

Rapid Communication

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Production of no-carrier-added radiobromine: new nickel selenide target and optimized separation by dry distillation

Abstract: Nickel(II) selenide (NiSe) was investigated as a new high-current target material for cyclotron production of radiobromine, as it contains a higher amount of selenium and has a lower melting point than the widely used Cu₂Se. Using a slanted target system, NiSe was successfully tested up to beam currents of 16 μ A so far. With regard to the isolation of no-carrier-added (n.c.a.) radiobromine from the target material, an improved dry distillation device with high yields of 76%–86% was developed. The implementation of a special custom-made quartz funnel decreased the dead volume of the apparatus and a quartz capillary for trapping the radiobromine allowed to concentrate the radioactivity in a small volume of less than 100 μ L of 0.1 M NaOH, ready for immediate subsequent radiosyntheses. Thus, the new apparatus improves the handling of the isolation procedure and the radioactive product. The radiochemical purity of the resulting solution of n.c.a. [⁷⁶Br]bromide was verified by radio-IC where no other species were detected.

Keywords: Radiobromine, non-standard PET nuclides, radionuclide production, targetry, radiochemical separation, dry distillation.

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1 Introduction

Radioisotopes of bromine have been of special interest in nuclear medical applications. The positron emitting isotopes ⁷⁵Br ($T_{1/2}$ = 1.6 h; β^+ = 75.5%) and ⁷⁶Br ($T_{1/2}$ =

16.2 h; β^+ = 57%) are useful for molecular imaging using PET, whereas the Auger electron emitters ⁷⁷Br ($T_{1/2}$ = 57.0 h) and ^{80m}Br ($T_{1/2}$ = 4.4 h) as well as the β^- -emitter ⁸²Br ($T_{1/2}$ = 35.3 h) are considered for internal radiotherapy. ⁷⁷Br is additionally suited for SPECT, thus representing a *theragnostic* radionuclide. From a chemical point of view, bromine, just as the other halogens, has the advantage to form covalent bonds to carbon. This makes it attractive for analogue labelling, especially of small molecules, but with distinct differences to fluorine and iodine. For example, the ⁷⁶Br-labelled molecules [⁷⁶Br]Bromo-2'-fluoro-2'-deoxyuridine ([⁷⁶Br]BFU), a potential proliferation marker for measurement of the local DNA synthesis rate *in vivo* [1, 2], and *meta*-[⁷⁶Br]Bromobenzylguanidine ([⁷⁶Br]MBBG), the bromine analogue of radioiodinated MIBG and a potential tracer for the norepinephrine transporter (NET) [3–8], belong to the best evaluated radiobrominated compounds up to now.

As a result of considerable amount of research and development work by the end of the 1980s, methods for the production of radiobromine as well as its use in labelling of molecules and the preparation of a few radiopharmaceuticals were established (for early reviews *cf.* [9–12]). Most of the production methods were based either on ³He- or α -particle induced reactions on arsenic or involved the decay of the β^+ emitting precursors ⁷⁵Kr, ⁷⁶Kr or ⁷⁷Kr produced in proton [13–15], deuteron [16, 17] or α -particle [18] irradiations of bromine. From late 1980s onwards, due to the development of a convenient method for nucleophilic labelling of molecules using aqueous [¹⁸F]fluoride [19], the importance of radiobromine decreased. About 15 years ago, new interest arose in the production of radiobromine using selenium as target material. In this context, several cross section measurements were performed (*cf.* [20–22]) and the data were evaluated (*cf.* [23, 24]).

Due to the higher availability of protons and deuterons compared to ³He- and α -particles, for the cyclotron production of radiobromine proton or deuteron bombardment of enriched selenium targets is generally favoured. The currently most widely used target material for the produc-

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tion of radiobromine is enriched Cu_2Se [25–28], which, however, has a rather low mass fraction of selenium of 38.3%. Therefore, nickel(II) selenide (NiSe) was investigated as a new potential high-current target material for radiobromine production. NiSe contains a significantly higher amount of selenium, thus higher radionuclide yields are to be expected related to identical target masses.

