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Assessment of organic contaminations in product radionuclide solutions after solvent extraction, and their subsequent removal using microcolumns

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ABSTRACT

Medical radionuclides such as Ga-68, Cu-64 or Ac-225 are usually produced by irradiation of enriched target materials in cyclotrons or nuclear reactors. After irradiation, the radionuclides need to be separated from their target. While this is mostly done by ion-exchange chromatography, an emerging separation method includes the use of (microfluidic) solvent extraction. However, the extent to which the chelators and organic solvents used during solvent extraction contaminate the final radionuclide-containing solution, including their potential impact on subsequent radiolabeling applications, has not been studied in detail. In this study, the potential contaminants N-benzoyl-N-phenylhydroxilamine (BPHA), dithizone (DIZ) and di(2-ethylhexyl)phosphoric acid (D2EHPA) were investigated, and a microcolumn purification method is proposed. It was found that contaminations with two of these chelators, BPHA and DIZ, significantly interfered with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) labeling. The applied microcolumn purification method eliminated the BPHA contamination from the Ga-68 solution completely, while simultaneously drastically reducing the total volume and acidity of the solution. It is therefore a promising purification method that can be included in an automated microfluidic solvent extraction procedure.

1. Introduction

In recent years, the world has seen a sharp increase in the use of medical radioisotopes for diagnostic, but even more so as radiotherapeutic agents for the treatment of advanced metastatic cancers. While Tc-99 m is still the workhorse of nuclear medicine (Filzen et al., 2017) other diagnostic radioisotopes such as Ga-68 (Lee et al., 2021) and Cu-64 (Suzuki et al., 2021) are finding their place in the medical landscape. Their form so-called 'theranostic pairs' with their chemically similar therapeutic counterparts, Lu-117 and Cu-67 respectively, allowing for personalized cancer imaging and treatment with higher accuracy. Furthermore, owing to its different decay characteristics and half-life, the alpha-emitter Ac-225 has been proposed as an attractive alternative to treatment with beta-emitters, and even demonstrated improved therapeutic efficacy when compared to Lu-177 (Perrone et al., 2025; Feuerecker et al., 2021) . Because of this ever increasing demand for medical radionuclides, radiochemists are extensively investigating different methods to produce a large range of medical radionuclides (Qaim and Spahn, 2018; Qaim, 2012). Various separation and purification methods are studied to optimize yield, automation and recyclability, including ion-exchange, solvent extraction, co-precipitation, electrochemical separation, as well as combinations of them (Qaim et al., 2022). One highly promising upcoming radionuclide purification method is microfluidic solvent extraction (Martini et al., 2019; Trapp et al., 2023a,b; Chakravarty et al., 2023). This method is not only characterized by the very high selectivity of the used chelators for the produced radionuclides, but also has the potential to allow for easier or direct target recycling. Finally, leveraging recent developments in microfluidic devices can enable the full automation of solvent extraction through the implementation of microfluidic chips, significantly decreasing potential radiation risks to the operators (Martini et al., 2019; Cote, 2025).

Clearly, these and other separation procedures of medical radionuclides need to comply with strict regulations (including good manufacturing processes (GMP) requirements) for their subsequent use as radiopharmaceuticals. Official requirements include a high radiochemical and radionuclidic purity, meaning that no other isotopes of the medical radionuclide and chemically different radionuclides

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are present, as well as requirements concerning the chemical purity (including metal-, buffer- and other chemical impurities) (International Atomic Energy Agency (Vienna), 2019; European Pharmacopoeia 10.0, 2007). While several studies have been published investigating the efficiency and selectivity of the solvent extraction process, including an assessment of common metal contaminations in the final solution (Pedersen et al., 2019; Chakravarty et al., 2023), potential organic contaminations after back-extraction have, to the best of our knowledge, not been considered to date. However, in addition to regulatory requirements and health safety standards, trace amounts of the extracting chelator in the final radionuclide product could potentially interfere with subsequent radiopharmaceutical labeling. An assessment of organic impurities combined with the development of further purification steps is therefore crucial.

