



Simplified and automatable radiochemical separation strategy for the production of radiopharmaceutical quality ^{86}Y using single column extraction chromatography



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HIGHLIGHTS

- Simple radiochemical separation using single column extraction chromatography.
- Separation strategy for production of high-quality theranostic Y-86 applications.
- Process allows for high recycling efficiency of the enriched target material.

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ABSTRACT

We present a simplified, automatable single-column radiochemical separation method using the extraction chromatographic branched-DGA resin for the production of no-carrier-added ^{86}Y with a radiochemical yield higher than 95%, an apparent molar activity of $1.4 \pm 0.4 \text{ Ci}/\mu\text{mol}$ (DOTA) and $2.3 \pm 0.7 \text{ Ci}/\mu\text{mol}$ (DTPA), and a run-to-run recycling efficiency of the isotopically-enriched target of $98 \pm 1\%$. These results enable the preparation of ^{86}Y radiopharmaceuticals for $^{86}\text{Y}/^{90}\text{Y}$ -based cancer theranostic applications.

1. Introduction

Targeted radionuclide therapy (TRT) for the treatment of cancer is rapidly gaining momentum in the US and Europe. Of several β^- -emitting isotopes employed in TRT, ^{90}Y plays an essential role thanks to its favorable chemical and dosimetric properties. Increasingly widespread utilization of ^{90}Y motivates the use of the β^+ -emitter ^{86}Y as an imaging surrogate in theranostic applications. Being chemically identical to ^{90}Y , the incorporation of ^{86}Y ($t_{1/2} = 14.7 \text{ h}$, 66% EC, 34% β^+ , $E_{\beta^+ \text{max}} = 3.2 \text{ MeV}$) into existing ^{90}Y -labeled radiopharmaceuticals is seamless and allows for the noninvasive investigation of the pharmacokinetic profile, tissue distribution, and radiation dosimetry of these compounds with positron emission tomography (PET) imaging (Qaim and Spahn, 2017; Rösch et al., 2017; Aluicio-Sarduy et al., 2018). To date, several methods for the production of ^{86}Y have been investigated (Qaim and Spahn, 2017; Rösch et al., 2017; Baimukhanova et al., 2018). Among them, cyclotron production based on the $^{86}\text{Sr}(p,n)^{86}\text{Y}$ nuclear reaction

has proven the most feasible route to obtain ^{86}Y with high radionuclidic and radiochemical purities. This route requires isotopically enriched ^{86}Sr (see Qaim and Spahn, 2017 and references therein), necessitating recycling of the expensive target material. In this work, we report a novel method that employs solid-phase extraction chromatography using a DGA resin to efficiently isolate ^{86}Y from enriched $^{86}\text{SrCO}_3$ targets, which significantly improves the radiochemical yield and provides ^{86}Y with apparent molar activities amenable to the radiolabeling of small molecules, nanoparticles, and antibodies for preclinical imaging of cancer. Importantly, near-quantitative recovery ($98 \pm 1\%$) of $^{86}\text{SrCO}_3$ is also achieved.

2. Materials and methods

Ultra-pure reagents were used for the radiochemical separation process and the recovery of the target material: Optima grade HCl and HNO_3 were purchased from Fisher Scientific; puratronic grade

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(NH₄)₂CO₃ (99.999%) was from Alfa Aesar; and isotopically enriched ⁸⁶SrCO₃ (96.40%) was obtained from Isoflex. All solutions were prepared using 18 M Ohm cm water. To ensure metal-free surfaces, the glassware and tools were washed with Alconox, treated with 1 M HNO₃, rinsed with 18 M Ohm cm water, and dried in an oven at 120 °C.

2.1. Target and bombardment

⁸⁶Y was produced using a 16 MeV GE PETtrace cyclotron via the nuclear reaction ⁸⁶Sr(p,n)⁸⁶Y from enriched ⁸⁶SrCO₃ targets covering the energy range E_p = 14.1–7.1 MeV. Before irradiation, the ⁸⁶SrCO₃ powder was pressed (250 kg/cm²) into a niobium crucible, which was covered with a 12.7 μm thick niobium foil to confine the target material and degrade the entrance energy of the proton beam to 14.1 MeV. With direct water-jet cooling on the back of the niobium crucible, typical irradiations were performed at currents of 5 μA for up to 2 h.

2.2. Separation of ⁸⁶Y from the ⁸⁶SrCO₃ targets

Following irradiation, the targets were allowed to decay for 4 h to reduce co-produced, short-lived ^{86m}Y (t_{1/2}: 48 min) in the final product. The target material was then dissolved in 5 mL of 9 M HCl, and the separation of ⁸⁶Y from the irradiated ⁸⁶SrCO₃ was carried out by single column extraction chromatography column using a resin functionalized with N,N,N',N'-tetrakis-2-ethylhexyldiglycolamide (branched DGA, Eichrom). The target solution was loaded onto the DGA column, and subsequent washes were performed using 9 M HCl (15 mL) and 0.5 M HNO₃ (15 mL) to remove the bulk strontium and traces of other metallic impurities. The no-carrier-added ⁸⁶Y was quantitatively eluted from the column with 0.1 M HCl (4 × 0.3 mL). All load, rinse, and elution solutions were passed over the column using a peristaltic pump flowing at 1.6 mL/min. The activity was assayed in a Capintec CRC-15R dose calibrator (setting #850/2)

2.3. Chemical and radiochemical analysis

Nuclear reactions, radiochemical yields, and the presence of radionuclidic impurities were evaluated by gamma-ray spectrometry using a calibrated high purity germanium (HPGe) detector (1.9 keV FWHM at 1333 keV). Trace metal analysis of the final eluate was performed by microwave plasma-atomic emission spectrometry (MP-AES) using an Agilent 4200 spectrometer. Typical detection limits of this technique vary by element and are sub-ppm for transition metals.

