

Comparative Radiolabelling of PSMA I&T and Somatostatin Analogues with ^{177}Lu and ^{90}Y : The Impact of SPE Purification

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Research Article

Keywords: Automated synthesis, Lu-177, Y-90, PSMA I&T, somatostatin analogue, solid phase extraction

Posted Date: August 12th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10585121/v1>

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Version of Record: A version of this preprint was published at EJNMMI Radiopharmacy and Chemistry on October 1st, 2026. See the published version at <https://doi.org/10.1186/s41181-026-00496-2>.

Abstract

Background

We report on comparison of two automated production processes for radiolabelling and formulation of three different radiopharmaceuticals [^{177}Lu]Lu-PSMA I&T, [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TOC. These processes were evaluated with and without C-18 solid phase extraction purification.

Methods

Radiopharmaceuticals were produced and formulated using single use cassette approaches on Eckert & Ziegler's Modular-Lab PharmTracer synthesis module. Quality control data from 20 to 30 batches for each radiopharmaceutical was used to evaluate these two production methods, including RP-HPLC, iTLC and GC analyses.

Results

Significant differences of product formulations were found in the amounts of unbound radiometal species as well as ethanol concentrations, although all batches analysed confirmed to pharmacopeial and internal specifications for product release. Radiochemical purity according to RP-HPLC showed no significant variations between the two production procedures. However, a slight increase in formation of a radiolytic side product during solid phase extraction purification of [^{177}Lu]Lu-PSMA I&T was noticeable.

Conclusions

Overall, in our setting omission of product purification from automated radiopharmaceutical production did not lead to any significant changes of the quality of the final products for all three radiotracers evaluated in this work. All batches analysed met specifications for product release. Thus, our data indicate that product purification is not required in all production procedures involving preparation of radiopharmaceuticals for radioligand therapy. However, this decision must be based on a case-by-case evaluation for each synthesis module and radiopharmaceutical in question.

1. Introduction

Radiopharmaceuticals based on radiometals are on the rise due to a marked increase in demand and very promising results in clinical application over the last two decades, especially when considering therapeutic applications for radioligand therapy (RLT) like [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]Lu-PSMA I&T or [^{177}Lu]Lu-DOTA-TATE and [^{177}Lu]Lu-DOTA-TOC. One method of synthesis and formulation for these radiopharmaceuticals is manual production [1, 2]. Clinics offering RLT are usually treating patients on a

regular basis, requiring production of multiple batches of these radiopharmaceuticals per month or even week. This places a steep radiation and time burden on personnel involved in the production [3, 4], especially when manual synthesis is performed. Additionally, in manual labour the risk of contamination of both personal and equipment is associated with significant risks and is difficult to mitigate. Consequently, this has given rise to automation of synthesis and dispensing procedures via specialised modules to prevent harm to workers and ensures compliance to regulatory limits for radiation exposure [5, 6]. Apart from radiation safety aspects, automated production also offers higher reproducibility, better process control as well as comprehensive documentation and in-process monitoring leading to a better traceability of the whole production process [7]. Recent development focus on the use of sterile single use cassette-based systems, that ensure high pharmaceutical standards and increase Good Manufacturing Practice (GMP) compliance by strengthening the Contamination Control Strategy. By eliminating the reuse of product-contact components, these systems remove concerns about cross-contamination and obviate laborious cleaning and cleaning validation—especially pertinent when long-lived radionuclides are used and components would otherwise be reused. [8].

Automated production of radiometal-based radiopharmaceuticals on synthesis modules usually consists of mixing the radiometal solution and the precursor ligand in a suitable buffer followed by incubation at pre-defined temperature and final formulation including sterile filtration [9, 10]. Some commercially available systems thereby include a purification step after incubation to ensure removal of unbound radiometal typically using solid phase extraction (SPE) cartridges, whereas others omit this purification step and formulate the final solution for parenteral application directly.

Here, we report on a comparative evaluation of two fully automated cassette-based synthesis processes for three different radiopharmaceuticals used for RLT: [^{177}Lu]Lu-PSMA I&T, [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TOC. These were radiolabelled and formulated with and without C-18 SPE using a commercial cassette-based synthesis module and we discuss the potential differences and impact on quality of the final radiopharmaceutical when using these different approaches.

2. Materials and Methods

2.1. Materials

PSMA I&T, DOTA-TATE and DOTA-TOC were obtained in bulk from piCHEM (Raaba-Grambach, Austria). Bulk peptides were dissolved in ethanol 50% and stored at -20°C as aliquots with a concentration of 1 mg/mL. [^{177}Lu]LuCl₃ was purchased in n.c.a. quality from ITM Medical Isotopes GmbH (EndolucinBeta®, Garching, Germany). [^{90}Y]YCl₃ was obtained from Eckert & Ziegler (Yttriga®, Eckert & Ziegler Radiopharma, Berlin, Germany).

2.2. Automated synthesis and product formulation

Radiopharmaceuticals were prepared on a Modular-Lab PharmTracer synthesis module (Eckert & Ziegler Radiopharma, Berlin, Germany). For automated synthesis with SPE purification, commercially available cassettes for Lu-177 (Eckert & Ziegler Radiopharma, Berlin, Germany) without alterations were used (Fig. 1). Synthesis without SPE was performed using custom-made cassettes (Eckert & Ziegler Radiopharma, Berlin, Germany), which were designed by the authors. The setup for the latter is depicted in Fig. 2.

Aliquots of PSMA I&T or DOTA-TATE were radiolabelled with [^{177}Lu]LuCl₃ or aliquots of DOTA-TOC were radiolabelled with [^{90}Y]YCl₃ corresponding to the required patient doses. Sodium ascorbate buffer to adjust the pH to 4.5 of the reaction solution was prepared using lyophilised sodium ascorbate kits (ASC-01, Polatom, Otwock, Poland), which were dissolved in 1 mL of water for injection (Fresenius Kabi, Graz, Austria). Radiolabelling was performed at 90°C for 14 min for [^{177}Lu]Lu-PSMA I&T, at 85°C for 20 min for [^{177}Lu]Lu-DOTA-TATE and at 95°C for 25 min for [^{90}Y]Y-DOTA-TOC.

After radiolabelling, 2 mL of physiological saline were added to the crude product. The solution was either then loaded onto a C18 Sep-Pak® Plus Light cartridge (Waters Corporation, Milford, MA, USA) or directly transferred to the product vial via a 0.22 µm sterile filter (Millex-GV® filter, 33 mm, Merck KGaA, Darmstadt, Germany). For synthesis carried out with SPE purification, the C18 cartridge was washed with physiological saline before eluting the radiotracer with 2.5 mL of ethanol 50% from the cartridge into the product vial by passing the solution through a 0.22 µm sterile filter (Millex-GV® filter, 33 mm). For both procedures, the product vial was pre-filled with ascorbic acid (Vitamin C-Injektapas®, Pascoe Pharmazeutische Praeparate GmbH, Enzersdorf, Austria) in an equivalent to 10 mg/GBq of Lu-177 or Y-90 and DTPA (Ditripentat-Heyl®, Berlin, Germany; diluted to 3 mg/mL) at a 20-molar excess over the peptide. The final product was diluted with 10 mL of physiological saline.