Additional purification steps are already commonly employed after conventional radiochemical separations, for instance using small volume ion-exchange columns, or HPLC (high performance liquid chromatography) based methods, which often also serve to decrease the volume of the radionuclide-containing solution for future radiolabeling procedures. Examples can be found in the routine production of radiolanthanides such as Lu-177 or Tb-161 after irradiation of Yb and Gd targets, respectively, where the first extraction chromatographic resin column results in elution volumes of several tens to hundreds of milliliters (Dartiguelongue et al., 2021). The concentration of these solution volumes is usually achieved by either additional anion-exchange resin columns or drying of the resulting solution (Le et al., 2008). Similarly, in the extraction of Ga-68 from ^{68}Ge/^{68}Ga generators, elution is typically achieved in 4–7 mL, followed by additional purification/concentration using cation-exchange resin columns (Zhernosekov et al., 2007; Asti et al., 2008; Rösch et al., 2006). Although these additional separate post-separation purification steps are often essential, they increase the overall processing time and further complicate automation of the separation and labeling process.

In earlier studies, we investigated microfluidic solvent extraction for the extraction of Ga-68 (Trapp et al., 2023a), Cu-64 (Trapp et al., 2023b) and Ac-225 (Trapp et al., 2024) using the chelators BPHA, DIZ and D2EHPA, respectively. This study aims to investigate the potential organic contamination in the solutions obtained after solvent extraction and to which extend they influence radiolabeling. It presents an automatable, single-use microcolumn-based method to further purify these solutions, which can also be extended to purification and concentration of solutions collected during separation methods other than solvent extraction.

2. Methods and materials

2.1. Organic contamination detection

To determine the presence of chelator contaminations, solutions obtained after back-extraction were analyzed by ultraviolet–visible spectroscopy (UV–Vis) using a UV-6300PC Double Beam Spectrophotometer. Back-extractions were done according to methods described in earlier works (Trapp et al., 2023a). However, the initial extraction step was skipped to avoid interferences with co-extracted metal ions during UV–Vis measurements. Therefore, no metals were present to back-extract, but the same experimental procedure was followed. The 'back-extractions' were done from three different chelator solutions due to their use in previous studies (Trapp et al., 2023a,b, 2024), namely (I) 0.2 M N-benzoyl-N- phenylhydroxylamine (BPHA; VWR International; CAS 304-88-1) in chloroform and back-extraction into 6 M HCl, (II) 0.01 M dithizone (DIZ; VWR International; CAS 60-10-6) in chloroform and back-extraction into 8 M HCl and (III) 10 v/v% di-2-ethylhexylphosphoric acid (D2EHPA, reagent grade < 98 %; Merck Sigma) in chloroform and back-extraction into 0.1 M HCl. The contact time during the back-extraction was 10 min. The obtained aqueous solutions were first measured by UV–Vis and afterwards slowly dried, redissolved in ultrapure water (MQ; Merck Milli-Q Advantage A10) and measured again, to compare the spectra and determine potential chloroform contamination. Analyses were done in quartz cuvettes over a wavelength range of 200–700 nm.

