

Temperature-dependent cation-exchange separation of terbium tracer from gadolinium using α -hydroxyisobutyric acid: relevance to ^{161}Tb production

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Abstract

Terbium-161 is a promising radionuclide for targeted radionuclide therapy because its decay characteristics combine therapeutic beta particles and short-range conversion and Auger electrons with gamma emissions suitable for imaging and dosimetry. Reactor production via the $^{160}\text{Gd}(n,\gamma)^{161}\text{Gd} \rightarrow ^{161}\text{Tb}$ pathway requires efficient separation of trace terbium from the bulk gadolinium target matrix. This study investigated the temperature dependence of terbium–gadolinium separation by cation-exchange chromatography using Dowex 50W-X8 resin and α -hydroxyisobutyric acid (α -HIBA) as a complexing eluent. Neutron-activated gadolinium and a radioactive terbium tracer were processed at column temperatures of 30, 50, and 70°C. The terbium tracer served as a chemical and radiometric surrogate for the terbium fraction associated with ^{161}Tb ; the direct yield of ^{161}Tb production was not determined. The eluent concentration was 0.3 M α -HIBA at pH 4.40. Fractions were collected at 5 mL intervals and analyzed by high-purity germanium gamma spectrometry. Terbium eluted before gadolinium at all temperatures investigated. Nominal terbium recovery increased from 97% at 30°C to 98% at 50°C and 99% at 70°C, whereas nominal gadolinium contamination decreased from 2.0% to 0.1%. The best separation was obtained at 70°C. Each temperature condition was tested once, so the results are descriptive rather than statistically replicated. Detector calibration uncertainty, background-spectrum uncertainty, and complete efficiency-calibration records were not available for reconstruction; consequently, the reported recovery and contamination values should be treated as nominal single-run values pending verification against the original laboratory records.

Introduction

Targeted radionuclide therapy uses a radionuclide attached to a biologically selective vector to deliver ionizing radiation to malignant cells. The therapeutic performance of the radionuclide depends on its half-life, particle emissions, tissue range, chemical properties, and compatibility with radiopharmaceutical chelators. ^{161}Tb has attracted considerable interest because it emits beta particles along with conversion and Auger electrons. These low-energy electrons can deposit energy over submicrometer distances and may be useful for treating small lesions and disseminated tumor cells. Its gamma emissions also enable imaging and post-therapy dosimetry [1–6].

The principal reactor-based production route for ^{161}Tb is the indirect neutron-capture reaction $^{160}\text{Gd}(n,\gamma)^{161}\text{Gd} \rightarrow ^{161}\text{Tb}$. The short-lived ^{161}Gd intermediate decays to ^{161}Tb [7–11]. Irradiation of enriched ^{160}Gd can therefore provide a route to high-activity terbium; however, the product is generated within a large quantity of gadolinium target material. The chemical similarity of neighbouring trivalent lanthanides complicates their separation, and inadequate removal of gadolinium may reduce the specific activity and chemical suitability of the terbium fraction.

Radiochemical separation methods investigated for terbium and gadolinium include cation-exchange chromatography, extraction chromatography, solvent extraction, high-performance liquid chromatography, and electrochemical separation. Cation-exchange chromatography is attractive

because it is comparatively simple and can exploit small differences in ionic radius and complex formation [10–13]. α -Hydroxyisobutyric acid is an effective complexing eluent for lanthanide separations. Under controlled pH and concentration conditions, the terbium– α -HIBA complex can be eluted before gadolinium [7, 11].

The separation depends on resin type and form, particle size, column dimensions, eluent concentration, pH, flow rate, target loading, and temperature [10–13]. The objective of this study was to investigate the effect of column temperature on the cation-exchange separation of a radioactive terbium tracer from gadolinium using Dowex 50W-X8 and α -HIBA. The study was designed as a laboratory-scale process-development experiment relevant to, but not equivalent to, direct production and purification of ^{161}Tb .

Materials and methods

Target materials and irradiation

Natural gadolinium oxide (Gd_2O_3) and natural terbium oxide (Tb_4O_7) were used as target and tracer materials, respectively. Approximately 6.19–6.44 mg of gadolinium oxide was sealed in aluminum foil and irradiated in the IRT-T research reactor at Tomsk Polytechnic University. The thermal neutron flux density was reported to be approximately $1.7 \times 10^{14} \text{ n cm}^{-2} \text{ s}^{-1}$. The gadolinium target was irradiated for two days, and the terbium oxide tracer was irradiated separately for four hours. The irradiated materials were subsequently processed in accordance with the facility's radiation-safety procedures.