2.3. Quality control procedures

80 automated radiopharmaceutical production batches from clinical routine with and without SPE purification were compared based on the results from quality control, with a focus on radiochemical purity (RCP) according to RP-HPLC analysis. Analytics were performed on an UltiMate 3000 system (Thermo Fisher Scientific, Vienna, Austria) consisting of a RS UHPLC pump, an auto sampler, a column compartment with oven temperature set to 25°C, as well as a variable wavelength detector and a Gabi Star radiodetector (Raytest, Straubenhardt, Germany) connected in series. Different columns and gradients were used depending on the radiotracer. Details are given in Table 1. UV signals were recorded at 200 nm for [^{177}Lu]Lu-PSMA I&T and at 220 nm for [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TOC.

Table 1

Stationary and mobile phases used for RP-HPLC of [^{177}Lu]Lu-PSMA I&T, [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TOC. Gradients are given as % of solvent B in the mobile phase at denoted time intervals.

[^{177}Lu]Lu-PSMA I&T	column for RP-HPLC	mobile phase	gradient & flow
	Phenomenex Jupiter 4 μm Proteo 90 Å, 250 x 4.6 mm (00G-4396-E0, Phenomenex, Aschaffenburg, Germany)	solvent A: phosphate buffer 0.03 M (pH 2.3) solvent B: acetonitrile	0–2 min: B 23% 2–10 min: B 23–30% 10–12 min: B 30–60% 12–14 min: B 60% flow = 1.0 mL/min
[^{177}Lu]Lu-DOTA-TATE	ACE 3 C18 150 x 3.0 mm (ACE-111-1503; Avantor, Radnor, Pennsylvania, USA)	solvent A: water/TFA 0.1% solvent B: acetonitrile/ TFA 0.1%	0–20 min: B 20% 20–21 min: B 20–60% 21–26 min: B 60% flow = 0.6 mL/min
	ACE 3 C18 150 x 3.0 mm (ACE-111-1503; Avantor, Radnor, Pennsylvania, USA)	solvent A: water/TFA 0.1% solvent B: acetonitrile/ TFA 0.1%	0–15 min: B 20% 15–16 min: B 20–60% 16–20 min: B 60% flow = 0.6 mL/min
[^{90}Y]Y-DOTA-TOC	ACE 3 C18 150 x 3.0 mm (ACE-111-1503; Avantor, Radnor, Pennsylvania, USA)	solvent A: water/TFA 0.1% solvent B: acetonitrile/ TFA 0.1%	0–15 min: B 20% 15–16 min: B 20–60% 16–20 min: B 60% flow = 0.6 mL/min

Apart from RP-HPLC, other quality control procedures according to pharmacopeial monographs or current scientific standards were performed as well. These included instant thin-layer chromatography (iTLC) using a Scan-RAM radio-TLC scanner with Laura radiochromatography analysis software (LabLogic Systems Ltd, Sheffield, UK) to determine unbound radiometal amounts. Silica gel (iTLC-SG, Agilent Technologies, Vienna, Austria) was used as stationary phase, with either sodium citrate 0.1 M (pH = 5.0, “mobile phase A”) or ammonium acetate 1M and methanol (1:1 v/v , “mobile phase B”) as mobile phase.

Gas chromatography was performed on a GC-2010 Plus gas chromatograph equipped with an AOC-20i autosampler (Shimadzu Austria, Korneuburg, Austria) to measure ethanol concentration in the final product. A Phenomenex Zebron ZB-624 column (7KM-G005-31) with FID temperature at 260°C and a flow rate of 3 mL/min was employed for analysis.

2.4. Batch analysis

For [^{177}Lu]Lu-PSMA I&T and [^{177}Lu]Lu-DOTA-TATE, three different levels of activity amounts were defined and five batches for each level were used for statistical evaluation and comparison between synthesis

procedures with and without SPE purification. For [^{177}Lu]Lu-PSMA I&T and [^{177}Lu]Lu-DOTA-TATE the three levels of starting activity were defined as “low”, “medium” and “high” activity.

For [^{90}Y]Y-DOTA-TOC only two levels of activity amounts were defined and five batches for each level were used for statistical evaluation and comparison between synthesis procedures with and without SPE purification. The two levels of starting activity were defined as “low” and “high” activity.

Activity yield was calculated as percentage of product activity in relation to starting activity of [^{177}Lu]LuCl₃ or [^{90}Y]YCl₃ used for each batch production.

2.5. Statistics and visualisations

Graphs and statistical analyses were performed using GraphPad Prism version 11.0.0 (GraphPad Software, San Diego, CA, USA). Statistical comparisons between two groups were performed using the Mann–Whitney *U* test. Differences were considered statistically significant at $p < 0.05$. Data are presented as the mean $\pm$ standard deviation (SD) of quintuplicate measurements ($n = 5$).

3. Results

3.1. Results for [^{177}Lu]Lu-PSMA I&T

For the three defined starting activity levels of 24.3 ± 0.5 GBq (“low activity”), 31.9 ± 0.7 GBq (“medium activity”) and 38.9 ± 1.4 GBq (“high activity”) for [^{177}Lu]Lu-PSMA I&T, results from RP-HPLC are summarised in Fig. 3. Mean values (of $n = 5$) with standard deviation for radiochemical purity are given in detail in the supplementary material (table S1).

RP-HPLC analysis of [^{177}Lu]Lu-PSMA I&T showed a statistically significant difference of RCP for all three levels of starting activity between syntheses without SPE versus those with SPE ($p \leq 0.01$ for all three quintuple pairs of batches). Overall, lower RCP is observed for production with SPE. All batches included in the analysis met the pharmacopeial limit for RCP of 95%. As shown in Fig. 4, a de-iodination product [11, 12] is visible at a t_R of around 6.0 minutes which is significantly reduced using the production method without SPE purification.

Results from iTLC showed no statistically significant difference between synthesis procedures and activity amounts, apart from iTLC with sodium citrate on the highest activity level. All values for unbound Lu-177 across all activity levels and synthesis methods were below 0.2%. Measurement and p-values from iTLC analysis are given in table S2 of the supplementary material.

GC analysis used to determine the ethanol concentration of the final product was not performed on all 30 batches included in the analysis. As expected, mean values $\pm$ SD across all activity levels were overall lower for synthesis without SPE purification ($0.50 \pm 0.19\%$, $n = 14$) compared to synthesis with SPE purification ($2.37 \pm 0.89\%$, $n = 13$).

Mean activity yield was calculated as $92.7 \pm 3.0\%$ for all batches with SPE purification compared to $94.6 \pm 3.7\%$ for all batches without SPE.

3.2. Results for [^{177}Lu]Lu-DOTA-TATE

For the three defined starting activity levels of 15.0 ± 2.9 GBq (“low activity”), 24.4 ± 0.4 GBq (“medium activity”) and 32.0 ± 0.7 GBq (“high activity”) for [^{177}Lu]Lu-DOTA-TATE, results from RP-HPLC are summarised in Fig. 5. Mean values (of $n = 5$) with standard deviation for RCP are given in detail in the supplementary material (table S3).

