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Liquid-liquid extraction in flow of the radioisotope titanium-45 for positron emission tomography applications†

Kristina Søborg Pedersen,[a,b§] Joseph Imbrogno[b§], Jesper Fonslet,[a] Marcella Lusardi[c], Klavs F. Jensen[b,c]*, and Fedor Zhuravlev[a]*

A continuous liquid-liquid extraction of ^{nat}Ti and its PET radioisotope ^{45}Ti into an organic phase from 12 M HCl is described. The extraction is completely selective with respect to Sc, which is commonly used as a cyclotron target for ^{45}Ti production. A membrane-based separator with integrated pressure control allowed for efficient, reproducible, and robust aqueous/organic phase separation in flow. Optimization studies established a guaiacol-anisole 9/1 (v/v) mixture and a flow rate ratio of 1/3 (aq. to org.), with a residence time of 13.7 s as the optimal extraction conditions. 90.3 ± 1.1% of ^{nat}Ti were consistently extracted from a 0.01 M solution of $^{nat}TiCl_4$ and $ScCl_3$, while 84.8 ± 2.4% of ^{45}Ti were extracted from 0.03-0.13 M $ScCl_3$ containing picomolar amounts of ^{45}Ti radionuclide, without extracting any Sc for either system. The organic phase can be directly used for ^{45}Ti-radiolabelling as demonstrated by the efficient radiosynthesis of the ^{45}Ti-radiolabeled antineoplastic [^{45}Ti](salan)Ti(dipic). This development opens a pathway to perform a continuous and efficient ^{45}Ti recovery and processing using an automated micro or millifluidics setup.

1 Introduction

Over the past several decades positron emission tomography (PET) has become a medical modality providing the best diagnostic options for cancer available today.[1] PET radiopharmaceuticals based on radiometals are gaining increasing popularity due to their ability to probe biological processes occurring on timescales from hours to days.[2] Convenient chelation chemistry and ready availability via the ^{68}Ge generator currently make ^{68}Ga radiometal the most popular choice for radiolabelling of peptides and antibody fragments.[3] ^{45}Ti is emerging as a promising PET radiometal due to its 85.7% positron branch, negligible secondary radiation, and facile production.[4] The 3-hour half-life of ^{45}Ti compares favorably with that of ^{68}Ga (68 min) and can allow for longer transport distances. Furthermore, the sharper PET images of ^{45}Ti due to its lower β^+ endpoint energy (1.04 MeV for ^{45}Ti vs. 1.90 MeV for ^{68}Ga) can be especially advantageous for a small-animal PET. A number of small molecule ^{45}Ti compounds were previously synthesized and used for PET imaging[5–7] and radiotracing.[8] Our research efforts are directed towards increasing the adoption of the ^{45}Ti PET by developing efficient ^{45}Ti recovery procedures and water-compatible chelation chemistry.

The bombardment of naturally monoisotopic scandium with low energy protons from a medical cyclotron via the ^{nat}Sc*(p,n)*^{45}Ti nuclear reaction is an attractive ^{45}Ti production route.[9–11] Recovery of a radiometal is the first post-production step, which for a highly hydrolyzable metal such as Ti, becomes critical. Currently, the solid phase extraction from acidic solutions onto a cation or anion-exchange resin is the predominant way to separate the ^{45}Ti from its Sc matrix. We and others previously used the PEG-functionalized diol,[8] cation-exchange[5–7] and hydroxamate[12] resins. With the recent advances and availability of automation, there is a strong drive to implement advanced chemical separation techniques compatible with micro and millifluidics.

One of these techniques is liquid-liquid extraction (LLE). In recent years LLE in micro-scale flow has received increasing attention[13]. Continuous extraction has been successfully demonstrated in rectangular microreactors[14], three-phase microfluidic chip[15], porous capillary[16], and capillary membrane-based devices[17] In the area of radiopharmaceutical production and research, LLE is underdeveloped since up until now LLE was primarily performed manually, entailing significant radiation exposure to personnel. Due to recent developments in flow chemistry, LLE can now be carried out continuously by exploiting the high mass transfer of slug flow followed by complete phase separation utilizing the wettability of polymer membranes.[18] This system has been used for multi-stage counter-current LLE of small organics and solvents,[19] solvent exchange and purification during continuous pharmaceutical synthesis,[20,21] and quantum dot purification.[22] In this work, LLE followed by a single stage of membrane-based phase separation was utilized to purify both non-radioactive and radioactive Ti from Sc metal continuously. This process does not require any manual operation after initial setup and therefore is highly applicable to radioactive systems, like the one described here.

