

A no-carrier-added $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator based on distillation

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Dedicated to the memory of Prof. Dr. Dr. h.c. Gerhard L. Stöcklin

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Summary. Arsenic-72 is a positron emitting isotope with promising properties for syntheses of ^{72}As -labelled radiopharmaceuticals for future application in positron emission tomography. This work describes the radiochemical separation of no-carrier-added ^{72}Se from cyclotron irradiated germanium targets and the development of a $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator, avoiding the addition of any selenium carrier. Using a vertical quartz tube device, no-carrier-added ^{72}As is nearly quantitatively released from various chloride salt solutions containing ^{72}Se within 10 min at a temperature of 100 °C in an HCl gas flow. The kinetics of the $^{72}\text{Se}/^{72}\text{As}$ isotope generator has been studied in relation to temperature, salt charge, and redox-stability. Under optimised conditions, ^{72}Se remains almost quantitatively (> 99.7%) in solution.

1. Introduction

^{72}As is a positron emitting arsenic isotope, with properties promising for possible application as ^{72}As -labelled radiopharmaceuticals. It has a positron emission rate of 88% with $E_{\beta+\text{max}} = 2.5$ MeV and $E_{\beta+\text{mean}} = 1.0$ MeV [1]. Although the positron emission decay is accompanied by photons of 834 keV (79.5%), 630 keV (7.9%), 1461 keV (1.1%) and others (< 0.5%), the long physical half-life of 26 hours may render ^{72}As as a PET radionuclide of choice for the quantitative imaging of biochemical and physiological processes with longer biological half-lives, e.g. immunoimaging and receptor mapping. In these cases, the half-life of ^{72}As may meet the radiopharmacological requirements resulting from the slower localization kinetics of the targeting vectors. The versatile chemistry of arsenic would permit the radiolabelling of a broad spectrum of potentially valuable pharmaceuticals.

The radionuclide ^{72}As can be produced directly at medium-energy cyclotrons via the $^{72}\text{Ge}(p, n)$, $^{72}\text{Ge}(d, 2n)$, $^{69}\text{Ga}(\alpha, n)$, $^{71}\text{Ga}(\alpha, 3n)$, and $^{71}\text{Ga}({}^3\text{He}, 2n)$ reactions. Indirectly, it can be produced as a daughter radionuclide of the relatively long-lived ^{72}Se ($T_{1/2} = 8.5$ d). Various ways for

the production of ^{72}Se have been described but mainly in the context of ^{73}Se production. Both deuteron- and proton-induced reactions on arsenic, and α - and ${}^3\text{He}$ -induced reactions on germanium have been investigated [2–4]. Alternatively, ^{72}Se can be obtained via proton induced spallation of RbBr [5] or other spallation processes.

Radionuclide generator systems play a key role in providing both diagnostic and therapeutic radioisotopes [6] for various applications in nuclear medicine, oncology and interventional cardiology. In particular, the application of positron emission tomography (PET) at centres lacking a cyclotron to produce the necessary radionuclides depends on the availability of biomedical PET radionuclide generators.

Fig. 1 illustrates the transient radionuclide generator kinetics for the system $^{72}\text{Se}/^{72}\text{As}$. The time where the daughter activity is maximum can be calculated to be 88.6 h. However, already after 48 h, i.e. every second day, it is theoretically possible to elute around 70% of the maximum daughter activity.

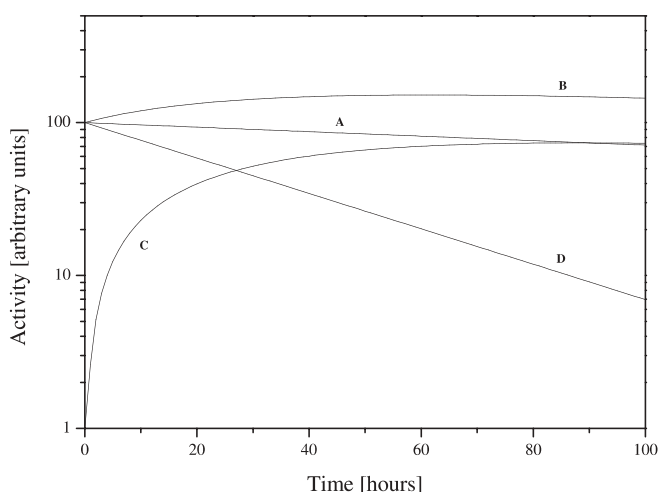


Fig. 1. Transient radionuclide generator kinetics for the system $^{72}\text{Se}/^{72}\text{As}$. A – independent activity of the parent isotope; B – growth of cumulative parent and daughter activity in a pure parent fraction; C – growth of daughter activity in a pure parent fraction; D – independent decay of the separated pure daughter fraction at maximum of generated activity.

