

Characterization of Rare Earth Elements used for Radiolabeling Applications by ICP-QQQ

Analysis of radiogenic REE isotopes in bulk REE matrices



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Introduction

Radiolabeling refers to a technique where a compound or substance is labeled (or tagged) with a radioactive isotope of an element. The labeled material can then be used for controlled delivery of the radiation emitted by the active isotope, or detected and traced from the radioactivity of the isotopic label.

The use of radiolabeled materials is growing steadily, with the market for radiolabeled pharmaceutical compounds expected to be worth over 5 billion US dollars by 2024 (1). Elements that can form useful radioisotopes include the lanthanides – also known as rare earth elements (REEs). Radio-lanthanide compounds are used in pharmaceutical and imaging applications.

To meet the rising demand for radio-lanthanides, there is a critical need for analytical techniques to support the production of traceable, high purity, labeled lanthanides (2). Production scale chemical purification and labeling of

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radio-lanthanides is challenging though, because all the lanthanides have similar chemical properties and tend to behave as a consistent group. To prepare a pure radio-lanthanide, it is necessary to accurately characterize the chemical composition of the non-radioactive natural or isotopically enriched starting material used. Before a candidate starting material can be used for routine radionuclide production, each batch must be tested and validated to ensure that radionuclide yields will be of the desired quantity and quality (3). To carry out this level of quality assurance (QA), accurate analytical procedures are needed, particularly to determine the level of trace lanthanide contaminants in the pure lanthanide starting material. Since any impurities need to be removed, the QA data is also useful to guide the design of robust, reproducible chemical separation methods (4). Determining the type and quantity of impurities present in the starting material also helps manufacturers predict whether unwanted radioactive side-products will be produced during irradiation.

Table 1 lists several radio-lanthanide product isotopes that have chemical and radioactive decay properties that make them suitable for applications in radiolabeling. In most of these examples, the starting material is a different element to the intended radio-lanthanide product isotope. This avoids the radio-lanthanide product isotope being affected by high concentrations of a stable isotope of the same element in the irradiated target, which cannot be removed by subsequent chemical separation. Typically, the radionuclides are produced by irradiating a lanthanide or lanthanide oxide starting material target at a nuclear reactor or cyclotron facility. For example, terbium-155 can be produced from gadolinium (III) oxide (Gd_2O_3) starting material in a cyclotron. The stable isotope ^{155}Gd is converted to the radioisotope ^{155}Tb via a (p, n) reaction, where a proton enters the nucleus and a neutron leaves the nucleus simultaneously.

Table 1. Starting materials and production route for radio-lanthanides used in labeling applications.

Radio-lanthanide	Starting Material*	Possible Nuclear Reaction Production Route**
^{153}Sm	^{152}Sm	$^{152}Sm(n, \gamma) \rightarrow ^{153}Sm$
^{149}Tb	^{151}Eu	$^{151}Eu(^3He, 5n) \rightarrow ^{149}Tb$
^{155}Tb	^{155}Gd	$^{155}Gd(p, n) \rightarrow ^{155}Tb$
^{161}Tb	^{160}Gd	$^{160}Gd(n, \gamma) ^{161}Gd \rightarrow ^{161}Tb + \beta^-$
^{166}Ho	^{164}Dy	$^{164}Dy(n, \gamma) ^{165}Dy(n, \gamma) ^{166}Dy \rightarrow ^{166}Ho + \beta^-$
^{169}Er	^{168}Er	$^{168}Er(n, \gamma) \rightarrow ^{169}Er$
^{177}Lu	^{176}Yb	$^{176}Yb(n, \gamma) ^{177}Yb \rightarrow ^{177}Lu + \beta^-$

* Starting materials are often isotopically enriched targets.

**n (neutron), p (proton), γ (gamma), 3He (helium-3).

The accurate characterization of REE materials is challenging for conventional single quadrupole ICP-MS. The REEs form hydride (MH^+), oxide (MO_x^+), and hydroxide (MOH^+) polyatomic ions in the plasma or during ion extraction, and these polyatomic ions can overlap the measured isotopes of other REEs. High intensity REE matrix element peaks can also cause peak tail overlaps on trace REE isotopes measured at adjacent masses. This peak tailing effect, known as the abundance sensitivity (AS), is different for different types of mass spectrometer. On commercial single quadrupole ICP-MS instruments, the AS is typically 10^{-7} , which means that every 10 million counts at a high intensity peak contributes one count to the adjacent masses. This AS performance means that an intense major element peak can cause peak tailing overlaps on trace analytes at adjacent masses when measured by single quadrupole ICP-MS.

