Development of a Chromatograpic Process for Large-Scale Production of No-Carrier-Added ^{177}Lu

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1. Introduction

No-carrier-added (N.C.A.) ^{177}Lu for targeted radionuclide therapy is produced via an indirect route using enriched ^{176}Yb targets (^{176}Yb(n,γ)^{177}Yb → ^{177}Lu), allowing the production of ^{177}Lu with high specific activity. This production route requires the separation of Lu from a large amount of chemically similar Yb, making the separation step essential in the overall process. Because Lu and Yb are adjacent lanthanides with similar chemical properties, their separation is challenging, particularly at higher Yb loading levels. For practical production, separation conditions applicable to gram-scale Yb targets must be established.

In this study, the chromatographic behavior of Lu and Yb was evaluated using stable isotopes under conditions relevant to scale-up. Cation-exchange chromatography was applied to examine the effects of eluent composition and column size on separation performance. The separation conditions were optimized by adjusting the eluent parameters and column dimensions..

2. Methods and Materials

A 0.07 M α-hydroxyisobutyric acid (α-HIBA) solution was prepared as the eluent by dissolving the reagent in distilled water under continuous stirring until complete dissolution was achieved. The pH of the solution was adjusted to 4.2 using ethanolamine. The prepared solution was then passed through a membrane filter prior to use to remove any particulate impurities. PAR (4-(2-pyridylazo)resorcinol) was used as the chromogenic reagent for lanthanide detection. To ensure optimal color development, PAR was dissolved in a pH 9.8 buffer solution prepared from acetic acid and ammonium hydroxide.

The stable isotopes of Lu and Yb used in the experiments were prepared by dissolving Lu_2O_3 and Yb_2O_3 in hydrochloric acid and heating to convert them into their chloride forms. After mixing $LuCl_3$ and $YbCl_3$, the solution pH was adjusted to approximately 2 using 0.1 M HNO_3, and the mixture was loaded onto a column packed with Dowex 50W-X8 resin. After connecting the Lu/Yb-loaded column to the separation column. The separation was carried out by using an LC pump. During the separation process, a color reagent was mixed with the effluent from the separation column via a mixing tee, allowing real-time monitoring of the separation by visual observation and UV/vis detection (Fig. 1).

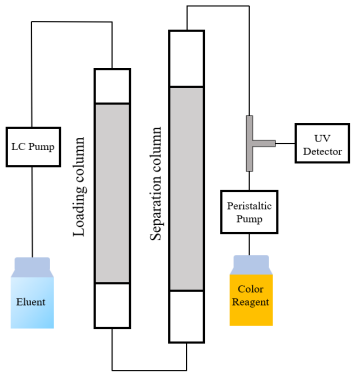

Fig. 1. Scheme of the Lu/Yb separation and detection system.

3. Results

3.1 Evaluation of Loading Column Capacity

The resin used in the loading column was Dowex 50W-X8, which is reported to possess a theoretical ion-exchange capacity of 1.7–1.9 meq/g and to exhibit high adsorption capacity at pH 2. To evaluate the practical ion-exchange capacity under the adsorption conditions, Yb_2O_3 dissolved in 0.1 M nitric acid was loaded onto the column. The experimental results indicated that approximately 7.95 g of resin was required for adsorption of 1 g of Yb_2O_3. Based on this result, quantitative determination was feasible under mixed Lu/Yb loading conditions (5 mg Lu and 1 g Yb).

3.2 Separation of Lu from Large-Scale Yb

The mixture containing 5 mg of Lu and 1 g of Yb was loaded onto a loading column (15 mm × 6.2 cm) packed with 10.2 g of resin and connected to a separation column (50 mm × 4 cm) containing 78.5 g of resin. The separation was carried out using 0.07 M α-HIBA as the eluent at a flow rate of 10 mL/min under a pressure below 100 psi. The effluent from the separation column was continuously mixed with 0.2

mM PAR via a mixing tee, and the separation was monitored in real time by absorbance measurement. As a result, Lu exhibited relatively lower affinity toward the resin and was eluted first, appearing as the leading peak. Yb was subsequently eluted, confirming the chromatographic separation of the two lanthanide elements. After the Yb peak was detected, the concentration of α-HIBA was increased to accelerate the complete elution of the remaining Yb from the column (Fig. 2).

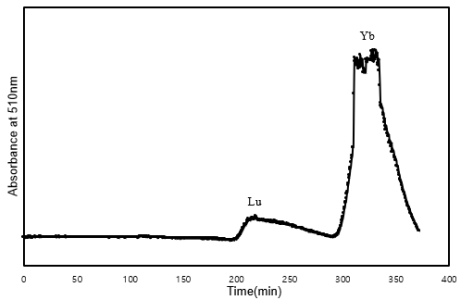

Fig. 2. Chromatographic separation of 1 g of Yb and 5 mg of Lu using 0.07 M α-HIBA (pH 4.2) as the eluent. The effluent was mixed with 0.2 mM PAR, and the absorbance was monitored at 510 nm using a UV/vis detector.

3. Conclusions

Stable isotopes were employed to evaluate a separation process relevant to the production of NCA ^{177}Lu. Using cation-exchange chromatography, Lu was successfully separated from gram-scale Yb targets, enabling the production of approximately 10 Ci of ^{177}Lu per batch under practical irradiation conditions. A loading column was implemented to enhance process robustness and ensure stable operation during scale-up. Based on these results, the optimized process is expected to contribute to the production and stable supply of high-purity NCA ^{177}Lu for clinical applications.

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