

## Article

# Selective and Efficient Separation of No-Carrier-Added $^{161}\text{Tb}$ from Gd/Dy Matrix Using P350@Resin for Radiopharmaceutical Applications

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## Abstract

Terbium-161 ( $^{161}\text{Tb}$ ) is an emerging  $\beta^-$ -emitting radionuclide of high interest for targeted radionuclide therapy. However, its reactor-based production presents significant challenges in the efficient separation of  $^{161}\text{Tb}$  from target  $^{160}\text{Gd}$  and co-produced  $^{161}\text{Dy}$ . In this study, the separation of  $^{161}\text{Tb}$  by a solvent-impregnated resin P350@resin has been evaluated. A combination of static adsorption and dynamic column experiments was conducted to investigate the separation behavior of  $\text{Gd}^{3+}$ ,  $\text{Tb}^{3+}$ , and  $\text{Dy}^{3+}$ . Optimal separation performance was achieved at 0.4–0.6 mol/L  $\text{HNO}_3$ , using a column bed height of 20–28 cm and flow rates of 0.5–1.0 mL/min. A two-step elution protocol enabled near-baseline resolution between Tb and Gd, Dy within 3 h, ensuring high-purity and fast product recovery. Comprehensive characterization using SEM-EDS, FT-IR, and XPS confirmed that metal ion uptake occurs via coordination with phosphoryl groups on the resin. The P350@resin thus enables a simple and selective separation platform for the production of no-carrier-added  $^{161}\text{Tb}$ , with high potential for clinical radiopharmaceutical manufacturing.

**Keywords:** terbium-161; lanthanides; extraction resin; radiopharmaceuticals

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## 1. Introduction

The targeted radionuclide therapy (TRT) has emerged as a potent strategy for cancer treatment, particularly for disseminated micrometastases [1,2]. Lutetium-177 ( $^{177}\text{Lu}$ ) is widely used for treating neuroendocrine tumors and prostate cancer [3,4]. As a medium-energy  $\beta^-$  emitter,  $^{177}\text{Lu}$  delivers cytotoxic radiation within a short path length, thereby minimizing damage to surrounding healthy tissues. However, its therapeutic efficacy against micrometastatic disease is limited by the relatively low number of low-energy electrons emitted per decay [3,5]. This limitation has spurred interest in other trivalent lanthanides that form stable complexes with macrocyclic chelators like DOTA [6,7]. Among these, terbium-161 ( $^{161}\text{Tb}$ ) has attracted considerable attention due to its highly favorable decay properties and its close chemical similarity to  $^{177}\text{Lu}$  [8,9]. With a half-life of 6.96 days,  $^{161}\text{Tb}$  emits medium-energy  $\beta^-$  particles (average  $E_{\beta^-} \approx 154$  keV) suitable for tumor irradiation [10]. Critically, each decay is also accompanied by the emission of approximately 12 low-energy Auger and conversion electrons, depositing a total of  $\sim 36$  keV within nanometer-scale distances. This results in high linear energy transfer (LET) at the subcellular level, enabling  $^{161}\text{Tb}$  to exert both crossfire effects on larger tumor masses and localized cytotoxicity against residual or microscopic disease [6]. These properties position

$^{161}\text{Tb}$  as a promising “drop-in” replacement for  $^{177}\text{Lu}$  in existing therapeutic frameworks, potentially enhancing efficacy without altering established clinical protocols.

The most efficient production route for  $^{161}\text{Tb}$  is the neutron irradiation of highly enriched  $^{160}\text{Gd}$  targets via the nuclear reaction  $^{160}\text{Gd}(n,\gamma)\rightarrow^{161}\text{Gd}\rightarrow^{161}\text{Tb}$  [11]. This indirect method yields no-carrier-added (NCA)  $^{161}\text{Tb}$  with high specific activity essential for radio-labeling. Because  $^{161}\text{Gd}$  has a short half-life ( $t_{1/2} = 3.65$  min), it decays almost completely during irradiation, minimizing byproduct formation [12]. Irradiation in high-flux research reactors such as SAFARI-1, ILL, or SINQ can produce 6 to 20 GBq depending on target mass, neutron flux, and irradiation duration [13]. The main challenge lies in post-irradiation purification: the mixture contains large quantities of unreacted  $^{160}\text{Gd}$  and co-produced  $^{161}\text{Dy}$ , chemically similar trivalent lanthanides that complicate separation. Efficient separation of  $^{161}\text{Tb}$  from these impurities is critical for achieving the radionuclidic and chemical purity required for clinical use, as  $^{161}\text{Dy}$  contamination reduces the apparent specific activity of  $^{161}\text{Tb}$ .

The conventional purification of  $^{161}\text{Tb}$  typically employs ion exchange chromatography with  $\alpha$ -hydroxyisobutyric acid ( $\alpha$ -HIBA) as the complexing agent [10,14]. This method exploits the subtle differences in complex stability among trivalent lanthanide [15,16].  $^{161}\text{Tb}$  elutes earlier than  $^{160}\text{Gd}$  due to its slightly stronger complexation with  $\alpha$ -HIBA; while  $^{161}\text{Dy}$ , having a smaller ionic radius, elutes later. Although effective, this technique requires precise control of pH and ligand concentration, uses slow gradients, and leaves residual ligand in the eluate, necessitating additional clean up. These factors result in long processing times and considerable radioactive liquid waste, limiting scalability for routine production.