The membrane separators used herein have been published for various applications, but are briefly described here.[18,19,22] The membrane separator module consists of two main components: a polymer microfiltration (MF) membrane and a thin plastic diaphragm (Fig. 1).

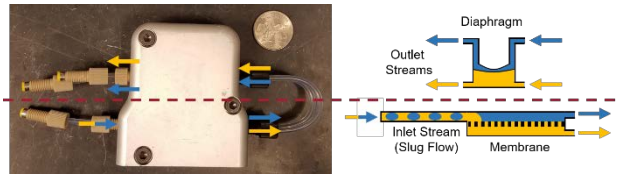

Fig. 1. Schematic diagram showing flow paths of membrane separator alongside a photograph of an actual separator. The aqueous phase is shown in blue (retained phase) and the organic phase is shown in yellow (permeated phase). U.S. quarter is shown for scale

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† Electronic Supplementary Information (ESI) available: Separator material optimization and solvent selection.

The diaphragm, a thin, chemically compatible perfluoroalkoxy alkane (PFA) polymer, acts to modulate the pressure between the aqueous and organic sides of the membrane. Various diaphragm thicknesses allow one to control the pressure the diaphragm exerts on the system, known as P_{dia}. The upper and lower bounds for operating this system while achieving complete phase separation correspond to the capillary, P_{cap}, and permeation pressures, P_{perm}, respectively. A more accurate model for the upper and lower pressure bounds that accounts for the pore size distribution and the tortuosity has been recently published.[23]

The interfacial tension between the two phases is also critically important since it cannot be varied without chemical additives or changing solvents. It is essential to stay within the operating range of the system; otherwise incomplete phase separation will occur. The capillary and permeation pressures are only the theoretical upper and lower limits, respectively, of the system; therefore it is important to note that the actual operating range where complete separation will occur usually exists in a smaller region when using a real system. Therefore, after the radioisotope of interest is selectively extracted into one of the phases (organic or aqueous), the membrane separator will completely separate the two phases, and the radioisotope-enriched phase can be used directly for downstream radiolabelling. By combining two or more membrane separators, multiple LLEs can be easily carried out in series, such as extraction into the organic phase and back-extraction into the aqueous phase.

In this contribution, we describe the use of a single membrane separator for the facile purification of the radioisotope ^{45}Ti in flow directly after production with a total system residence time less than 1 min and a residence time of ≤ 15 s for the LLE mixing step. To demonstrate that the extracted ^{45}Ti can be used directly for radiolabelling after the LLE in flow, we performed a radiosynthesis of [^{45}Ti](salan)Ti(dipic), an anti-tumour compound previously used for ^{45}Ti-radiotracing.[8]

2 Experimental

2.1 Materials

Guaiacol, anisole (99%), 1-octanol (99%), titanium (IV) chloride (neat), titanium (IV) chloride solution (0.09 M in 20% HCl), hydrochloric acid (37%), sulfuric acid (95.0-98.0%), and pyridine-2,6-dicarboxylic acid (dipic) (98%) 1,2-decandiol (98%), 2,3-napthalene diol (98%) , α,α,α-trifluorotoluene (99%), 1,1,1,3,3,3-hexafluoropropanol (99 %), 1*H*,1*H*,2*H*,2*H*-perfluoro-1-octanol were purchased from Sigma Aldrich and used without further purification. TLC plates (Silica gel on TLC Al foil) were also purchased from Sigma Aldrich. Scandium (III) chloride (anhydrous, 99.9%) and scandium foil (250 µm, 99.9% pure, rare earth analysis) were purchased from Alfa Aesar. Custom Ti and Sc ICP standards were purchased from Inorganic Ventures (100 ppm of each metal in a 5% HCl solution). Salan[24] and (salan)Ti(dipic)[25] were synthesized according to the literature procedures. The membrane separator module was similar to those manufactured by Zaiput Flow Technologies. Pall PTFE membranes were used for all experiments (47 mm diameter, 0.1/0.2/0.5 µm pore size, polypropylene (PP) support for the 0.1/0.2 µm pore sizes). PFA diaphragms (0.001”/0.002”/0.005” (0.0254/0.0508/0.1270 mm)) were purchased from McMaster Carr. All PFA tubing (1/16” OD, 0.03” ID) was purchased from Idex Health and Science. PTFE static mixers were purchased from Stamixco. The 15 mL plastic centrifuge tubes with screw caps were purchased from VWR.

