Method of Separating Carrier-Free Ho-166 and Purification using Chromatography

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1. Introduction

This Study is about the separation and purification of Holmium-166(Ho-166) using chromatographic methods, and suggest a method that can significantly improve the purity of Ho-166 by indirect producing process.

Ho-166, one of main nuclides produced nuclear reactor, is remarkable therapeutic effect in the fields of nuclear medicine. Ho-166 shows good candidate for theranostic effects, because it emits a proper γ-energy(80keV) for diagnosis and therapeutic β-energy(E_β = 665.7keV). Ho-166 can be produced directly and indirectly like below.

Direct production [(n,γ) reaction]:
$^{165}Ho(n,\gamma)^{166}Ho$
Indirect production [(n,γ)β reaction]:
$^{164}Dy(n,\gamma)^{165}Dy(n,\gamma)^{166}Dy \rightarrow {}^{166}Ho + \beta^-$

Generally, most of the medical studies have been carried out with direct produced Ho-166 using neutron irradiation with stable Ho-165. This system contains a large amount of inactive holmium and as a results large amounts of ligands was required in the labeling process. Representatively, ^{166}Ho-DOTMP for bone seeker and ^{166}Ho-RMHA for synovectomy have been studied, and radioembolizing agents for liver cancer have been evaluated.

In the 2000s, as the development of radiolabeling technique on antibodies was established, high purity radionuclides have been required to improve labeling yield. Compare to direct production, indirect production can provide the highly purified radionuclides but it go through a rather sophisticated separation process. It is necessary to selectively separate a trace amount of elements(Ho-166) generated by neutron irradiation from the target element(Dy-164)

Dy-166 as parent nuclide can be produced by double neutron capture reaction of stable Dy-164. Ho-166 produced by β decay from Dy-166 [$T_{1/2}$=81.5 h, E^{β}_{max}=486.8 keV, E^{β}_{av}=130 keV] can be separated from Dy-166 since two elements have slightly different chemical properties.

To induce a change in chemical properties between Dy and Ho, several papers have reported that the ionic character change of lanthanides complexing with appropriate chelating agents can isolate the target lanthanides [1-3]. These specific agents to the metal ion are called as complexing agents.

F, De Corte et al suggests the importance of the secondary reaction interference in double neutron capture and shows the reaction scheme like below.[4]

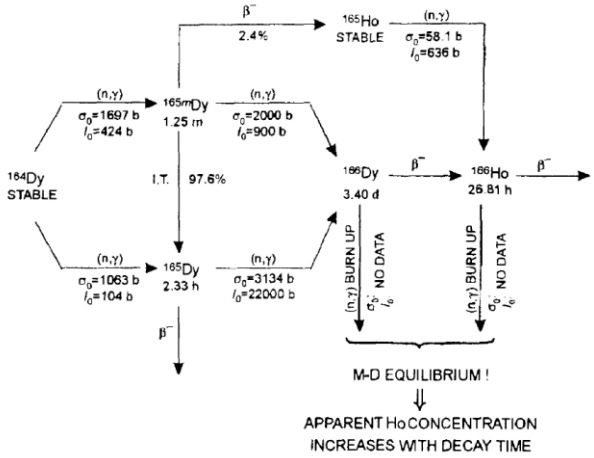

Fig. 1. Nuclear Reaction of Dy-164 target.

At the end of bombardment, there can be mainly two nuclide groups in the target. One is holmium group in which Ho-166 and Ho-165 are present, the other is dysprosium group in which Dy-164, Dy-165, Dy-165m, and Dy-166 are present. Susanta Lahiri separated Ho-166 from Dy-166, but it can be said that it is not exactly carrier free state since Ho-165 is also included. In order to obtain carrier free Ho-166, the separation is carried out first, and secondary separation should be performed after the time laps for new radioactive equilibrium.

RI handling works such as establishment of optimal separation conditions always result in radiation exposure risk and may generate radiowaste. To minimize these drawback, KAERI has developed separating and simultaneously identification technique from two lanthanides by using coloring agents and ion-pairing agents under conditions that do not need RI. KAERI also has developed an automated system for separating pure target radioisotopes, which is aimed to protect operators from harmful radiation as well as to reduce the separation time. The separation of the RI can be confirmed by the RI detection part to control the RI separation.