2.4. Apparent molar activity measurements

The apparent molar activity was determined by titrimetric complexation of the purified ⁸⁶Y with varying concentrations of DOTA and DTPA chelators (Yoo et al., 2005). Briefly, 100 μL aliquots of diluted ⁸⁶Y stock solution (100 μCi at the end of bombardment; EOB) were added to vials containing 50 μL of 0.5 M NaOAc buffer solution (pH = 4.5). Increasing concentrations of DOTA and DTPA (100 μL, 0–100 μg/mL) in water were added to the vessels, which were then vortexed and incubated for 60 min at 80 °C and room temperature, respectively. The percentage of the radionuclide complexed in each sample was monitored by thin layer chromatography (TLC) using silica gel plates run using 1:1 MeOH:10% NH₄OAc (w/v) as mobile phase. Evaluation of the TLC plates was performed by autoradiography on a Packard Cyclone phosphor-storage plate. The retention factor of free ⁸⁶Y was 0 and chelated ⁸⁶Y-DOTA/DTPA was 1.

2.5. Recovery of the enriched target material

After separating the ⁸⁶Y activity, the recovery of the enriched target material was performed via a series of precipitation/decantation steps in saturated (NH₄)₂CO₃ solutions (Rösch et al., 1993). Briefly, the ⁸⁶Sr

contained in the 9 M HCl eluted fractions (load and rinse) was precipitated as carbonate by dropwise addition of freshly prepared solution of saturated (NH₄)₂CO₃, until no more precipitate formation was observed. Afterward, the ⁸⁶SrCO₃ was separated by centrifugation and dried at 120 °C in inert gas atmosphere.

3. Results and discussion

3.1. Irradiation and production yield

The original energy of the proton beam was 16 MeV, but the beam energy was degraded to 14.1 MeV after passing the Nb foil target window. To minimize decomposition of the target material, irradiations were performed by slowly increasing the beam current to the desired value. Production runs lasted an average of 2 h at proton currents up to 5 μA. No apparent damage to the Nb window encasing the target material was observed, and an ⁸⁶Y production yield of 0.11 ± 0.02 GBq/μA h (n = 3) was obtained after irradiating 130–160 mg/cm² ⁸⁶SrCO₃ targets, a physical yield that is comparable to prior literature report. At beam intensities > 5 μA, scorching of the target ⁸⁶SrCO₃ was visible, so beam intensities were limited to 5 μA thereafter.

3.2. Separation of ⁸⁶Y from ⁸⁶Sr

Fig. 1a depicts the separation strategy employed for the radiochemical isolation of ⁸⁶Y using a single branched-DGA extraction chromatography column. The branched DGA resin was selected instead of the normal DGA because large volumes of diluted HCl were required to elute ⁸⁶Y from the latter (Fig. S1) (Pawlak et al., 2013). Owing to the differential affinity of Sr²⁺ and Y³⁺ ions for the branched DGA resin at varied hydrochloric acid concentrations, the selective loading of the Y³⁺ ions from the 9 M HCl solutions used for target dissolution was possible (Horwitz et al., 2005). The poor retention of Sr²⁺ ions allowed the collection of the bulk target material as effluent during the column loading and subsequent 15 mL 9 M HCl washing steps. Load and wash eluents were preserved for later recovery of the expensive ⁸⁶SrCO₃. Additionally, low affinity (K_d < 10) metal impurities such as Cu were also partially eluted at this step (Horwitz et al., 2005).

Next, the column was washed with 0.5 M HNO₃ to elute trace metal impurities of Fe, Zn, and the remaining Cu (Fig. 1b). The removal of these metal impurities is crucial to achieve high radiolabeling yields, particularly when promiscuous chelating agents such as DOTA or DTPA are employed. An affinity constant lower than 2 for all these metals over a wide range of HNO₃ concentrations allows their quantitative removal with this rinse (Horwitz et al., 2005; Pourmand and Dauphas, 2010). However, the lowest 0.5 M HNO₃ was selected to reduce the acidity of the final eluate while avoiding ⁸⁶Y activity losses during the wash.

Finally, the resin's relatively lower affinity (K_d ~ 50) for ⁸⁶Y in dilute HCl (0.1 M) was leveraged to elute ⁸⁶Y in a small volume (≤ 600 μL) with a resulting separation factor of 10⁵, and a radiochemical yield of 96 ± 2% (n = 3).

3.3. Radionuclidic and chemical impurities

The isotopic composition of the enriched ⁸⁶Sr target (0.01% ⁸⁴Sr; 96.4% ⁸⁶Sr; 1.33% ⁸⁷Sr; and 2.28% ⁸⁸Sr) influences the radionuclidic purity of the final product. For a 2 h irradiation, the major radionuclidic impurities relative to the ⁸⁶Y activity at EOB were ^{86m}Y (173%), ⁸⁷Y (0.22%), ^{87m}Y (1.7%), and ⁸⁸Y (0.1%). A cooling period of 4 h after EOB allowed for the decay of ^{86m}Y (99.31% branching ratio to ⁸⁶Y). Following subsequent radiochemical separation, the radioisotopic impurities relative to the ⁸⁶Y activity at the end of chemistry EOC (ca. 5 h post-EOB) were 2.87% ^{86m}Y, 0.27% ⁸⁷Y, 1.62 ^{87m}Y and 0.12% ⁸⁸Y, measured by γ-ray spectrometry (Fig. 2).

The levels of Sr and other common metals affecting the ⁸⁶Y apparent

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