To overcome the limitations associated with conventional  $\alpha$ -HIBA-based ion exchange chromatography, recent research has focused on extraction chromatography using solvent-impregnated resins (SIRs) [17,18]. This approach combines the selectivity of solvent extraction with the operational simplicity, reusability, and mechanical stability of solid-phase supports. TrisKem’s TK-series resins (TK211, TK212, and TK221) incorporate organophosphorus extractants into polymeric matrices and have enabled  $^{161}\text{Tb}$  production with >99.99% radionuclidic purity [19]. Despite these advantages, SIR-based strategies present their own challenges. These include partial overlap in resin selectivity, complications in column regeneration, and potential radiochemical losses during sequential elution. Moreover, ensuring scalability and reproducibility in routine production requires thorough system validation and process optimization. In the broader rare earth industry, numerous high-efficiency solvent extractants, such as D2EHPA [20], PC-88A [21], and Cyanex 272 [22], have been successfully developed and, in some cases, formulated into SIRs with demonstrated effectiveness in lanthanide separation [23,24]. However, most of these systems have not yet been applied to  $^{161}\text{Tb}$  production. Introducing highly selective and efficient SIRs based on these extractants could enable more modular, scalable, and clinically adaptable purification workflows for  $^{161}\text{Tb}$  and other medically relevant radiolanthanides.

In this context, P350@Resin—functionalized with phosphite ester groups—emerges as a promising alternative for the purification of  $^{161}\text{Tb}$ . Although P350 has demonstrated strong affinity and separation efficiency for rare earth elements [25,26] and actinides [27–29] across various chemical and environmental applications [30], its use in  $^{161}\text{Tb}$  purification has not yet been explored. The present study seeks to address this gap by systematically evaluating the separation performance of P350@Resin toward Gd, Tb, and Dy, with the goal of establishing its feasibility as a single-resin platform for  $^{161}\text{Tb}$  production. Furthermore, we investigate the underlying separation mechanisms through comprehensive physico-chemical characterizations. This work lays the groundwork for a robust, efficient, and clinically translatable purification protocol, supporting the broader adoption of  $^{161}\text{Tb}$  in targeted radionuclide therapy.

## 2. Materials and Methods

The Analytical-grade lanthanide salts, including  $\text{Gd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{Tb}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ , and  $\text{Dy}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ , were obtained from Shanghai Adamas Reagent Co., Ltd. (Shanghai, China) and used as non-radioactive surrogates for radiochemical separation experiments. The P350@resin was supplied by Beijing Realkan Separation Technologies Co., Ltd. (Beijing, China). This resin consists of a polystyrene-divinylbenzene copolymer matrix, impregnated with a dialkyl phosphite ester mixture (50 wt.% of the resin). The size distribution of the resin is 200–400 mesh. All nitric acid solutions were prepared using concentrated  $\text{HNO}_3$  (65–68%, GR, Sinopharm Chemical Reagent Co., Ltd., Shanghai, China) diluted with ultrapure water. All other reagents were of analytical grade and used without further purification.

Batch adsorption experiments were conducted to evaluate the affinity and selectivity of P350@resin for  $\text{Gd}^{3+}$ ,  $\text{Tb}^{3+}$ , and  $\text{Dy}^{3+}$  under varying chemical conditions. In each experiment, 0.1 g of resin was equilibrated with 10 mL of single-ion solution containing 1 mmol/L of each metal ion in nitric acid at defined concentrations ranging from 0.01 to 1.0 mol/L. The mixtures were agitated at room temperature for 2 h with a shaking frequency of 300 rpm using a thermostatic shaker. After equilibration, the suspensions were filtered, and the supernatants were analyzed for residual metal content by inductively coupled plasma-atomic emission spectroscopy instrument (ICP-OES, iCAP PRO, ThermoFisher, Waltham, MA, USA). The sorption efficiency ( $E\%$ ), equilibrium sorption capacity ( $Q_e$ , mg/g), distribution coefficient ( $K_d$ , mL/g), separation factor ( $SF$ ), were calculated according to the following equations:

$$E\% = \frac{C_i - C_e}{C_i} \times 100\%, \quad (1)$$

$$Q_e = (C_i - C_e) \times \frac{V}{m}, \quad (2)$$

$$K_d = \frac{C_i - C_e}{C_e} \times \frac{V}{m}, \quad (3)$$

$$SF = \frac{K_{d,A}}{K_{d,B}}, \quad (4)$$

where  $C_i$  and  $C_e$  are the initial and equilibrium concentrations of the element in the aqueous solution, respectively.  $V$  is the volume (mL) of the aqueous solution, and  $m$  is the mass (g) of the solid sorbents.

Chromatographic separation experiments were conducted using polypropylene columns (1 cm inner diameter) packed with P350@resin to bed heights ranging from 8 to 28 cm (corresponding to 6–22 mL bed volume). A mixture containing 1.0 mg each of  $\text{Gd}^{3+}$ ,  $\text{Tb}^{3+}$ , and  $\text{Dy}^{3+}$  was adsorbed into the column, followed by elution using nitric acid solutions of varying concentrations (0.4–1.2 mol/L) at controlled flow rates between 0.5 and 2.0 mL/min. Eluate fractions of 10 mL were collected sequentially. The element concentrations of selected fractions were further analyzed by ICP-OES. Based on breakthrough profiles, a two-step selective elution protocol was developed: after sample (a simulated feed solution composed by stable isotopes of 200 mg  $^{160}\text{Gd}$ , 40  $\mu\text{g}$   $^{161}\text{Tb}$ , and 40  $\mu\text{g}$   $^{161}\text{Dy}$ ) loading, the column was first eluted at a flow rate of 1.0 mL/min with 0.4 mol/L  $\text{HNO}_3$  to selectively remove  $\text{Gd}^{3+}$ , followed by 0.6 mol/L  $\text{HNO}_3$  to recover  $\text{Tb}^{3+}$  while retaining  $\text{Dy}^{3+}$  on the column. Stable isotopes of Gd, Tb, and Dy were used in this study to simulate post-irradiation conditions. Because lanthanide isotopes exhibit identical chemical behavior, these model experiments provide a reliable indication of  $^{161}\text{Tb}$  separation performance [3,6,10,19]. The activity levels of related  $\beta^-$ -emitters, such as  $^{177}\text{Lu}$ , are well below thresholds that would degrade polymer resins, and  $^{161}\text{Tb}$  has a comparable emission profile and half-life. It is therefore reasonable to infer that the beta radiation from  $^{161}\text{Tb}$  would

likewise not damage the resin or affect binding. Future work will extend this protocol to irradiated targets to further confirm the resin's performance under radioactive conditions.