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Several $^{72}\text{Se}/^{72}\text{As}$ generator systems have been proposed previously. Al-Kouraiishi and Boswell [7] were able to obtain ^{72}As from a coagulated form of carrier-added ^{72}Se on a Dowex 50 column in 15 ml of water. Due to the presence of selenium carrier, the separation yields were less than 70%. Electrolytic generators with ^{72}Se deposited on Pt electrodes as Cu^{72}Se have been reported [8, 9]. Another process involving addition of selenium carrier in the form of selenic acid uses the cyclic reduction of selenium to Se° and a separation of ^{72}As by filtration with subsequent oxidative dissolution of Se° using H_2O_2 prior to each separation cycle [5].

The aim of this work was to develop a $^{72}\text{Se}/^{72}\text{As}$ generator without any addition of selenium carrier. The system should be reliable for the routine separation of ^{72}As to allow investigations on syntheses of ^{72}As -labelled radiopharmaceuticals and their evaluation.

2. Materials and methods

Isotope production

^{72}Se was produced at the compact cyclotron CV28 of the Forschungszentrum Juelich *via* the $(^3\text{He}, 3n)$ nuclear reaction on natural germanium. Irradiation was done with 36 MeV ^3He -particles at a beam current of 5 μA for 12 h, giving a yield of about 185 MBq (5 mCi). To simulate the behaviour of ^{72}Se , ^{75}Se was used in some experiments, which was produced in a carrier-added (ca) form of specific activity 0.52 GBq/ μmol *via* the (n, γ) -reaction in the nuclear research reactor BERII at the HMI Berlin ($\Phi = 4.0 \times 10^{14}$ n/cm 2 s).

Analogously, to simulate the behaviour of no-carrier-added (nca) ^{72}As , ^{77}As was used, which was produced in a nca state *via* the $^{76}\text{Ge}(n, \gamma)^{77}\text{Ge}$ ($T_{1/2} = 11.30$ h) \rightarrow ^{77}As ($T_{1/2} = 1.618$ d) reaction on natural germanium at the TRIGA reactor of the Institute of Nuclear Chemistry of the University of Mainz ($\Phi = 4.0 \times 10^{12}$ n/cm 2 s).

Radiochemical separation of ^{72}Se

To isolate ^{72}Se , the irradiated 100 mg germanium targets are dissolved in 5 ml aqua regia and transferred to a two-necked flask. GeCl_4 is removed from the solution *via* distillation in an N_2 flow (10 ml/min), while conc. HCl is added continuously (10 drops per minute) at a temperature of 130 $^\circ\text{C}$. The distilled GeCl_4 is trapped in an ice-cooled flask, filled with 20% H_2SO_4 and precipitates as GeO_2 . No-carrier-added ^{72}Se as well as the already generated ^{72}As remain in the flask quantitatively. The neutron-irradiated germanium and the neutron irradiated selenium are treated analogously.

Cyclic separation of nca ^{72}As from nca ^{72}Se

For constructing the present distillative radionuclide generator system, an apparatus was adopted which has been shown to be versatile and adequate for a variety of thermochromatographic and distillative separations of generator radionuclide pairs. This apparatus, first developed to separate the positron emitter $^{94\text{m}}\text{Tc}$ from the irradiated molybdenum oxide within 25 minutes [10], was subsequently improved and used more universally for separations of the sys-

