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A new method for radiochemical separation of arsenic from irradiated germanium oxide

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Abstract

Radioarsenic labelled radiopharmaceuticals could be a valuable asset to Positron Emission Tomography (PET). In particular, the long half-lives of ^{72}As ($T_{1/2} = 26$ h) and ^{74}As ($T_{1/2} = 17.8$ d) allow to investigate slow physiological or metabolical processes, like the enrichment and distribution of antibodies in tumor tissue. This work describes the direct production of no-carrier-added (nca) arsenic isotopes *As, with * = 71, 72, 73, 74 or 77, the reaction to [*As]AsI_3 and its radiochemical separation from the irradiated solid germanium oxide via polystyrene-based solid-phase extraction. The germanium oxide target, irradiated at a cyclotron or a nuclear reactor, is dissolved in concentrated HF and Ge is separated almost quantitatively (99.97%) as $[GeF_6]^{2-}$. [*As]AsI_3 is formed by addition of potassium iodide. The radiochemical separation yield for arsenic is >90%. [*As]AsI_3 is a versatile radioarsenic labelling synthon.

Keywords: As-71; As-72; As-73; As-74; As-77; Radiochemical separation; Solid-phase extraction

1. Introduction

The recent increasing interest in the element arsenic in environmental sciences (The U.S. Geological Survey Workshop on arsenic in the environment, available at wwwbrr.cr.usgs.gov/Arsenic/, 2004), toxicology and carcinogenesis (Evans et al., 2004) and medicine, particularly in the treatment of promyelocytic leukaemia (Ravandi, 2004; Miller et al., 2002; Zhu et al., 2002, 2003, 2001, 1997; Chen et al., 1996, 1997; Shen et al., 1997; Wang, 2001), stimulates a need to develop convenient and reproducible methods to trace this element and its compounds in subtoxic and subpharmaceutical concentrations. Arsenic has several radioisotopes of interest for molecular/medical or environmental application (cf. Table 1).

Several approaches to develop an easy and practical system to separate these isotopes from cyclotron or

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Table 1
Decay data of the most relevant arsenic isotopes (National Nuclear Data Center, 2004)

Property	^{71}As	^{72}As	^{73}As	^{74}As	^{76}As	^{77}As
$T_{1/2}$ [d]	2.7	1.1	80.3	17.8	1.1	1.6
Mode of decay (%)	EC (70) β^+ (30)	EC (12.2) β^+ (87.8)	EC (100)	EC (66) β^+ (29)	β^- (100)	β^- (100)
Most abundant γ-lines [keV]	175.0 (82.0%)	834.0 (79.5%) 629.9 (7.9%)	53.4 (10.0%)	595.8 (59.0%) 634.8 (15.4%)	559.1 (45.0%) 657.1 (6.2%)	239.0 (1.6%) 520.6 (0.5%)
Mean positron energy [keV]	350	1170		440		

reactor irradiated germanium or germanium oxide targets have been described in the past (Basile et al., 1984; Byrne, 1984; Mausner et al., 2004; Ward et al., 1970). In addition, 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 using ^{74}As labelled antibodies directed against the apoptotic marker phophatidylserine (PS) in a Dunning R2337 AT1 prostate cancer model (Jennewein et al., 2004a, b) clearly demonstrate the potential of these radioarsenic isotopes. This strengthens the motivation to develop adequate and reliable radiochemical separations.

The decay properties of radioactive arsenic isotopes are summarized in Table 1.

^{71}As has a half-life of 65 h. It decays by 70% through electron capture and has a positron emission rate of 30% with $E_{\beta^+mean} = 350$ keV. It can be produced by the ^{70}Ge(d,n)^{71}As reaction (Beard, 1960) and by Ge(p,xn)^{71}As processes (Basile et al., 1984).