Compared to single quadrupole ICP-MS, Agilent triple quadrupole ICP-MS (ICP-QQQ) instruments offer superior resolution of polyatomic interferences using reactive cell gases. This performance improves accuracy in complex sample types, including analysis of trace REEs in geological samples and materials applications (5, 6). Also, Agilent ICP-QQQ instruments use a tandem mass spectrometer configuration (MS/MS) with two full-sized quadrupole mass analyzers, Q1 and Q2, both housed in high vacuum regions. Two mass filtering steps reduce peak tail overlaps, as the overall AS in MS/MS is the product of the AS of the two quadrupoles, so $10^{-7} \times 10^{-7}$, or 10^{-14} (7).

Previous studies suggest that ICP-QQQ methods can improve the accuracy of analysis of trace impurities in the lanthanide starting materials/targets used for radio-lanthanide production. Also, assessment of the concentration of impurities in the starting material recovered after chemical separation of the radioisotope could allow for re-use of the recovered material.

The chemical separation methods used to purify radio-lanthanide isotopes can be designed and optimized using stable isotopes of each lanthanide, rather than the radioactive material. ICP-QQQ can be used to measure the intended lanthanide product element at trace (ppt) levels in the presence of a high concentration (ppm level) of the bulk target material. This capability enables realistic testing of the separation scheme while using cheap, safe, and readily available natural REE materials.

In this study, several pairs of trace REE analytes and adjacent mass neighboring REE matrix elements relevant to radio-lanthanide production were measured by ICP-QQQ. The samples included materials that are typically used as

irradiation targets for radio-lanthanide production. The use of ICP-QQQ for optimizing radiochemical separation of target lanthanides, and for measuring REE impurities in irradiated targets, was also demonstrated. The developed methods will enable end users to compile a REE impurity profile of materials of relevance to the production of radionuclides for labeling applications.

Experimental

Sample preparation

For the detection limit (DL) study, calibration standards from 1 ppt to 100 ppb were prepared for each trace REE in solutions containing 10 ppm of the neighboring REE matrix element. All solutions were stabilized with 2% HNO₃. These bulk-trace lanthanide pairs are summarized in Table 2. Similar solutions were prepared to test the extraction chromatography-based chemical separation procedures.

Table 2. Pairs of natural REE matrix elements and trace REE analytes used for preparation of calibration standard sets to test resolution of adjacent mass interferences.

Bulk REE Matrix (Isotopic abundance, %)	Trace REE Analyte (Isotopic abundance, %)
¹³⁹ La (99.91)	¹⁴⁰ Ce (88.45)
¹⁴⁰ Ce (88.45)	¹⁴¹ Pr (100)
¹⁵⁸ Gd (24.84)	¹⁵⁹ Tb (100)
¹⁶⁴ Dy (28.18)	¹⁶⁵ Ho (100)
¹⁶⁵ Ho (100)	¹⁶⁶ Er (33.61)
¹⁶⁸ Er (26.78)	¹⁶⁹ Tm (100)
¹⁷⁴ Yb (31.83)	¹⁷⁵ Lu (97.41)

The performance of the ICP-QQQ MS/MS method with O₂ cell gas was investigated using analysis of Tb in the presence of a Gd matrix. Gadolinium (III) oxide powder (Gd₂O₃, 99.999 % purity) was gently dissolved in 8 M HNO₃, evaporated to dryness, and then redissolved in 2% HNO₃ to give a final concentration of 10 ppm Gd.

Irradiated Gd₂O₃ targets were dissolved in concentrated HNO₃. To determine the target radio-lanthanide activity levels and any other radionuclides produced, an aliquot was taken for measurement by gamma spectrometry. Following this analysis the sample was left for enough time to allow short-lived radionuclides to decay, after which the stable REE impurities were determined by ICP-QQQ.