The works to obtain carrier fee Ho-166 are carried out in two step as like below. The first step is to perform the first column separation to obtain the Dy-fraction after melting the irradiated target (Dy target). The second step is to collect n.c.a Ho-166 through the

secondary column separation after radioactive equilibrium is established. The obtained Ho mixture is subjected to washing process and drying to obtain carrier free Ho.

In this presentation, we will discuss the cold separation studies for lanthanides and real-time metal ion detection. Based on these research, the production of Ho-166 was carried out and discussion will be conducted.

2. Experiments

2.1. Instrumentation with the post-column reaction system

The HPLC instrument consisted of a high pressure pump and a six-port Rheodyne valve equipped. The lanthanide sample was injected into the mobile phase HIBA delivered at a flow rate of 1.0 ml/min. The eluted metal ions were mixed in a mixing-tee with the post-column reagent added using a syringe pump with a flow rate of 0.7 ml/min. Then, the mixed solution was monitored using a UV-vis spectrophotometer. The absorbance according to time-interval was checked and plot the absorbance like below.

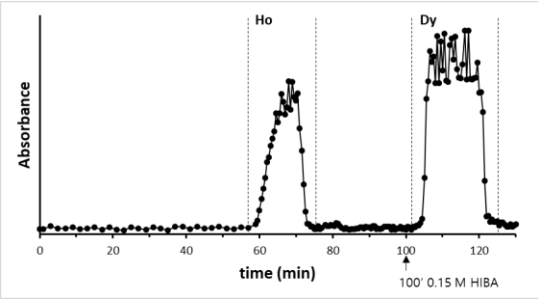

Fig. 2. Chromatogram of separated Ho and Dy

2.2. Automated system for lanthanide separation

The system is composed of four main parts: high pressure pump, switching/selection valve, RI detection, and controller.

2.3. Separation and purification of Ho-166

1 ml of sample, including 30 mg of Dy, is injected into the prepared column under isocratic condition in which the eluent α-HIBA is flowing at 3 ml/min. When the first elution of Dy is identified, replace with high concentration eluents to get a Dy fraction. The obtained fraction is adsorbed into small column containing cation exchange resin. After 1 day, small column connects the separation column. After obtain Ho fraction by doing secondary separation process, crude Ho is adsorbed into small column and washing it. Detaching process was done by using high concentrated acid.

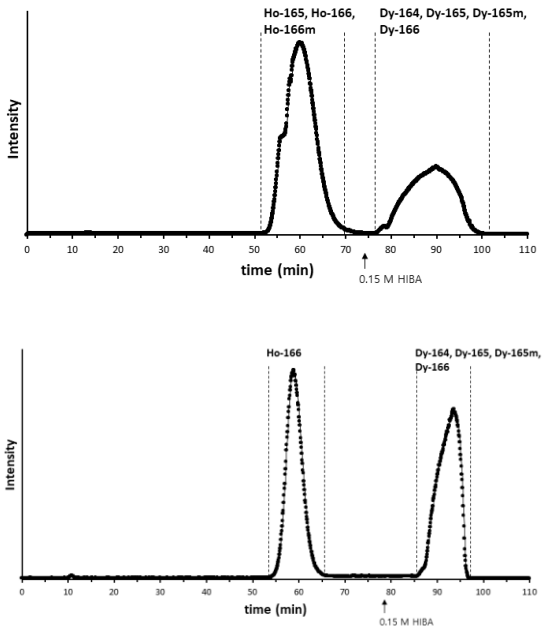

Fig. 3. Chromatogram of separated Ho-166 and Dy target(above : 1st column separation, below : 2nd column separation)

3. Results and Discussion

Ho-166, developed through this study, was provided to two research institutes in KOREA, and research like radiopharmaceutical evaluation is currently being conducted. In the future, the study of large capacity production will be carried out and it will expand the pilot supply in KOREA

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