RP-HPLC analysis of [^{177}Lu]Lu-DOTA-TATE showed no significant difference of RCP across all three levels of starting activity between syntheses without SPE versus those with SPE. All batches included in the analysis met a pre-defined RCP limit of 95% for product release. Sample chromatograms for both synthesis approaches are given in Fig. 6.

iTLC analysis showed low levels of unbound Lu-177 across all batches, with a statistically significant difference between the two synthesis processes for iTLC with sodium citrate on low and medium starting activity levels. No statistical significance was observed between iTLC results with methanol/ammonium acetate or sodium citrate for the highest activity level. Measurement and p-values from iTLC analysis are given in table S4 of the supplementary material.

GC analysis used to determine the ethanol concentration of the final product was not performed on all 30 batches included in the analysis. Similar to [^{177}Lu]Lu-PSMA I&T analysis, lower mean values $\pm$ SD across all activity levels were confirmed for synthesis without SPE purification ($0.14 \pm 0.06\%$, $n = 9$) compared to synthesis with SPE purification ($2.61 \pm 0.79\%$, $n = 10$).

Mean activity yield was calculated as $92.3 \pm 2.4\%$ for all batches with SPE purification compared to $94.7 \pm 4.2\%$ for all batches without SPE.

3.3. Results for [^{90}Y]Y-DOTA-TOC

For the two defined starting activity levels of 4.0 ± 0.5 GBq (“low activity”) and 7.3 ± 1.6 GBq (“high activity”) for [^{90}Y]Y-DOTA-TOC, results from RP-HPLC are summarised in Fig. 7. Mean values (of $n = 5$) with standard deviation for RCP are given in detail in the supplementary material (table S5).

RP-HPLC analysis of [^{90}Y]Y-DOTA-TOC showed no significant difference of RCP across both levels of starting activity between syntheses without SPE versus those with SPE. All batches included in the analysis met a pre-defined RCP limit of 95% for product release. Sample chromatograms for both synthesis approaches are given in Fig. 8. An additional peak at a retention time of 10.7 minutes, which was not further characterised, was apparent in the batches without SPE amounting to 0.5% of radiochemical impurity.

iTLC analysis showed low levels of unbound Y-90 across all batches, with a statistically significant difference between the two synthesis processes for iTLC with sodium citrate on both activity levels. No statistical significance was observed between iTLC results with methanol/ammonium acetate for the higher activity level. Measurement and p-values from iTLC analysis are given in table S6 of the supplementary material.

GC analysis used to determine the ethanol concentration of the final product was not performed on all 20 batches included in the analysis. Similar to analysis of [^{177}Lu]Lu-PSMA I&T and [^{177}Lu]Lu-DOTA-TATE, mean values $\pm$ SD across both activity levels were confirmed to be lower for synthesis without SPE purification ($0.19 \pm 0.004\%$, $n = 6$) compared to synthesis with SPE purification ($3.25 \pm 0.62\%$, $n = 8$).

Mean activity yield was calculated as $80.2 \pm 4.4\%$ for all batches with SPE purification compared to $86.8 \pm 5.5\%$ for all batches without SPE.

4. Discussion

Today, many commercial systems applying single-use cassettes are available for the automated preparation of radiopharmaceuticals. Several of them also promote their application for the synthesis of therapeutic compounds for RLT, including the radiopharmaceuticals described in this manuscript [9, 13–16], but also for different targeting structures [16–24] and other radionuclides like Ac-225 [25, 26], Pb-212 [27] or Tb-161 [28]. Even though these synthesis products are proposed for the same applications, these systems have technical variations. The main difference between the various synthesis modules is whether these systems include purification steps or not. To date, no validation data are available to assess the performance quality of these different approaches.

Within this work, data on the direct comparison of automated synthesis of three radiopharmaceuticals ([^{177}Lu]Lu-PSMA I&T, [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TOC) on the same Modular-Lab PharmTracer module using two different radiolabelling approaches, one with SPE purification and one without could be obtained.

Overall, for all three radiolabelled compounds and activity levels RP-HPLC analysis showed no relevant differences of product release parameters between the synthesis procedure using SPE for radiotracer purification vs. synthesis without SPE. The main focus was the quantification of unbound radiometal species, because skipping SPE purification during synthesis could potentially lead to increased amounts of unbound metallic impurities in the final product. The European Pharmacopeia specifies a limit of $< 2\%$ unbound radiometal in its monographs on [^{177}Lu]Lu-PSMA I&T [29] and other metal radiotracers [30, 31]. The same limit is given also in EANM guidelines on clinical use of therapeutic radiopharmaceuticals for RLT [32, 33]. Although there was a trend of slightly increased unbound radiometal amounts, evident from both RP-HPLC and iTLC data when SPE was excluded, especially for the two radiotracers with DOTA chelators, values were below 1% for all evaluated batches.

A statistically significant difference in radiochemical purity was found in RP-HPLC analysis of [^{177}Lu]Lu-PSMA I&T formulations. A main impurity peak was apparent at a retention time of around 6.0 minutes. As previously reported, this impurity is most likely a de-iodination product caused by radiolysis of this radiotracer [11, 12]. A main variation between the two described synthesis processes is the longer residence time of the radiolabelled molecule on the C-18 cartridge during SPE purification, with no protective effect of ascorbic acid or ethanol during washing steps. As further evidence, we provide the radiochromatogram of a batch production of [^{177}Lu]Lu-PSMA I&T, not included in the batch analysis of this work, with prolonged residence time of the product on the C-18 cartridge in the supplementary material. In figure S1 a major increase in the main radiochemical impurity with a retention time of around 6.0 minutes is deducible. Therefore, it seems plausible that the observed difference in radiochemical purity is a result of radiolytic degradation happening during the SPE purification step of the automated production process, resulting in de-iodination of [^{177}Lu]Lu-PSMA I&T.

As expected, ethanol concentration in the final products differed significantly between the two production methods for all three radiopharmaceuticals analysed, independent of activity levels, as the main source for ethanol in the final product is ethanol 50% used for elution of the radiotracer from the C-18 cartridge post-labelling. Minor amounts of ethanol were still detectable in the product solution of batches without SPE purification, which were a result of dissolution of the precursors in ethanol prior to synthesis.

Apart from lowering ethanol concentrations in the final product, synthesis without SPE purification also allows for reduced size of single-use cassettes, therefore reducing overall radioactive waste for routine RLT production. The simpler fluidic path on these smaller cassettes can furthermore lead to increased process reliability and fewer potential points of failure. Another positive aspect of omitting SPE is the slightly reduced synthesis time of around 30% less by skipping cartridge activation, product fixation and elution. There was also a slight trend towards higher activity yield across all three radiopharmaceuticals included in this work.