^{72}As is a positron emitting arsenic isotope, with properties suitable for application in ^{72}As-labelled PET-radiopharmaceuticals. It has a positron emission rate of 88% with $E_{\beta^+mean} = 1.17$ MeV. 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 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 is commensurate with the radiopharmacological requirements resulting from the relatively slow localization kinetics of the labelled species. These virtues are comparable to those of ^{124}I ($T_{1/2} = 4.18$ d), but note that this radioisotope has a β^+-branching of only 22%. In addition to production from a generator following the reaction ^{70}Ge(α,2n)^{72}Se $\rightarrow$ ^{72}As (Al-Kourashi and Boswell, 1978; Jennewein et al., 2004a, b, 2005; Phillips, 1994; Phillips et al., 1991, 1992; Rösch et al., 2002; Rösch and Knapp, 2003), it can be produced directly in high yields, e.g. via the ^{72}Ge(p,n)^{72}As reaction using small-sized cyclotrons (Basile et al., 1984).

^{73}As has a half-life of 80.3 d and decays exclusively via electron capture, emitting only a γ-ray of 53.4 keV. Because of the long half-life, it is mainly applied as a tracer for environmental sciences. It is currently produced via the Ge(p,xn)^{73}As reaction with subsequent distillation and purification on a cation exchange column (Mausner et al., 2004).

^{74}As is also a positron emitter, but has a much longer half-life ($T_{1/2} = 17.8$ d) than ^{72}As. It thus represents one of the longest-living positron emitters with sufficient β^+ branching. It has a positron emission rate of 29% with a low positron energy of $E_{\beta^+mean} = 440$ keV and an electron emission rate of 34.2% and $E_{\beta^-mean} = 137$ keV. The low positron energy provides a high local resolution, comparable to that of ^{18}F, when measured via PET, as shown in Fig. 1. Here the spatial resolution in dependency of positron energy was measured at the Small Animal PET of the University of Texas Southwestern Medical Center at Dallas for point sources ($\varnothing = 1$ mm) of ^{72}As, ^{74}As, ^{124}I, ^{18}F and ^{22}Na.

^{74}As was one of the first isotopes used in the very preliminary stages of PET in the 1950s and 1960s (Sweet and Brownell, 1955; Leicester and Vanderfield, 1966; Mealey, 1963; Wilcke, 1965a, b; Wilcke and Brock, 1965) called positrocephalography at that time. Due to its long half-life, it is more appropriate for animal use than human use, but could also provide a useful tool for the study of long-lasting metabolic processes, like antibody-antigen interactions or, in general, long term pharmacokinetics of developmental drugs. ^{74}As can be produced best by the ^{74}Ge(p,n)^{74}As or ^{73}Ge(d,n)^{74}As reaction at a small-sized cyclotron. Excitation functions

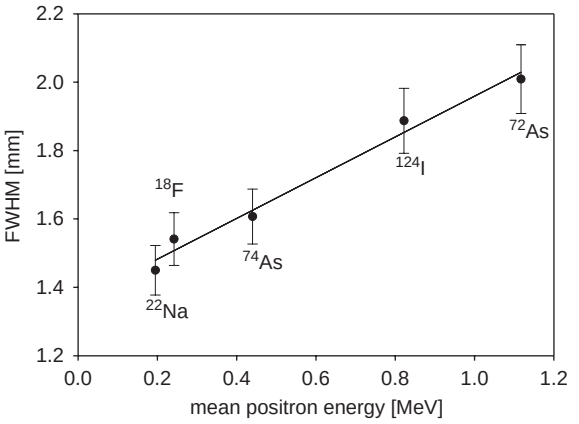

Fig. 1. Spatial resolution for different positron emitting isotopes versus their positron energy. Measurements were done at the Small Animal PET of the UTSW Medical Center at Dallas using equal-sized point sources, $\varnothing = 1$ mm.

and target yields were described in detail previously (Basile et al., 1984).

^{77}As is a 100% electron emitting isotope with a half-life of 1.6 d and $E_{\beta^- mean} = 226$ keV. This isotope could be of future use in arsenic based endoradiotherapeuticals. ^{77}As can be produced at nuclear reactors via the ^{nat}Ge(n,γ)^{77}Ge reaction, ^{77}Ge decaying to ^{77}As with a half-life of 11.3 h. In addition, also deuteron induced reactions on enriched ^{76}Ge targets could provide pathways for direct or indirect production of ^{77}As.