The concentration of  $H^+$  in the aqueous sample was quantified through acid-base titration. The morphology and surface elemental distribution of P350@resin before and after lanthanide adsorption were examined by scanning electron microscopy (SEM, Regulus 8230, Hitachi, Tokyo, Japan) with energy-dispersive X-ray spectroscopy (EDS) for elemental mapping. Fourier-transform infrared (FT-IR, INVENIO R, Bruker, Billerica, MA, USA) spectra were collected over the wavenumber range of 400–4000  $cm^{-1}$  to identify functional groups and monitor potential shifts in bonding modes after metal ion binding. X-ray photoelectron spectroscopy (XPS) was carried out on a Bruker S2 Puma system (Bruker, Billerica, MA, USA) with Al  $K\alpha$  radiation to analyze the chemical states of surface elements, with particular attention to changes in the O 1s and P 2p regions indicative of metal–ligand interactions.

### 3. Results and Discussion

#### 3.1. Adsorption and Separation Performance of P350@Resin Toward $Gd^{3+}$ , $Tb^{3+}$ , and $Dy^{3+}$

The adsorption behavior of P350@resin toward  $Gd^{3+}$ ,  $Tb^{3+}$ , and  $Dy^{3+}$  was systematically investigated, and the results are summarized in Figure 1. The adsorption efficiency for all three lanthanide ions increased with the solid-to-liquid (S/L, g/mL) ratio, exceeding 90% when the ratio surpassed 6 g/L. Among the three ions,  $Dy^{3+}$  consistently exhibited the highest adsorption efficiency across all S/L values, followed by  $Tb^{3+}$  and  $Gd^{3+}$ . This trend reflects the resin's preferential binding toward heavier lanthanides, attributable to the increasing charge density and decreasing ionic radius along the lanthanide series.

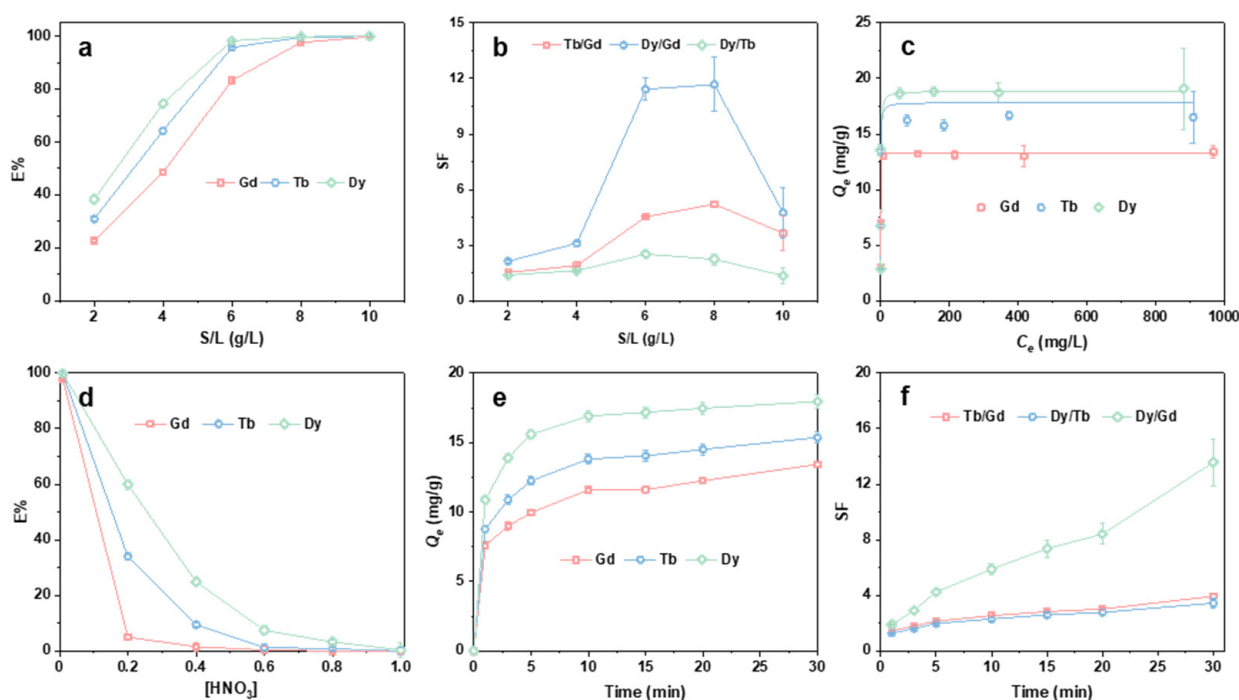


**Figure 1.** The static adsorption performance of P350@resin for  $Gd^{3+}$  /  $Tb^{3+}$  /  $Dy^{3+}$ . Effect of solid-to-liquid ratio on (a) adsorption efficiency and (b) separation factor, (c) adsorption isotherm, (d) effect of aqueous nitrate concentration, effect of contact time on (e) adsorption capacity and (f) separation factor.