2.2. DOTA radiolabeling

The chelator dodecane tetraacetic acid (DOTA; CAS 60239-18-1) was chosen for radiolabeling studies with Ga-68, Cu-64 and Ac-225, due its frequent application in radiopharmaceuticals (Baranyai et al., 2019). Ga-68 was eluted from an Eckert & Ziegler IGG100 Ge-68/Ga-68-generator (generously supplied by Erasmus MC) and Ac-225 was supplied by Eckert & Ziegler. Cu-64 was produced at the Hoger Onderwijs Reactor (HOR) in Delft (the Netherlands) by neutron activation of a Zn metal foil with a thermal neutron flux of 3.5×10^{13} $s^{-1}m^{-2}$ for 5 h. After irradiation the Zn foil was dissolved in 8 M HCl and Cu-64 was separated from the solutions using a DOWEX 2 × 8 200/400 mesh resin (Merck). After pre-conditioning of the column, Cu-64 was adsorbed to the column and subsequently eluted in 1 M HCl. To obtain chelator-contaminated solutions, extractions and back-extractions of Ga-68, Cu-64 and Ac-225 were executed as described in earlier studies (Trapp et al., 2023a). The labeling of the radionuclides to DOTA was performed in a solution consisting of 120 µL acetic acid buffer (pH 4.2), 25 µL 0.42 mM DOTA in MQ and 10–30 kBq of Ga-68, Cu-64 or Ac-225, either obtained from the extraction process or used directly from the source (therefore without potential organic contaminants). The solutions were equilibrated in a thermoshaker for 15 min, at 90 °C and 300 rpm. Labeling efficiencies were determined by instant-thin layer chromatography (iTLC). Herefore, instant thin layer chromatography strips (iTLC-SG Agilent) were applied, using acetonitrile 5% v/v (CAS 75-05-08; Central warehouse L&M) as the mobile phase. After the (labeled) radionuclide solutions were pipetted onto the strip, they were left to dry for 30 min, before being submerged 1 cm into acetonitrile 5% v/v. The mobile phase was left to run for 5 min and the strips were dried afterwards for another 30 min before measurements. During this chromatography step, the DOTA-labeled radionuclides were separated from the unlabeled radionuclides on the strip. To determine the radiolabeling efficiency, the strips were cut in half and both the top (A_{top}) and bottom (A_{bottom}) of the strip were measured separately for their radioactivity with the Wallac Wizard 2480 automatic gamma counter (Perkin Elmer). The DOTA labeling efficiency (LE%) was calculated as follows:

$$LE\% = \frac{A_{top}}{A_{bottom} + A_{top}} * 100\% \quad (1)$$

While Ga-68 and Cu-64 were measured directly, Ac-225 was measured indirectly using the 211 keV γ-ray emitted by its daughter Fr-221 after >30 min of equilibration time.

2.3. Phosphor imaging

For visual representation of the labeled and unlabeled Ga-68 activity, the iTLC strips were imaged with a Typhoon Trio+ phosphor imager (Amersham GE) and images were analyzed with ImageQuant TL. The screen of the phosphor imager was exposed to the iTLC strips for 10 min, and subsequently placed into the phosphor imager. The phosphor images of the iTLC strips were taken with a pixel size of 50 µm.

2.4. Microcolumn purification

For the specific case of the Ga-68 solution with BPHA contamination, a purification method was developed consisting of an ion-exchange resin-based microcolumn. The microcolumn was fabricated by mixing PDMS elastomer and its curing agent with a mass ratio of 10:1 and pouring the mixture onto a 4-inch silicon wafer with a

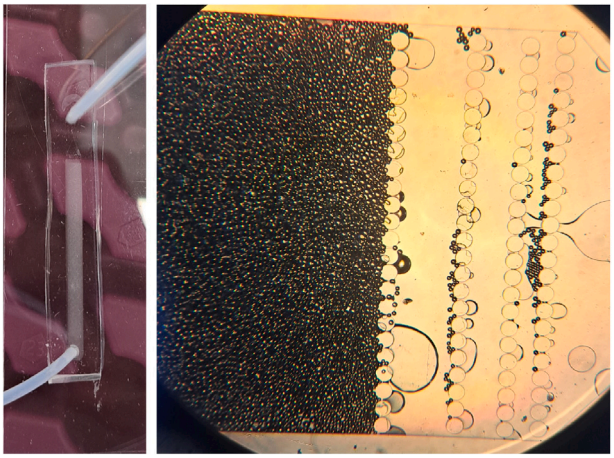

Fig. 1. Left: Image of 2 mm wide column containing ~8 mg of AG 1-X8 resin. Right: Microscopic images of 5 mm wide microcolumn containing AG 1-X8 resin.

