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Lu-177 preparation for radiotherapy application

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HIGHLIGHTS

- A separation study has been performed using an organo-ceramic hybrid material for the production of NCA ^{177}Lu.
- A remote separation system with a dedicated program for a Yb/Lu pair has been developed.
- This method is suitable for preparation of the NCA ^{177}Lu by using a few mg of enriched Yb target.

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ABSTRACT

A separation study using a ^{176}Yb target for the preparation of nca ^{177}Lu, which is a beta-emitting nuclide used not only in radioimmunotherapy applications but also in the treatment of various lesions, has been performed. A material having a better selectivity and separation efficiency for Lu than Yb was developed, and the separation conditions of ^{177}Lu were derived using this from a neutron irradiated ^{176}Yb target. The separation material was an organo-ceramic hybrid material containing a phosphate group. Adsorption behavior was determined through batch experiments, and ^{177}Lu separation from the Yb target was evaluated through column experiments. The Yb target, with a 99.72% in ^{176}Yb, was irradiated in the irradiation hole of HANARO, which has a thermal neutron flux of 1.6E+14 n cm^{-2} s^{-1}. The batch experiments revealed that the organo-ceramic hybrid material (Sol-POS) had a separation factor of 1.6 at 0.5 M HCl. Separation was performed through extraction chromatography using a 5 mg enriched Yb target, and the separation yield of the NCA ^{177}Lu was about 78%. If the amount of Yb target is increased to produce curies level ^{177}Lu, additional purification will be needed.

1. Introduction

In radioisotope-based therapy, various attempts are being made to develop radiopharmaceuticals, which utilize labeled compounds, antibodies, and peptides to transfer beta- and alpha-emitting nuclides to specific lesions (Bergsma et al., 2012; Beylergil et al., 2013). For in vivo treatment, the use of highly specific activity radionuclides is essential, and lanthanides, such as samarium (Sm), terbium (Tb), holmium (Ho), and lutetium (Lu), etc., are highly favored (Knapp et al., 2005; Lehenberger et al., 2011). Among them, ^{177}Lu is a representative nuclide, and can be mass produced in research reactors. ^{177}Lu can be prepared directly using ^{176}Lu as a target, or indirectly using ^{176}Yb. The former involves a simple chemical process after irradiation and can produce mass amounts of ^{177}Lu, but the ^{177}Lu product includes ^{177m}Lu with a long half-life and nonradioactive isotopes of Lu contained in the target material. Therefore, the specific activity of ^{177}Lu is comparatively low. Indirectly-prepared ^{177}Lu on the other hand has a specific activity that is at least 10-times higher than that of directly-prepared ^{177}Lu, and is more suitable for radioimmunotherapy using biomaterials such as monoclonal antibodies. As such, the preparation of ^{177}Lu from the ytterbium (Yb) target is more widely studied in related fields (Horwitz et al., 2005).

The key for the preparation of no-carrier added (NCA) ^{177}Lu using an indirect method is a successful separation of ^{177}Lu from a macro amount of Yb target, which have similar chemical properties as the final product. In the past, solvent extraction with organo-phosphorous extractants, carboxylic acids and other amines or ion exchange chromatography with resin containing has been used in the separation of individual lanthanides from a Yb/Lu pair (Lahiri et al., 1998; Cha et al., 1997). Extraction chromatography, which has a combination of solvent extraction and ion-exchange chromatography, has recently emerged as another method (Horwitz et al., 2005; Van So and Morcos, 2008; Van So and Morcos, 2008a, 2008b).

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In this paper, we describe the separation technology based on chromatography using a chelating reaction in a column for preparation of NCA ^{177}Lu from the ^{176}Yb enriched target. The sorbent materials containing phosphate groups were selected for this experiment and its applicability was experimentally evaluated using the irradiated targets at a research reactor (HANARO).

2. Materials and measurement

The target materials used were ^{176}Lu, ^{168}Yb and ^{176}Yb in oxide form, and their isotopic enrichment were 74.1% in ^{176}Lu, 20.1% in ^{168}Yb and 99.72% in ^{176}Yb, respectively. They were purchased from Trace-Sciences International Inc., USA. The solid phase extractants as the column material were used as organophosphorus-functionalized silica developed at the Korea Atomic Energy Research Institute (KAERI) (Lee et al., 2009). They had an average particle size of 50–75 μm. All chemicals used in this work were at least of ACS reagent grade. The quantitative analysis of radioactive samples was performed using HPGe gamma spectroscopy (ORTEC Inc. GEM 20P4-70). The elution profile of ^{177}Lu and Yb nuclides from the column was checked by the Radio-Isotope Separation System (RISS).

3. Experimental

3.1. Irradiation target design

A triple container, which was specially designed, was used for irradiation of the target material Yb_2O_3 at HANARO (30 MW multipurpose research reactor located at Daejeon, Republic of Korea). The target material Yb_2O_3 was primarily sealed in a quartz ampoule, and sealed two more times in Al containers. The designed capsule was assessed for thermal stability, such as the expected heat generation and temperature, during irradiation at the IP-15 hole (thermal flux: 1.6E+14 n cm^{-2} s^{-1}), which has the highest neutron flux among the on-power loading irradiation holes of HANARO.