2.2 Instrumentation

The solutions for the continuous membrane-based separation were pumped using either the KDS 100 Legacy Syringe (radioactive experiments) or the Harvard Apparatus PHD 2000 Programmable and Infusion syringe pumps (non-radioactive experiments). The NMR spectra were taken on Agilent 400 MR operating at 400.445 MHz (^{1}H). The radioactivities were measured on the CRC-55tR, CII Capintec, Inc. dose calibrator. Radio-TLC was performed with a Raytest MiniGita TLC scanner using chloroform /ethyl acetate (1/1, v/v) as a mobile phase. The HPLC and radio-HPLC analyses were performed on a Hitachi Chromaster equipped with a Carrol&Ramsey 105-S radio-detector and a Hitachi 5430 double diode array detector. Column: Phenomenex Luna 3µ C18(2) (100 Å, 100 mm × 2.00 mm). Flow: 0.5 mL/min. Eluents: (A) 0.1% (v/v) CF_3COOH in Milli-Q water, (B) 0.1% (v/v) CF_3COOH in CH_3CN. The radiochemical identity of [^{45}Ti](salan)Ti(dipic) was established by comparing its retention time with that of its natural abundance isotopomer. The radiochemical conversion (RCC) was determined by radio-HPLC or radio-TLC and calculated as: RCC = ($Area_{product}$/Total Area) * 100%.

The extent of extraction (Extraction % in Fig. 4-5) was determined relative to titanium initially present in the aqueous phase (100%*$[Ti]_{(org)}$ / $[Ti]_{(aq)}$) using inductively coupled plasma atomic emission spectroscopy (ICP-AES, Agilent 5100 Dual View) of the aqueous phase. Samples of the aqueous phase were collected before the LLE and after 5, 15, 30, and 45 minutes of LLE. 0.35 mL of each sample was digested in 5 mL with 10 % (v/v) H_2SO_4 for 6 hours at 160 °C. 2.7 mL of the digested sample was diluted up to 10 mL with Milli-Q water to reach a total acid concentration of 5 % (v/v). Calibration standards (Inorganic Ventures) were prepared to match the sample matrix with concentrations of 22.2, 18, 15, 10, and 5 ppm Ti and Sc and run prior to every set of samples. Samples were analyzed in radial view at a viewing height of 8 mm. Because organic solutions are not directly amenable to the ICP analysis, the extraction to the organic phase was calculated from the concentration of Ti and Sc in the aqueous phase ($C^{Ti,Sc}$) before and after the LLE by $E = ((C^{Ti,Sc}_{\text{before LLE}} - C^{Ti,Sc}_{\text{after LLE}})/C^{Ti,Sc}_{\text{before LLE}}) \cdot 100$ %.

2.3 Radiochemistry

^{45}Ti was produced by 10-20 µA proton irradiation of 30-60 mg scandium foil, for 5-15 min using a GE PETtrace cyclotron. To

minimize coproduction of the ^{44}Ti (half-life = 60.0 years), a 500 µm thick aluminium foil was used to degrade the incidental 16 MeV beam to approximately 13 MeV. The ^{45}Ti-loaded foils were dissolved in 3 mL 12 M HCl, and the reaction mixture was filtered through a glass frit and further diluted with 12 M HCl to a total of 10-20 mL. The radioisotope ^{45}Ti was extracted from its HCl solution into the organic phase using either shaking/spinning (batch) or slug flow (continuous) procedures. The organic phase was separated and mixed with a 0.06 M solution of salan and dipic in pyridine. The solution was stirred at 60°C for 15 min to complete the formation of [^{45}Ti](salan)Ti(dipic) and then analyzed.

2.4 Batch LLE and separation

For the non-radioactive work, 0.5 mL 0.01 M $TiCl_4$ and 0.01 M $ScCl_3$ in 37 % HCl was mixed with 1.5 mL guaiacol/anisole, 9/1 (v/v), and shaken for 2 minutes in a centrifuge tube. The phases were allowed to separate by gravity. The concentration of Ti and Sc in the aqueous phase before and after the LLE was measured by ICP-AES.