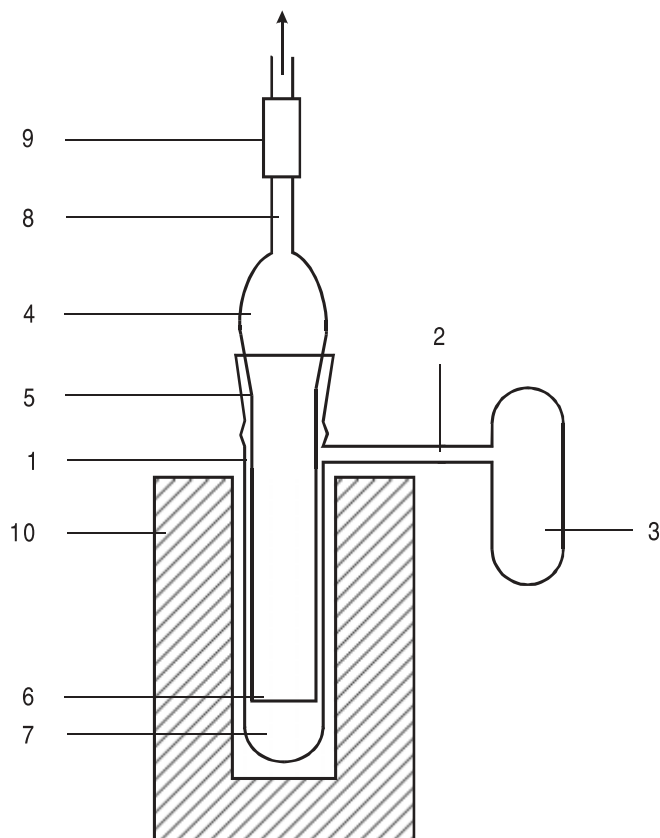


Fig. 2. Sketch of the $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator apparatus. 1 – outer quartz or glass tube; 2 – inlet of HCl; 3 – HCl vessel; 4 – inner quartz or glass tube; 5 – ground joint; 6 – open lower end of the inner tube; 7 – ^{72}Se fraction; 8 – upper end of the inner tube; 9 – adsorber; 10 – heating device, lead shielding.

tems $^{110}\text{Sn}/^{110}\text{In}$, $^{186}\text{W}/^{186}\text{Re}$, $^{188}\text{W}/^{188}\text{Re}$ [11, 12]. For a recent review on thermochromatographic separations cf. [13].

The 5 ml HCl solution containing ^{72}Se is transferred to a quartz or glass tube system as shown in Fig. 2, which is inserted vertically into a heated oil-bath. 1.0 g of a chloride salt and 1.0 ml of conc. HCl are added. The following chlorides were tested: KCl, LiCl, NaCl, AlCl_3 , CaCl_2 , NH_4Cl , BaCl_2 and hydrazine dihydrochloride. As the volume of the loaded generator is a critical parameter, the salts have not been used in equimolar amounts, but with the same mass of 1.0 g. Hydrochloric acid is passed through the inlet into the apparatus with a variable flow rate of 20–120 ml/min. The temperature at the position of the ^{72}Se fraction inside the tube can be raised up to 140 $^\circ\text{C}$. The ^{72}As is volatilised as AsCl_3 and transported with the stream of hydrochloric acid. It is adsorbed on a cartridge, containing a suitable material (*e.g.* charcoal). To determine HCl flow rates, the charcoal cartridge was substituted by a 100 ml glass-syringe.

Two types of experimental setups have been used to record the distillation kinetics of nca radioarsenic trichloride ($^{72}\text{AsCl}_3$ and $^{77}\text{AsCl}_3$). The generator glass tubes were placed at room temperature into the oil bath, which was subsequently heated up to a defined end-temperature [protocol (i)]. The radioarsenic content in the containment was measured on-line *via* γ -ray spectroscopy. For this purpose, a NaI-detector was integrated into the lead shielding, with the detector head close to the lower end of the generator. Alternatively, the generator glass tubes were placed in

a pre-heated oil-bath [protocol (ii)] at an already defined constant temperature and the distillation kinetics were measured analogously to protocol (i).

3. Results and discussion

Separation of ^{72}Se and recovery of macroscopic Ge-targets

The radiochemical procedure used to separate nca ^{72}Se (or nca ^{77}As) from irradiated natural germanium targets is based on the formation of volatile GeCl_4 which is distilled at temperatures above 130°C and precipitates in cold 20% H_2SO_4 as GeO_2 . During this procedure the nca radioselenium exists in a non-volatile oxidation state. The overall radiochemical yield of nca ^{72}Se is $90 \pm 4\%$. The germanium content of the residue is less than 1%. The $^{77}\text{Ge}/^{77}\text{As}$ separation was performed analogously with comparable ^{77}As yields.