Natural gadolinium was used as an economical chemical surrogate rather than an enriched ^{160}Gd production target. The radioactive terbium tracer was used as a surrogate for the terbium fraction. Consequently, the present experiment evaluates the separation chemistry and does not provide direct measurements of the production yield of ^{161}Tb , specific activity, or radionuclide purity.

Dissolution of the irradiated gadolinium target

The irradiated gadolinium oxide was transferred to a borosilicate glass vessel and dissolved in hydrochloric acid. Initially, 2 mL of 0.04 M HCl was added, and the suspension was heated for 30 min at approximately 130–140°C until it evaporated and solidified. Irradiated gadolinium oxide was transferred into a borosilicate glass vessel and dissolved in hydrochloric acid. In the first step, 2 mL of 0.04 M HCl was added, and the suspension was heated at about 130–140°C for 30 min until it had evaporated and solidified. The residue was then treated with 2 mL of 6 M HCl and heated under the same conditions. The dissolution and evaporation cycle was repeated twice to improve the conversion of the oxide target into a soluble chloride form. After cooling, the final residue was dissolved in 2 mL of 0.04 M HCl.

The terbium tracer target was processed using a similar procedure. The irradiated terbium oxide was treated repeatedly with 6 M HCl and heated at approximately 145°C. Hydrogen peroxide was added

during the dissolution procedure to assist conversion of the target material. The final terbium tracer solution was prepared in 2 mL of 0.04 M HCl.

Preparation of the α -HIBA eluent

0.3 M solution of α -HIBA was prepared by dissolving 62.4 g of α -hydroxyisobutyric acid in 2 L of distilled water. The pH of the solution was adjusted to 4.40 with NH_4OH solution. To measure the pH accurately, a pH meter was used to monitor the pH-dependent elution order of lanthanides, as higher-atomic-number lanthanides (e.g., Tb) form more stable complexes and elute earlier than lower-atomic-number elements (e.g., Gd) at this pH.

Cation-exchange column

Dowex 50W-X8 strong-acid cation-exchange resin in the ammonium form was used for the separation. The resin (200–400 mesh) was packed into a 20cm chromatographic column and conditioned before sample loading. The column was connected to a temperature-controlled fractionation system. Cation-exchange procedures using strong-acid resins and α -HIBA have previously been used to separate terbium from gadolinium and related lanthanide matrices [7, 10–13]. The same general column procedure was applied at 30, 50, and 70°C.

Chromatographic separation

For each experiment, a model solution was prepared by combining the gadolinium solution with the radioactive terbium tracer. The model solutions contained approximately 100 μL of gadolinium tracer and 2 μL of terbium tracer. Gadolinium oxide masses were 6.19, 6.22, and 6.44 mg for the 30, 50, and 70°C experiments, respectively. The model solution was loaded onto the conditioned column using a peristaltic pump. The column was rinsed with 10 mL of distilled water. Elution was performed using 0.3 M α -HIBA at pH 4.40. Fractions of 5 mL were collected using an automated fraction collector. Elution continued until measured activity approached background. The experimental conditions are summarized in Table 1.

Table 1
Experimental conditions for terbium-gadolinium separation

Experiment	Gadolinium oxide mass (mg)	Dissolution temperature (°C)	Separation temperature (°C)
1	6.19	130	30
2	6.22	135	50
3	6.44	140	70

The three temperature conditions were single experiments, not replicate groups. Accordingly, no inferential statistical comparison was performed, and the temperature-dependent values are reported descriptively.

Gamma-spectrometric analysis

The activity of the target solutions and collected fractions was measured using a high-purity germanium (HPGe) detector (Canberra GC2018). The gamma spectra were used to identify and quantify the terbium- and gadolinium-containing fractions. Gadolinium was identified via its characteristic photon peak at 97 keV, corresponding to ^{153}Gd , while terbium (^{160}Tb) was identified by the peak at 298 keV. The measurement data from the detector are shown in Table 2–4. The measured count rates were corrected for radioactive decay and background. The percentage activity in each fraction was calculated as follows.

$$A_i (\%) = \frac{C_{i, \text{corrected}}}{\sum C_{i, \text{corrected}}} \times 100 \quad (1)$$

where $C_{i, \text{corr}}$ is the decay-corrected count rate for fraction i .