However, not including a product purification step in a radiolabelling procedure has its disadvantages as well. As mentioned above, a trend towards higher amounts of unbound radiometal species was found in our product analyses by both RP-HPLC and iTLC in syntheses without SPE purification. Although all of the batches included in our work were well within the pharmacopeial limit, incomplete radiolabelling during synthesis, i.e. as a result of errors during synthesis preparation or technical problems during transfers in the automated process, could potentially lead to unbound radiometal amounts above acceptable limits in the final product. SPE would remove these unwanted radiometal species and most likely still result in a sufficiently pure product, albeit with a somewhat lower yield. Another important drawback of not including product purification in the automated synthesis procedure is the presence of all starting materials in the product formulation. This means that all reagents including the radionuclide solution and buffer for pH adjustment used for synthesis will ultimately be administered to patients without further purification, apart from sterile filtration. Consequently, all buffers and additives as well as the radionuclide solution itself must be defined as excipients and therefore must meet the

corresponding requirements [34]. Employing product purification during synthesis allows the use of reagent grade chemicals for radiolabelling as the vast majority of these reagents is removed by SPE.

Considering all of these factors, the decision whether or not product purification should be included in an automated production process of a radiopharmaceutical therefore cannot be generalised for different modules or radiotracers. Careful evaluation and validation must be conducted for each radiopharmaceutical and synthesis module on a case-by-case basis. Responsibility for this process ultimately rests with the local department overseeing radiopharmaceutical production and product release.

5. Conclusion

This work shows that automated synthesis of [^{177}Lu]Lu-PSMA I&T, [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TOC on a Modular Lab PharmTracer module does not necessarily require product purification steps to meet pharmacopeial standards for clinical use of these radiotracers. Although SPE allows to decrease the amount of unbound radiometal species in the synthesis product, omitting this process step from the synthesis does not have a significant effect on radiochemical purity according to European Pharmacopeia requirements. Omitting final product purification also has added benefits of a possible reduction in single-use cassette size, slightly shorter synthesis time and elimination of ethanol from the synthesis process. In the case of [^{177}Lu]Lu-PSMA I&T, not including SPE purification even decreased the risk of other radiolytic side products, thereby even slightly increasing radiochemical purity. On the other hand, without purification all reagents used during the synthesis process will end up in the final product formulation, leading to stricter requirements for the chosen starting materials. The decision on whether to use a process including a final purification step, however, needs to be based on consideration of several parameters and should include a solid risk assessment followed by appropriate validation of the process. Such validation cannot be delegated to commercial suppliers of synthesis modules, but lie in the responsibility of the producing facility and the personnel in charge of production, quality control and product release.

Declarations

Acknowledgements

The authors would like to thank Alexander Wurzer and Leonora Gamper from the Department of Nuclear Medicine, Medical University of Innsbruck for their valuable contribution in performing quality control on [^{177}Lu]Lu-PSMA I&T, [^{177}Lu]Lu-DOTA-TATE and [^{90}Y]Y-DOTA-TOC batches used in this publication.

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Funding

Not applicable.

Availability of data and materials

Supporting information is provided containing further data. Additional data are available from the corresponding author upon reasonable request.

Declarations Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest statement

The authors declare no conflicts of interest.

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Figures

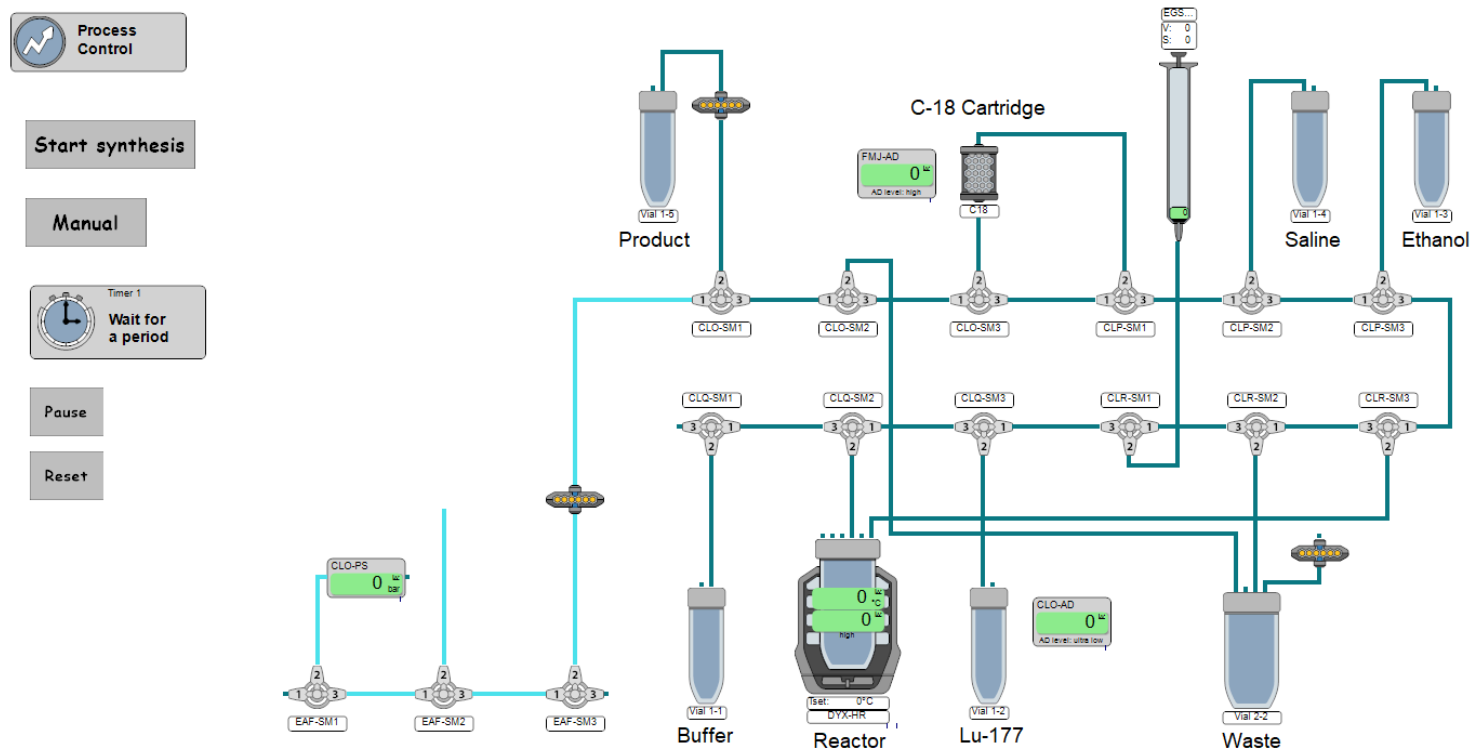


Figure 1

Schematic representation of the setup for automated synthesis of $[^{177}\text{Lu}]\text{Lu-PSMA I\&T}$ and $[^{177}\text{Lu}]\text{Lu-DOTA-TATE}$ with SPE using a C-18 cartridge for product purification. The setup for automated synthesis of $[^{90}\text{Y}]\text{Y-DOTA-TOC}$ is identical. "Lu-177" denotes $[^{177}\text{Lu}]\text{LuCl}_3$. "C-18 Cartridge" indicates the cartridge position used for SPE purification