2. Separations

All the production routes mentioned both at accelerators and nuclear reactors share the radiochemical separation of nca radioarsenic from macroscopic germanium targets. The radiochemical procedures for germanium are described in detail by Mirzadeh (Mirzadeh and Kahn, 1986; Mirzadeh et al., 1981; Mirzadeh and Lambrecht, 1996). Only a few alternative radiochemical separations for radioactive arsenic isotopes have been reported to date. Schindewolf and Irvine (1958) and Basile et al. (1984) dissolved the irradiated germanium target in conc. HF and used at first an anion exchange column to separate As(III) from Ge(IV) which is retained by the resin as hexafluorocomplex. A second anion exchange column with HF/HCl gradients was required for purification. Mukhopadhyay et al. (2002) produced nca radionuclides of arsenic and selenium in an ^{16}O irradiated cobalt target matrix. The initial products, formed by ^{59}Co(^{16}O,xn)$^{70-73}$Br reactions, decayed promptly to arsenic and selenium radionuclides, which were subsequently separated by liquid-liquid extraction (LLX) using di-(2-ethylhexyl) phosphoric acid (HDEHP) and trioctylamine (TOA) as liquid ion exchangers. The radiochemical separation of ^{77}As from ^{77}Ge using thin-layer chromatographic and electrophoretic methods is described by Halpern et al. (1964) and Maki and Murakami (1974). Other radiochemical separations of As from Ge used an oxidative distillation followed by a reductive distillation (Beard, 1960). The major drawback of all the previous methods, however, was that they lacked the option of using the separated nca radioactive arsenic isotopes for a following labelling chemistry of biomolecules.

The aim of the present work was to develop a more convenient radiochemical separation method for radioactive arsenic isotopes from reactor or cyclotron irradiated germanium oxide targets with optimized radiochemical yields, separation efficiencies and radiochemical product purity. Moreover, the transfer of the separated and purified radioarsenic fractions to a chemical form (synthon), optimum for future labelling chemistry, should represent an important feature of the separation to allow investigations and application of radioarsenic-labelled radiopharmaceuticals. The system should be reliable for the routine separation of the arsenic isotopes, and finally, the handling time should be reduced to a minimum.

A radiochemical procedure based on the formation of soluble [GeF_6^{2-}] in concentrated hydrofluoric acid and the reaction to [*As]AsI_3 through addition of KI is described to separate nca *As (* = 71,72,73,74,77) from irradiated germanium oxide targets.

3. Materials and methods

3.1. Isotope production

^{74}As was produced by the ^{nat}Ge(p,x)^{74}As reaction [$E_p = 20$ MeV] on 100 mg GeO_2 pellets (850 μm equivalent Ge thickness) pressed at 10 t and placed in water-cooled stainless steel target holders and covered by a thin pure Al-foil. To avoid excessive burning of the target material by the energy deposition of the 16 MeV incident proton beam, the particle current was limited to 8 μA in a homogeneous beam. The thick target yield under these conditions is 2.5 MBq/μAh (at EOB) for production of ^{74}As with high levels of ^{72}As contamination.

^{77}As was produced in nca state via the ^{76}Ge(n,γ)^{77}Ge $\rightarrow$ β^-($T_{1/2} = 11.30$ h)$\rightarrow$^{72}As processes 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). All irradiations were performed using 100 mg of $^{nat}GeO_2$.

3.2. Materials

Germanium(IV)oxide (99.9999% pure, PURA TREM) was 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 sorbent mass of 50 mg and a volume of 1 ml were purchased from Varian.

3.3. Radiochemical separation

Irradiated germanium oxide targets were dissolved in 5 ml conc. HF at room temperature for 1 h. Subsequently, potassium iodide was added and stirred for 10 min. The amount of KI was varied between 0.1 and 10 mg/ml HF. The mixture was transferred to an ENV-solid phase extraction cartridge. The cartridge-holder and fittings to standard size syringes were made in the machine-shop of the Institute of Nuclear Chemistry, University of Mainz. The ENV cartridge was preconditioned with 5 ml of MeOH, 5 ml H_2O and 5 ml conc. HF containing potassium (1 mg/ml). The nca [*As]AsI_3 was fixed to the solid phase, while the macroscopic $[GeF_6]^{2-}$ was eluted quantitatively with the mobile phase. After the fixation of [*As]AsI_3, excess HF was removed with a nitrogen-flow over the cartridge for 5 min. The elution of [*As]AsI_3 was performed with 500–1000 μl of various organic solvents (toluene, chloroform, dichloromethane, hexane, cyclohexane and ethanol). If the subsequent labeling chemistry requires anhydrous solvent conditions, a $CaCl_2$ drying cartridge could be used.