Instrumentation

An Agilent 8800 ICP-QQQ was used in this study. The 8800 was equipped with a standard sample introduction system comprising a glass concentric nebulizer, a quartz spray chamber, a quartz torch with 2.5 mm i.d. injector, and nickel-tipped interface cones. The general instrument operating conditions are summarized in Table 3.

Table 3. ICP-QQQ operating parameters.

Parameter	Setting
Scan Mode	MS/MS
Plasma Conditions	Low matrix
RF Power (W)	1550
Extract 1 (V)	0
Extract 2 (V)	-175
Reaction Cell Gas	Oxygen
Oxygen Flow Rate (mL/min)	0.3 (30% of full-scale)
Octopole Bias (V)	-5.0
Energy Discrimination (V)	-7.0
Octopole RF (V)	200

Results and discussion

Instrument sensitivity and interference removal

To remove the matrix element hydride and peak tailing interferences for each of the trace REE analytes investigated, the 8800 ICP-QQQ was operated in MS/MS mode with O₂ cell gas. To compare the performance of single quadrupole ICP-MS, the measurements were also performed using the 8800 in single quad mode, where Q1 does not perform any mass selection.

Using the example of trace Tb analysis in a Gd matrix, Tb was measured as the product ion ¹⁵⁹Tb¹⁶O⁺ at *m/z* 175 using mass shift. In single quad mode, the ¹⁵⁸Gd¹H and ¹⁵⁸Gd tailing interferences were not effectively avoided using O₂ cell gas. A 10 ppm Gd standard gave a signal at *m/z* = 175 of approximately 1.3×10⁶ counts per second (cps). This high background meant Tb could not be measured at concentrations below 100 ppt.

Using MS/MS mode with Q1 and Q2 set to *m/z* = 159 and 175, respectively, the *m/z* 175 background signal in the 10 ppm Gd matrix was reduced to ~4,400 cps, which enabled accurate low-level Tb measurement. Using MS/MS, a detection limit of 2.1 ppt was achieved for Tb in the 10 ppm Gd matrix with background subtraction (Figure 1).

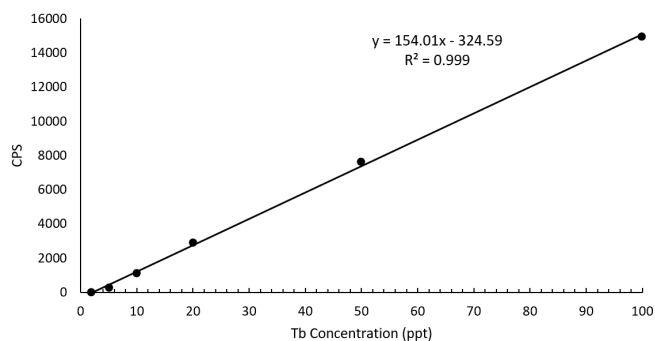


Figure 1. Calibration for Tb in the presence of 10 ppm ^{158}Gd . Tb measured as $^{159}\text{Tb}^{160+}$ by ICP-MS/MS in O_2 mass-shift mode.

A similar trend was seen for the other trace lanthanides listed in Table 4. Operating the 8800 in MS/MS with on-mass or mass-shift mode using O_2 cell gas, DLs in the low ppt range were achieved for most analytes. Only Ho (measured at m/z 165) in a Dy (164) matrix and Er (166) in a Ho (165) matrix showed higher DLs, up to 1.1 ppb in the case of Ho in Dy. The ppt level DLs are equivalent to purity levels of up to 2.1×10^{-7} relative to the 10 ppm concentration of each respective matrix element. This sensitivity is significantly better than the purity information currently provided by the manufacturers of lanthanide powders. The purity analysis also provides valuable information about possible radionuclides that may be formed from contaminants during irradiation of the lanthanide starting material powders.

The single O_2 cell gas mode used for this study gave acceptable data for all trace lanthanides studied. The DLs for some REEs, e.g., trace Ho in Dy, could be improved by further optimizing the cell conditions or using an alternative reaction gas such as N_2O or NH_3 (6).

Table 4. Detection limits achieved by 8800 ICP-QQQ for trace REEs in REE matrices. Analysis based on measurement of natural, stable isotope elemental standards.