microcolumn pattern. The pattern was printed on the silicon wafer using a soft lithography technique. Two microcolumns were made with differing width of 2 mm and 5 mm, both 3 cm long and 0.1 mm high. The ion-exchange resin AG 1-X8 (Bio-Rad) was preconditioned in 6 M HCl and loaded into the microcolumn with a syringe via flexible tubing until filled, resulting in a content of approximately 8 mg in the 2 mm wide column and 21 mg in the 5 mm wide column. A picture of the 2 mm wide column as well as a microscope image of the 5 mm wide column are shown in Fig. 1. The Ga-68 solution was obtained in 6 M HCl from batch back-extractions as described earlier, and the total Ga concentration was adjusted by addition of $Ga(NO_3)_2$ to be at 1 pM to simulate a realistic concentration of several GBq Ga-68. The 5 mL solution was loaded into a syringe, and connected to the microcolumn via flexible tubing. An AL-1000 Programmable Syringe Pump (941-371-1003; World Precision Instruments Inc.) was used to push the solution through the microcolumn at a set flow rate. The radioactivity of the solution was measured before ($A_{initial}$) and after adsorption (A_{after}) of Ga-68 to the microcolumn and adsorption efficiencies ($AE\%$) were calculated as:

$$AE\% = (1 - \frac{A_{after}}{A_{initial}}) * 100\% \quad (2)$$

These experiments were done in triplicate and uncertainties are given as one standard deviation of the mean.

After adsorption of Ga-68 to the microcolumn, elution was done into MQ. The solution was collected in small fractions (of 50 μL in the 5 mm wide column and approximately 20 μL in the 2 mm wide column) to evaluate the elution profile, and thus determine the minimum amount of solution necessary for complete elution. Additionally, the above-mentioned steps were repeated with a 6 M HCl solution obtained from the back-extraction process with BPHA and chloroform but without Ga-68, to investigate the MQ solutions eluted from the microcolumn for any residual BPHA contamination. Measurements of the BPHA contamination in the 6 M HCl solution and the obtained MQ solutions were done by UV–Vis spectroscopy as described above.

During radionuclide production, final radionuclide products are often contaminated with common metal contaminants, including Zn, Fe and Cu (Ramogida et al., 2019; Pandey et al., 2019; Oehlke et al., 2015). To investigate the potential of the developed microcolumn in reducing the concentrations of these contaminants during the microcolumn purification experiments, a 2.5 mL solution containing 5 mg/L $ZnCl_2$, $FeCl_2$ and $CuCl_2$ in 6 M HCl was pushed through the column and eluted into 250 μL MQ. The metal concentrations before adsorption ($C_{initial}$) and after elution ($C_{elution}$) were measured by inductively coupled plasma optical emission spectroscopy (ICP-OES; Optima 8000 from Perkin Elmer) and the total recovery (R%) was calculated as shown below:

$$R\% = (1 - \frac{C_{elution}}{C_{initial}}) * 100\% \quad (3)$$

3. Results and discussion

3.1. Organic contamination detection

To determine the presence of chloroform, BPHA, DIZ or D2EHPA in the aqueous solutions, UV–Vis measurements were first done on solutions obtained after the back-extraction process. Fig. 2 displays the measured spectra of the solutions collected after back-extraction, showing contaminations with (a) BPHA, (b) DIZ and (c) D2EHPA, before and after being dried to evaporate the chloroform contamination. The most prominent peaks can be seen in the spectra of BPHA. It has been reported that BPHA is soluble in water at levels detectable by UV–Vis (Morroni et al., 2004), and its presence was therefore expected in the solutions. After evaporating the chloroform, the peak representative for BPHA (Morroni et al., 2004) can be seen at around 270 nm. The significant difference in the spectra before evaporation is due to the presence of chloroform contaminations and the resulting interaction between chloroform and BPHA.

