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$^{76/77}$Br Production Using CoSe Cyclotron Targets for Small Molecule Radiopharmaceuticals

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HIPPO
Horizon-Broadening Isotope Production Pipeline Opportunities

Motivation and Objectives

Diagnostic positron emitter ^{76}Br ($t_{1/2}$=16.2 h) and therapeutic Auger emitter ^{77}Br ($t_{1/2}$=57.0 h) have benefits over radioiodine:

1. Less dehalogenation = more stable carbon-halogen bonds due to the higher electronegativity of bromine (2.8) v. iodine (2.5). This means that it is a stronger polar covalent bond.

$$^{\delta+}C\text{-}Br^{\delta-} > {}^{\delta+}C\text{-}I^{\delta-}$$

This lends greater stability to brominated compounds in vivo.[1]

2. Less dosimetric burden on patient due to more diffusive distribution. Unlike iodide, bromide does not accumulate in the thyroid but remains in the blood. Similarly, bromide's rapid distribution means that it yields close to its final distribution after only five minutes. Its biological half-life in humans is 9-12 days.[1]

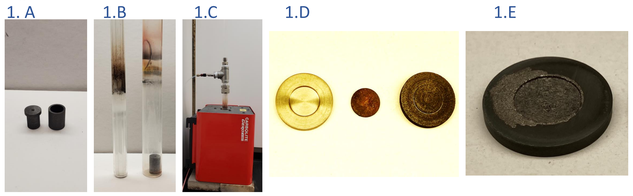
These are some of the reasons why $^{76/77}$Br are a promising theranostic pair. To harness this possible use, proper procedures for cyclotron production, radiochemical isolation and radiosynthesis of radiobromine is required.

Main objective: develop and optimize the production of clinical quality ^{76,77}Br.

Cyclotron Production Methods

Production of Co^{76,77}Se Intermetallic Cyclotron Targets

Figure 1



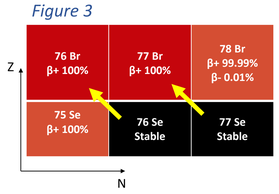
After forming enriched Co^{76}Se or Co^{77}Se at 1100°C in sealed quartz ampoules, the amorphous CoSe is formed into a 10 mm ⌀ disc inside a graphite crucible (Fig. 1.A-1.C). To complete the target coin, this disc is hot-pressed into a 19 mm ⌀ pocketed niobium disc (Fig. 1.D-1.E).

Figure 2

Subsequently, a customized ARTMS Quantm Irradiation System (QIS)™ capsule houses the CoSe coin and niobium backing. (Fig. 2)

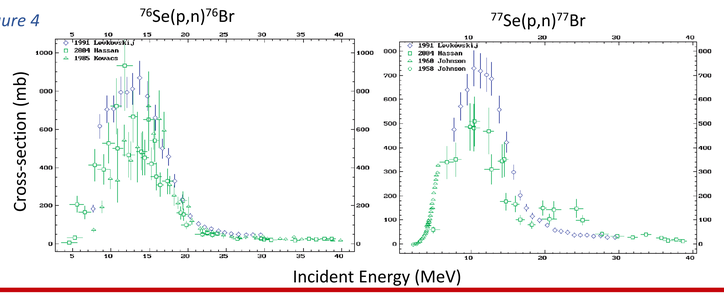
Cyclotron Production of $^{76/77}$Br

Figure 3



$^{76/77}$Br is produced by 40 μA 12.5 MeV proton irradiation (Fig. 3) using a GE PETtrace cyclotron.
Fig. 4 shows the excitation functions for enriched ^{76}Se(p,n)^{76}Br and ^{77}Se(p,n)^{77}Br.[2]

Figure 4

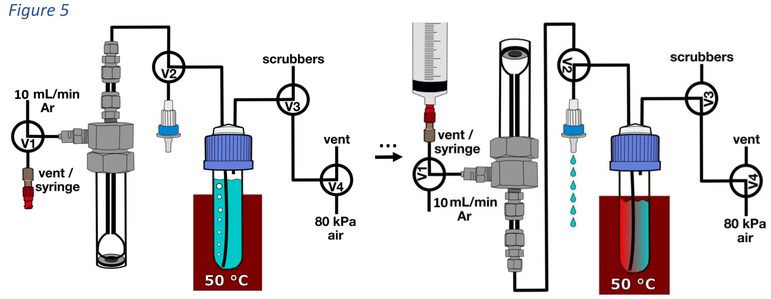


Radiochemical Methods

Radiochemical isolation of radiobromine

$^{76/77}$Br is isolated from the target material using a vertically oriented thermal chromatographic or "dry" distillation method. In this procedure, the $^{76/77}$Br is rinsed into an H_2O trap, followed by trapping on a quaternary methyl ammonium (QMA) anion exchange cartridge.

Figure 5



Distillation → Quench → Flip → Vent → Rinse x 5 → Load QMA

New QMA preparation and elution conditions for [$^{76/77}$Br]bromide isolation were investigated using tetraethylammonium bicarbonate (NEt_4HCO_3), which has established compatibility for radiochemical halogenation of iodonium ylide precursor molecules.