To evaluate the selectivity of the resin, SF for  $Dy/Gd$ ,  $Dy/Tb$ , and  $Tb/Gd$  pairs were calculated and are presented in Figure 1b. The highest SF values were observed at an S/L ratio of 8 g/L, reaching above 10 for  $Dy/Gd$  and above 2 for  $Dy/Tb$ , highlighting the

strong discriminatory capability of P350@Resin, particularly for  $\text{Dy}^{3+}$ . The SF for Tb/Gd peaked at about 4, indicating a moderate yet useful separation potential between these two chemically similar ions. Adsorption isotherms (Figure 1c) further confirmed these trends. At saturation, the maximum  $Q_e$  of P350@Resin were approximately 19.5 mg/g for  $\text{Dy}^{3+}$ , 15.5 mg/g for  $\text{Tb}^{3+}$ , and 12.5 mg/g for  $\text{Gd}^{3+}$ . These results are consistent with the higher affinity of the resin for lanthanides of higher atomic number.

The effect of nitric acid concentration on adsorption efficiency is shown in Figure 1d. As acid concentration increased, E% decreased sharply for all ions. Above 0.3 mol/L  $\text{HNO}_3$ , E% fell below 10% for all ions, indicating effective elution under higher acid concentrations and enabling controlled desorption during column operation. From Figure 1e, the adsorption of all three ions rapidly reached near equilibrium within 10 min, followed by a very slow increase. The relative adsorption capacities ( $\text{Dy}^{3+} > \text{Tb}^{3+} > \text{Gd}^{3+}$ ) were consistent with the isotherm data. Importantly, separation factors also increased over time (Figure 1f), with Dy/Gd reaching a maximum SF of over 16 at 30 min, suggesting that kinetic control may further enhance selectivity.

These results demonstrate that P350@Resin exhibits strong, selective, and tunable adsorption for lanthanide ions, particularly favoring  $\text{Dy}^{3+}$  over  $\text{Tb}^{3+}$  and  $\text{Gd}^{3+}$ , making it well-suited for use in  $^{161}\text{Tb}$  purification from irradiated  $^{160}\text{Gd}$  targets and the co-produced  $^{161}\text{Dy}$ .

### 3.2. Chromatographic Separation of $\text{Gd}^{3+}$ , $\text{Tb}^{3+}$ , and $\text{Dy}^{3+}$ Using P350@Resin

To assess the chromatographic performance of P350@resin under dynamic conditions, elution profiles of  $\text{Gd}^{3+}$ ,  $\text{Tb}^{3+}$ , and  $\text{Dy}^{3+}$  were obtained using columns with varying bed heights. At a column height of 8 cm (Figure 2a), all three lanthanides eluted in close succession, with significant peak overlap between  $\text{Gd}^{3+}$  and  $\text{Tb}^{3+}$  and incomplete resolution of  $\text{Dy}^{3+}$ . Although the elution sequence ( $\text{Gd} < \text{Tb} < \text{Dy}$ ) was retained, the insufficient bed volume limited band dispersion, leading to poor separation and high risk of cross-contamination—rendering the setup impractical for radiochemical purification.

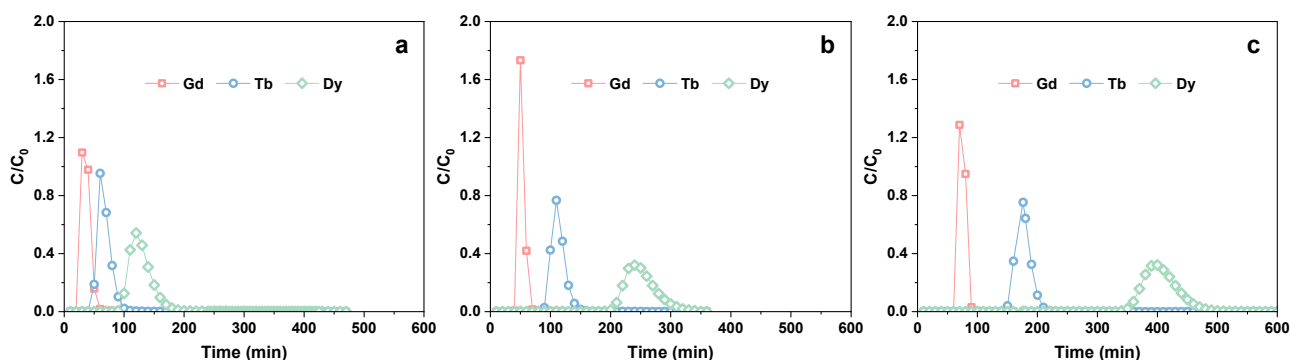


**Figure 2.** The effect of the different heights of P350@Resin column on  $\text{Gd}^{3+}/\text{Tb}^{3+}/\text{Dy}^{3+}$  separation (column diameter is fixed as 1 cm). (a) 8 cm, (b) 18 cm, (c) 28 cm. 0.6M  $\text{HNO}_3$  as the eluent. The flow rate of the eluent was 0.5 mL/min.

When the column height was increased to 18 cm (Figure 2b), substantial improvement in resolution was observed, which is attributed to enhanced mass transfer and increased interaction time with the resin matrix, allowing better utilization of selectivity differences among the lanthanides. At a bed height of 28 cm (Figure 2c), baseline separation of all three ions was achieved.  $\text{Gd}^{3+}$  eluted sharply,  $\text{Tb}^{3+}$  was well-separated around 180 min, and  $\text{Dy}^{3+}$  appeared as a broad peak between 350 and 450 min. The increased column efficiency and extended interaction path promoted sharper elution gradients and wider peak spacing. Importantly, the separation between  $\text{Gd}^{3+}$  and  $\text{Tb}^{3+}$  was sufficient to allow

the collection of high-purity  $^{161}\text{Tb}$  with minimal Gd breakthrough—an essential criterion for radiopharmaceutical-grade  $^{161}\text{Tb}$  production suitable for DOTA chelation.

