TRISKEM INFOS

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Dear User,

In this new issue of our TKI newsletter - already the 20th! - you will find more information on our ongoing work on the separation of nca Lu-177, and nca Tb-161, from their respective irradiated targets of elevated size. The presented work was mainly performed using, in addition to the TK221 Resin presented in our last TKI19, three new resins called TK211, TK212 and TK213, you will find more information about these resins on the following pages.

We are also introducing the new Guard Resin, an alternative to the Prefilter Resin for the removal of organic impurities with higher hydrophobicity. It is further finding use in a Ge-68 separation method that is currently being optimized.

Finally, we are very glad to announce our very first virtual Users Group Meeting! It will be organized on the 24th of November in cooperation with the NPL (Teddington, UK) as part of their virtual CARM conference. We would be very glad if you would participate to this new experience!

Michaela Langer, CEO

TK211/212/213 Resins

The TK211, TK212 and TK213 Resins are based on different mixtures of organophosphoric, organophosphonic and organophosphinic acids. It could be shown that under certain conditions and for certain lanthanide pairs, such mixtures can show increased selectivity compared to the respective pure compounds.

The organic phase further contains a small amount of a long-chained alcohol that will act as radical scavenger to increase the radiolysis stability of the resin. The inert support onto which the organic phase is impregnated contains aromatic groups which will also contribute to the increase of the radiolysis stability of the resins.

The inert support further shows an elevated capacity for the extractants, accordingly this allows the TK211/2/3 Resins to have a higher extractant load compared to e.g. the LN Resin series.

The TK211/2/3 Resins show, like the LN Resins, differences in their respective acidities. TK211 is the most acidic resin, accordingly it will extract lanthanides, and other elements, at higher acid concentrations than e.g. TK212 and TK213. TK212 on the other hand is more acidic than TK213 (order of acidity: TK211 > TK212 > TK213). The selectivity and retention of the lanthanides is generally very similar in HNO_3 and HCl on all three resins, accordingly both acids may be employed for the separation of lanthanides.

This difference in the relative acidity of the resins can be exploited to facilitate otherwise more complex lanthanide separations [1]. This will particularly be the case for the separation of very small amounts of one lanthanide from a large excess of its neighbouring lanthanide.

Typical examples are the production of nca Lu-177 (separation from irradiated Yb-176 targets) and nca Tb-161 (separation from irradiated Gd-160 targets).

By performing a first separation on a less 'acidic resin' such as TK212 followed by direct elution of the lanthanide fraction to be further purified onto a more 'acidic resin' such as TK211 for further purification ("sequential separation") it is possible to eliminate intermediary steps such as the use of TK221 (or DGA) Resin to convert the lanthanide fraction from higher acid concentration to low acid concentration.

In an ideal case even a fully sequential three column separation might be possible (TK213 => TK212 => TK211).

Two examples of the use of such sequential separation steps will be shown in the following.

The production of nca Lu-177 is rapidly gaining importance due to its increased use in nuclear medicine. Reliable, preferably easy to automize methods that allow for its separation from irradiated Yb-176 targets of elevated size (≥500 mg) are thus of increasing importance.

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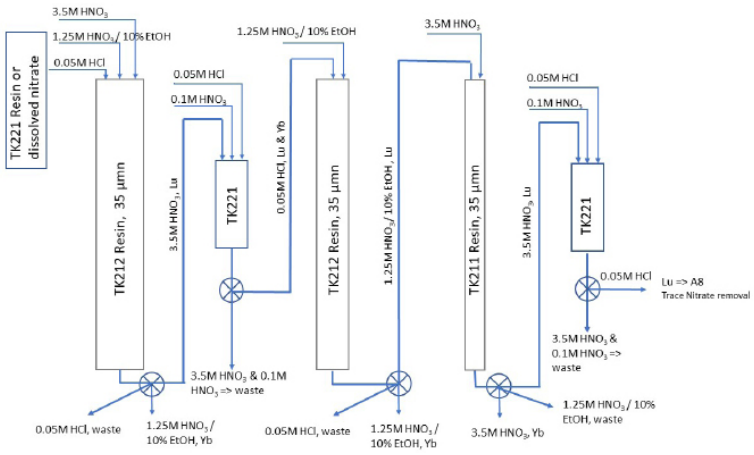


Figure 1: Scheme of a method for the separation of Lu from 500 mg Yb using TK212, TK221 and TK211

Horwitz et al. [2] describe a method based on three LN2/DGA cycles for the separation of nca Lu-177 from 300 mg Yb-176 targets. While this method gives good yields (~73%) in a short separation time (~4h) the fact that an elevated number of columns are required complicates its automatization. Further it has only been tested for up to 300 mg of target material.

By introducing a sequential separation step this method can be partially simplified (Figure 1).

