

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

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Summary. ^{72}As -labelled radiopharmaceuticals could be a valuable resource for Positron Emission Tomography (PET). In particular, the long half-life of ^{72}As ($T_{1/2} = 26$ h) facilitates the observation of long-term physiological or metabolic processes, such as the enrichment and distribution of antibodies in tumor tissue. This work describes the primary radiochemical separation of no-carrier-added (nca) ^{72}Se from cyclotron irradiated germanium targets and the development of a polystyrene type solid-phase extraction based $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator, avoiding the addition of any selenium carrier. The irradiated germanium target is dissolved in HF_{conc} and selenium is reduced with hydrazine dihydrochloride. The nca $^{72}\text{Se}^{(0)}$ is adsorbed on a solid-phase extraction cartridge, representing the generator column. The ^{72}As is eluted using various aqueous solvents with 40%–60% yield and $< 0.1\%$ ^{72}Se content. To be able to study the radiopharmaceutical arsenic chemistry, subsequent chemical modification of the nca ^{72}As eluates to nca $^{72}\text{As}[\text{AsI}_3]$ provides a versatile radioarsenic labelling synthon.

1. Introduction

The recent increasing interest in the element arsenic in environmental sciences [1], toxicology and carcinogenesis [2] and medicine [3, 4] stimulates development of convenient and reproducible methods to trace this element and its compounds in subtoxic and subpharmaceutical concentrations. Arsenic has several isotopes of interest for medical or environmental application (cf. Table 1).

A number of approaches to develop an easy and practical system to separate these arsenic isotopes from cyclotron or reactor irradiated germanium or germanium oxide targets have been described [5–8]. In parallel, a $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator has been studied [9–15]. Strategies towards a versatile radioarsenic labelling chemistry were developed to generate arsenic isotopes in chemical forms suitable for future application in labelling chemistry, radiopharmacy and, ultimately, for molecular imaging using Positron

Emission Tomography (PET). Recent advances in the use of ^{74}As labelled antibodies, directed against the apoptotic marker phosphatidylserine (PS) in a Dunning R2337 AT1 prostate cancer model [16], clearly demonstrate the potential of those radioarsenic isotopes. This enhances the motivation to develop adequate and reliable radiochemical separations.

^{72}As is a positron emitting arsenic isotope, with properties suitable for possible application in ^{72}As -labelled PET-radiopharmaceuticals. It has a positron emission rate of 88% with $E_{\beta^+ \text{max}} = 2.5$ MeV and $E_{\beta^+ \text{mean}} = 1.2$ MeV [17]. Although the positron emission is accompanied by the emission of 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 those cases, the half-life of ^{72}As is commensurate with the radiopharmacological requirements resulting from the slower localization kinetics of the labelled species. These advantages are comparable to those expected from ^{124}I ($T_{1/2} = 4.18$ d), but note that that radionuclide has a β^+ branching of 22% only. On the other hand, compared to established radiohalogenation strategies, a versatile chemistry of arsenic is required to permit the radiolabelling of a broad spectrum of potentially valuable pharmaceuticals.

In addition to direct production routes, the radionuclide ^{72}As can be obtained as a daughter of the relatively long-lived ^{72}Se ($T_{1/2} = 8.5$ d). Various methods for the production of ^{72}Se have been described, but mainly in the context of ^{73}Se production [18–22]. The deuteron- and proton-induced reactions on arsenic, and α - and ^3He -induced reactions on germanium have been investigated. Alternatively, ^{72}Se can be obtained *via* proton induced spallation of e.g. RbBr [11].

Radionuclide generator systems play a key role in providing both diagnostic and therapeutic radionuclides for various applications in nuclear medicine, oncology and interventional cardiology. In particular, centers lacking a cyclotron to produce the necessary radionuclides might benefit substantially from the availability of biomedical PET radionuclide generators [15]. Several $^{72}\text{Se}/^{72}\text{As}$ generator systems have been proposed previously. Al-Kouraiishi and Boswell [9]

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Table 1. Most interesting radioisotopes of arsenic and their decay data [24].