3.4. Determination of radionuclidic purity and radiochemical separation yields

The radionuclidic purity and radiochemical separation yields were determined using γ-ray spectroscopy. Aliquots of the dissolved target were measured and quantitatively compared with the γ-ray spectra of the solid phase extraction cartridges, eluates and waste-solutions. The γ-ray spectroscopy was performed using an Ortec HPGe detector system, and the GammaVision 5.0 software by Ortec was used for peak area analysis.

4. Results and discussion

4.1. Target dissolution

For optimum target dissolution, it is important to use precipitated germanium oxide and not burned germanium oxide as target material, as the latter is not soluble at room temperature. Higher temperatures should be avoided, since an increased temperature leads to the formation of arsine (AsH_3) and thus to significant volatilization of activity (>60%, $T_b(AsH_3) = -62.5\,^{\circ}C$ (Smith, 1973)). Low temperatures, fast target dissolution and the quantitative formation of nca [*As]AsI_3 minimize the formation of arsine and loss of activity due to volatilization. The use of metallic germanium was also evaluated, but GeO_2 is preferable, since the macroscopic Ge is already in the oxidation state +IV. However, to date isotopically enriched germanium is only available as metal. If metallic germanium is used as target material, small amounts of HNO_3 must be added to the HF solution to oxidise $Ge^{(0)}$ to $Ge^{(IV)}$ and thus to dissolve the target. Heating of the target accelerates the dissolution process significantly, but leads also to a loss of arsenic activity, due to the formation of *AsH_3 as described above. *AsH_3 formation and volatilization was not observed at room temperature. However, the oxidizing conditions after addition of HNO_3 in the target solution lead to the formation of free iodine when adding potassium iodide in an exothermic reaction. The procedures described in this article therefore are not applicable to metallic germanium targets. If isotopically enriched target material is used, an oxidation prior to irradiation is crucial.

Following both p- and n-irradiation of 100 mg $^{nat}GeO_2$ targets, the optimum dissolution was achieved at room temperature after 20 min.

A comparison of γ-spectroscopically measured As contents of the target solution before and after the solid-phase extraction gives separation yields >90% for *As, independent of the produced arsenic isotope. The amount of Ge separated from the cartridge is >99.97%.

4.2. Formation and fixation of [*As]AsI_3

Macroscopic AsI_3 is dark orange, the melting point is 140.4 °C and the boiling point 371 °C (Smith, 1973). Its solubility in polar solvents is limited and therefore it is slightly soluble in water, but well soluble in organic solvents, like CS_2, benzene, toluene, xylene and chloroform (Zingaro, 1994). The formation of macroscopic AsI_3 under these conditions was observed when adding equimolar amounts of KI and macroscopic As_2O_3 to conc. HF. The dark orange AsI_3 precipitated immediately and quantitatively. AsF_3 can also be formed in conc. HF from As_2O_3, but not without the addition of concentrated H_2SO_4 (Shriver et al., 1997).

The amount of KI necessary for quantitative formation of nca [*As]AsI_3 was evaluated (cf. Fig. 2). After the addition of 2 mg KI per ml $HF_{conc.}$ (12 μmol/ml), the yield was 95 ± 5% and did not change with the increase in the KI concentration.