It could be shown [1] that the method described in Figure 1 allows for separating Lu from up to 500 mg of Yb with elevated Lu recovery (~85%) and a very low amount of residual Yb in the final Lu fraction.

News

New Guard Resin.

The Guard Resin is a hydrophobic, highly crosslinked, porous polydivinylbenzene based adsorbent. Due to its high hydrophobicity it will remove certain organic impurities, notably organic impurities that are hydrophobic, more efficiently than e.g. the Prefilter Resin. The resin shows high mechanical and chemical stability, and it can be used over the whole pH range.

Another application of the Guard Resin is the separation, in combination with the ZR Resin, of Ge-68 from GaNi or GaCo targets.

The Guard Resin is TSE/BSE/GMO free.

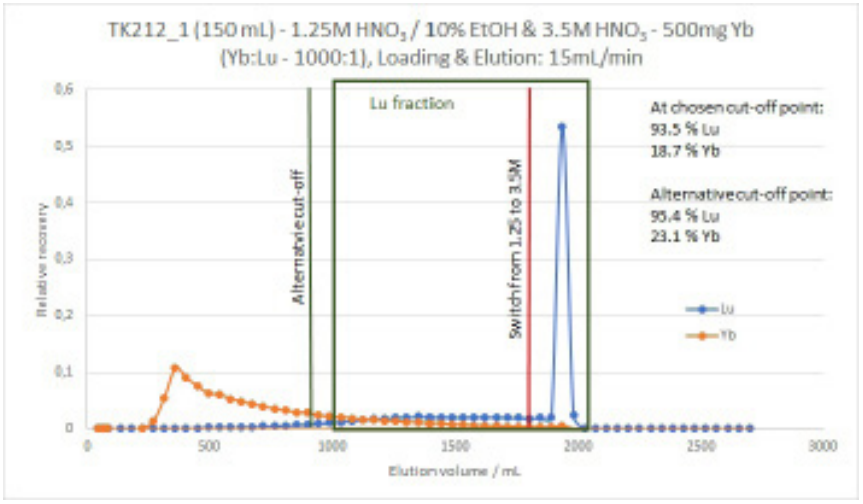


Figure 2: Example of a Lu separation from 500 mg Yb on a TK212 column (2.5 x 30 cm, 150 mL) using 1.25M HNO_3 / 10% EtOH and 3.5M HNO_3

The increased Lu recovery is, other than the use of TK212 instead of LN2, also due to the adjustment of the eluting agent used for the chromatographic separation of Lu and Yb on the first TK212 column from 1.3M HNO_3, as suggested by Horwitz et al., to 1.25M HNO_3 / 10% EtOH.

It should be noted that adding EtOH only showed an improvement for the 1.25M HNO_3 but not for the 3.5M HNO_3. Further, mixing 3.5M HNO_3 with EtOH should be strictly avoided for safety purposes.

Figure 2 – Figure 4 show typical chromatograms obtained during the separation of Lu from 500 mg of Yb (initial Lu:Yb ratio: 1:1000). All experiments were performed using stable elements, fractions of defined sizes were collected, diluted, and analysed off-line by ICP-MS. Relative recoveries were calculated for Lu and Yb and plotted against the elution volume.

It should be noted that the switch to 3.5M HNO_3 in the given example was made at a rather late stage of the separation. In the final version of the process it should take place earlier, ideally triggered via radiation detection, close to the chosen cut-off point (left end of the green frame). Indeed, the moment of the switch will have, especially on the first column, a considerable influence on the Lu recovery and Yb carry-over. This is mainly due to the large tailing introduced by the macro-amount of Yb.

The fractions comprised in the green frame ("Lu fractions") were combined and passed through a 5g TK221 cartridge for conversion to ≤0.05M HCl. The Lu fraction thus obtained in dilute HCl was then loaded onto the next TK212 column (1.5 x 30 cm, 53 mL).