Although different wet-chemical separation methods, such as distillation [14, 29–35], precipitation as $\text{AgCl}[*\text{Br}]$ and subsequent cation exchange [36, 37] or separation by anion exchange [38] have been described earlier, the dry distillation concept has become prevalent regarding the isolation of n.c.a. radiobromine from the target material. Compared to the wet-chemical techniques, the dry distillation is fast, easier to handle and usually a one-step procedure. Furthermore, the target remains intact and is immediately reusable for the next irradiation. Under these conditions elaborate recovery chemistry is most often not required, which is especially advantageous in the case of highly enriched target material. Several dry distillation devices have been reported in the literature up to now [25–28, 39–41]. However, there was still a demand for optimization, partially concerning targetry or handling and partially concerning the recovery yield or the volume of solvent containing the isolated radioactivity. Therefore, in this work an improved dry distillation procedure was developed using NiSe as target material with regard to both the volume of the final bromide solution for subsequent radiosyntheses and the handling of radioactivity, thus aiming at less radiation exposure to the operator and enhancement of safety.

2 Targetry

With regard to large scale production of radiobromine for nuclear medical applications, NiSe was investigated as a new high-current target material. Targets were pre-

pared by melting commercially available, crystalline NiSe (230–310 mg/cm^2) of natural isotopic composition (99.9%, supplied by Alfa Aesar, Germany) onto custom-made nickel backings ($\varnothing$ 25 mm), designed with a 0.5 mm deep cavity and a spot-welded nickel net for better adherence of the target material (Figure 1). Various mesh sizes were tested, and the most homogenous layer of NiSe was obtained by using a net with a coarse size of 558 mesh/ cm^2 . The nickel foil (99.8%) for preparation of the backing as well as the nickel net (99+%) were purchased from ChemPUR, Germany. For melting the NiSe onto the Ni-backing, a conventional tube furnace in combination with a specially developed temperature program ($T_{\text{max}} = 1010^\circ\text{C}$) was used. The melting process was performed under a constant flow of argon (15 mL/min) in order to avoid oxidation of the target material.

All irradiations were carried out at the cyclotron BC1710 of the INM-5, Forschungszentrum Jülich, with 17 MeV protons. For radiochemical studies a beam current of 3 μA and an irradiation time of 1.5 h were chosen. That way, about 25 MBq ^{76}Br , 9.25 MBq ^{77}Br and 6.25 MBq ^{82}Br were produced, corresponding to a percentage isotopic distribution of radioactivity of 60 : 25 : 15 (^{76}Br : ^{77}Br : ^{82}Br) at EOB. All development processes and tests were executed and analyzed using a mixture of these isotopes.

Irradiations were performed using a slanted target holder, where the beam hits the target material at an angle of 20° (see Figure 2). As discussed earlier, the use of a slanted target has several advantages: (a) the larger surface area reduces the effective power density in the target material during the irradiation, (b) the primary proton energy of the cyclotron can be utilized entirely, as no front cooling is mandatory, (c) the enhancement of the effective target thickness results in an increased interaction of the projectiles with the target nuclei and thus in higher production yields, while (d) the minimization of the target thickness ensures a nearly quantitative release

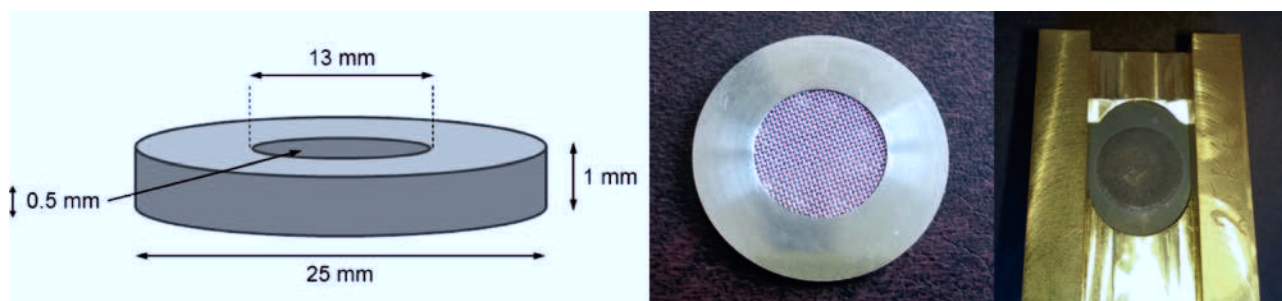


Fig. 1: Left: schematic drawing of the Ni backing; right: picture of the Ni backing with coarse mesh size, and readily prepared NiSe target in the slanted holder.

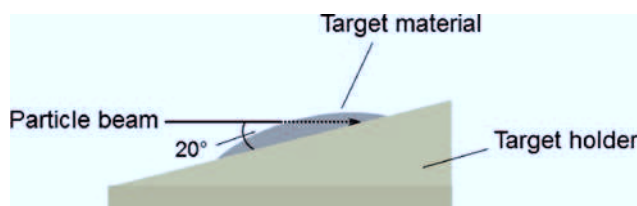


Fig. 2: Cross-sectional scheme of the slanted target holder indicating orientation of incident beam.

