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Isolation of Gadalonium /Terbium using Extraction chromatography approach for therapeutic issues

N. Salek[1*], S. Vosoughi[2], P. Afshar[3], M. Salehi Barough[3], M. Mehrabi[2]

[1] *Nuclear Fuel Research School, Nuclear Science and Technology Research Institute (NSTRI), P.O. Box 1439-5836, Tehran, Iran*
[2] *Radiation Application Research School, Nuclear Science and Technology Research Institute (NSTRI), P.O. Box 1439-5836, Tehran, Iran*
[3] *Department of Medical Radiation, Engineering Faculty, Central Tehran Branch, Islamic Azad University, Post Code 1955-847781, Tehran, Iran*

ABSTRACT

^{161}Tb is a promising radionuclide, which is a suitable radionuclide with favorable properties for small treatment size of cancer. NCA ^{161}Tb can be produced by the indirect method through ^{160}Gd(n,γ) ^{161}Gd→^{161}Tb nuclear reaction. To obtain the NCA radionuclides, the existence of an effective Gd/Tb separation method is critical. In this study, isolation of Tb from Gd/Tb matrix using Ln resin column based on extraction chromatography method has been carried out. Fractions eluted from the column containing Gd/Tb matrix were identified and quantified using ICP. The optimization of different experimental parameters for the effective separation of Gd/Tb, such as concentration of eluting solutions and flow rate of load and elution, was investigated. The results showed that optimum Gd/Tb isolation condition was obtained using HNO_3 solution with a concentration of 0.8 and 3 N to separate gadolinium and terbium isotopes, respectively. The separation yield of Tb and Gd was obtained at 83.51 % and 81.8%, respectively.

***Keywords*:** No Carrier Added, Extractin choromatography, Therbium-161, Targeted therapy

I. Introduction

Advances in nuclear medicine, such as external radiotherapy and targeted radionuclide therapy, have led to a dramatic increase in the availability and development of new methods of cancer treatment [1]. External radiation therapy with ionizing radiation is cancer patients' most common radiation therapy. This approach treats the primary tumor and the surrounding area with high-energy X-rays. Targeted radiotherapy is a promising and evolving method of cancer therapy in which cancer cells are destroyed using biological vectors and appropriate radionuclides [2]. Selectiveness in delivering the radiation to the target without fewer side effects and the possibility of assessing the tumor's uptake before the therapy are considered advantages of this approach [3]. Appropriate therapeutic radionuclide selection is one of the most important parts of this procedure which is

**Corresponding Author name:* N. Salek
E-mail address: nsalek@aeoi.org.ir

achived by considering several factors like short physical half-life and high dose rate. The physical half-life of the radionuclide must match the biological turnover of the ligand in vivo. A high dose rate is more suitable for rapidly dividing tumors [4-5]. The theranostic approach in nuclear medicine couples diagnostic imaging and therapy purposes by targeting one specific tumor receptor [6]. Theranostic radio-lanthanides like ^{153}Sm, ^{177}Lu, ^{166}Ho, and ^{161}Tb, have recently drawn great attention in targeted radionuclide therapy [7-9]. Among the theranostic radio-lanthanides, auger-electron emitters, especially in non-carrier added form, have a significant impact on the treatment of tumors because of the relatively short range in the tissue, severe local damage, high cytotoxicity effects and high specific activity, which required in carrier molecules radiolabeling for therapy [10-11]. Several factors influence the selection of an appropriate therapeutic radioisotope.

Terbium-161 (^{161}Tb) with favorable nuclear properties like beta irradiation with energy of 0.55 keV, γ-rays with energy of 26-55 keV (63%), which is suitable for imaging, proper half-life of 6.88 days, and emission of a larger number of conversion and Auger electrons with energies 40-49 keV(54%), 17-26 keV(51%) and 1.5-8 keV (259%) can be considered as a good candidate for small treatment size of cancer. The direct method is not preferred to produce ^{161}Tb, because the only stable isotope of terbium is ^{159}Tb. The NCA ^{161}Tb can be produced indirectly through a $^{160}Gd(n,\gamma)$ $^{161}Gd \rightarrow ^{161}Tb$ nuclear reaction. Due to differences between Gd and Tb nuclides, their separation is achievable, making it feasible to produce NCA 161Tb radionuclide without including cold isotopes [12-13]. There are a number of separation methods described in the literature for the separation of individual lanthanides, which are based mostly on ion-exchange chromatography, solvent extraction, extraction chromatography (EXC), cementation, and electrochemical process. Methods of ion-exchange chromatography and, extraction chromatography (EXC) were successfully used for lanthanides isolation. In this study, isolation of Tb and Gd elements by Extraction Chromatography (EXC) was investigated to achieve a successful methodthat can also be used for active nuclides.

II. Experimental Materials

Natural Gd_2O_3 and Tb_2O_3 were purchased from sigma-Aldrich chemical Company, UK..LN2 resin (25-53μm particle size) was obtained from Eichrom Company. HNO_3(65%) and other chemical materials were obtained from Merck Company. All chemical reagents were of analytical grade. This research used the standard peristaltic pump model 1-S100-1L produced by Longer company.