The spectrum obtained for DIZ shows a peak at 250 nm which is not in line with literature reports of DIZ spectra (having peaks at around 445 nm and 590 nm (Rauf et al., 2015)). This peak likely represents an oxidation product of dithizone as shown by von Eschwege et al. (2011). Since DIZ is known to have a low temperature and photostability (Thiagarajan and Subbaiyan, 1992), the concentration decreases during open tabletop heating, resulting in a lower concentration in the measurement after drying. D2EHPA is not present as a contamination in a concentration within the detection range of the UV–Vis spectrophotometer (<1 ppm), although this of course does not fully exclude its presence. The spectra of the DIZ and D2EHPA solutions before drying also show a steep absorbance at wavelengths between 200 and 230 nm, indicating minor chloroform contaminations Wang and Asher (2012).

From these measurements it can be concluded that some chelators contaminate the aqueous solution after back-extraction, a fact that has not been discussed in the literature yet (Chakravarty et al., 2023). This result is consistent with our previous study (Santoso et al., 2025), where we studied the release of chelator-impregnated beads. On silica beads, the 8-h releases of BPHA, DIZ and D2EHPA in Milli-Q water and 12 M HCl were in the range of tens to hundreds of mg per gram water, depending on their solubility. The solubility of the chelators is usually approached using octanol-water partition and pKa.

3.2. DOTA radiolabeling

From the previous experiments it was clear that the BPHA and DIZ chelators, as well as the chloroform, can contaminate the aqueous solution during back-extraction to varying degrees. The potential interference of chelator contamination was therefore investigated during the labeling of the radionuclides Ga-68, Cu-64 and Ac-225 to DOTA. The results (Fig. 3) indicate that BPHA interferes with the labeling of Ga-68 to DOTA. Interference of DIZ during Cu-64 radiolabeling to DOTA can be assumed from the results. For Ac-225, no significant difference can be seen during the radiolabeling to DOTA, indicating that no interfering D2EHPA contamination was present, which was expected based on the UV–Vis results shown in Fig. 2 (c). While the radiolabeling of Ga-68 to DOTA yielded a LE% of 99.58 ± 0.70% in absence of BPHA contamination, in its presence the LE% drops significantly depending on the amount of BPHA contamination. Phosphor imaging of the iTLC strips and corresponding UV–Vis spectra (Fig. 4) indicate the correlation between differing labeling efficiencies and concentration of BPHA contamination. The LE% of Cu-64 radiolabeled to DOTA also

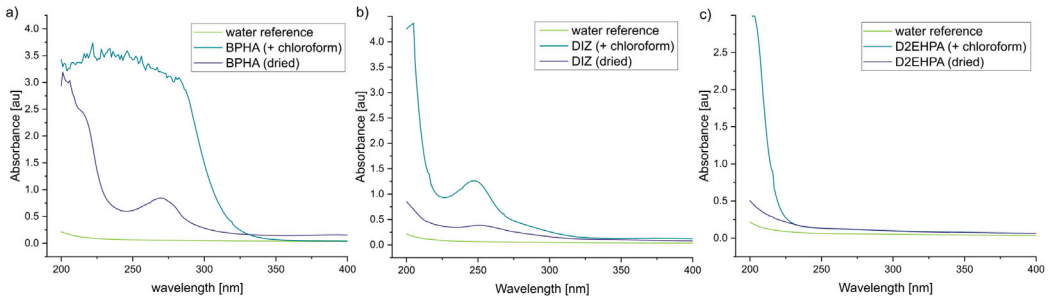

Fig. 2. UV–VIS spectra showing the presence or absence of contaminations after back-extraction by (a) BPHA, (b) DIZ and (c) D2EHPA, before (light blue) and after (dark blue) evaporation (and re-dissolution) to indicate the difference with and without chloroform contamination.