Terbium recovery was calculated as:

$$R_{\text{Tb}} (\%) = \frac{\sum A_{\text{Tb, selected}}}{A_{\text{Tb, loaded}}} \times 100 \quad (2)$$

Table 2
Measurement data for 30°C

Test-tube No	Gd	Tb	Dead time %	Date	Time	V (ml)	Measurement Time (s)
5	0	0	0.03	10.04.26	10:45	5	300
6	0	9.80E + 02	0.12	10.04.26	10:52	5	300
7	0	4.61E + 04	3.9	10.04.26	11:02	5	300
8	2.29E + 03	2.94E + 03	0.32	10.04.26	11:11	5	300
9	2.65E + 04	4.30E + 02	0.63	10.04.26	11:20	5	300
10	5.44E + 04	3.11E + 02	1.2	10.04.26	11:28	5	300
11	26900	1.98E + 02	0.62	10.04.26	11:37	5	300
12	6.62E + 02	1.76E + 02	0.06	10.04.26	11:45	5	300
13	3.98E + 02	1.21E + 02	0.05	10.04.26	11:53	5	300
14	2.98E + 02	8.50E + 01	0.05	10.04.26	12:01	5	300
15	1.53E + 02	4.35E + 01	0.04	10.04.26	12:08	5	300
16	1.05E + 02	4.05E + 01	0.03	10.04.26	12:16	5	300
17	8.24E + 01	2.74E + 01	0.03	10.04.26	12:24	5	300
18	1.41E + 02	3.90E + 01	0.04	10.04.26	13:43	5	300
19	2.12E + 02	5.40E + 01	0.04	10.04.26	13:57	5	300
20	2.93E + 01	0	0.03	10.04.26	12:46	5	300
21	1.45E + 02	0	0.03	10.04.26	14:20	5	300

Test-tube No	Gd	Tb	Dead time %	Date	Time	V (ml)	Measurement Time (s)
22	8.07E + 01	0	0.03	10.04.26	14:53	5	300

Table 3
Measurement data for 50°C

Test-tube number	Gd	Tb	Dead time %	Date	Time	V (ml)	Measurement time (s)
5	0	0	0.03	15.04.26	11:03	5	300
6	0	0	0.03	15.04.26	11:09	5	300
7	0	8.04E + 01	0.04	15.04.26	11:16	5	300
8	0	3.10E + 04	2.66	15.04.26	11:24	5	300
9	0	3.28E + 04	0.72	15.04.26	14:59	5	300
10	7.31E + 01	4.35E + 02	0.07	15.04.26	11:39	5	300
11	5.19E + 03	2.23E + 02	0.16	15.04.26	11:47	5	300
12	2.59E + 04	1.74E + 02	0.59	15.04.26	11:55	5	300
13	4.55E + 04	1.14E + 02	0.99	15.04.26	12:03	5	300
14	3.19E + 04	7.56E + 01	0.71	15.04.26	12:11	5	300
15	4.08E + 02	3.35E + 01	0.04	15.04.26	12:19	5	300
16	1.93E + 02	3.31E + 01	0.03	15.04.26	12:27	5	300
17	6.06E + 02	6.78E + 01	0.04	15.04.26	14:13	5	300
18	9.70E + 01	0	0.04	15.04.26	12:43	5	300
19	7.43E + 01	0	0.03	15.04.26	12:51	5	300
20	2.00E + 00	0	0.03	15.04.26	12:58	5	300
21	4.55E + 01	0	0.03	15.04.26	13:06	5	300
22	0	0	0.03	15.04.26	14:37	5	300

Table 4
Measurement data for 70°C

Test-tube number	Gd	Tb	Dead time %	Date	Time	V (ml)	Measurement time (s)
5	0	0	0.03	22.04.2026	10:51	5	300
6	0	0	0.03	22.04.2026	10:57	5	300
7	0	0	0.03	22.04.2026	11:04	5	300
8	0	0	0.04	22.04.2026	11:10	5	300
9	0	1.46E + 03	0.16	22.04.2026	11:16	5	300
10	0	2.10E + 04	1.7	22.04.2026	11:23	5	300
11	0	2.05E + 04	1.71	22.04.2026	11:31	5	300
12	0	2.09E + 03	0.08	22.04.2026	14:16	5	300
13	1.51E + 02	2.66E + 02	0.06	22.04.2026	11:45	5	300
14	1.85E + 03	1.50E + 02	0.07	22.04.2026	11:53	5	300
15	6.01E + 03	9.35E + 01	0.17	22.04.2026	12:01	5	300
16	1.65E + 04	6.68E + 01	0.39	22.04.2026	12:11	5	300
17	1.15E + 05	2.08E + 02	0.63	22.04.2026	14:40	5	300
18	2.94E + 04	3.10E + 01	0.64	22.04.2026	12:29	5	300
19	6.87E + 04	7.82E + 01	0.39	22.04.2026	15:04	5	300
20	3.33E + 03	0.00E + 00	0.04	22.04.2026	12:44	5	300
21	1.38E + 02	0.00E + 00	0.04	22.04.2026	12:52	5	300
22	1.08E + 02	0.00E + 00	0.03	22.04.2026	13:00	5	300
23	8.08E + 01	0.00E + 00	0.04	22.04.2026	13:08	5	300