	^{72}As	^{73}As	^{74}As	^{76}As	^{77}As
$T_{1/2}$ [d]	1.1	80.3	17.8	1.1	1.6
Mode of decay [%]	EC (12.2) β^+ (87.8)	EC (100)	EC (71) β^+ (29.0)	β^- (100)	β^- (100)
Most abundant γ -rays [keV]	834.0 (79.5)	53.4 (10.0)	595.8 (59.0)	559.1 (45.0)	239.0 (1.6)
Intensity in (%)	629.9 (7.9)			657.1 (6.2)	

eluted ^{72}As from a coagulated form of carrier-added ^{72}Se on a Dowex 50 column in 15 ml of water. Electrolytic generators with ^{72}Se deposited on Pt electrodes as Cu^{72}Se were reported [12, 13]. Another process using addition of selenium carrier in the form of selenic acid uses the cyclic reduction of selenium to $\text{Se}^{(0)}$ and a separation of ^{72}As by filtration with subsequent oxidative dissolution of $\text{Se}^{(0)}$ using H_2O_2 prior to each separation cycle [11]. As published recently, our group developed a no-carrier-added generator based on distillation [10, 23]. Following the $\text{Ge}(^3\text{He}, 3n)^{72}\text{Se}$ process, the irradiated Ge was dissolved in aqua regia and germanium was removed *via* distillation as GeCl_4 . The remaining solution of ^{72}Se in conc. HCl was transferred to a vertical quartz tube device. In the presence of various chloride salts in the ^{72}Se solution, no-carrier-added ^{72}As was nearly quantitatively released within 10 min at temperatures of 100 °C in an HCl gas flow.

The aim of this work was to develop a $^{72}\text{Se}/^{72}\text{As}$ generator, still without any addition of selenium carrier, but which should be more practicable and convenient compared to previously published systems. Moreover, transfer of the separated and purified ^{72}As fraction to a chemical form (synthon) optimum for future labelling chemistry should represent an important feature of the radionuclide generator system to allow investigations of ^{72}As -labelled radiopharmaceuticals. The system should be reliable for the routine separation of ^{72}As , and finally, the handling time should be reduced to a minimum.

2. Experimental

2.1 Isotope production

^{72}Se was produced at the compact cyclotron CV28 at the Forschungszentrum Jülich *via* the $^{nat}\text{Ge}(^3\text{He}, 3n)$ nuclear reaction. 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 (3.1 MBq/mAh). ^{72}Se was also produced *via* the $^{70}\text{Ge}(\alpha, 2n)^{72}\text{Se}$ reaction with a bombarding energy of 36.5 MeV. The beam current was 4.5 μA and irradiations of 5 h resulted in an activity of about 185 MBq (8.2 MBq/mAh). All irradiations were performed on natural or isotopically enriched germanium or on natural germanium oxide.

2.2 Radiochemical separation of ^{72}Se and generator setup

To isolate ^{72}Se from the irradiated germanium targets, 100 mg of irradiated metallic germanium is dissolved in 5 ml HF_{conc} and 500 μl $\text{HNO}_{3\text{conc}}$ at room temperature

within 3 hours. The amount of $\text{HNO}_{3\text{conc}}$ necessary could be reduced with a prolonged dissolution period, *e.g.* to 50 μl , if the target is stirred overnight in 5 ml HF_{conc} prior to the addition of the oxidizing acid. Germanium oxide targets can be dissolved directly in 5 ml HF_{conc} without using HNO_3 . The subsequent procedures are performed analogously. In order to reduce $\text{Se}^{(\text{VI})}$ to $\text{Se}^{(0)}$, 10 mg of hydrazine dihydrochloride or SO_2 is added to the solution.

A polystyrene based (Varian ENV, 500 μl bed volume) solid phase extraction cartridge is preconditioned with 5 ml of CH_3OH , 5 ml H_2O and 5 ml HF_{conc} before the mixture is transferred to the cartridge. While macroscopic Ge is eluted with the mobile phase as $[\text{GeF}_6]^{2-}$, $^{72}\text{Se}^{(0)}$ is adsorbed on the solid phase, thus becoming the generator column. After first setup of the generator column, the remaining HF is removed with N_2 and the cartridge is stored in a sealed container in N_2 atmosphere for the next elution.