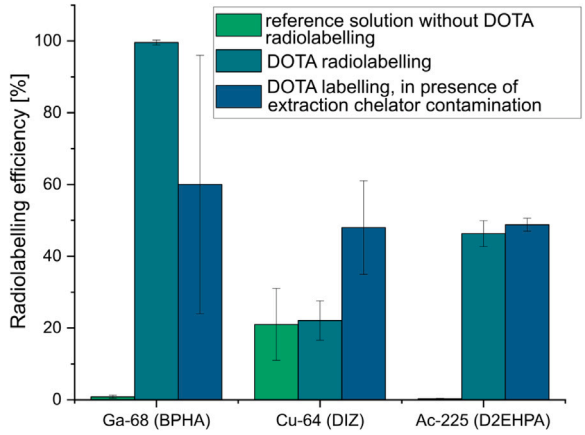

Fig. 3. Labeling efficiencies of Ga-68, Cu-64 and Ac-225 to DOTA in the presence and absence of contamination by extraction chelators BPHA, DIZ and D2EHPA, respectively. Experiments have been performed in triplicate, with the uncertainties given as one standard deviation of the mean.

demonstrates the interference of organic chelator contamination. The reference solution without DOTA but with DIZ contamination shows a labeling efficiency of 21 ± 10 %, showing that the ^{64}Cu-DIZ complex moves on the iTLC strip in the same way ^{64}Cu-DOTA does. The DOTA labeling without DIZ contamination resulted in 22.1 ± 5.5%. When repeated with presence of DIZ contamination the LE% increased to 48 ± 13 %, which is not an improvement of the DOTA radiolabeling, as the radiolabeling conditions are identical, but indicates the presence of DIZ labeled Cu-64. Since the DOTA concentration in the solution was high enough to exceed radionuclide concentrations by several orders of magnitude, metallic contaminations cannot be the cause of the drop in labeling efficiencies (usually nanomolar DOTA concentrations are sufficient to account for interfering metal contaminations (Breeman et al., 2003; Mueller et al., 2003)). These radiolabeling results in the presence of BPHA and DIZ contaminations showcase the interference of these contaminants with radiopharmaceutical labeling procedures.

3.3. Microcolumn purification

To prevent the presence of chelator contaminations in the radionculide solutions, an additional clean-up step after solvent extraction is essential. Commonly, HPLC-based methods are used for purification of both radionuclides and radiopharmaceuticals (Bokolo et al., 2025), although these are difficult to automate in conjunction with earlier extraction steps, and relatively time-consuming. This is why we developed a microcolumn-based clean-up method that can directly be integrated in an automated solvent extraction procedure.

As a case study, the purification of a Ga-68 in 6 M HCl solution after solvent extraction with BPHA in chloroform is further discussed in detail. First, two different microcolumn sizes were packed with AG 1-X8 ion-exchange resin, as shown in Fig. 5 (a). Adsorption efficiencies exceeding 98 % were achieved with both microcolumns using flowrates of 20 and 50 μL/min. Only at 100 μL/min a decrease in adsorption efficiency to 90.59 ± 0.48% was observed in the 2 mm wide column. Elution of Ga-68 was accomplished into MQ and elution profiles are shown in Fig. 6. From both microcolumns, around 98 % of Ga-68 could be eluted. However different volumes of MQ were needed, namely 90 μL and 150 μL for the 5 mm wide column and the 2 mm wide column, respectively. Fig. 5 (b) shows the UV–Vis absorption spectra of the 6 M HCl solution before the microcolumn purification step, exhibiting a significant amount of BPHA contamination, as well as a MQ solution obtained after elution from the microcolumn, with no indication of residual BPHA contamination. These spectra indicate the ability of the microcolumn to purify solutions from chelator and chloroform contaminations. Additionally, a significant reduction of acidity (from 6 M HCl to MQ) and volume (from 5 mL to below 150 μL) could be achieved during the microcolumn purification. This is particularly important as small volumes and specific pH are needed for radiopharmaceutical labeling. The elution in MQ allows for easy buffering to obtain the optimal pH (Zhernosekov et al., 2007).