The concentration of nitric acid plays a critical role in dictating the elution sequence and resolution of lanthanide ions during chromatographic separation. At 0.4 M  $\text{HNO}_3$  (Figure 3a), strong retention was observed, resulting in well-separated peaks:  $\text{Gd}^{3+}$  (100–200 min),  $\text{Tb}^{3+}$  (350–450 min), and  $\text{Dy}^{3+}$  (700–850 min). Despite the extended run time, this condition provided baseline resolution, ideal for applications requiring high radionuclidic purity.

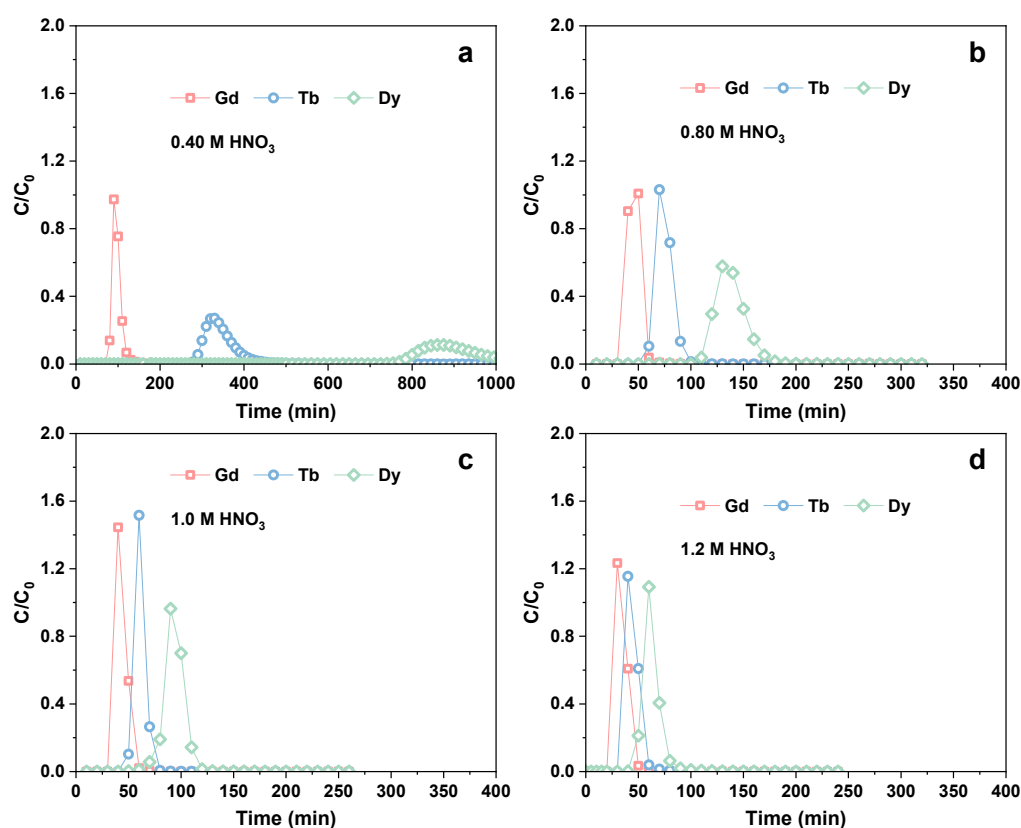


**Figure 3.** The effect of the concentration of the eluting acids on  $\text{Gd}^{3+}/\text{Tb}^{3+}/\text{Dy}^{3+}$  separation. (a) 0.4 M  $\text{HNO}_3$ , (b) 0.8 M  $\text{HNO}_3$ , (c) 1.0 M  $\text{HNO}_3$ , (d) 1.2 M  $\text{HNO}_3$ . The flow rate of the eluent was 0.5 mL/min.

With the increasing nitric acid concentration, elution occurred more quickly. Moderate resolution was maintained but with reduced selectivity, peaks were further compressed with partial overlap between  $\text{Tb}^{3+}$  and  $\text{Dy}^{3+}$ , indicating weakened selectivity due to increased coordination competition from nitrate ions. At 1.2 M (Figure 3d), all ions eluted nearly simultaneously within 60 min. The co-elution indicated saturated resin sites and was unsuitable for selective purification but may be used for column regeneration.

To further refine dynamic chromatographic conditions, the effect of eluent flow rate was investigated. At the lowest tested flow rate (0.5 mL/min, Figure 4a), excellent peak resolution was observed.  $\text{Gd}^{3+}$  eluted first with a narrow and sharp peak centered around 50–150 min.  $\text{Tb}^{3+}$  followed at approximately 300–400 min, with minimal overlap with  $\text{Gd}^{3+}$ .  $\text{Dy}^{3+}$ , in turn, was eluted significantly later (~700–1000 min), and well-separated from both  $\text{Gd}^{3+}$  and  $\text{Tb}^{3+}$ . The long residence time at this low flow rate allowed equilibrium-driven interactions between the lanthanide ions and the resin to reach near-completion, thereby maximizing selective retention and band separation. This condition yielded the highest theoretical plate numbers and provided baseline resolution among the three lanthanides.