2.3 Elution of nca ^{72}As from the nca ^{72}Se loaded generator cartridge

The generated daughter ^{72}As can be subsequently eluted using various aqueous solvents. In this work, HF, aqua regia, pure H_2O , 0.1 and 1.0 molar NaOH and $\text{MeOH}/\text{H}_2\text{O}$ gradients have been used to find the optimum elution conditions. The effect of various liquids and/or gases under which the generator is stored between two successive elutions was studied. The generators were eluted daily and every 48 h. Fractions of 100 μl were collected and ^{72}As and ^{72}Se contents were determined using γ -ray spectroscopy.

2.4 Reaction to produce $^{72}\text{AsI}_3$

The combined eluate fractions ($V = 2$ ml) are diluted with 3 ml HF_{conc} at room temperature in a Teflon flask containing 10 mg of KI. The solution is stirred for 10–15 minutes, until it develops a slight yellowish colour. The mixture is then transferred to a second, identical ENV-solid phase extraction cartridge preconditioned with 5 ml of MeOH , 5 ml H_2O and 5 ml HF_{conc} containing potassium iodide at a concentration of 1 mg/ml. The nca $[\text{AsI}_3]$ is adsorbed on that cartridge. Subsequently, $[\text{AsI}_3]$ can be eluted with ethanol or other organic solvents. Some following chemistry may require a water-free environment. In this case, the nca $[\text{AsI}_3]$ can be eluted with chloroform and dried with CaCl_2 before further reactions.

2.5 Determination of radionuclidic purity and radiochemical separation yields

Radionuclidic purity and radiochemical separation yields were obtained using γ -ray spectroscopy. Aliquots of the dissolved target were measured and quantitatively compared with the γ -ray spectra of the loaded generator, eluates and waste solutions. The γ -ray spectroscopy was performed using an ORTEC high-purity germanium detector system and the Gamma Vision 5.0 software by ORTEC for analysis.

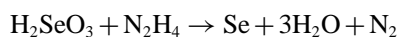
2.6 Materials

Metallic germanium (99.9999% grade) and germanium(IV)-oxide (99.9999% grade, PURA TREM) were purchased from Strem Chemicals Inc.. Concentrated hydrofluoric acid (48%) and potassium iodide were purchased from Aldrich. BOND ELUT ENV solid phase extraction cartridges with a bed volume of 500 ml were purchased from Varian. Isotopically enriched germanium was purchased from Campro Scientific, with 96.4% ^{72}Ge content.

3. Results and discussion

3.1 Separation of ^{72}Se

The radiochemical procedure used to separate nca ^{72}Se from irradiated germanium targets (natural or isotopically enriched) is based on the formation of soluble $[\text{GeF}_6]^{2-}$ in concentrated hydrofluoric acid and the reduction of ^{72}Se to $^{72}\text{Se}^{(0)}$ by hydrazine. This reduction is a standard reaction for the gravimetric estimation of macroscopic selenium (IV) and (VI) in aqueous solutions, cf. e.g. [23].



Other reducing agents described are sulphur dioxide or tin(II) chloride [23]. In order to avoid addition of other metals, we evaluated only sulphur dioxide and hydrazine dihydrochloride. Both approaches gave comparable separation yields of $98 \pm 2\%$ nca ^{72}Se . However, SO_2 causes a significant loss ($> 30\%$) of ^{72}Se -activity, due to volatilization together with excess sulphur dioxide, which was not observed while using hydrazine dihydrochloride as the reducing agent.

The oxidation state of the target material is important. The use of GeO_2 is preferable, since macroscopic Ge is already in the oxidation state +IV. However, to date isotopically enriched germanium as target material is only available as metal. Thus while using metallic germanium as target material, besides HF small amounts of HNO_3 have to be added to oxidise $\text{Ge}^{(0)}$ to $\text{Ge}^{(\text{IV})}$ and to dissolve the target. Heating the mixture accelerates the dissolution significantly, but it also results in some loss of selenium, as under these conditions the volatile SeF_4 is formed. The formation of SeF_4 ($T_b = 100^\circ\text{C}$) is negligible at room temperature. A comparison of the the γ -ray spectroscopically measured ^{72}Se contents of the target solution before and after reduction, and before and after solid-phase extraction, indicate separation yields $> 95\%$ for ^{72}Se using hydrazine dihydrochloride. The amount of Ge separated from the initial cartridge is $> 99\%$.

