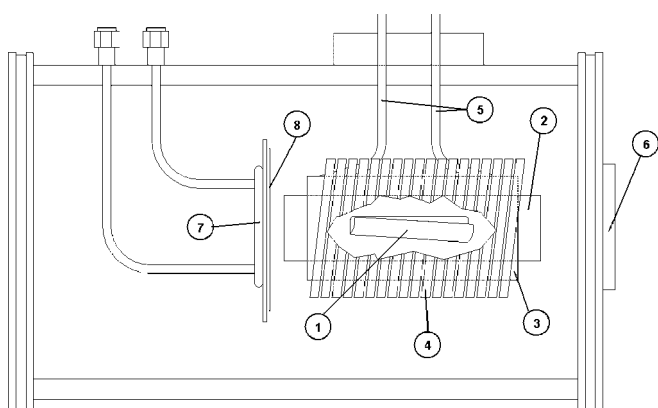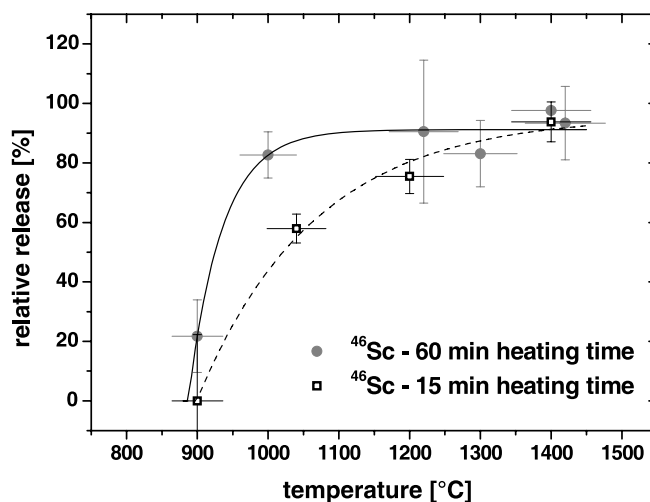

Fig. 1. Scheme of the vacuum release setup. (1) Titanium foil in a (2) tantalum crucible centered by a (3) corundum space holder which is wrapped by the (4) copper coil of the induction furnace. (5) Water cooling of the induction furnace. The closed end of the tantalum crucible points towards the (6) vacuum window to measure its temperature with the pyrometer. The open end of the tantalum crucible points towards the (7) cooled carrier holding the (8) tantalum foil to collect the released products.

Fig. 2. The relative amount of scandium released from titanium metal *vs.* the temperature at varied heating times 15 min (black open squares) and 60 min (grey points). A distinct heating time dependence and a maximum release above 1200 °C are observed. The horizontal error bars are showing the temperature uncertainty in the sample during the heating time. The vertical error bars are calculated standard uncertainties from the γ-measurements. Lines were drawn to guide the eye.

Table 1. The relative release for the different scandium isotopes from a titanium matrix.

	No.#	Temp. (°C)	^{44m}Sc (%)	^{46}Sc (%)	^{47}Sc (%)	^{48}Sc (%)
60 min	1	900 ± 36		22 ± 12		
	2	1000 ± 40		82.7 ± 7.8		
	3	1220 ± 49	98.0 ± 7.2	91 ± 24		
	4	1300 ± 52		83 ± 11		
	5	1400 ± 56	98.0 ± 2.8^a	97.60 ± 0.35^a	97.40 ± 0.12^a	98.8 ± 1.8^a
	6	1420 ± 57	95.7 ± 3.6	93 ± 12		
15 min	7	900 ± 36		$0^b \pm 22$		
	8	1040 ± 42		58 ± 4.9^a		
	9	1200 ± 48		75.5 ± 5.8		
	10	1400 ± 56		93.8 ± 6.7		

a: Neutron irradiated titanium foil with. higher activity;
b: Value lower than background.