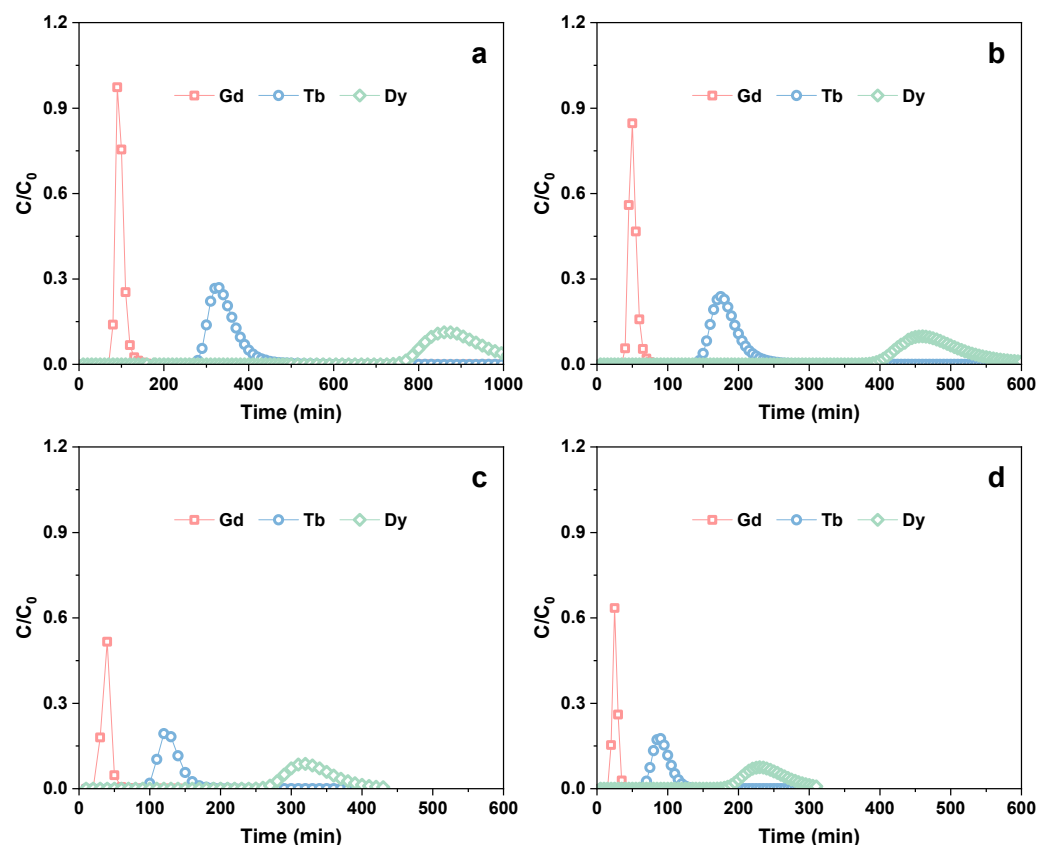


**Figure 4.** The effect of eluent flow rate on Gd<sup>3+</sup>/Tb<sup>3+</sup>/Dy<sup>3+</sup> separation. (a) 0.5 mL/min, (b) 1.0 mL/min, (c) 1.5 mL/min, (d) 2.0 mL/min. 0.4 M HNO<sub>3</sub> as the eluent.

As the flow rate increased, the elution peaks showed only minor changes in shape but remained largely consistent in width. The Gd<sup>3+</sup> peak shifted slightly earlier, and Tb<sup>3+</sup> also eluted earlier, with a small degree of overlap with Dy<sup>3+</sup> emerging at higher flow rates. At the highest flow rate tested (2.0 mL/min, Figure 4d), these effects were most noticeable: the Gd<sup>3+</sup> peak appeared very early, the Tb<sup>3+</sup> peak showed a modest reduction in intensity, and Dy<sup>3+</sup> eluted sooner with slight tailing. These subtle changes reflect reduced contact time between the solution and resin functional groups, leading to a slight decrease in separation selectivity. While the overall resolution remained acceptable, the highest flow rate provided less optimal conditions for collecting highly pure <sup>161</sup>Tb fractions.

In conclusion, under low-acidity conditions (0.4–0.8 M HNO<sub>3</sub>), flow rates of 0.5–1.0 mL/min offer the best compromise between resolution and efficiency for isolating high-purity <sup>161</sup>Tb. These conditions, in conjunction with prior column height and acidity optimizations, provide a solid foundation for method standardization and scale-up in radiopharmaceutical applications.

### 3.3. Adsorption Mechanism of P350@Resin

To elucidate the adsorption mechanism of P350@resin toward lanthanide ions, a comprehensive characterization was performed before and after Gd<sup>3+</sup>, Tb<sup>3+</sup>, and Dy<sup>3+</sup> loading. As shown in Figure 5a, the original P350@resin exhibits uniform spherical morphology with smooth surfaces, suggesting good synthesis reproducibility and structural integrity. EDS elemental mapping revealed homogeneous distribution of C, O, and P elements, indicating successful incorporation of functional groups across the resin matrix, which is critical for effective metal ion coordination. No significant signals from other elements (e.g., S or F) were detected, indicating that any impurities, if present, are only trace-level and unlikely to influence lanthanide adsorption. This indicates that the sorption behavior

is primarily attributable to the designed phosphoryl sites, which are critical for effective metal ion coordination.