3.2. Preparation of radioactive solution

For preliminary experiments, the radioactive ^{177}Lu and ^{175}Yb solutions were obtained by the irradiation of $^{176}Yb_2O_3$ enriched target. After neutron irradiation, the target was dissolved in a 1.5 ml solution of 6 M HCl added with a few drops of 35% H_2O_2 with heating on a hot plate. Next, the target solution was reconditioned through several cycles of the dry evaporation and the addition of distilled water. The final adjustment was made with 0.1 M HCl. In column experiments, the enriched $^{176}Yb_2O_3$ was irradiated for 7 days in the same irradiation hole and processed as described earlier.

3.3. Determination of adsorption behavior through batch experiments

Batch experiments were performed to evaluate the behavior of Yb and Lu based on changes in the concentration of HCl. Seven flasks containing a 25 ml HCl solution, each (0.01 M, 0.05 M, 0.1 M, 0.2 M, 0.5 M, 1 M and 2 M) itself containing a mixture of 1 mg Yb and 1 mg Lu spiked with radioactive ^{175}Yb and ^{177}Lu were used. Then, 0.2 g of each adsorbent were added into each flask. The two types of organophosphorus-functionalized silica named Sol-POS (functionalized by RO-P=(-R)-OH) and Sol-PSO (functionalized by R-P=$(OH)_2$) were used as an adsorbent. After stirring for 2 h, suspended materials were removed using a 0.25 μm filter. The Radioactivity was compared to the initial solution to calculate the distribution coefficient and adsorption rate for each nuclide.

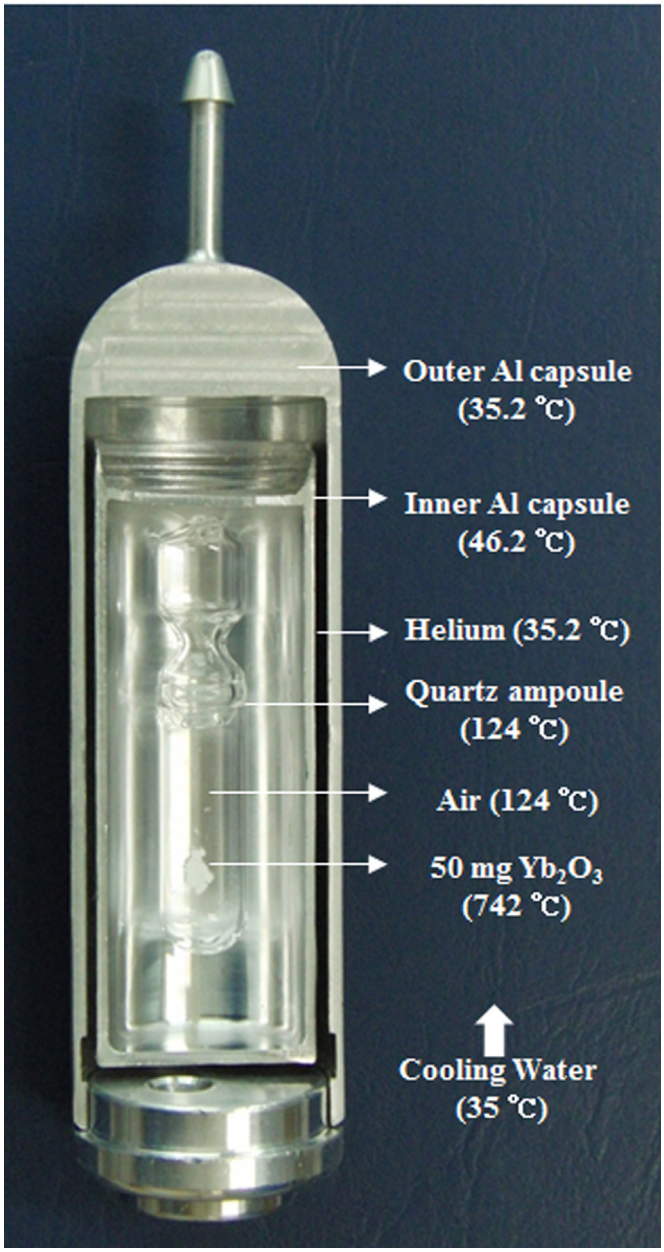

Fig. 1. Temperature distribution in target capsule during the neutron irradiation.

3.4. ^{177}Lu separation through column experiments

Based on the concentration of eluents obtained from the batch experiments, the elution rate was fixed at 2.6 ml cm^{-2} min^{-1} at room temperature. Lu and Yb separation conditions were examined while varying the packing height of the organophosphorus-functionalized silica. Considering the amount of Lu produced by irradiation of the Yb target at HANARO, the radioactive ^{175}Yb and ^{177}Lu were added as tracers to a stock solution in which Yb and Lu were mixed at a ratio of 1:10^{-3}. Five mg of enriched Yb target was irradiated for 7 days at the IP-15 irradiation hole and allowed to decay for a certain period of time before using it. The radioactivity measurement of each isotope was performed by HPGe gamma spectroscopy (ORTEC Inc. GEM 20P4-70) using 396 keV of gamma rays emitted from ^{175}Yb ($T_{1/2}$=4.19 days) and