Trace Element (Measured isotope)	Q1 / Q2	Matrix Element (10 ppm)	DL of Trace Element (ppt)
Ce (140)	140/156	^{139}La	12.2
Pr (141)	141/157	^{140}Ce	11.9
Tb (159)	159/175	^{158}Gd	2.1
Ho (165)	165/181	^{164}Dy	1100
Er (166)	166/182	^{165}Ho	186
Tm (169)	169/185	^{168}Er	2.3
Lu (175)	175/191	^{174}Yb	9.3

Measurement of lanthanide oxide samples

The concentrations of trace lanthanides in a solution containing 10 ppm Gd_2O_3 powder were determined using the 8800 ICP-QQQ with O_2 cell gas. As shown in Figure 2, most REEs were measured on-mass. Only ^{159}Tb , ^{172}Yb , and ^{175}Lu were measured as oxide product ions in mass-shift mode to avoid interferences from $^{158}\text{Gd}^1\text{H}$ at m/z 159, $^{156}\text{Gd}^{16}\text{O}$ at m/z 172, and $^{158}\text{Gd}^{16}\text{O}^1\text{H}$ at m/z 175 (Figure 2).

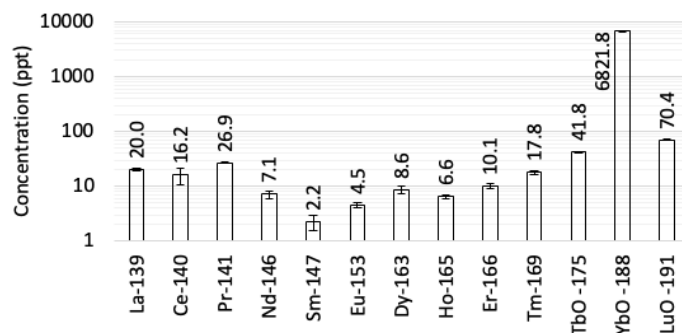


Figure 2. Impurity profile and ICP-MS measurement uncertainties (2σ) of Gd_2O_3 powder used for irradiation.

Elemental standard solutions are used to test chemical separation procedures, so the same ICP-QQQ method was used to measure impurities in a Gd single-element ICP standard. The results are shown in Figure 3. The relatively high measured concentration of YbO in the powder and ICP standard suggests that the interference from $^{156}\text{Gd}^{16}\text{O}$ and $^{156}\text{Gd}^{16}\text{O}_2$ on ^{172}Yb and $^{172}\text{Yb}^{16}\text{O}$, respectively, were not fully resolved. Yb is also not very reactive with oxygen cell gas, leading to low sensitivity for the YbO^+ product ion. The method could potentially be improved through further optimizing the cell conditions or using an alternative cell gas such as N_2O or NH_3 (6, 7).

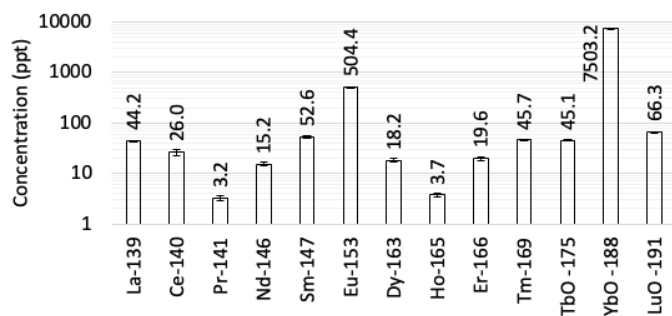


Figure 3. Impurity profile and ICP-MS measurement uncertainties (2σ) of a Gd ICP standard using 8800 ICP-QQQ in MS/MS mode with O_2 cell gas.

Chemical separation results

Operating the 8800 in MS/MS mode with O₂ cell gas and using stable element analogs in place of short-lived radioactive samples enables the optimization of separation procedures under realistic conditions. Realistic conditions refer to the separating of a trace level target lanthanide in the presence of high concentrations of a neighboring lanthanide. This approach enables the development of robust radiochemical procedures before testing with active samples. It also avoids the cost and safety issues of handling active materials during method development.