$^{72}\text{Se}/^{72}\text{As}$ generator

The concept of the $^{72}\text{Se}/^{72}\text{As}$ isotope generator is based on the high volatility of AsCl_3 formed at temperatures above 80°C in the presence of chloride salts and HCl gas (AsCl_3 $b_p = 130^\circ\text{C}$), while selenium remains in the residue as a non-volatile complex. The selenium chloride Se_2Cl_2 ($b_p = 130^\circ\text{C}$; decomposition), having a boiling point similar to AsCl_3 is not formed under those experimental conditions. The thermal volatility of SeCl_4 ($b_p = 191^\circ\text{C}$; sublimation and almost complete dissociation to lower chlorides and chlorine in the vapour) and of oxochloride SeOCl_2 ($b_p = 177^\circ\text{C}$) is low at temperatures below 120°C . However, the stoichiometry of those selenium species might be affected by the chloride salts cations. Hexachloroselenates of type M_2SeCl_6 are known for alkali chloride salts or for other cations and compounds such as $\text{SeCl}_4 \cdot \text{AlCl}_3$, cf. Fig. 7 [14].

Fig. 3 shows the results observed while using the experimental set-up described in protocol (i). The lower group of plots shows the increase of ^{72}As in the absorber at increasing temperatures from 110°C to 140°C . The upper group shows

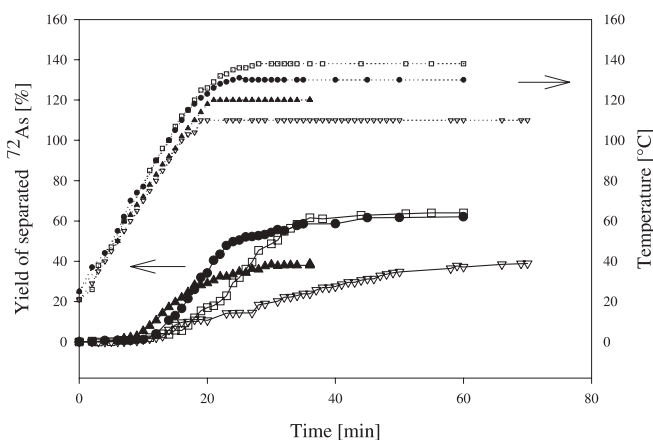


Fig. 3. Kinetics of distillative ^{72}As separation depending on the temperature; protocol (i). The lower group of graphs shows the increase of ^{72}As in the absorber (9), the upper group shows the temperature profiles in the generator flask.

the temperature profiles in the generator flask for the corresponding end temperatures from 110 to 140°C . The highest yield observed is 60% after 30 min at 140°C . At lower temperatures, such as 110°C , only 20% yield of separated ^{72}As is achievable after 40 min. This procedure can be repeated as soon as no-carrier-added ^{72}As is formed again (see also Fig. 1).

The advantage of the experimental set-up described in protocol (ii) is a significantly reduced distillation time necessary to separate the nca radioarsenic. Fig. 4 shows the results of the kinetic measurements, performed as described in protocol (ii). At a temperature of 140°C , $> 98\%$ yield was achieved already after 7 minutes. In terms of the retention of the nca radioselenium generator charge, it is, however, necessary to compromise between generator running time and temperature. At a temperature of 80°C , the maximum yield of ^{72}As of about 95% was reached after only 17 minutes, and the kinetics obviously are much slower than at higher temperatures. Fig. 5 shows the time needed for 50% and 100% ^{72}As separation yield at different temperatures. A temperature of 105°C seems to be optimum which is the inflection

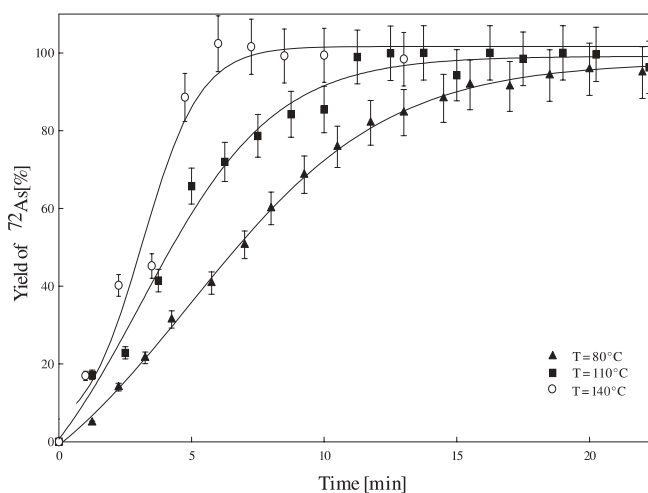


Fig. 4. Distillation kinetics of $^{77}\text{AsCl}_3$; protocol (ii). $T = 80, 110$ and 140°C , HCl flow rate = 60 ml/min .