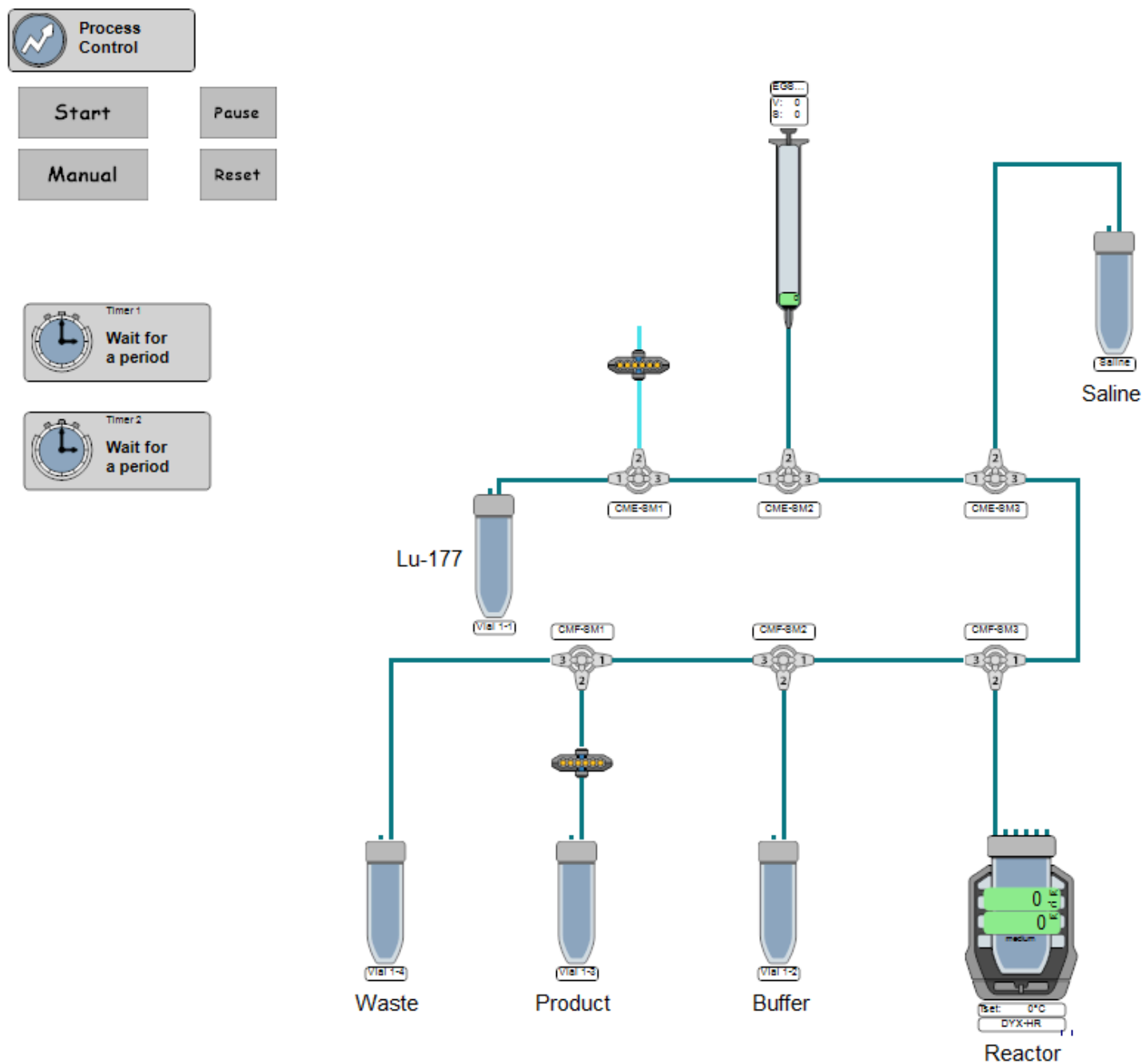


Figure 2

Schematic representation of the setup for automated synthesis of $[^{177}\text{Lu}]\text{Lu-PSMA I\&T}$ and $[^{177}\text{Lu}]\text{Lu-DOTA-TATE}$ without SPE purification. The setup for automated synthesis of $[^{90}\text{Y}]\text{Y-DOTA-TOC}$ is identical. “Lu-177” denotes $[^{177}\text{Lu}]\text{LuCl}_3$.