Test-tube number	Gd	Tb	Dead time %	Date	Time	V (ml)	Measurement time (s)
24	2.35E + 02	6.75E + 00	0.03	22.04.2026	15:28	5	300
25	3.44E + 01	0.00E + 00	0.03	22.04.2026	13:21	5	300
26	1.01E + 00	0.00E + 00	0.04	22.04.2026	15:51	5	300

The first four fraction test-tubes not shown contained no measurable activity across all tables.

Results

Elution behavior

Terbium eluted before gadolinium at all three investigated temperatures. At 30°C, the terbium activity maximum occurred at approximately 30–35 mL and the gadolinium maximum at approximately 45–50 mL (Fig. 1). Partial overlap was observed. At 50°C, the terbium maximum occurred at approximately 35–40 mL and the gadolinium maximum at approximately 55–65 mL (Fig. 2). At 70°C, terbium was distributed mainly between approximately 40 and 65 mL, whereas gadolinium was retained until approximately 95 mL, and activity extended to approximately 105 mL (Fig. 3).

Recovery and gadolinium contamination

The separation results are shown in Table 5.

Table 5
Effect of temperature on terbium recovery and gadolinium contamination

Separation temperature (°C)	Main terbium elution region (mL)	Terbium recovery (%)	Gadolinium contamination (%)
30	30–35	97	2.0
50	35–40	98	0.1
70	40–65	99	0.1

The terbium recovery increased from 97% at 30°C to 99% at 70°C. At the same time, the gadolinium contamination decreased from 2.0% at 30°C to 0.1% at 50°C and remained at 0.1% at 70°C. Based on the measured recovery and contamination values, 70°C yielded the best overall separation performance.

Discussion

Dowex 50W-X8 cation-exchange chromatography with α -HIBA separated the radioactive terbium tracer from gadolinium under the investigated conditions. The observed elution order is consistent with the use of a complexing eluent to exploit differences in the chemical behaviour of neighbouring trivalent lanthanides. Under the selected pH and eluent concentration, terbium eluted before gadolinium [7, 11, 12].

Temperature had a clear effect on the separation profile. At 30°C, the terbium and gadolinium peaks were relatively close and partially overlapped. Increasing the temperature to 50°C increased the separation between the principal activity regions and reduced nominal gadolinium contamination. At 70°C, gadolinium activity was retained for a considerably larger elution volume than the main terbium fraction. These observations are consistent with the sensitivity of lanthanide separations to resin properties, eluent composition, pH, and chromatographic operating conditions [10–13].

The temperature effect may result from changes in complex-formation kinetics, mass-transfer rates, resin–ion interactions, and the relative mobility of the metal– α -HIBA complexes. These explanations remain mechanistic hypotheses because distribution coefficients and thermodynamic parameters were not measured independently in this study.

The 70°C result-99% nominal terbium recovery with 0.1% nominal gadolinium contamination is encouraging for development of a process relevant to ^{161}Tb production. However, natural gadolinium was used instead of enriched ^{160}Gd , and a radioactive terbium tracer served as a surrogate. The experiment therefore demonstrates separation chemistry but does not establish the production yield, specific activity, radionuclide purity, or radiochemical purity of reactor-produced ^{161}Tb [1, 5–9].

The experiments were performed at tracer or small laboratory scale, and each temperature was tested once. Resin capacity, target loading, radiation damage, heat-transfer behaviour, and reproducibility may differ during higher-activity processing. The reported gadolinium contamination was based on gamma-spectrometric activity measurements; elemental gadolinium contamination should also be quantified by a validated analytical method such as ICP-MS.