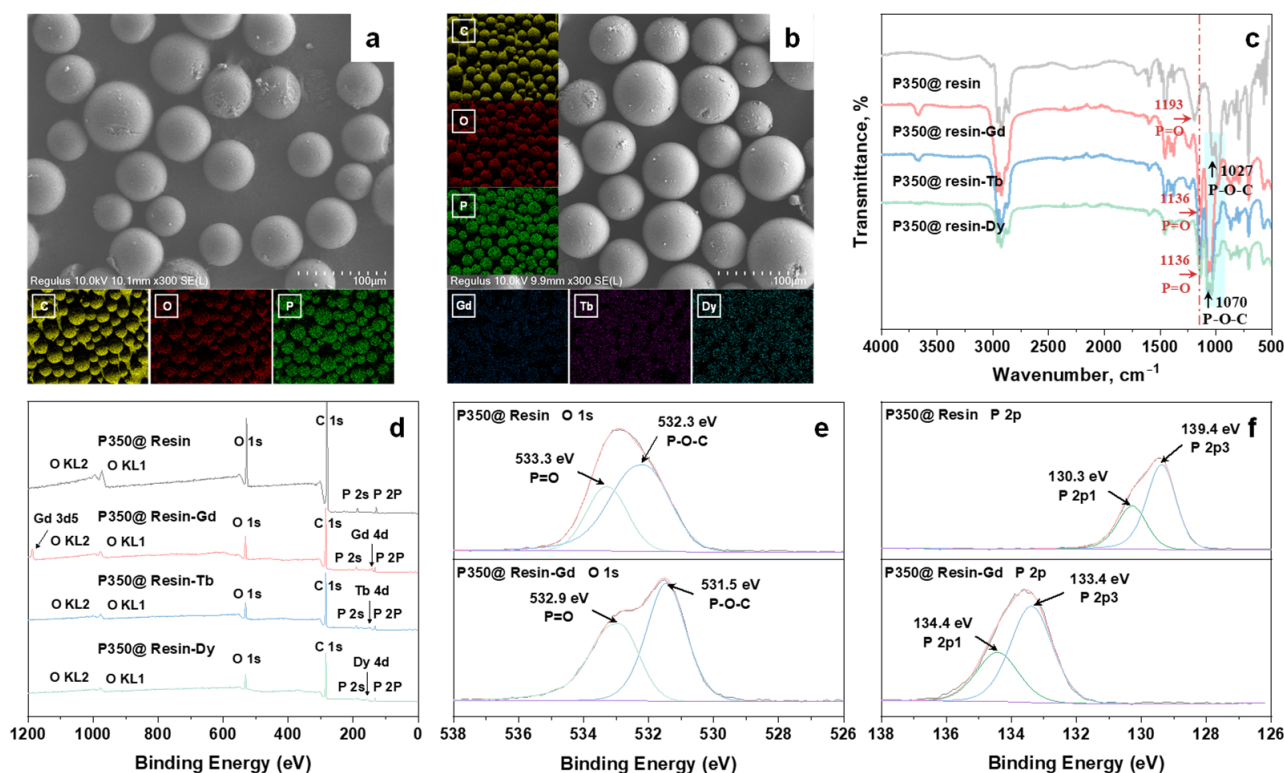


**Figure 5.** Characterization of P350@resin before and after  $\text{Gd}^{3+}$ / $\text{Tb}^{3+}$ / $\text{Dy}^{3+}$  adsorption (a) SEM and EDS mapping of the resin before adsorption, (b) SEM and EDS mapping of the resin after adsorption, (c) FT-IR analysis and (d–f) XPS analysis of the resin before and after adsorption. Different colors represent deconvoluted peaks corresponding to individual chemical states: red—total fitted curve; blue/green—component peaks.

Following lanthanide adsorption (Figure 5b), EDS confirmed the presence of Gd, Tb, and Dy on the resin surface. Their uniform distribution across the matrix indicates efficient and homogeneous uptake. Importantly, the spherical morphology of the resin remained intact, demonstrating excellent mechanical and chemical stability during the adsorption process, which is favorable for repeated chromatographic use. FT-IR analysis (Figure 5c) was conducted to investigate changes in functional group vibrations after lanthanide loading. The characteristic stretching bands of the P=O group (originally at  $\sim 1136 \text{ cm}^{-1}$ ) and the P–O–C linkage ( $\sim 1070$ – $1193 \text{ cm}^{-1}$ ) exhibited noticeable red shifts in the  $\text{Ln}^{3+}$ -loaded samples. These shifts are indicative of coordination interactions between lanthanide ions and the phosphoryl of P350 on the resin [31].

XPS spectra provided further evidence of chemical binding. The survey spectra (Figure 5d) confirmed the presence of Gd 3d, Tb 4d, and Dy 4d signals in the loaded resin, verifying successful adsorption. Importantly, in the pristine resin no peaks corresponding to elements other than C, O, and P were detected in the XPS survey, confirming that the resin's composition is limited to its polymer backbone and functional groups. High-resolution O 1s spectra (Figure 5e) showed two peaks in the original resin at 533.3 eV (P=O) and 532.3 eV (P–O–C). After  $\text{Gd}^{3+}$  adsorption, these peaks shifted to 532.9 eV and 531.5 eV, respectively, indicating redistribution of electron density due to metal coordination. Similarly, the P 2p spectrum (Figure 5f) displayed two characteristic peaks in the original resin at 130.3 eV (P 2p<sub>1/2</sub>) and 129.4 eV (P 2p<sub>3/2</sub>). Upon  $\text{Gd}^{3+}$  loading, these peaks shifted to 134.4 eV and 133.3 eV, respectively, further confirming participation of the phosphoryl in the chelation

process. These changes are consistent with previously reported organophosphorus extractants used for rare earth separation [32,33], in which the electron density shifts reflect the chemical nature of metal–ligand bonding.

Collectively, the SEM, EDS, FT-IR, and XPS results confirm that P350@resin binds lanthanide ions via coordination with phosphoryl. The stable morphology, homogeneous elemental distribution, and clear spectral shifts indicate that the resin maintains structural integrity and functional group accessibility during adsorption.

### 3.4. Simulated $^{161}\text{Tb}$ Production Process

To apply the P350@Resin into a practical protocol for purifying  $^{161}\text{Tb}$  from neutron-irradiated  $^{160}\text{Gd}$  targets, a stepwise elution strategy using discrete nitric acid concentrations was developed with a simulated feed solution containing stable isotopes of Gd, Tb, and Dy. In the first step, Gd was gradually eluted under low-acid conditions to maximize separation from Tb. In the second step, Tb and Dy were eluted more rapidly under higher acidity to minimize processing time. The elution behavior was first assessed using individual lanthanide solutions. As shown in Figure 6a, initial elution with 0.4 M  $\text{HNO}_3$  during the 0–80 min interval resulted in complete and selective removal of  $\text{Gd}^{3+}$ . A subsequent switch to 0.6 M  $\text{HNO}_3$  enabled efficient elution of  $\text{Tb}^{3+}$  between 80 and 130 min, followed by  $\text{Dy}^{3+}$  from 130 to 200 min. This two-step profile offered faster elution than continuous operation at 0.4 M  $\text{HNO}_3$  (Figure 3a), while maintaining sufficient resolution between  $\text{Tb}^{3+}$  and  $\text{Dy}^{3+}$  compared to 0.8 M  $\text{HNO}_3$  (Figure 3b).