Lastly, high purity germanium (HPGe) gamma spectrometry and dose calibrator measurements assessed the radionuclidic purity and radiochemical yield of the distillation.

Results

Figure 6

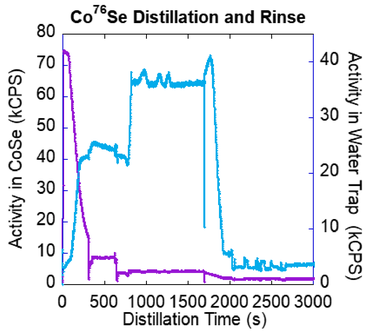
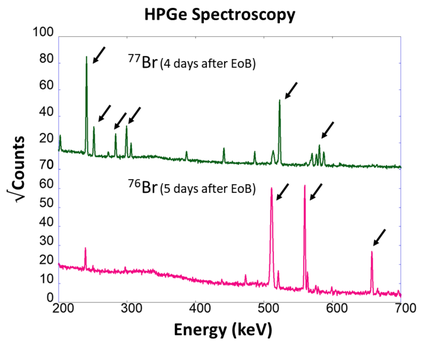


Figure 7



- Elemental cobalt and selenium powder readily fused into solid pieces (270 ± 20 mg) in 1 h at 1200 °C inside a vacuum ampule. Typical mass losses to the ampule walls were 6 ± 4% (n = 10).[3]
- Cyclotron production yields were 103 ± 10 MBq·μA^{-1}·h^{-1} for ^{76}Br and 17 ± 1 MBq· ·μA^{-1}·h^{-1} for ^{77}Br.
- The distillation in (Fig. 6) demonstrates how radiation travels from the Co^{76}Se coin into the water trap. The importance of rinsing is exemplified by the significant increase of activity at 900 s.
- Moreover, the average decay corrected yield of the radiobromide recovered from the H_2O trap is 70 ± 13% (n = 26).
- Using HPGe spectroscopy (Fig. 7), the end of bombardment (EoB) radionuclidic purity was measured to be 99.7% and 99.6% for ^{76}Br and ^{77}Br, respectively.

Results

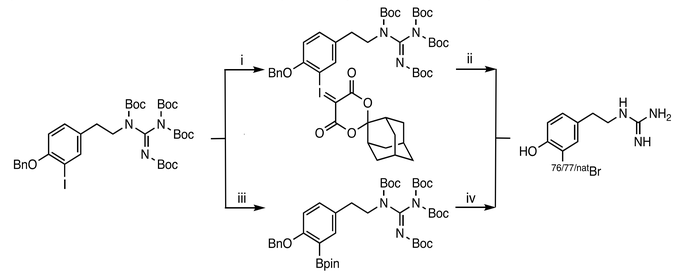
Figure 8

	QMA Equilibration Agent	$^{76/77}$Br Trapping (%)	QMA Elution Agent	$^{76/77}$Br Eluted (%)	*n*
Mixdorf, 2023[4]	$NaHCO_3$ (0.5 M)	99 ± 0.5% n= 9	Me_2NH (0.1 M)	94 ± 6%	6
New	$NaHCO_3$ (0.5 M)	95 ± 3.4% n = 4	NEt_4HCO_3 (0.014 M)	96 ± 3.3%	4

QMA loading tests with NEt_4HCO_3 elute for $^{76/77}$Br demonstrate a high recovery yield of 96.6 ± 3.3% (n = 4). The new preparation and elution combination seem to have comparable results to previous procedures. This data represents various configurations of QMA elution. One configuration used acetonitrile (MeCN) as the organic base for the elution agent, azeotropically dried with argon. Meanwhile the other configuration used N,N-dimethylformamide (DMF) and was azeotropic drying-free.

Conclusions & Future Work

In conclusion, this work has demonstrated a viable method to produce clinical quality $^{76/77}$Br using novel CoSe cyclotron targets and a dry distillation method for radiochemical isolation. This has been used to synthesize ^{77}Br-labeled PARP-1 inhibitors and further studies will expand its application to radiopharmaceuticals targeting norepinephrine transporter. The precursor will be an aryliodonium ylide precursor molecule, based on an improved synthesis of [^{18}F]3F-pHPG.[5]



i. a) Dimethyldioxirane, AcMe, AcOH, 0 °C, b) SPIAd, EtOH, Na_2CO_3, H_2O
ii. a) $Et_4N[^{76/77/nat}Br]Br$, DMF, 120 °C, 10 min, b) 3 M HCl, 120 °C, 15 min.
iii. Bis(pinacolato)diboron, $PdCl_2$dppf, KOAc, DMSO, 80 °C, 2 h.
iv. a) $[^{76/77/nat}Br]$, $Cu(py)_4(OTf)_2$, 3,4,7,8-tetramethyl-1,10-phenanthroline, MeOH, rt, 30 min, b) 3 M HCl, 120 °C, 15 min

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Acknowledgements

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