In this study, Tb was separated from Gd using an extraction chromatography column packed with a LN (lanthanide) resin (50–100 μm particle size, Triskem International). Figure 4 shows an elution profile for Gd and Tb at a 4.5×10⁴ excess of Gd. Gd was expected to elute with 0.75 M HNO₃, while Tb was expected to be retained until conditions were switched to 1.0 M HNO₃ (8). To check if the separation scheme had been effective, each 1 mL fraction was collected and measured using ICP-MS/MS in O₂ mass-shift mode. The results showed that a small amount of ¹⁵⁹Tb was recovered in the ¹⁵⁸Gd fraction.

The effectiveness of the ICP-QQQ method to resolve Tb from Gd has been demonstrated using trace Tb standards in a Gd matrix. This performance gives confidence that the signal at *m/z* 159 seen in the Gd fraction was due to trace ¹⁵⁹Tb eluting together with the Gd, rather than an interference from ¹⁵⁸Gd¹H. Also, based on the starting concentration of Tb added to the column, the total Tb recovery was <100%, suggesting little or no contribution from Gd to the measured Tb signal.

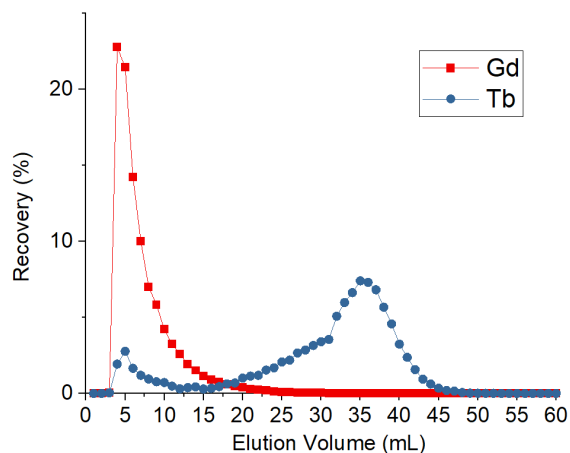


Figure 4. Elution profile for Tb and Gd.

Measurement of impurities in irradiated samples

A compacted Gd₂O₃ powder target was irradiated to produce ¹⁵⁵Tb (half-life of 5.32 days). The irradiated target was then dissolved in concentrated HNO₃ and an aliquot was used to measure the activity level of ¹⁵⁵Tb and other short-lived radionuclides by gamma spectrometry. After leaving the sample enough time for the radioisotopes to decay, the stable REE isotopes remaining in the Gd₂O₃ sample were measured using ICP-QQQ.

Lanthanum and Ce were the only REE contaminants detected in the final sample at concentrations of ~13.1 and 3.5 ppm, respectively. However, the concentration of both La and Ce was reduced to below background levels after chemical separation. The detection of La and Ce in the irradiated Gd₂O₃ powder shows the potential for stable and long-lived radionuclide impurities to be formed during irradiation. The findings illustrate the importance of chemical separation in the production of high purity radio-lanthanides.

The ICP-QQQ method can be used for post-separation analysis of the final radio-lanthanide product to assess the concentration of stable impurities still present, and to help assess the effectiveness of the chemical separation. Depending on the application, enriched or recycled target materials may be used that contain lanthanides at non-natural abundances, which will affect the level of impurities that can be measured. The measurement of such impurities is important as a QA measure, as high concentrations of impurities can lead to competition for the chelating agent used, which can reduce the radiolabeling efficiency.

Conclusion

The use of radio-lanthanides is of increasing interest in pharmaceutical and imaging applications. Preparation of high purity radio-lanthanides often requires separation of the low concentration target isotope from the high concentration stable REE matrix. To check the purity of the starting REE materials, the Agilent 8800 ICP-QQQ was operated in MS/MS mode with O₂ cell gas to measure all REE impurities in high-purity REE matrices. The ICP-QQQ method was much more effective at removing REE matrix-based polyatomic and peak tailing interferences compared to single quadrupole ICP-MS.

The measurement of trace levels of Tb in the presence of bulk Gd was used as an example. The results obtained from analyzing stable element standards showed that the method was useful for a range of radio-lanthanides.

Overall, the ICP-MS/MS method improved accuracy and confidence of the measurements needed for a complete REE impurity profile of materials used in the production of radionuclides for pharmaceutical and imaging applications. The study has shown that the method is suitable for:

- The measurement of REE impurities in the starting powders used for irradiation.
- Optimizing chemical separation conditions using stable element analogs.
- Assessing the REE impurities present in the irradiated target material post-irradiation.

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