For the ^{45}Ti work, a centrifuge tube was charged with 2 mL of the solution of ^{45}Ti (10-50 MBq) in 37% HCl and 2 mL of the organic phase. The mixture was shaken vigorously, spun for 15 minutes, and centrifuged at 4000 rpm to separate the phases. Then, the radioactivity in each phase was measured.

2.5 Continuous membrane-based LLE and separation

The LLE and phase separation in flow were performed using a membrane-based separator with a PFA diaphragm for integrated pressure control (with this design, the transmembrane pressure is intrinsically linked with the back-pressure applied by the diaphragm). A flow schematic of the experimental setup is shown (Fig. 2). The two phases passed

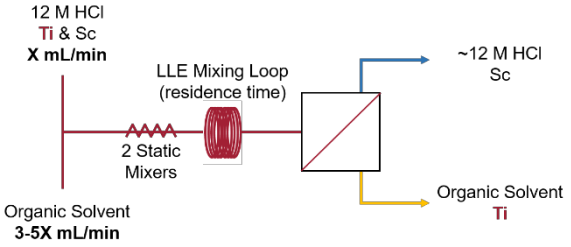


Fig. 2. Schematic of the setup used for continuous phase separation. The aqueous and the organic phases were combined through a tee and mixed with two static mixers and mixing tubing. The aqueous phase was retained by the membrane, while the organic phase permeated through the membrane. Ti was selectively extracted over Sc into the organic phase.

through PFA tubing (1/16" OD, 0.03" ID) and were mixed in a PEEK tee, followed by two 10 element PTFE static mixers (3.4 cm total length, placed inside of a short length of 1/8" OD, 1/16" ID PFA tubing) and various lengths of PFA mixing tubing, which were used to control the residence time of the LLE. After the static mixers, steady slug flow was developed and passed through the LLE mixing loop and finally into the membrane separator, where the organic phase permeated the membrane while the aqueous phase was retained. Different diaphragm thicknesses, membranes, and flow rates were tuned to achieve complete separation of the aqueous and organic phases.

3 Results and discussion

3.1 LLE in batch mode: preliminary experiments

Several practical considerations merit emphasis at the outset. In radiochemistry, ^{45}Ti is obtained as a strongly acidic solution after digestion of the cyclotron-irradiated Sc foil in concentrated HCl. High acidity is necessary because when [H^+] < 11 M the titanium speciation diagram becomes populated by titanyl species,[26] unusable for radiolabelling. Such a high acidity limits the choice of extractants and diluents to non-basic compounds. The oxophilicity of titanium further narrows it down to O-donors, such as alcohols, diols, and phenols, and certain organic acids. Finally, high acid concentration increases the phase miscibility and lowers the interfacial tension, making phase separation potentially more complicated.[26] Our preliminary screening experiments were performed in batch using gravity separation and were inspired by a report claiming that ^{45}Ti can be extracted from aqueous HCl into 1-octanol, presumably as [^{45}Ti]Ti *n*-octyloxide [**1**] (Fig. 3).[27]

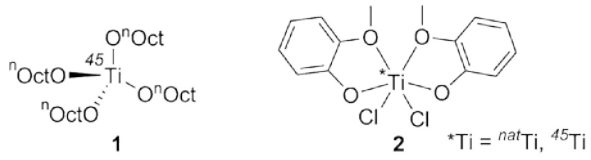


Fig. 3. The putative Ti species extracted in 1-octanol (**1**) and guaiacol (**2**).

Table 1. Liquid-liquid batch extraction of ^{45}Ti from cyclotron-irradiated Sc foil digested in 37% HCl, except entry 1[a]. EE is the extraction efficiency, EE = 100% * $A_{(org)}$ / $A_{(org+aq)}$, where $A_{(org)}$ *and* $A_{(org+aq)}$ is the activity of ^{45}Ti in the organic and organic + aqueous layers, correspondingly, as measured by a radiation detector

Entry	Extraction system (organic phase)	EE(%)
1	1-octanol, neat[a]	4
2	1-octanol, neat	47
3	1,2-Decanediol, 0.1M in 1-octanol	54
4	2,3-naphthalene diol, 0.1 M in 1-octanol	52
5	$C_{10}F_{21}CH_2CH(OH)CH_2OH$[b]	< 0.1
6	Guaiacol, neat	75

[a]20% HCl; [b]trifluorotoluene/hexafluoropropanol (1/1, v/v)