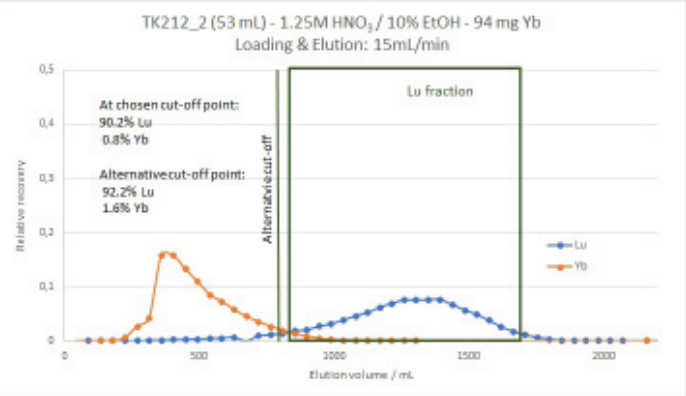
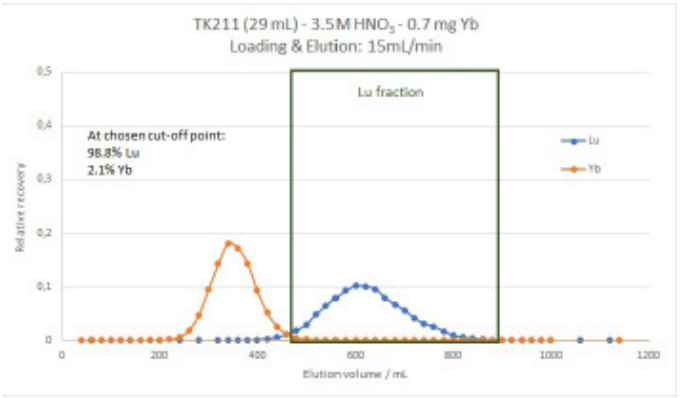


Figure 3: Example of a Lu separation from 94 mg residual Yb (obtained from a first separation on TK212) on a second TK212 column (1.5 x 30 cm, 53 mL) using 1.25 M HNO_3 /10% EtOH.

Due to the lower of amount of Yb present on the column the tailing of the Yb and Lu elution is less pronounced than on the first TK212 column.

Although this would be possible, in this example the Lu containing fractions (green frame) are not eluted in HNO_3 of elevated concentration (as described in the Horwitz method), passed through a TK221 (or DGA) cartridge and eluted in dilute HCl for another load onto TK212.



Example of a Lu separation from <1 mg residual Yb (obtained from the second separation on TK212) on a TK211 column (1.1 x 30 cm, 29 mL) using 3.5 M HNO_3

Instead the combined fractions are directly loaded onto a TK211 column (1.1 x 30 cm, 29 mL) for the final purification of the Lu.

Lu is finally obtained following separation/elution e.g. with 3.5M HNO_3.

In the final step the obtained Lu fractions (as indicated in the green frame) were combined and loaded onto a 2 mL TK221 cartridge, any last potentially present impurities are removed through consecutive rinsed with 3.5M HNO_3 and 0.1M HNO_3. Lu is then finally eluted using ≤0.05M HCl.

Last traces of nitrates that might still be present will be removed via a 1 mL anion exchange cartridge (A8 Resin).

A further upscale of this separation process is currently being finalized

Another radiolanthanide increasingly finding use is Terbium. As Tb isotopes may be used for PET imaging (Tb-152), SPECT imaging (Tb-155), alpha therapy (Tb-149) and beta therapy (Tb-161) it is also referred to as the 'swiss army knife' of nuclear medicine [3,4]. Particularly the interest in Tb-161 is currently increasing significantly, accordingly methods for the separation of Tb from irradiated Gd targets of elevated size are needed. The development, and later upscale, of methods for the separation of Tb from 500mg Gd is currently on-going. Figure 5 shows a scheme of a suggested separation process. As may be seen the separation is more straightforward compared to the separation of Lu from Yb targets (Figure 1).

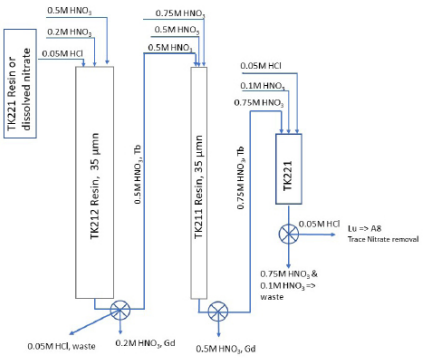


Figure 5: Scheme of a method currently under development for the separation of Tb from 500 mg Gd using TK212 and TK211

Figure 6 and Figure 7 show typically obtained chromatograms (stable Gd, Tb and Dy, with an original ratio of 1000:1:1).

Like for the Lu separation the separations were performed using stable elements, fractions of defined volumes were taken and analysed by ICP-MS.

A first separation is performed on a TK212 column. This step allows for an initial separation of Tb from Gd and Dy.

The obtained Tb fractions (indicated by the orange frame) were then combined and directly loaded onto a TK211 column for final purification of the Tb.

Agenda

Please find here below a listing of the conferences at which we'll participate this year. The majority of the conference, we had planned to attend, have been postponed for security reasons. We understand and support these measures.

You'll find an updated list with the new conference dates (if known) on our web site under: https://www.triskem-international.com/ma/events.

We will participate with a virtual booth to the EANM and the WMIC. Please don't hesitate to contact Dr. Steffen HAPPEL **(shappel@triskem.fr)** to organize a video conference or chat during these events. An overview over some recent work in the separation of radionuclides for use in nuclear medicine and radiopharmacy can be found in the "Presentations" section of our website (https://www.triskem-international.com/posters-and-presentations.php).