Bond Elut ENV, a high-purity styrene divinyl benzene (SDVB) polymer has been optimized for the extraction of polar organic residues, such as herbicide metabolites and explosives from large volume water samples. Although primarily developed for environmental applications, it can also be used for clinical purposes such as the extraction of metabolites from human fluids. Bond Elut ENV features a 125 μm highly cross-linked spherical polymer with a surface area of 500 m^2/g and

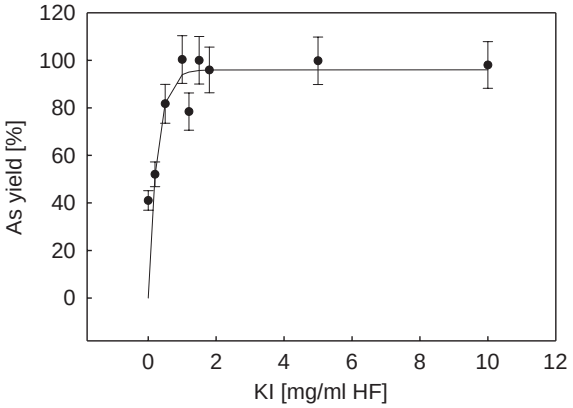

Fig. 2. Yield of nca [*As]AsI_3 versus the potassium iodide content in conc. HF. Nca [*As]AsI_3 was eluted with chloroform after fixation on an ENV solid phase extraction cartridge.

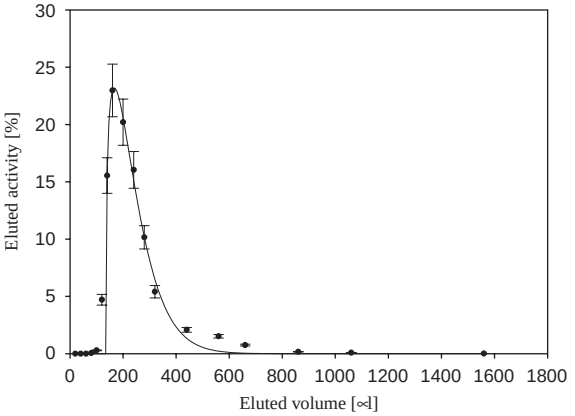

Fig. 3. Typical elution profile of a nca $^{77}AsI_3$ loaded polystyrene ENV cartridge (eluted with ethanol, percentage of eluted activity based on the activity-balance of all the fractions, total elution volume 1.8 ml).

a pore volume of 1.3 ml/g. The absence of secondary interactions on the polymer surface eases the elution of a wide range of molecular species. The cartridges are resistant to concentrated hydrofluoric acid. Using these cartridges, >90% of the nca [*As]AsI_3 could be fixed.

5. Elution

Various organic solvents were studied to elute the fixed [*As]AsI_3 activity. We observed similar elution yields, independent of polarity and lipophilicity of the tested solvents (toluene, chloroform, dichloromethane, hexane, cyclohexane and ethanol). Yields were >95% in a volume of 1000 µl for all solvents, with >80% of the eluted [*As]AsI_3 obtained in the first 500 µl (Fig. 3). Thus, the solvent for the elution should be chosen based on the requirements of the intended subsequent labelling chemistry. In an antibody labelling study, prior to studies in vitro and in vivo (Jennewein et al., 2004a, b), the elution was performed with ethanol. The solution could be concentrated to 50 µl after elution at 50 °C and a slow nitrogen flow in 20 min to keep the antibody from precipitating and to reduce the ethanol burden, which was injected in animals. If the nca [*As]AsI_3 should be used later in a nonaqueous labeling environment, e.g. for synthesis of organometallic compounds (Jennewein et al., 2003a, b), it can be eluted with chloroform and dried with chemically inert $CaCl_2$ before further reaction. The use of sodium thiosulfate as drying reagent was also evaluated, but the high affinity of arsenic for sulfur leads to a loss of arsenic activity (>80%) and therefore has to be avoided. A typical elution profile for ^{77}As is given in Fig. 3.