A DOTA labeling experiment was repeated with the purified Ga-68, as described above, which resulted in a radiolabeling efficiency of 98.3% ± 1.8%. This showcases again the successful elimination of the BPHA contamination by the microcolumn purification method. After production of Ga-68 by either elution from a ^{68}Ge/^{68}Ga generator or after irradiation of Zn-68 in a cyclotron with subsequent separation of Ga-68 via cation-exchange, an extra purification/concentration step is often necessary, as done in this study. Elution from a generator usually results in volumes of 4 to 7 mL (Asti et al., 2008; Zhernosekov et al., 2007). The most commonly used approach for this step includes the use of cation-exchange columns with subsequent elution of Ga-68 in a solution containing high amounts of acetone (Asti et al., 2008; Zhernosekov et al., 2007; Rösch et al., 2006; Ocak et al., 2010). Rösch et al. obtained 97% of Ga-68 in 400 μL in a 97.6% acetone/0.05 M HCl solution (Rösch et al., 2006) using a cation exchange micro-chromatography column filled with 50 mg of AG 50W-X8 resin (BioRad). Even if Ga-68 was produced via cyclotron irradiation with subsequent separation by cation exchange columns, it is often further purified and concentrated using the same method by Zhernosekov et al. (2007) as described above, including the use of an acetone/HCl solution (Alves et al., 2017). The presented microcolumn purification method therefore presents a successful alternative to existing purification/concentration methods, while avoiding the use of organic solvent for elutions and resulting in an even smaller elution volume. These results show that the method is not only useful for the integration into a solvent extraction procedure, but also as a purification step for Ga-68 solutions obtained from other production and separation routes, such as generator elutions and cation exchange after cyclotron production.

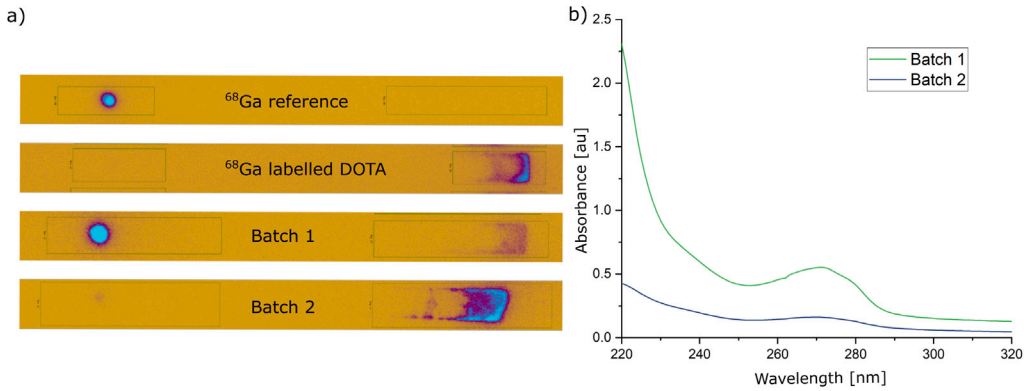

Fig. 4. (a) iTLC strips showing the effect of BPHA contamination during radiolabeling of DOTA. Labeling was executed with DOTA in the absence and presence of varying concentrations of BPHA, as shown by the UV–Vis spectra in (b).