WMIC virtual 2020, virtual booth, 07 – 10/10/2020, https://www.wmicvirtual.org/

Virtual EANM20, virtual booth, 22 – 30/10/2020, Vienna (Austria), https://eanm20.eanm.org/

TrisKem UGM 2020: Our first virtual Users Group Meeting, 24 November 2020 from 13h to 17h CET. The meeting will be a part of the virtual CARM conference organized by the National Physical Laboratory (NPL) from November 23rd to 27th, to subscribe: https://www.eventbrite.co.uk/e/virtual-conference-on-applied-radiation-metrology-vcarm-registration-116885598973

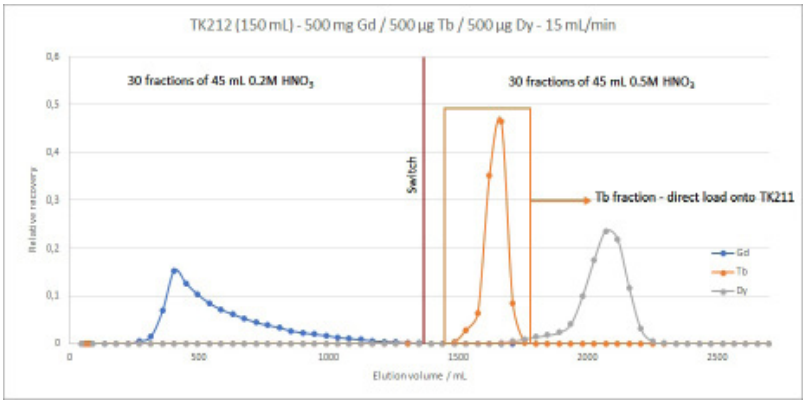


Figure 6: Example of a Tb separation from 500 mg Gd on a TK212 column (2.5 x 30 cm, 150 mL) using 0.2M HNO_3 and 0.5M HNO_3

As may be seen in Figure 7 under the chosen conditions most of the Gd is breaking through during the load, any Gd remaining on the columns is rinsed of with 0.5M HNO_3.

It could be shown for the Lu separation process that the addition of small amounts of EtOH (10% v/v) improves the separation, this is currently also being tested for the Tb separation.

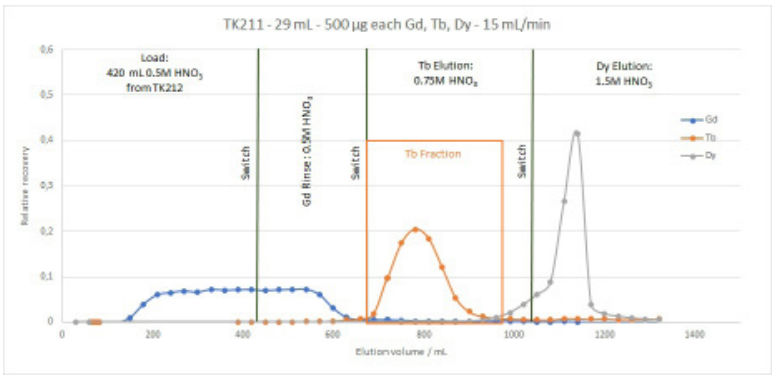


Figure 7: Example of a Tb separation from 500 µg Gd on a TK211 column (1.1 x 30 cm, 150 mL) using 0.5M HNO_3 and 0.75M HNO_3

Increasing the concentration of the mineral acid (in this example to 0.75M HNO_3) will lead to the elution of Tb, leaving potentially remaining traces of Dy on the column. In case the presence of Dy can be ruled out this elution can be performed at higher acid concentrations, thus lowering the elution volume.

As a final step the Tb will be concentrated on a 2 mL TK221 cartridge, any last potentially present impurities are removed through consecutive rinses with 0.75M HNO_3 and 0.1M HNO_3. Tb is then finally eluted using ≤0.05M HCl. Last traces of nitrates that might still be present will be removed via a 1 mL anion exchange cartridge (A8 Resin).

Main applications:
- Lanthanide separation

The indicated method is currently undergoing further optimisation and upscale to ≥1g.

Prepacked TK211/212/213 columns of various sizes (e.g. 150 mL, 53 mL and 29 mL) are currently being developed.

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- C Müller et al.:"A Unique Matched Quadruplet of Terbium Radioisotopes for PET and SPECT and for a- and b2-Radionuclide Therapy: An In Vivo Proof-of-Concept Study with a New Receptor-Targeted Folate Derivative" J. Nucl. Med. 53, 1951 (2012)
- CERNCOURRIER: "Terbium: a new 'Swiss army knife' for nuclear medicine", 28/01/2013, accessed 23/08/2020

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