We observed little extraction when a solution of ^{45}Ti in 20% HCl was used (Table 1, entry 1). Using 37% HCl (12 M) significantly improved the extraction. 1,2-Decanediol used as co-extractant as a 0.1 M solution in 1-octanol gave only a slight improvement over neat 1-octanol. 2,3-naphthalene diol, reported to extract Ti at pH=4,[28] showed similarly modest performance. (Table 1, entries 3 and 4). During these batch extractions, we noticed a significant increase in the volume of the 1-octanol phase suggestive of conc. HCl migrating into the organic phase. In an attempt to improve the phase separation we turned to perfluorinated extractants.[29] Disappointingly, the

fluorous analog of 1-octanol, $CF_3(CF_2)_5CH_2CH_2OH$ formed an emulsion. A 0.05 M solution of $C_{10}F_{21}CH_2CH(OH)CH_2OH$ in trifluorotoluene / hexafluoropropanol (1/1, v/v) failed to extract any ^{45}Ti. (Table 1, entry 5). Previously, it was reported that guaiacol (o-methoxyphenol) easily forms a moisture-sensitive but isolable complex cis-[$TiCl_2(\eta^2$-guaiacolato$)_2$] with titanium tetrachloride.[30] Gratifyingly, using neat guaiacol as an extractant, we were able to extract 75% of activity into the organic phase, presumably as [**2**] (Fig. 3). Next, we translated the batch experiments into fully continuous flow experiments.

3.2 LLE of ^{nat}Ti in flow: system optimization

In order to find the optimum extraction conditions, the diaphragm thickness, membrane pore size, organic phase composition, flow rate ratios, and residence times were varied. Once the optimal materials and conditions were determined, a study was conducted to determine the shortest residence time, thereby minimizing the dead volume and overall processing time, while still maintaining high extraction. The residence time was varied by varying the length of the mixing tubing after the static mixers while maintaining a constant flow rate. All systems were operated for 60 min each and samples were collected every 15 min.

Complete separation requires both the diaphragm thickness and membrane pore size to be chosen so that P_{dia} lies between the P_{cap} and P_{perm} pressures. In general, low interfacial tension mixtures often require smaller pore size membranes and thinner diaphragms. In these experiments, polytetrafluoroethylene (PTFE) membranes were tested using the following pore sizes 0.1, 0.2, and 0.5 µm. Three different diaphragm film thicknesses were also tested: 0.001", 0.002", and 0.005" (0.025 mm, 0.051 mm, and 0.127 mm).

Since guaiacol had shown the most selective and highest extraction efficiency for Ti over Sc in batch, it was chosen as a candidate for translation into flow. A solution of 0.01 M $TiCl_4$ and 0.01 M $ScCl_3$ in 37% HCl was extracted into guaiacol using the membrane separator. Occasional retention and/or breakthrough of the aqueous into the organic phase was observed with a 0.2 µm PTFE/PP membrane, 0.002" diaphragm thickness, and 0.2 mL/min total flow rate. The situation was remedied by adding various amounts of anisole, which is structurally similar to guaiacol but acted to increase the interfacial tension. The COSMO-RS calculations[31] showed that the interfacial tension is expected to increase linearly with the increase in the volume fraction of anisole (Figure S1, see the ESI†). These organic mixtures were used to extract Ti, (0.01 M) from 37% HCl at a total flow rate of 0.20 mL/min and aqueous to organic flow rate ratios of 1/5, 1/3, and 1/1 (v/v). Corresponding flow rates and extraction performance are shown in Table S1, see the ESI†. To determine the scalability of the process, the total flow rate was then increased five-fold. Therefore, a total flow rate of 1.00 mL/min was used, while maintaining the same flow rate ratios and residence times.

The separation results for both 1-octanol and 1/1 guaiacol/anisole using different membranes and diaphragm thicknesses are shown in Table S2, see the ESI†. Although the guaiacol/anisole mixture performed much better than 1-octanol, its extraction efficiency was not high enough. Therefore, the ratio of guaiacol to anisole was varied as well, as summarized in Table 2. After an optimal system was developed, the residence time of mixing was varied to minimize the dead volume and decrease the total amount of time spent in the system. This was achieved by increasing or decreasing the length of the PTFE tubing used for mixing. The following lengths were tested with their corresponding residence times at 0.20 mL/min: 10 cm (13.7 s), 25 cm (34.2 s), 54 cm (73.9 s), 108 cm (147.8 s), 216 cm (295.6 s).