Table 1: Comparison of Cu_2Se with the new target material NiSe.

Target material	Stoichiometric fraction of Se [%]	Mass fraction of Se [%]	Melting point [°C]
Cu_2Se	33.3	38.3	1113
NiSe	50	57.4	959

of radiobromine in the subsequent dry distillation process (cf. [42]).

The slanted target is cooled by a 2π -water cooling from the backside, with the additional option to attach a more powerful helium cooling system for irradiations at higher beam currents. Concerning its capability to withstand high-current irradiations, the new target material NiSe was successfully tested up to proton currents of 16 μA so far. After first irradiations with beam times of 20 min, no loss of material or deterioration of structure or mechanical consistency was observed. Further tests at higher beam currents are envisaged.

Compared to the conventionally used Cu_2Se , NiSe contains an about 17% higher molar amount of selenium, corresponding to a factor of 1.5 and an about 20% higher mass fraction (see Table 1). Assuming analogue beam conditions and equal target masses, these criteria will con-

tribute to a significant enhancement of the production yield of radiobromine.

With regard to the subsequent dry distillation procedure for separation of the n.c.a. product from the target material another great advantage of NiSe is the approximately 150 °C lower melting point. As a result, the dry distillation of radiobromine is already possible at temperatures well below 1000 °C, thus reducing material stress and contributing to operational safety.

The work performed so far with natural selenium serves as proof of principle. Since for medical applications radiobromine is required in isotopically pure form, the use of enriched target material will be mandatory. Thus, investigations on synthesizing isotopically enriched ^{76}Se are warranted.

3 Dry distillation procedure

Aiming at routine production, the already known dry distillation procedure for the isolation of n.c.a. radiobromine from the target material lent itself mostly to be optimized by developing an improved apparatus. Figure 3 shows a schematic drawing of the set-up. For heating, a conventional tube furnace with an external control unit was used. All quartz elements were custom-made in house. It became soon apparent, that radiobromine generally condenses or adsorbs in ground joints and adapter pieces, especially in reducers. Therefore, it was of great relevance for the development of the dry distillation apparatus to avoid such elements. Inspired by the dry distillation apparatus for ^{123}I -production constructed earlier at the University in Essen [43], this finally led to the application of an inserted and separately detachable quartz capillary. Although different materials like platinum or stain-

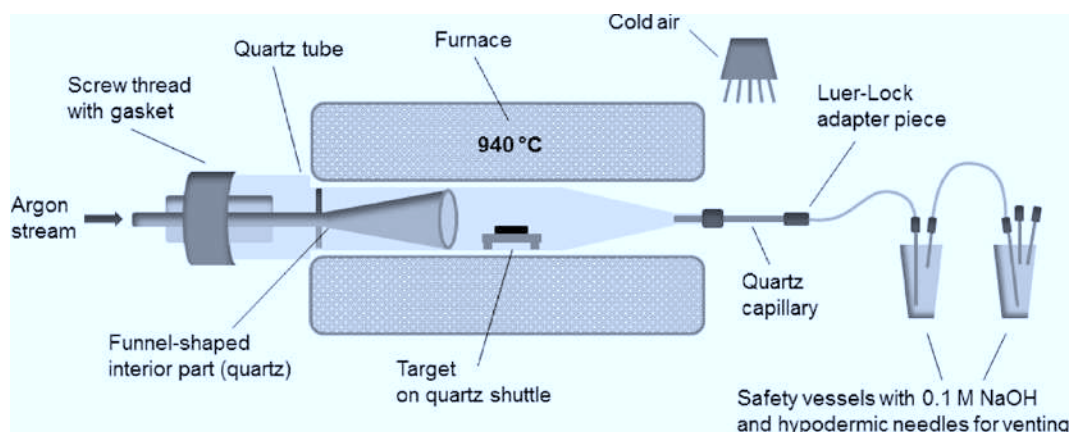


Fig. 3: Schematic drawing of the modified dry distillation apparatus.

Table 2: Temperature program for the dry distillation of radiobromine from NiSe.

Stage	Furnace temperature [°C]	Dwell time [min]
1	150	5
2	500	5
3	900	10
4	940	5

Table 3: Radioactivity balance in the optimized dry distillation procedure.