3.2 $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator

From the transient radionuclide generator kinetics, the time during which the daughter activity reaches the maximum is calculated to be 88.6 h. However, after 48 h, i.e. every second day, it is theoretically possible to elute about 75% of the maximum daughter activity ($\sim 40\%$ to elute every 24 h) [10]. Fig. 1 shows a γ -ray spectrum in linear scale of the loaded generator at equilibrium. The characteristic γ -lines of ^{72}As , besides the 511 keV annihilation radiation, are 834.0 keV (79.5%) and 629.9 keV (7.92%). ^{72}Se can only be identified by its low energy γ -ray at 46.0 keV (58.0%).

The radiochemical separation yields were evaluated as a function of different solvents for the elution of the daughter activity over a wide pH range. From the individual γ -ray spectra of each aliquot, the peak areas for ^{72}As and ^{72}Se were determined before and after each separation step. Table 2 shows the ^{72}As yield and ^{72}Se breakthrough for 4 eluents.

Deionized water as eluent gives the highest ^{72}As separation yield of 60%. The breakthrough of the mother radionuclide is minimum when eluting with HF_{conc} , however, the ^{72}As yield of 50% is significantly lower than with the deionized water. A change of pH using NH_3 or phosphoric acid as eluent does not increase the ^{72}As elution yield. To keep the eluate volume small, the generator was eluted with a volume of 1 ml, irrespective of the solvent. Higher yields could be obtained with larger volumes (comparable to the volume of 15 ml used by Al-Kourashi and Boswell [9]), but a higher volume could result in difficulties during the subsequent labelling chemistry.

Table 2. ^{72}As yield and ^{72}Se breakthrough for 4 types of eluents [$V = 2$ ml].

Eluent	^{72}As yield (%)	^{72}Se breakthrough (%)
HF_{conc}	50 ± 5	< 0.1
H_2O	60 ± 5	1.9
NH_3 , 1.3%, pH = 11.5	30 ± 5	0.4
Phosphoric acid, 1.3%, pH = 0.5	30 ± 5	1.2

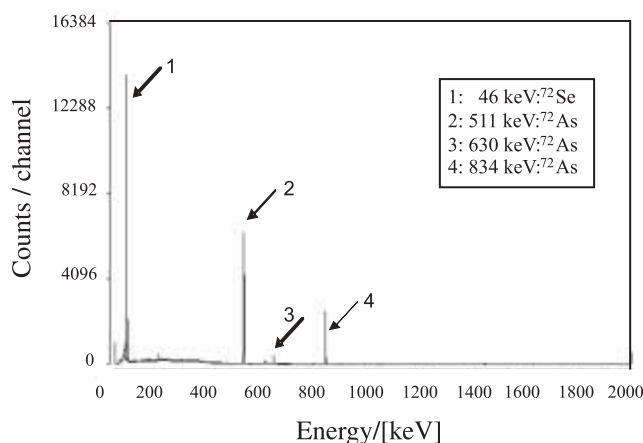


Fig. 1. γ -ray spectrum of a 100 μCi $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator before elution.

The initial content of ^{72}Se in the generator eluate is relevant for a possible medical application. However, there are two further processing steps to consider, namely (a) formation of $[\text{}^{72}\text{As}]\text{AsI}_3$ including an ENV cartridge separation process, and (b) final labelling of the biomolecules of interest with $[\text{}^{72}\text{As}]\text{AsI}_3$. Both processes will further reduce the level of ^{72}Se in the final ^{72}As fractions. This further reduction is 5fold for process (a), as selenium generally does not react with iodides [23].

Thus, the ^{72}Se breakthrough appears to be more relevant in terms of the overall $^{72}\text{Se}/^{72}\text{As}$ generator activity. By an average breakthrough of 1% the generator load losses are negligible compared to the loss by the decay of ^{72}Se . Therefore, we suggest choosing the eluent based on the solvent-requirements for the following experiments.