Extraction Chromatography of Gd/Tb

EXC is a separate procedure that combines the selectivity of solvent extraction with the ease of operation and rapidity of column chromatography. This system (figure 1)

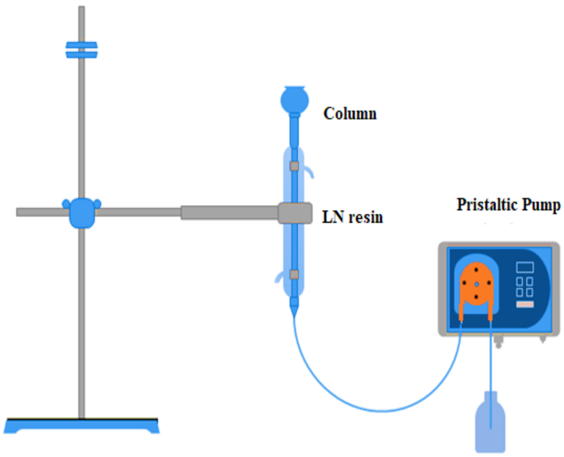

Fig. 1. Extraction chromatography separation system.

consists of a glass column with an inner diameter of 8 mm and a bed height of 18 cm that a layer of glass wool was inserted as top bed support. A peristaltic pump and a polyethylene tube are used to pass the solutions through the column. To obtain optimal conditions for this separation, about 10 g of LN-resin (particle size: 25-53 µm) was wetted in 0.1 N nitric acid for one week and then the column was filled with it. The column was preconditioned by 50 ml of distilled water, 50 ml of 0.1 N nitric acid, and 50 ml of distilled water, respectively. 5 mg of Gd2O3 and 1 mg of Tb2O3 were dissolved in 5 mL of 0.1 M HNO3 and were loaded on the column at a flow rate of 2 ml/min.

Optimization of experimental parameters

Among the experimental parameters such as concentration of eluting solutions and flow rate of load and elution, which influence the selective separation of Tb/Gd, the main separation parameter is the concentration of eluting solutions as the mobile phase of the column.

III. Results and discussion

The effect of elution concentration on Tb/Gd EXC

A continuous sequence of elution concentrations of HNO_3 solutions (0.3M to 4M) was selected to evaluate the isolation of Gd/Tb elements. The eluted solutions were collected in 2.5mL bed volume and analyzed by ICP analysis. Fig. 2 shows the separation profile of Tb and Gd on the Ln resin Column. It can be concluded that in the ranges of 0.5-0.8 M and 2-3 M HNO_3 concentrations, the highest separation was observed for gadolinium nuclei and terbium nuclei, respectively. With increasing acidity concentration up to 4 M, no significant change in the separation process occurred. In the range of 0.8 M, a small peak of terbium is probably related to the continuous trend of increasing concentrations.

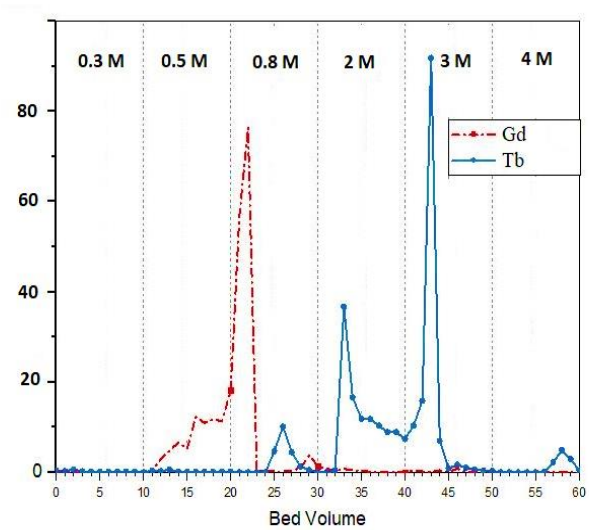

Fig. 2. Separation profile of Tb and Gd on the Ln resin based on ICP analysis.

Also, in this study, various combinations of HNO_3 concentrations were used to obtain the optimum conditions for separation. The EXC column was eluted with each 50 mL of 0.3–4 N; 0.5–2 N; 0.8–3 N, and 2–3 N HNO_3 solutions. The separation yields of Tb and Gd that were obtained from the separation with various combinations of HNO_3 concentrations are summarized in Table 1.

The results show that considering all the conditions, the concentrations of 0.8-3 M are the best choice for separating terbium and gadolinium.

Table 1. The separation yield of Tb and Gd eluted from the column using various combinations of HNO_3 concentrations.

The combination of HNO_3 concentrations (N)	Tb yield (%)	Gd yield(%)
0.3–4	44.12	22.16
0.5–2	61.4	58.7
0.8–3	83.51	81.8
2–3	82.62	21.97

The effect of the flow rate of load and elution on Tb/Gd EXC

The effect of the flow rate of loading and elution on the separation of Gd and Tb is shown in Table 2. A peristaltic pump was used to adjust the flow rate to obtain the optimized conditions for loading and eluting.

Table 2. The effect of the flow rate of load and elution.

The flow rate of loading (ml/min)	The flow rate of eluting (ml/min)	Time of separation (minute)	Separation yield (%)
1	1	110	75.6
1	1.5	77	83
1	1.7	70	79

IV. Conclusions

In summary, the separation of Gd/Tb has been done by extraction chromatography using Ln resin as a stationary phase and nitric acid solution as a mobile phase. The results showed that in order to achieve efficient separation, some factors such as elution concentration must be considered and optimized. In this study, the concentrations of 0.8-3 M are considered the best separation yield to isolate gadolinium and terbium isotopes.

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