Distribution of radioactivity	A/A_0 [%]
Target	< 2
Dead volume of apparatus	≈ 10–20 (1% of it in the safety vessels)
Trapping in capillary	78–88
Overall isolation yield	76–86

less steel were tested as well, quartz capillaries proved to be the most suitable concerning trapping efficiency, elution yield and cost factor.

By applying a special temperature program (see Table 2) n.c.a. radiobromine was distilled from the target at an oven temperature of $\approx 940^\circ\text{C}$. Under constant argon flow of 10 mL/min the radioactivity was carried into a quartz capillary (100 mm $\times$ 2 mm $\times$ 0.8 mm; length $\times$ $\varnothing_{\text{outside}} \times \varnothing_{\text{inside}}$) and condensed at the interior surface. After a short cooling period the capillary could be detached and rinsed with an aqueous solution of (e.g. 0.1 M) NaOH. This separation procedure takes about 1 h in total and the target is immediately reusable for the next irradiation.

By using NiSe targets with a maximum mass of 308 mg/cm² only about 2% of the produced radioactivity remains in the target. The implementation of a funnel-shaped interior part drastically reduced the dead volume of the device and hence the loss of radioactivity. Conservatively estimated, about 10%–20% of the whole radioactivity got lost in the dead volume; only 1% thereof was found in the safety vessels. In total the described apparatus allows for high, reproducible isolation yields of 76%–86% (see Table 3).

Rinsing the quartz capillary with less than 100 μL NaOH solution enables the recovery of about 96% of the trapped radioactivity in the first elution. In the scope of this proof-of-principle investigation, about 80 MBq ^{76}Br , 33 MBq ^{77}Br and 20 MBq ^{82}Br were obtained 1.5 h after EOB of a 3 h irradiation at 10 μA . Thus, the volume of the bromide solution was significantly reduced compared

to earlier procedures. The obtained n.c.a. [$^{*}\text{Br}$]bromide could immediately be used for subsequent radiosyntheses without further purification or volume reduction steps and is hence particularly suited for applications in mini-synthesizers or microfluidic systems. Furthermore, the application of the easily removable capillary for trapping the radiobromine markedly improved the handling of the distillation method.

4 Quality control of separated n.c.a. radiobromide

The radionuclidic composition as well as the amount of radioactivity in the n.c.a. radiobromide solution was determined by γ -ray spectrometry on HPGe detectors and subsequent peak area analysis using the program *GammaVision 6.01* (EG&G Ortec, USA). No non-isotopic radioactive impurities were found in the radioactive solution. Due to the use of $^{\text{nat}}\text{Se}$ as target material for radiochemical studies the control of the isotopic purity was irrelevant, as discussed above in the targetry section.

Specification of radiochemical purity was done via radio-IC (ion chromatography) measurements by detection of conductivity and radioactivity (NaI detector) for non-radioactive and radioactive species, respectively. Measurements were performed using the IC-system 882 *Compact IC Plus* of Metrohm, Germany, in combination with a Metrosep A Supp 5 250/4.0 anion exchange column at an eluent composition of 3.2 mM CO_3^{2-} / 1 mM HCO_3^- (0.7 mL/min). In the IC spectra only one radioactive signal at the retention time of bromide was observed and the presence of other non-radioactive ionic species could be excluded within the detection limit of the used IC system (< 1 $\mu\text{g/L}$).

5 Conclusion

With respect to an efficient cyclotron production of the medically interesting bromine isotopes ^{75}Br , ^{76}Br , ^{77}Br , $^{80\text{m}}\text{Br}$ and ^{82}Br a new NiSe target was developed. Compared to the conventionally used Cu_2Se , this new target material contains a markedly higher amount of selenium. Thus, under analogous experimental conditions significantly higher radionuclide yields are to be expected when using NiSe as target material. In addition, its approximately 150 $^\circ\text{C}$ lower melting point contributes to operational safety and handling. Using a water-cooled slanted target system, NiSe was successfully tested up to beam cur-

rents of 16 μA protons. Here, no deterioration of the target material was observed, making NiSe exceedingly suited for large scale production of radiobromine. Synthesis of enriched Ni^{*}Se for isotope specific production is warranted.

Furthermore, an optimized dry distillation device for the isolation of n.c.a. [⁷⁶Br]bromide allowed for nearly quantitative removal of radiobromine from the target material and for an improved handling. Using a quartz capillary, radiobromide was obtained in a small volume of less than 100 μL aqueous NaOH and is ready for subsequent radiosyntheses without further purification. After the separation procedure the NiSe target is immediately reusable for the next irradiation.

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