Table 2. Phase separation performance for different guaiacol to anisole ratios in the organic phase using different aqueous to organic flow rate ratios.

Org. Phase Guaiacol/Anisole (v/v)	Aq. Flow Rate [mL/min]	Org. Flow Rate [mL/min]	Performance [-]
Aqueous Phase: 37% HCl (12 M) 0.2 µm PTFE membrane and 0.002" Diaphragm thickness			
10/90	0.10	0.10	Complete Sep.
75/25	0.05	0.15	Complete Sep.
	0.10	0.10	
	0.10	0.30	
	0.25	0.75	
90/10	0.03	0.17	Complete Sep.
	0.05	0.15	
	0.25	0.75	
95/05	0.10	0.10	Retention/ Breakthrough

3.3 Optimization of Continuous LLE and Phase Separation in Flow Using Non-Radioactive Metals

Due to the harsh nature of both the aqueous and organic solvents used for this extraction, both the membrane and diaphragm had to be extremely stable. Therefore, PTFE membranes were used for all experiments described herein. Since a 0.2 µm membrane and a 0.002" diaphragm was the only combination that led to complete phase separation, it was used for all of the optimization experiments.

The composition of the organic phase needed to both selectively extract only Ti and have a high enough interfacial tension with the HCl phase that complete separation could be achieved. It was determined that extraction was directly correlated with guaiacol concentration, that is a higher guaiacol concentration led to higher extraction up to a maximum Ti extraction of 90% with 90% guaiacol. Guaiacol concentrations above 90% led to incomplete phase separation. A summary of the phase separation performance using various organic phase compositions is shown in Table 2.

In addition to the composition of the organic phase, the relative ratios of aqueous to organic flow rates were also varied. When comparing relative flow rate ratios of 1/1, 1/3, and 1/5 (v/v) (aq. to org.) it was determined that 1/1 gave the lowest extraction. A ratio of 1/3 gave a higher extraction, but 1/5 did not yield a further increase in performance (see Table S1, ESI†). All ratios where the aqueous flow rate was higher led to lower extraction efficiency. Therefore, a flow rate ratio of 1/3 was chosen as to avoid using excess solvent.

In order to determine the scalability and stability of the extraction, the total flow rates were scaled five-fold to a total flow rate of 1.00 mL/min, while maintaining the same flow rate ratios and residence times. The extraction performance was identical to the original scale, and the maximum extraction of 90% was still achieved at 90% guaiacol and a flow rate ratio of 1/3 (Fig. 4).

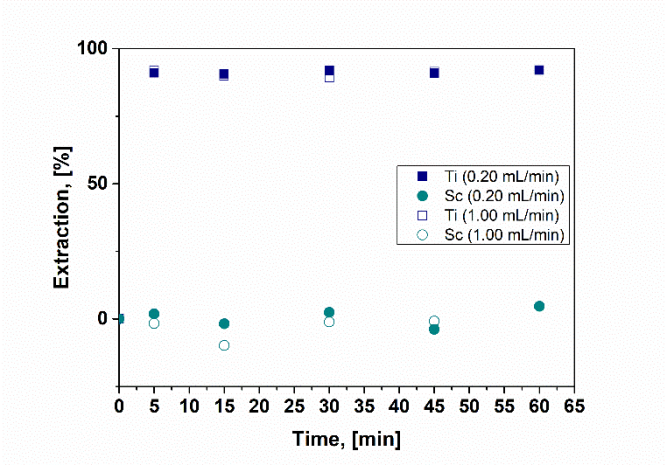


Fig. 4. Extraction performance over time for a total flow rate of 0.20 mL/min (solid symbols) and for a five-fold scale-up at a 1.00 mL/min (open symbols). These data show the ability for facile scale-up of the system.

The total production time is a critical parameter in this system since the radioactive Ti is continuously undergoing decay back to Sc ($t_{1/2}$=3 hours). Therefore, the shortest residence time is desirable. Residence times of the mixing tubing were varied from 13.7 s up to ~5 min. The extraction efficiency was the same for all residence times. Therefore the shortest residence time was the most optimal (Fig. 5). This performance is due to the enhanced uniform mixing imparted by t-mixing, helical static mixing, and segmented flow, which allows for the equilibrium stage to be reached quickly. Overall, an organic phase consisting of 90% guaiacol 10% anisole, total flow rates of 0.20 or 1.00 mL/min, an aqueous to organic flow rate ratio of 1/3, and a residence time of 13.7 s led to highest and most efficient extraction resulting in 90.3±1.1% extraction of Ti. No scandium extraction (whithin experimental error) was detected.