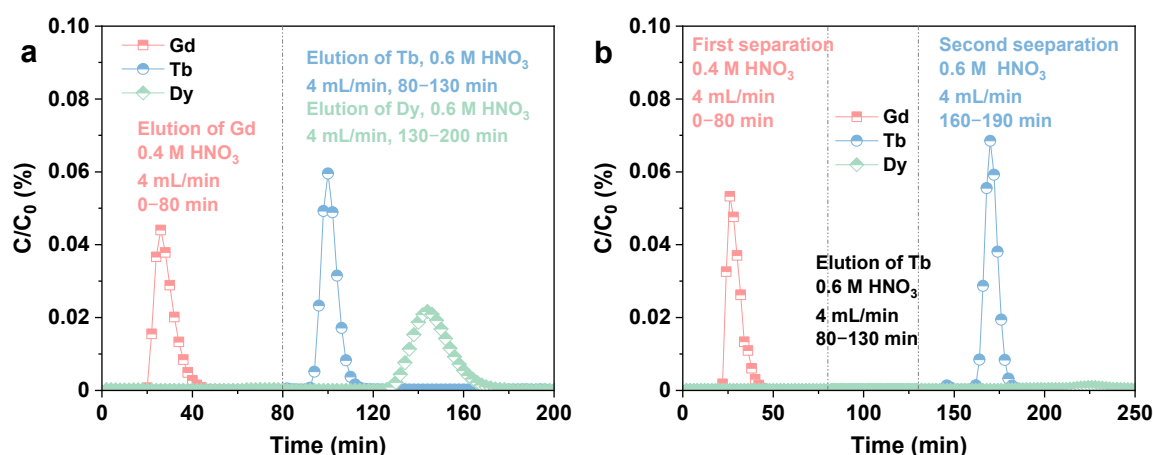


**Figure 6.** (a) Evaluation of the elution time of  $\text{Tb}^{3+}$  using 0.6 mol/L nitric acid. (b) Elution curve of  $\text{Gd}^{3+}/\text{Tb}^{3+}/\text{Dy}^{3+}$  in continuous separation process. The column size is 16 mm  $\times$  30 cm.

To further evaluate the strategy under realistic dynamic conditions, a continuous step-gradient operation was conducted. As shown in Figure 6b,  $\text{Gd}^{3+}$  was sharply eluted during the first 50 min and was completely removed before the acid concentration change.  $\text{Tb}^{3+}$  eluted cleanly in the 80–190 min interval, exhibiting a symmetrical peak with negligible  $\text{Dy}^{3+}$  overlap.  $\text{Dy}^{3+}$  remained strongly retained beyond 250 min, confirming the resin's selectivity under continuous operation. The collected Tb fraction achieved a purity of  $98.67 \pm 0.28\%$ , very close to the  $\geq 99\%$  threshold typically required for radiopharmaceutical applications; with further optimization of column parameters and elution protocols, this value can be expected to reach or exceed that benchmark. Although the total processing time ( $\sim 3$  h) results in only  $\sim 1.24\%$  decay of  $^{161}\text{Tb}$ , this is significantly lower than the decay loss associated with conventional industrial cation exchange resin methods ( $\sim 3.72\%$  over 475 min) [10]. TK resins allow faster purification ( $\sim 90$  min,  $\sim 0.62\%$  decay) but require three columns and complex transfer steps, increasing operational burden and risk of

$^{161}\text{Tb}$  loss [19]. In contrast, the P350@Resin approach processes a much larger Tb load (200 mg vs. 10 mg for TK resin studies) and manages a more challenging feed composition (Gd:Tb:Dy ratio of 5000:1:1), which explains the slightly longer elution time. These results demonstrate the feasibility of implementing a two-step elution protocol without requiring multiple columns or complex gradient systems. The process offers well-defined elution windows, operates under mild acidity, and achieves rapid throughput, making it a practical and efficient approach for producing  $^{161}\text{Tb}$  with high radionuclidic purity suitable for clinical applications.

#### 4. Conclusions

This work systematically demonstrates the suitability of P350@resin for the radiochemical purification of no-carrier-added  $^{161}\text{Tb}$  from neutron-irradiated  $^{160}\text{Gd}$  targets. The resin exhibits selective and strong affinity for trivalent lanthanides, with a separation trend of  $\text{Dy} > \text{Tb} > \text{Gd}$  under diluted nitric acid conditions. Static batch experiments confirmed high adsorption capacity (17 mg/g for Tb) and favorable separation factors (4 of Tb/Gd and 2 of Tb/Dy), while dynamic column tests revealed that column height, acid concentration, and flow rate are key parameters governing separation efficiency. Under optimized conditions: 0.4–0.6 mol/L  $\text{HNO}_3$ , 20–28 cm bed height, and a flow rate of 0.5–1.0 mL/min. Separation of  $\text{Tb}^{3+}$  from  $\text{Gd}^{3+}$  and  $\text{Dy}^{3+}$  was consistently achieved. A two-step elution protocol was established that yielded high-purity Tb fractions with minimal cross-contamination from stable isotopes simulated solution. SEM, EDS, FT-IR, and XPS analysis confirmed that the binding mechanism involves coordination between lanthanide ions and the phosphoryl functional groups of P350. These results highlight the effectiveness of P350@resin for  $^{161}\text{Tb}$  purification, providing a scalable and practical foundation for producing clinical-grade  $^{161}\text{Tb}$ -based radiopharmaceuticals.

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