The radionuclidic purity of the eluted ^{77}As was determined using γ-ray spectroscopy analysing the fractions eluted with ethanol. The spectrum obtained was compared with that of an aliquot of the target solution (Fig. 4a–b). Whereas in the target sample the γ-rays of ^{77}Ge, e.g. at 211 keV (29.2%) and 216 keV (27.1%) could clearly be observed, these lines are not detectable in the separated ^{77}As fractions, as demonstrated in the expanded part of the spectrum (note the longer measurement time for the ^{77}As spectrum of 10 h compared to 1 h for the target spectrum). Integrating the spectroscopic data for the 211 and 216 keV γ-ray lines, the amount of Ge remaining in the ^{77}As fraction was calculated to be lower than 0.0002%, which is <2 µg for a 100 mg GeO_2 target. At 264 keV a small γ-ray line is visible in the enlarged view of the spectrum of the separated ^{77}As fraction, which also is part of the ^{77}Ge γ-emissions. However, this γ-ray line also represents radioselenium impurities. ^{74}Se has only a 0.89% natural abundance, but a high (n,γ) cross section of 46 barn. As the (n,γ) reaction to ^{77}Ge has a cross section of only 0.06 barn, even small impurities of selenium could have a measurable effect, as the 264.7 keV line is the highest intensity γ-ray line of ^{75}Se with 58.9% abundance. Therefore the 264 keV γ-ray line was not used for the determination of the radiochemical purity of the separated ^{77}As.

6. Apparatus

A schematic representation of the separation system is shown in Fig. 5. It essentially comprises a temperature controlled Teflon reactor with a stirrer and a polystyrene based ENV solid phase extraction cartridge. All parts are resistant to concentrated hydrofluoric acid and organic solvents. Reservoirs are available for all