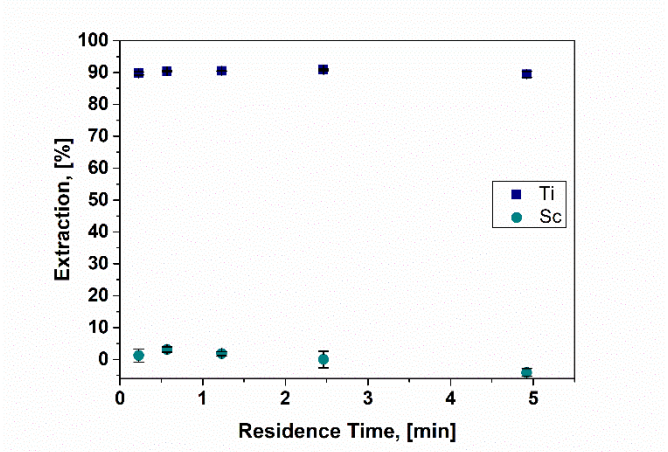


Fig. 5. Extraction performance for various different residence times (time for LLE in mixing loop from Fig. 2). The maximum Ti extraction (90%) was achieved for all residence times, down to the shortest residence time of 13.7 s.

3.4 LLE of ^{45}Ti in flow and radiosynthesis of [^{45}Ti](salan)Ti(dipic)

With the extraction conditions optimized for ^{nat}Ti, we turned to the radioactive isotopomer, ^{45}Ti. While the concentration of Sc was comparable in both non-radioactive and radioactive cases (0.01 M vs. 0.03-0.13 M correspondingly) the concentration of the radiometal in the Sc-containing matrix solution was lower than that of its natural abundance isotopomer by 10 orders of magnitude, ranging from 1 to 10 picomoles. At these concentrations, even the trace levels of impurities or water could potentially lead to side-reaction or hydrolysis and as a consequence, change the extraction efficiencies of ^{45}Ti. To our delight, the LLE of ^{45}Ti in flow using a 90% guaiacol 10% anisole mixture and a flow rate ratio of 1/3 (aq. to org.), with a residence time of 13.7 s showed that the extraction efficiency of ^{45}Ti was consistent with that of ^{nat}Ti (84.8±2.4% and 90.3±1.1% correspondingly), (Fig. 6). The ICP-AES analysis of the aqueous phase before and after the LLE confirmed that no Sc was extracted into the organic phase.

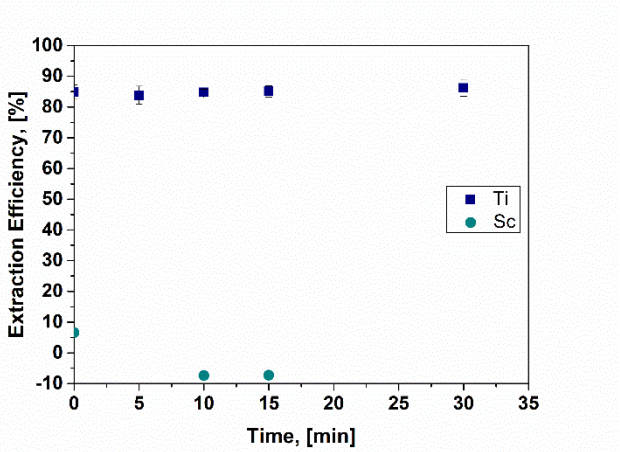
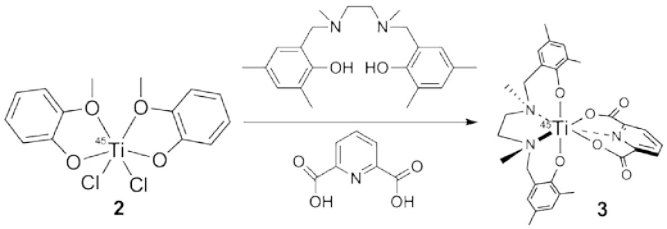


Fig. 6. Continuous LLE of ^{45}Ti at a flow rate ratio of 1/3 (aq. to org.) with 90 % guaiacol 10 % anisole. ^{45}Ti extraction efficiency calculated from the radioactivity measurements and Sc extraction calculated from ICP-AES.