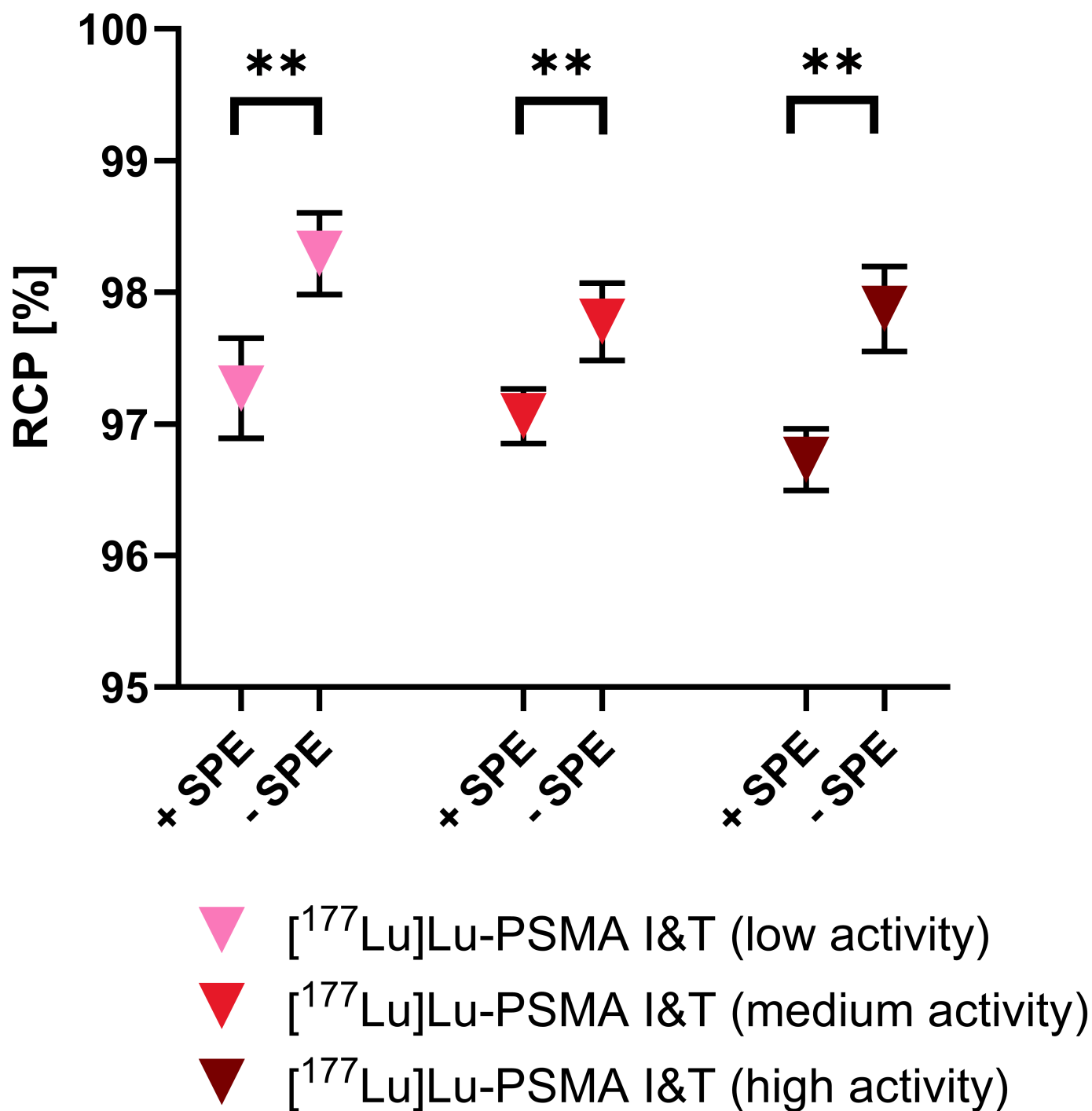


Figure 3

Results from RP-HPLC analysis of $[^{177}\text{Lu}]\text{Lu-PSMA I\&T}$. RCP is given as mean values $\pm$ standard deviation with $n=5$ batches for each data set for the three defined levels of starting activity (exact values are stated in the text). Statistically significant difference is denoted with ** ($p \leq 0.01$). RCP = radiochemical purity. SPE = solid phase extraction.

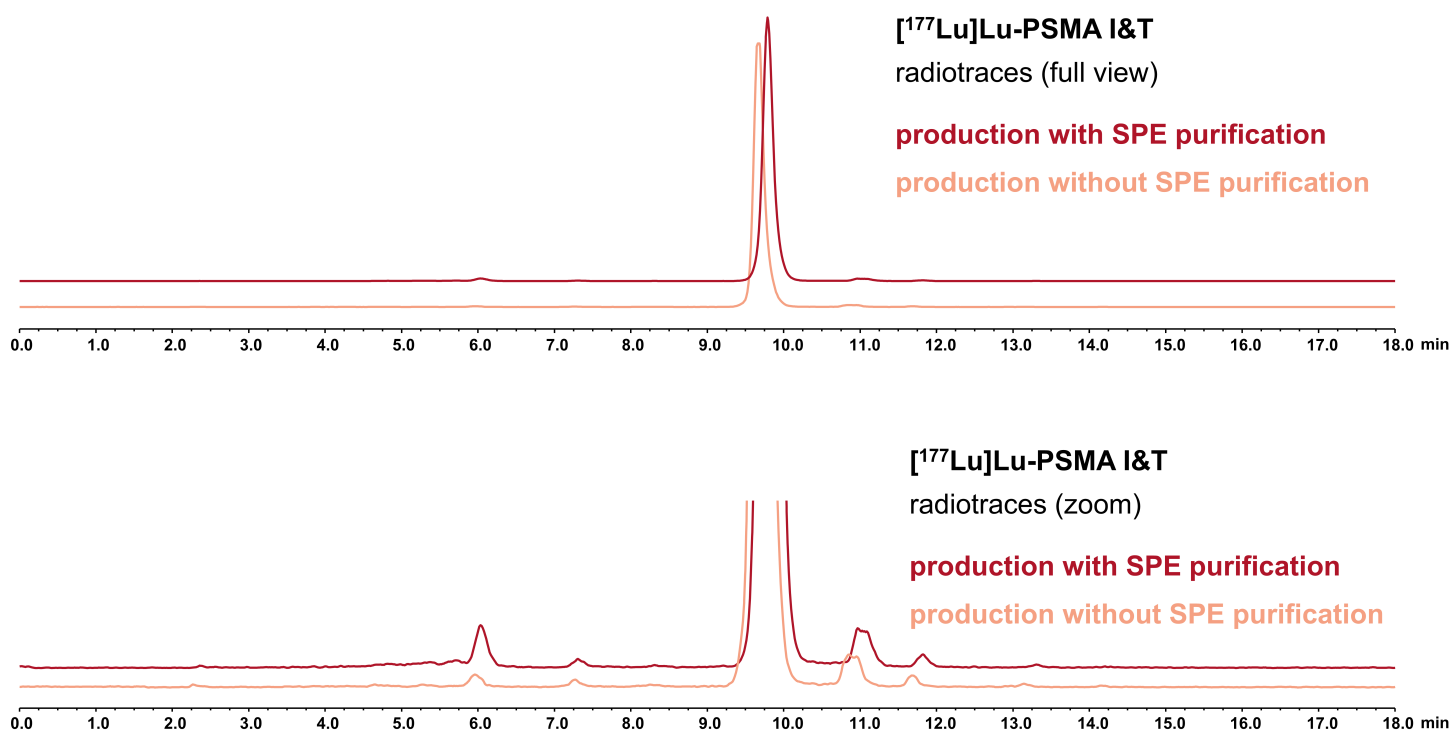


Figure 4

Results from RP-HPLC analysis of [¹⁷⁷Lu]Lu-PSMA I&T. RCP is given as mean values $\pm$ standard deviation with $n=5$ batches for each data set for the three defined levels of starting activity (exact values are stated in the text). Statistically significant difference is denoted with ** ($p \leq 0.01$). RCP = radiochemical purity. SPE = solid phase extraction.