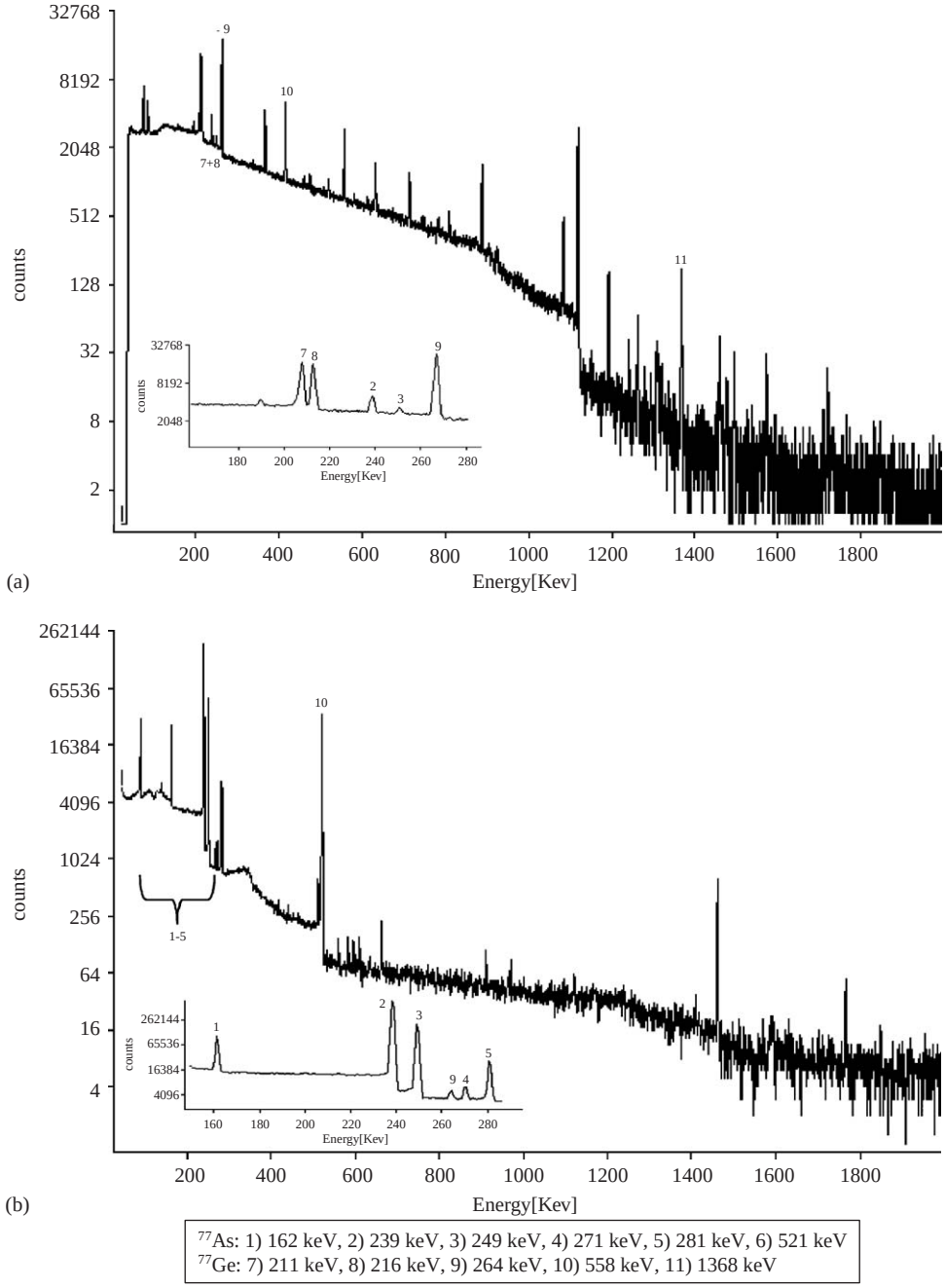

Fig. 4. Radiochemical purity of the separated nca $^{77}AsI_3$ in ethanol: (a) γ-ray spectrum of the target after dissolution in conc. HF; measurement time = 1 h; (b) γ-ray spectrum of ^{77}As; measurement time = 10 h.

solutions necessary and the apparatus can be flushed with nitrogen. This system is well suited for future automation.

The separation method introduced here was exemplified by ^{77}As and ^{74}As, but the main impact may lie in the separation of ^{72}As. In previous works of our group, the radionuclide generator system $^{72}Se/^{72}As$ was described (Jennewein et al., 2004a, b, 2005). The idea of a generator seems to be very appealing in a clinical environment without a cyclotron. However, the produc-

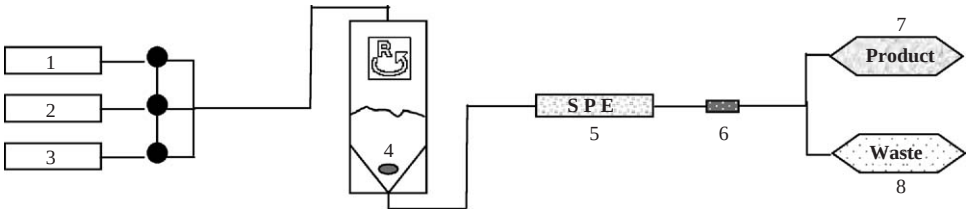

Fig. 5. Scheme of the described extraction system for the separation of nca radioactive arsenic isotopes from reactor or cyclotron irradiated germanium oxide targets: 1. Nitrogen; 2. HF with KI; 3. Organic solvent; 4. Reactor with target; 5. cartridge for separation of [^{72}As]AsI_3; 6. Drying cartridge; 7. Product, nca [^{72}As]AsI_3; and 8. Waste.

tion yields of ^{72}Se (Basile et al., 1984; Horiguchi et al., 1983; Dmitriev, 1986) are rather low from the viewpoint of preparing generators for a sufficient supply of ^{72}As. In contrast, the production yields in the direct production of ^{72}As via the ^{72}Ge(p,n)^{72}As reaction would be relatively high. From the systematics, the maximum of the excitation function is expected to be between 9 and 15 MeV, which is covered by small-sized medical cyclotrons. A batch yield of several GBq of ^{72}As could be obtained, which would be sufficient for systematic medical applications. Even commercial distribution seem to be feasible.

7. Conclusion

A new method was developed to separate radioactive arsenic isotopes from reactor or cyclotron irradiated germanium oxide targets. Following initial target dissolution, the arsenic reacts on addition of KI to form [*As]AsI_3. This nca radioarsenic triiodide is fixed on a polystyrene based solid phase extraction column. Macroscopic Ge is separated as $[GeF_6]^{2-}$. Nca [*As]AsI_3 can be obtained in yields $>85\%$ with a contamination from germanium of less than 0.01%. This approach suggests a convenient technological realisation with rather low operation costs, and would be easy to automate for routine use. Compared to previously described radioarsenic separations from macroscopic germanium, the method allows an efficient route to *As labelling of molecules relevant to biochemistry and medicine via the labelling synthon [*As]AsI_3. This approach might be in particular relevant to the large-scale production of ^{72}As following ^{72}Ge(p,n)^{72}As reaction on highly enriched $^{72}GeO_2$.

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