Fig. 2 shows a typical elution profile of a 100 μCi $^{72}\text{Se}/^{72}\text{As}$ isotope generator, eluted with HF_{conc} . The daughter activity concentration has its maximum after 200 μl and it is possible to elute the whole activity in 500 μl .

The radionuclidic purity of the eluted ^{72}As was determined *via* γ -ray spectroscopy of the eluted fraction (Fig. 3). All the peaks are attributed to ^{72}As . The 46 keV γ -ray from ^{72}Se is not detectable after 1 h measurement time. Using these spectroscopic data, the ^{72}Se -breakthrough was calculated to be less than 0.1%.

The radiochemical purity is very much dependent on the storage conditions of the generator between subsequent elutions. The reduced $\text{Se}^{(0)}$ on the cartridge is sensitive to oxidation. In the case that the generator is stored also under HF_{conc} , but under air instead of nitrogen for 2 days without elution, up to 10% of the ^{72}Se load breaks through. This can be avoided by removing excess HF_{conc} with nitrogen after elution, and storing the generator in a sealed nitrogen-filled container. Another option is to store the generator column under reducing conditions filled with 0.1 M hydrazine dihydrochloride containing HF_{conc} solution. While this option works well for the development of radiochemical processes, hydrazine dihydrochloride might interfere when the eluted activity is used for subsequent chemical reactions.

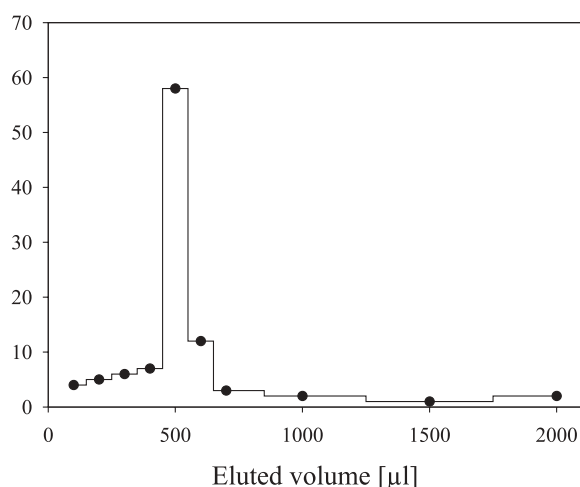


Fig. 2. Typical elution profile of a 100 μCi $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator (eluted with HF_{conc} ; percentage of eluted activity is based on the activity summation of the combined fractions, total elution volume 2 ml).

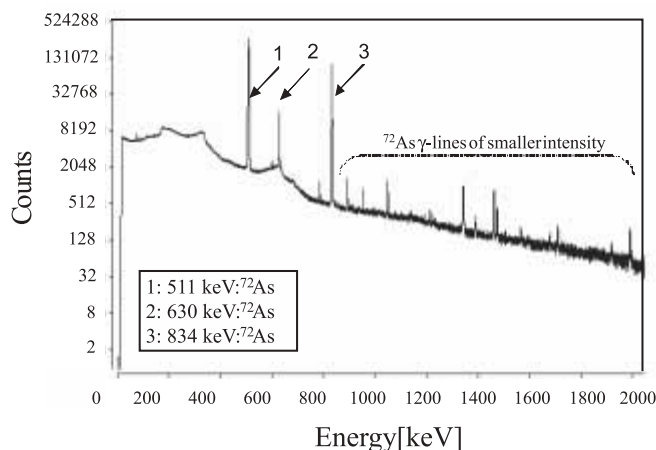


Fig. 3. γ -ray spectrum of eluted ^{72}As , shown on a logarithmic scale.

3.3 Conversion to $[\text{}^{72}\text{As}]\text{AsI}_3$

The eluted ^{72}As activity reacts on addition of potassium iodide and forms $[\text{}^{72}\text{As}]\text{AsI}_3$. This process can also be observed when adding macroscopic amounts of As_2O_3 and KI to a HF solution. The bright orange AsI_3 is immediately precipitated. The yield for the cold reaction is > 95%. Elution with HF has the advantage that $[\text{}^{72}\text{As}]\text{AsI}_3$ is soluble in organic solvents and therefore can easily be separated from the HF_{conc} solution by liquid-liquid or solid phase extraction. The formation of $[\text{}^{72}\text{As}]\text{AsI}_3$ transforms the generator eluate to a definite chemical form and its solubility in organic solvents makes $[\text{}^{72}\text{As}]\text{AsI}_3$ a very useful synthon for subsequent labelling chemistry.