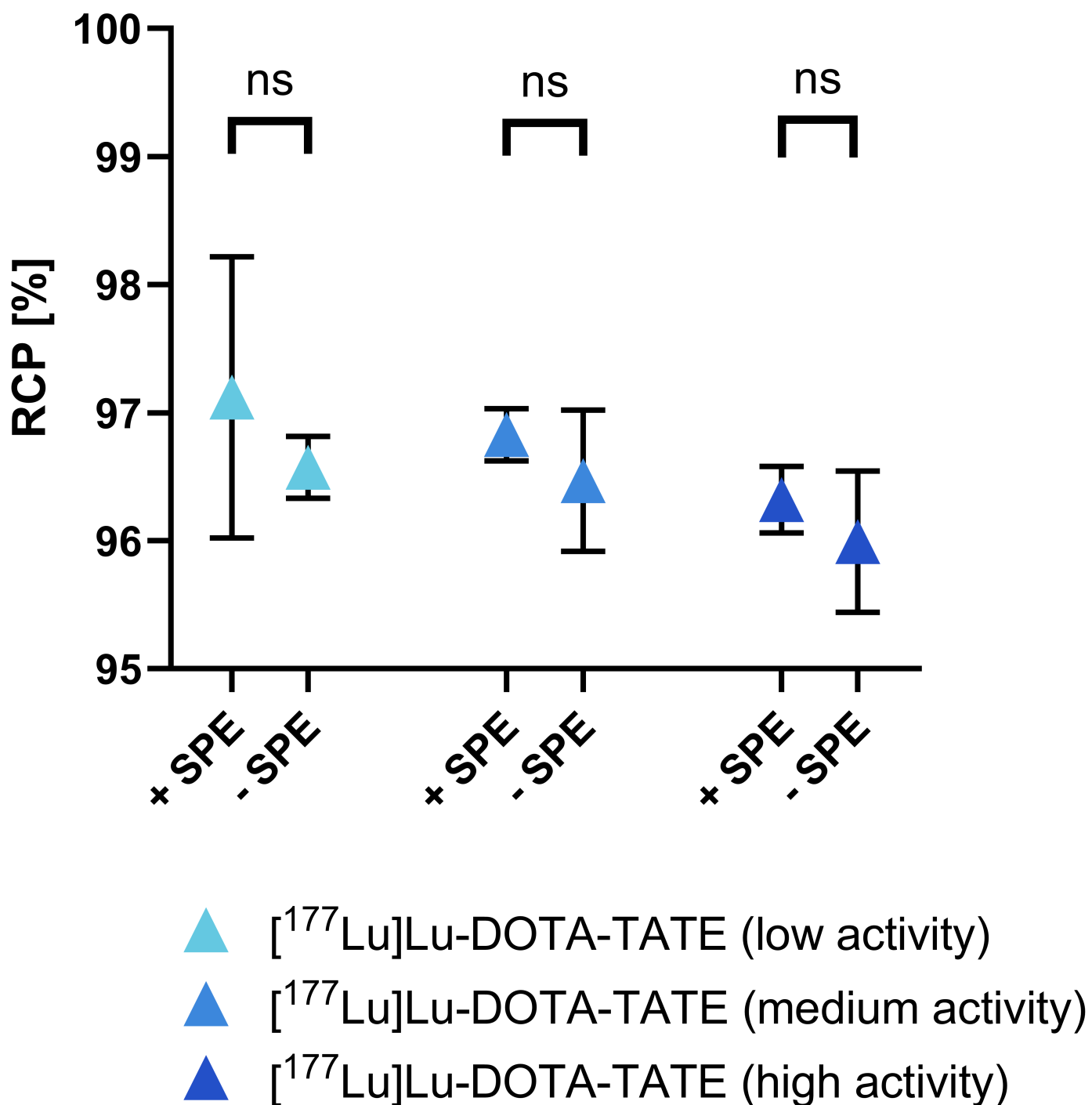


Figure 5

Results from RP-HPLC analysis of $[^{177}\text{Lu}]\text{Lu-DOTA-TATE}$. RCP is given as mean values $\pm$ standard deviation with $n=5$ batches for each data set for the three defined levels of starting activity (exact values are stated in the text). RCP = radiochemical purity. SPE = solid phase extraction. ns = not statistically significant.

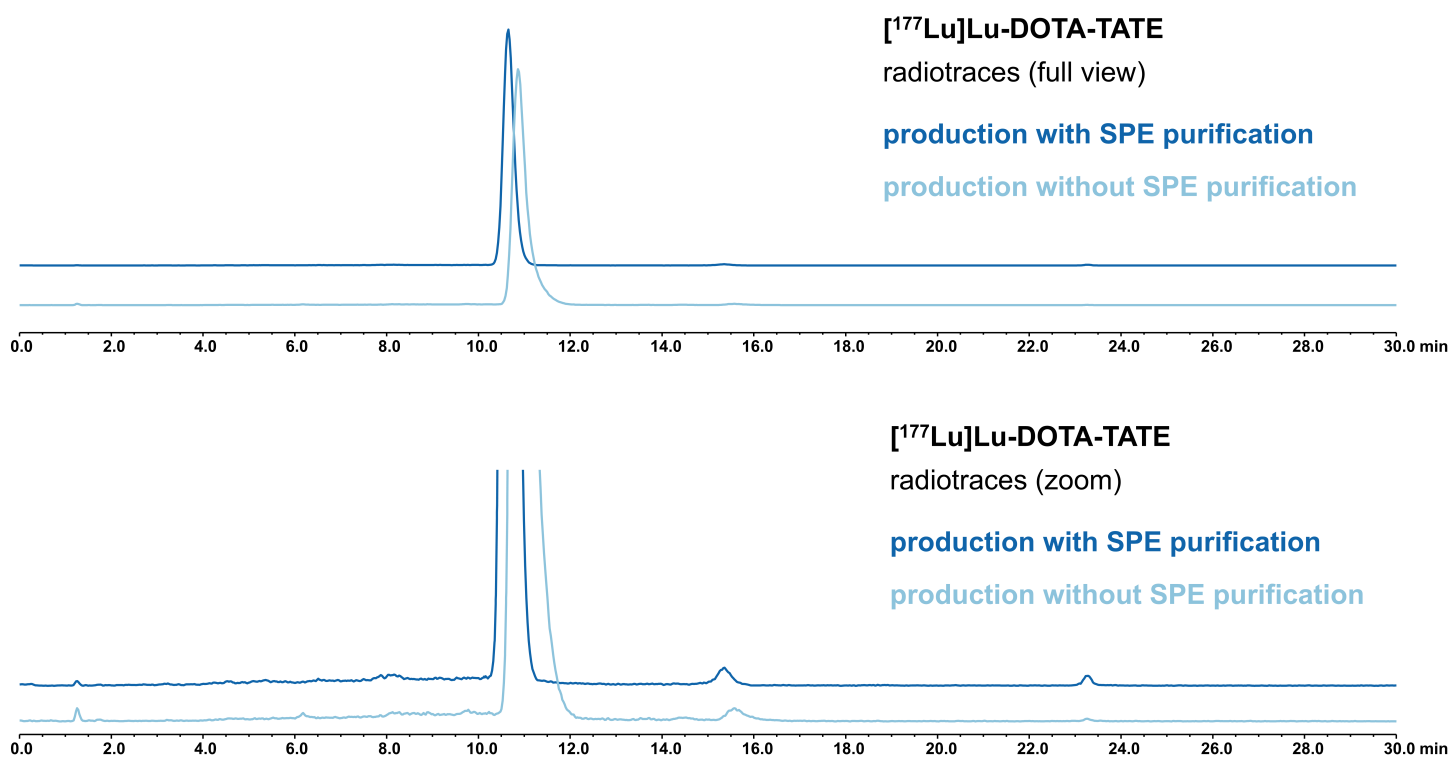


Figure 6

Representative radiochromatograms of [¹⁷⁷Lu]Lu-DOTA-TATE for production with SPE purification (dark blue) and without SPE purification (light blue). In the upper panel the full chromatograms are visible, whereas the lower panel is zoomed in to give a detailed view of impurity peaks.