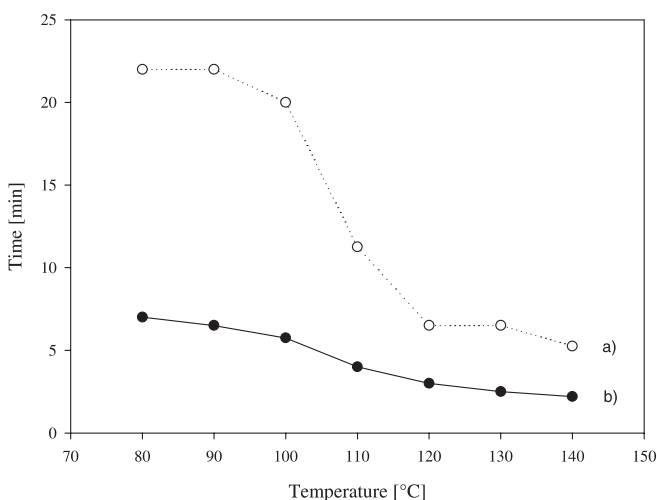


Fig. 5. Determination of optimum distillation temperature of the $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator for 100% ^{72}As separation yield (a) and for 50% ^{72}As separation yield (b).

point (zero point in the second derivative) of the graphs shown in Fig. 5.

The influence of the HCl flow rate on the distillation kinetics of $^{77}\text{AsCl}_3$ was studied in more detail, as illustrated in Fig. 6. A tripling of the HCl flow rate is followed by an approximate tripling in the nca radioarsenic volatilization at $t = 10$ min. At a lower flow rate of 20 ml/min the ^{72}As separation yield of 100% cannot be achieved. A maximum of 80% yield is achieved after 40 minutes distillation time. Consequently, a constant HCl flow rate of 60 ml/min was adjusted for routine use. This indicates the importance of a reproducible maintenance of the HCl flow. This is, however, a technical problem, because of the fast and severe oxidation of the pressure reducer at the gas cylinder outlet valve.

The effect of salt additives on the nca separation of ^{72}Se fraction has been systematically studied using the following salts: KCl, NaCl, AlCl_3 , NH_4Cl , CaCl_2 , BaCl_2 and hydrazine dihydrochloride. The results are illustrated in Fig. 7. Although usage of equimolar amounts of different salts seemed to be quite adequate, this was not possible because of the fixed volume of the generator apparatus, resulting in a constant volume of liquid solution in which an equimolar amount of salt *e.g.* AlCl_3 , would have not been soluble. Therefore, we used 1 g of compound per salt tested. The different chlorides were used to vary the chlorine ion

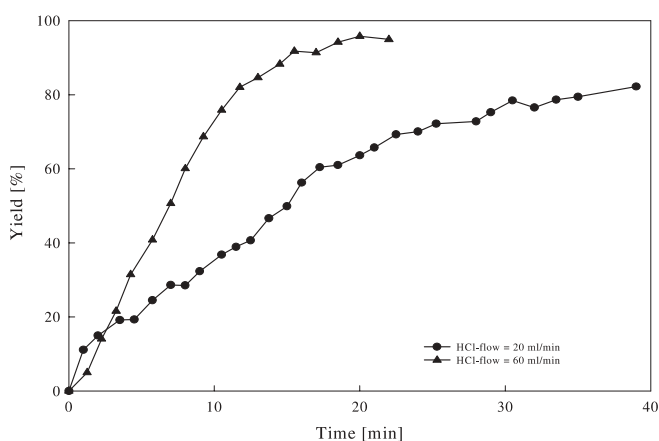


Fig. 6. Distillation kinetics of $^{77}\text{AsCl}_3$ at different HCl flow rates, $T = 90^\circ\text{C}$.