3.4 Apparatus

A schematic representation of the $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator system is shown in Fig. 4. It consists of two Teflon reactors and the two corresponding polystyrene based ENV solid phase extraction cartridges. The first cartridge represents the generator column and the second one is used for the solid phase extraction based separation of nca $[\text{}^{72}\text{As}]\text{AsI}_3$ from the radionuclide generator eluate. Reservoirs are there for all the above described necessary solutions and the apparatus can be flushed with nitrogen. This system is well suited for automation.

4. Conclusion

Following radiochemical separation of ^{72}Se from irradiated Ge or GeO_2 targets, nca ^{72}Se was used to design a convenient solid phase extraction radionuclide generator. After initial reduction of radioselenium, nca $\text{Se}^{(0)}$ is fixed on a polystyrene based solid phase extraction column. Macroscopic Ge is separated as $[\text{GeF}_6]^{2-}$. Depending on the eluent, ^{72}As can be obtained with yields > 60% and a selenium contamination of less than 0.1%.

In addition to radionuclide generator performance, two other aspects are important. Compared to previously described $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator designs, the method has two advantages. (A) it allows an efficient route to ^{72}As labelling molecules relevant to biochemistry and

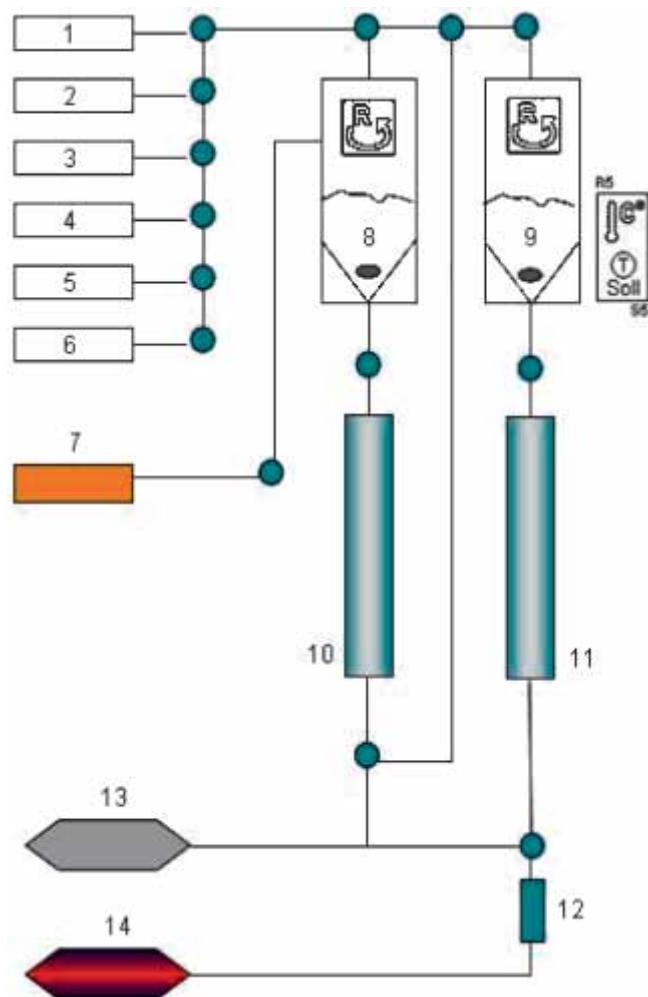


Fig. 4. Scheme of a $^{72}\text{Se}/^{72}\text{As}$ radionuclide generator based on solid phase extraction.

medicine via the labelling synthon $[^{72}\text{As}]\text{AsI}_3$ and (B) it represents a convenient technological realisation with rather low operation costs and easy to automate for routine use. 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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