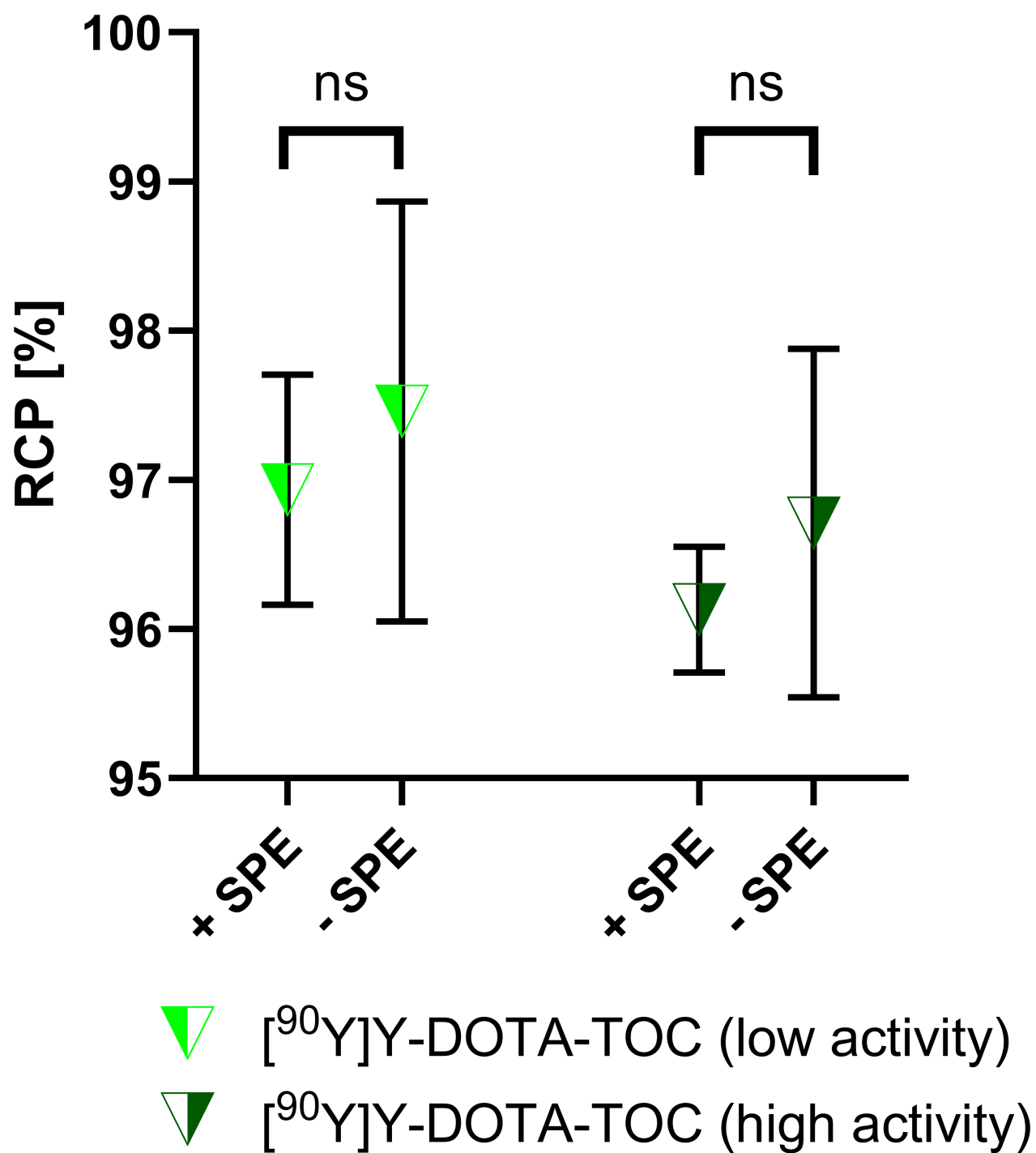


Figure 7

Results from RP-HPLC analysis of $[^{90}\text{Y}]\text{Y-DOTA-TOC}$. RCP is given as mean values $\pm$ standard deviation with $n=5$ batches for each data set for the two defined levels of starting activity (exact values are stated in the text). RCP = radiochemical purity. SPE = solid phase extraction. ns = not statistically significant.

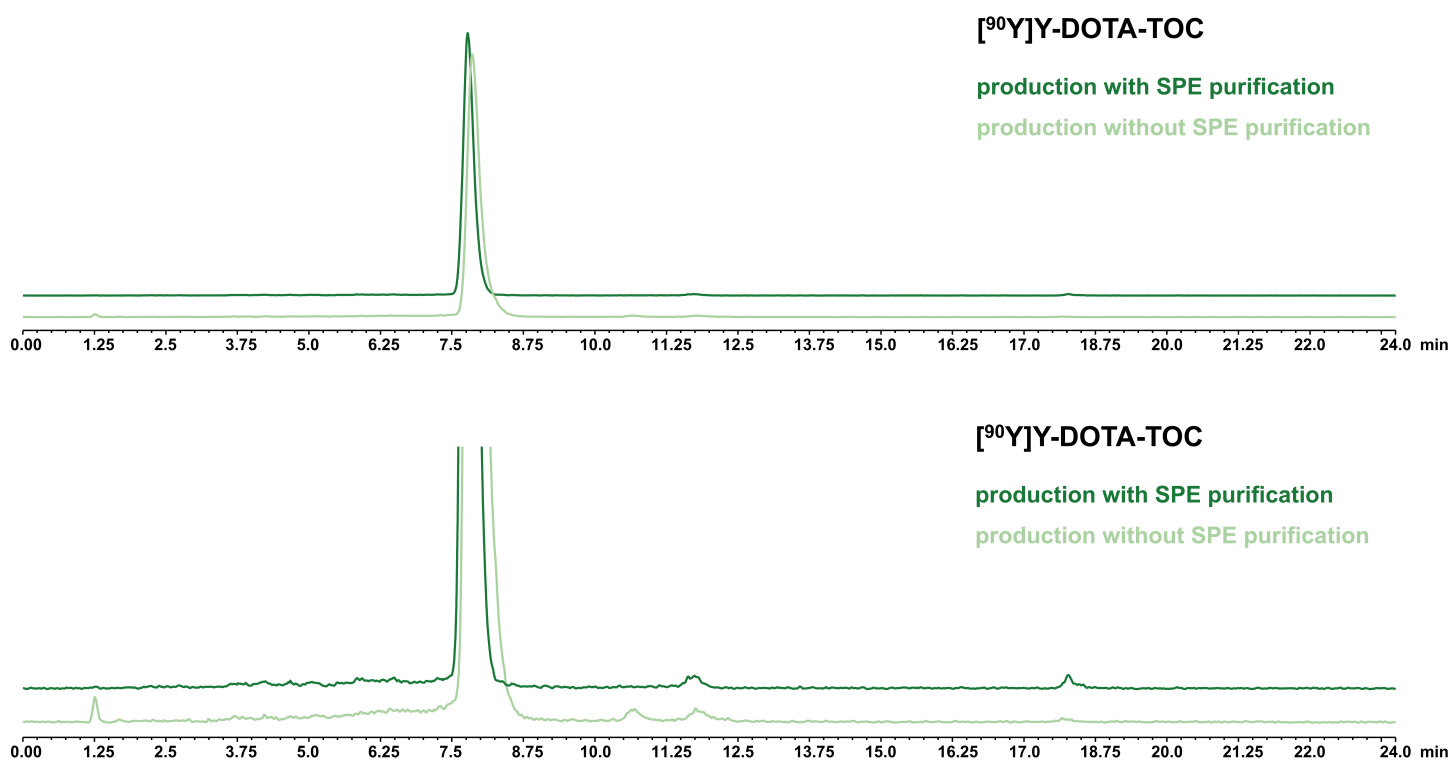


Figure 8

Representative radiochromatograms of $[^{90}\text{Y}]\text{Y-DOTA-TOC}$ for production with SPE purification (dark green) and without SPE purification (light green). In the upper panel the full chromatograms are visible, whereas the lower panel is zoomed in to give a detailed view of impurity peaks.

Supplementary Files

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- [SupplementaryMaterialComparativeRadiolabelling260728.docx](#)