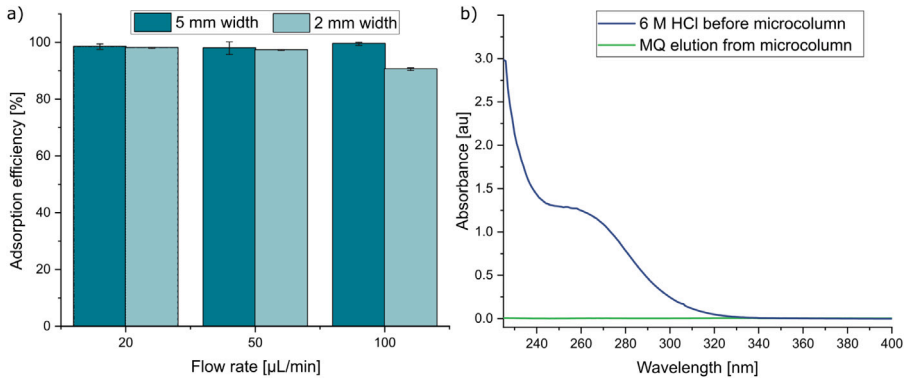

Fig. 5. (a) Adsorption efficiency of Ga-68 from 6 M HCl at varying flowrates in two different microcolumn widths. (b) UV–Vis spectra of 6 M HCl solution before loading of the microcolumn and MQ elution from the microcolumn afterwards, showing no BPHA contamination.

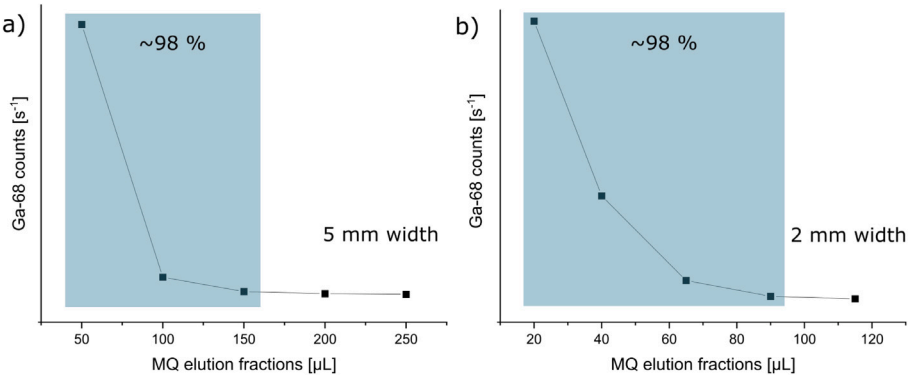

Fig. 6. Ga-68 elution was achieved into MQ at a flowrate of 100 µL/min from (a) a 5 mm wide microcolumn with 21 mg of AG 1-X8 resin and (b) a 2 mm wide microcolumn with 8 mg of AG 1-X8 resin. The total eluted Ga-68 percentage was determined as the ratio of Ga-68 activity in the elution fractions vs. the total added Ga-68 activity.

3.4. Distribution of common metal contaminants

Finally, the distribution of Zn, Fe and Cu contamination was measured, due to their frequent occurrence in irradiated targets (Pandey et al., 2019; Oehlke et al., 2015). Of special interest was the radionuclide Cu-61, which can be co-produced during irradiation of Zn-68 for the production of Ga-68 (Oehlke et al., 2015). The total recovery of Zn, Fe and Cu after adsorption and elution was found to be 97.6 ± 3.5%, 77.9 ± 3.8% and 5.8 ± 0.9%, respectively, showing that especially Cu contamination (including Cu-61) can be reduced significantly by almost 95 %.

4. Conclusion

It was shown that solvent extraction of medical radionuclides from their target solutions can result in contamination with the used chelators in the product radionuclide solution which will further be used for radiolabeling of pharmaceuticals. Specifically the chelators BPHA and DIZ were found to cause a contamination that demonstrably interfered with subsequent DOTA radiolabeling. Implementation of a microcolumn purification step using the AG 1-X8 resin allowed for the elimination of the BPHA contamination, wile reducing the total acidity of the solution from 6 M HCl to MQ, the volume from 5 mL to less then 150 µL, and the Cu contamination by almost 95 %. This microcolumn

purification method is extremely promising also for other separation methods that result in high volumes or acidities, to circumvent the necessity of drying down the highly radioactive solutions.

CRediT authorship contribution statement

Svenja Trapp: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Brenda Giling:** Investigation. **Esmee Spuijbroek:** Investigation. **Albert Santoso:** Investigation, Formal analysis. **Elisabeth Paulssen:** Supervision. **Robin de Kruijff:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Elisabeth Paulssen reports financial support was provided by Dutch Research Council (NWO) under Project Number 16913. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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