detection system. Below 1000 °C the release of scandium decreases. Presumably, almost no release can be expected at heating temperatures below 600 °C. As seen in Fig. 2 the heating time is of minor importance at high temperatures. The lower the temperature the slower is the diffusion and the more important it is to heat for a sufficient long time to get a quantitative release [17]. For both heating times the maximum release takes place at 1200 °C. The measured release at 1220 °C and 60 min heating time (measurement 3 in Table 1) is in very good agreement with the results shown in the work of Alekseev *et al.* [15]. Due to the experimental setup shorter heating times could not be investigated, because of the slow cooling process and the hereby increased inaccuracy of the heating time. In particular the metal foil needs at least 1 min to cool down from 1420 to below 870 °C and then about 15 min from 870 to 100 °C.

The measured relative release of the different scandium isotopes from the titanium metal are compiled in Table 1. The accuracy of the data does not allow for the observation of isotopic effects. All errors for the relative release are given as standard uncertainty values from counting statistics. This explains the smaller errors of the measurements No. 5 and 7, which were done using neutron irradiated titanium yielding a much higher scandium activity compared to those produced by the cyclotron irradiation. The temperature errors are representing the temperature interval in which the experiment took place.

If the initial distribution of the products is known and the speed of the diffusion is the most relevant factor for the release, diffusion coefficients may be determined from the release rates [18, 19]. Unfortunately, there is no easy way to determine the distribution of the scandium activity in the foils. A more or less even distribution of the scandium activity in the titanium can be assumed due to the selected production paths of the scandium activity in our experiments. However, Matzke [20] suggested in his work that, if the relative release yield is larger than 0.3 (30%) and the concentration of the products on the surface is zero, diffusion coefficients may be calculated even without the exact knowledge of the distribution function. He postulates that during the heating process a distribution is formed that is less dependent on the initial distribution but more dependent on the principal condition of zero concentration at the sur-

face. For high release rates as for measurements No. 2–9 of Table 1, a homogeneous initial distribution may be assumed,

$$F = 1 - \frac{8}{\pi^2} \exp\left(-\frac{Dt}{d^2}\right) \tag{1}$$

(where F is the relative release, D the diffusion coefficient, t the heating time, and d the thickness of the foil) and diffusion coefficients of $(4.56 \pm 0.81) \times 10^{-9}$ and $(2.68 \pm 0.78) \times 10^{-9}$ cm^2/s were determined for measurement No. 8 (1040 °C) and No. 2 (1000 °C) respectively. These data are in agreement with data from [17], showing diffusion coefficients of scandium in titanium as 5.37×10^{-9} cm^2/s for 1021 °C and 4.51×10^{-9} cm^2/s for 997 °C.

Finally, the investigation of the collected scandium sample, using an inductively coupled plasma-optical emission spectroscopy device (ICP-OES), revealed a Ti transfer of less than 10^{-6} from the initial mass of the heated Ti-matrix to the final sample. This is a upper limit which can be decreased easily by optimizing the process and the handling procedures.

4. Conclusion

Generally, a possibility was detailed for the clean and efficient separation of carrier-free scandium from titanium metal. The investigated approach might be applicable for the separation of ^{44}Sc from a ^{44}Ti/^{44}Sc generator system for radiopharmaceutical use. This method favors the production path using neutron irradiated metallic ^{nat}Ti-foil. The ^{nat}Ti can just be stored until all unwanted Ti-isotopes decay ($T_{1/2}$ of ^{45}Ti is about 3 h) and can subsequently be heated up for the first time to remove the unwanted Sc contaminations. A release temperature of > 1000 °C at a heating time ≥ 15 min is required. This release procedure can be optimized using permanent heating of the Ti and installing a retractable sampling device in front of the opening of the release crucible. A crucial requirement for a long term use of metallic Ti in this release procedure is gas pressure well below 10^{-6} mbar preventing the embrittlement of the material and its partial oxidation. A simultaneously operated replaceable permanently hot titanium getter with a large surface would keep the oxygen, nitrogen as well as the water partial pressure

within the release structure sufficiently low for a stable long term operation.

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