For radiopharmaceutical application, additional quality-control measurements would be required, including complete radionuclide analysis, radiochemical purity, chemical purity, specific or molar activity, residual α -HIBA concentration, and radiolabeling performance with a suitable chelator such as DOTA [2, 4, 6, 8, 14]. Recent work on terbium purification and automated processing further indicates that enriched-target validation, decontamination performance, process reproducibility, and GMP-compatible handling are important before clinical translation [2–4, 6, 8].

The study should therefore be regarded as a laboratory-scale process-development investigation. It identifies 70°C as a promising operating temperature for the Dowex 50W-X8/ α -HIBA system and provides a basis for future experiments using enriched ^{160}Gd , replicate columns, complete detector calibration, and automated hot-cell processing.

Conclusion

A temperature-dependent cation-exchange procedure was investigated for separation of terbium tracer from gadolinium using Dowex 50W-X8 resin and 0.3 M α -HIBA at pH 4.40. Terbium eluted before gadolinium at 30, 50, and 70°C. Increasing the column temperature improved the separation profile and increased nominal terbium recovery from 97% to 99%. Nominal gadolinium contamination decreased from 2.0% at 30°C to 0.1% at 50 and 70°C. The best observed separation was obtained at 70°C, where the terbium fraction was concentrated mainly between approximately 40 and 65 mL, and gadolinium was retained until approximately 95 mL. The method provides a laboratory-scale separation basis for further investigation of ^{161}Tb production and purification. Validation using enriched ^{160}Gd , replicate experiments, complete radionuclide analysis, elemental impurity measurements, detector-efficiency calibration, numerical uncertainty estimates, and radiolabeling tests is required before the method can be considered for production of material intended for medical applications.

Declarations

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Conflict of interest

The authors declare no conflicts of interest.

Ethical approval

No human participants or animals were involved in this study.

Author Contribution

S.B: conceptualization, methodology, investigation, data analysis, writing the original draft, and visualization. I.A.U: conceptualization, supervision, writing-review and editing, and resources. L.Z: investigation, and resources. K.B: data curation, formal analysis, writing and review K.H: validation and editing.