Finally, to examine if the extracted solution of ^{45}Ti can be directly used for radiolabelling, we attempted a synthesis of [^{45}Ti](salan)Ti(dipic) [**3**], a Ti-antineoplastic, previously used for

animal ^{45}Ti-PET and *ex vivo* radiotracing.[8]



Scheme 1. Radiosynthesis of [^{45}Ti](salan)Ti(dipic) from ^{45}Ti extracted in the organic phase directly after LLE in flow.

To that end, the organic phase after the continuous LLE of ^{45}Ti was collected and reacted with an equimolar solution of salan and 2,6-pyridinedicarboxylic acid (dipic) in pyridine at 60°C (Scheme 1). An essentially complete (98.7%) conversion to the desired product [**3**] was observed within 15 min as evidenced by radio-TLC (red peak for the product [**3**] and only traces of unreacted [**2**], green peak), proving the high quality and reactivity of extracted ^{45}Ti (Fig. 7, inset). The HPLC/radio-HPLC further confirmed the identity of the product [**3**] matching its retention time to that of the independently synthesized non-radioactive [^{nat}Ti](salan)Ti(dipic) determined by the HPLC equipped with the UV-detector (Fig. 7).

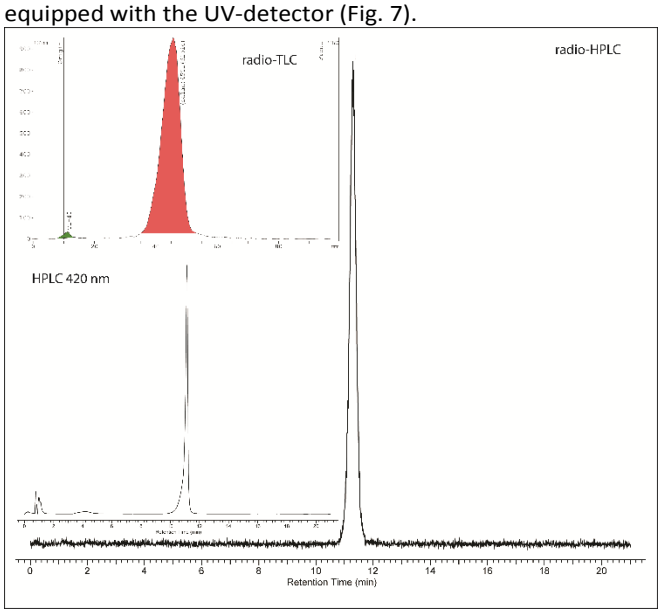


Fig. 7. Radio-HPLC of [^{45}Ti](salan)Ti(dipic), retention time= 11.3 min. Bottom: HPLC of (salan)Ti(dipic) at 420 nm, retention time= 11.2 min, insert: Radio-TLC of [^{45}Ti](salan)Ti(dipic) **3**, R_f=0.49, red peak, and **2**, baseline, green peak.

Conclusions

We have reported a selective liquid-liquid extraction of ^{nat}Ti and its PET radioisotope (^{45}Ti) into an organic phase from a solution containing various amount of Sc in 37% (12 M) HCl. A membrane-based separator with integrated pressure control allowed for continuous aqueous/organic phase separation in flow. Optimization studies established a 90% guaiacol 10% anisole mixture and a flow rate ratio of 1/3 (aq. to org.), with a residence time of 13.7 s as the optimal extraction conditions. 90.3%±1.1 of ^{nat}Ti were consistently extracted from a 0.01 M solution of $TiCl_4$ and $ScCl_3$, while 84.8±2.4% of ^{45}Ti were extracted from 0.03-0.13 M $ScCl_3$ containing picomolar amounts of the ^{45}Ti radionuclide. As a process, the LLE in flow of ^{45}Ti was reproducible and robust. Additionally, the throughput demonstrated in this work would be capable of meeting the demand in a hospital or industrial setting. The organic phase can be directly used for ^{45}Ti-radiolabelling as demonstrated by the efficient radiosynthesis of [^{45}Ti](salan)Ti(dipic) resulting in a 98.7% conversion.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Separator material optimization and solvent selection.

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