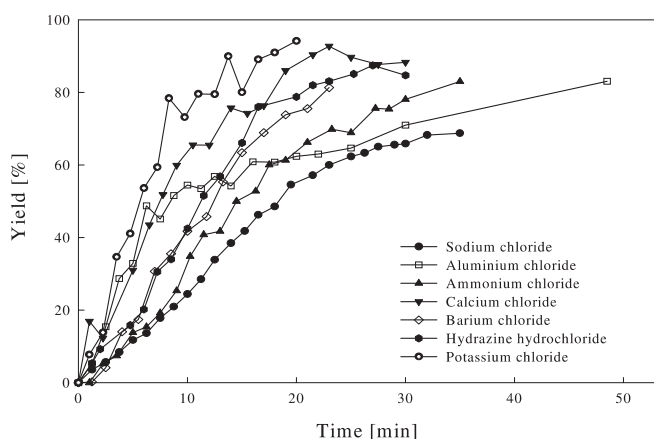


Fig. 7. Distillation kinetics of $^{72}\text{AsCl}_3$ with varying salts in the generator charge, $T = 100^\circ\text{C}$; HCl flow rate = 60 ml/min.

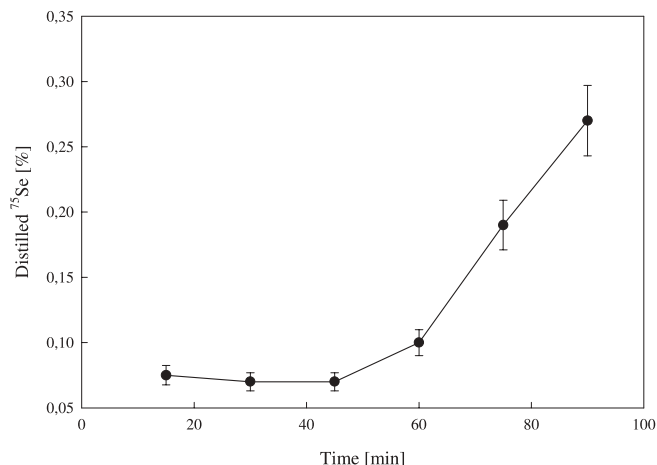


Fig. 8. Se-retention of the $^{72}\text{Se}/^{72}\text{As}$ generator after re-oxidation, $T = 80^\circ\text{C}$; HCl flow rate = 60 ml/min. The result shown here relates to the small amount of ^{75}Se distilled over in a simulation experiment.

density in the solution, while hydrazine dihydrochloride was used to observe whether the addition of a reducing agent has an effect on the nca $^{72}\text{AsCl}_3$ formation or not. The amount of chlorine ions per ml generator charge varied from 3.4 mmol for NaCl to 1.0 mmol for BaCl_2 . Obviously this is not reflected in the measured results, where KCl (2.7 mmol/ml generator charge) showed the best distillation kinetics and NaCl the worst. A possible explanation for this result is the lower solubility of NaCl compared to KCl in hot HCl, which could be visibly observed, but is not described in the literature. For routine use of the generator, KCl is recommended.

On the contrary to nca radioarsenic, which is always present as AsCl_3 under these reaction conditions, different oxidation states seem to be possible for selenium, resulting in significant differences in retention in the generator system. Prior to transferring the radioselenium to the generator apparatus, it was completely oxidised *via* refluxing for 2 h in 5 ml aqua regia. Fig. 8 shows that the selenium breakthrough is very low within the first hour of the separation process. The procedure is therefore good for the separation of nca radioarsenic. The selenium retention for suggested separation periods of less than 10 minutes is $> 99.9\%$.

A longer separation period will possibly result in the reduction of selenium, yielding volatile radioselenium compounds. This is indicated by an increase of the selenium breakthrough at $t > 60$ min (see Fig. 8). Thus, a complete oxidation with aqua regia is recommended prior to subsequent generator utilisation. When the generator was used one day after the previous separation without pre-oxidation, the selenium breakthrough was $> 75\%$ at a temperature of 80°C after 20 minutes of the separation process. This could easily be avoided by adding 0.5 ml of concentrated HNO_3 prior to each generator run and heating the system up for 1 hour, before turning on the HCl gas flow.

4. Conclusion

A $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator utilising a distillation concept has been optimised. It could be automated for future

use as a biomedical generator. At an optimum temperature of 105 °C, more than 99% of the nca ^{72}As is separated in less than 10 minutes at a nca ^{72}Se contamination level below 0.05%. Systematic chemical investigations on the labelling chemistry of no-carrier-added radioarsenic, however, are required prior to the application of ^{72}As labelled compounds.

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