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Figures

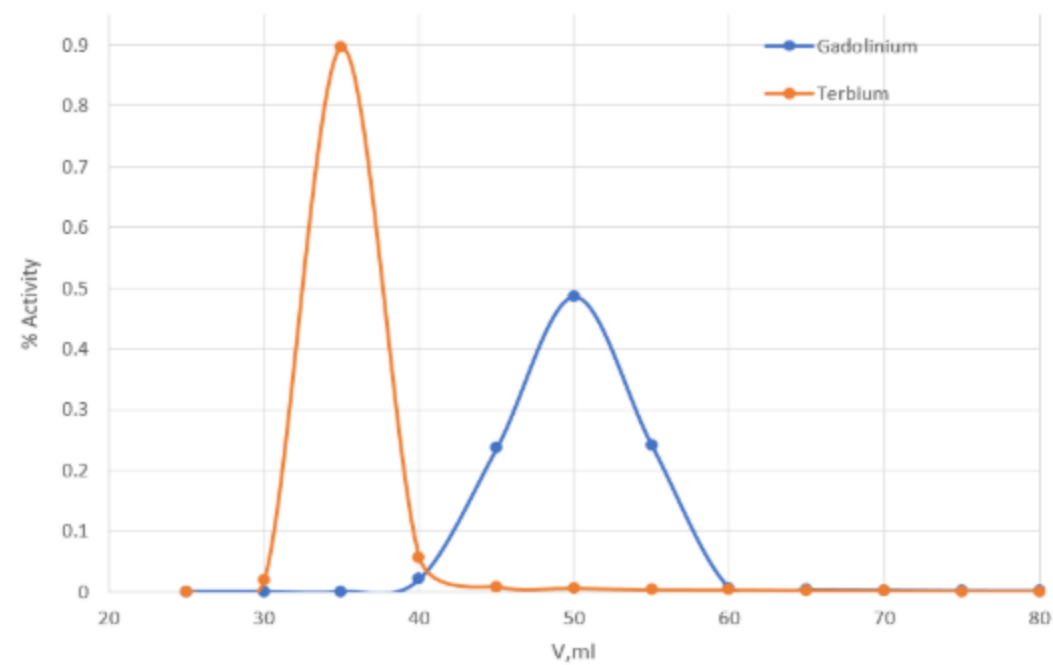


Figure 1
Elution curve of the Gd/ Tb separation at 30 °C

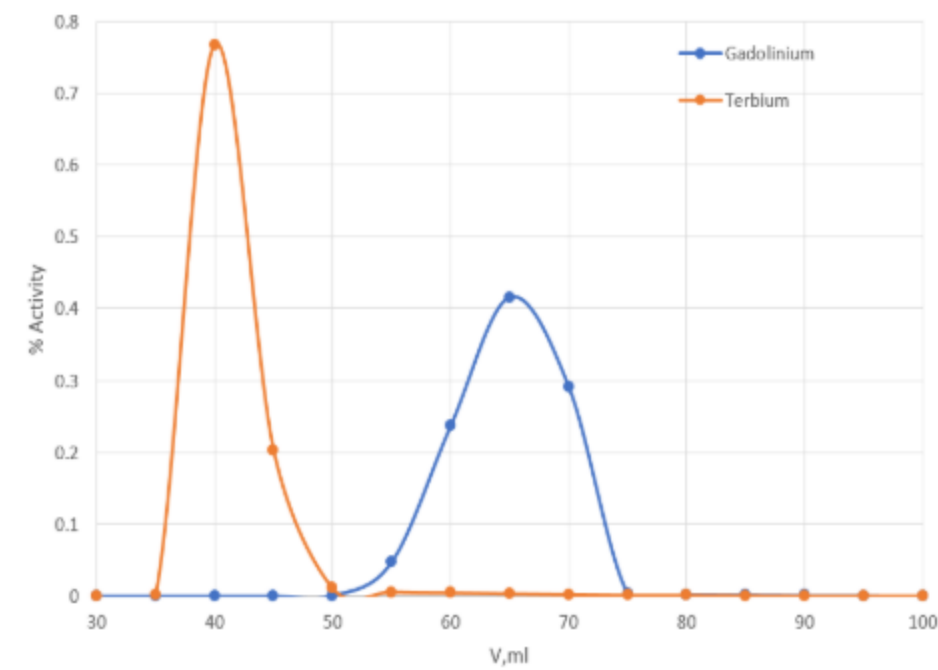


Figure 2
Elution curve of the Gd/ Tb separation at 50 °C

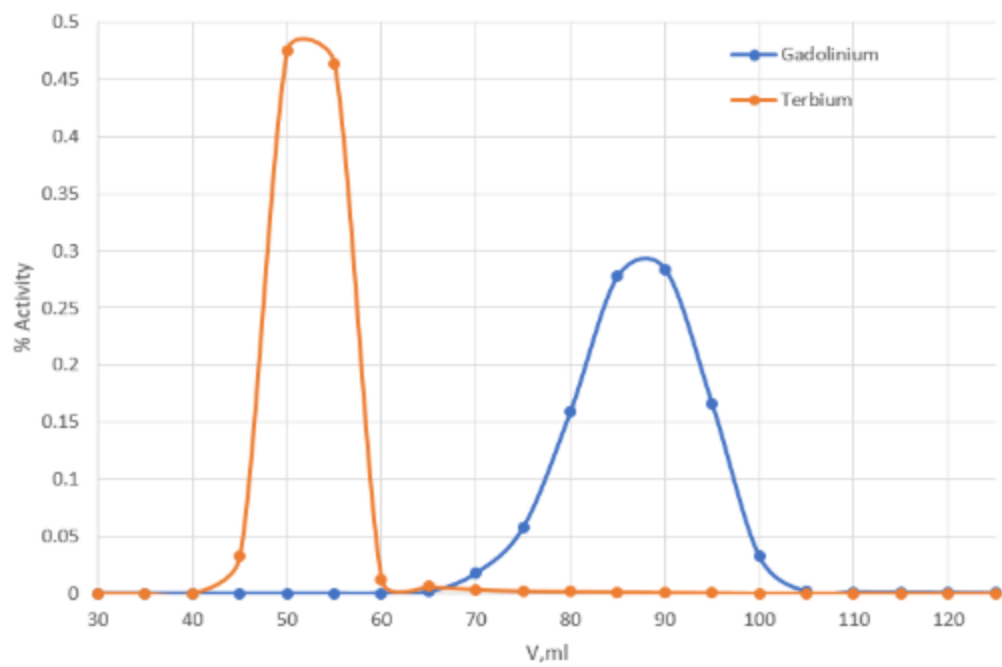


Figure 3

Elution curve of the Gd/ Tb separation at 70 °C