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Semi-automated system for concentrating ^{68}Ga-eluate to obtain high molar and volume concentration of ^{68}Ga-Radiopharmaca for preclinical applications

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ABSTRACT

Introduction: ^{68}Ga-radiopharmaceuticals are common in the field of Nuclear Medicine to visualize receptor-mediated processes. In contrast to straightforward labeling procedures for clinical applications, preclinical in vitro and in vivo applications are hampered for reasons like e.g. volume restriction, activity concentration, molar activity and osmolality. Therefore, we developed a semi-automatic system specifically to overcome these problems. A difficulty appeared unexpectedly, as intrinsic trace metals derived from eluate (Zn, Fe and Cu) are concentrated as well in amounts that influence radiochemical yield and thus lower molar activity.
Methods: To purify Gallium-68 and to reduce the high elution volume of a ^{68}Ga-generator, a NaCl-based method using a column containing PS-H$^+$ was implemented in a low volume PEEK system. Influence on reducing osmolality, acidity and the amount of PS-H$^+$ resin (15–50 mg) was investigated. [^{68}Ga]Ga was desorbed from the PS-H$^+$ resin with acidified 2-5 M NaCl (containing 0.05 M of HCl) and ^{68}Ga-activity was collected. DOTA-TATE was used as a peptide model. All buffers and additives used for labeling were mixed with Chelex 100 (~1 g/50 mL) for >144 h and eventually filtered using a 0.22 μm filter (Millipore). Quantification of metals was performed after labeling by HPLC (UV).
Results: Gallium-68 activity could be desorbed from PS-H$^+$ cation column with 3 M NaCl, and >60% (120–180 MBq) of [^{68}Ga]Ga was collected in <0.3 mL. Taking into account the used amount of ^{68}Ga-eluate, buffer and other excipients, the overall amount of trace metal per labeling was <1.5 nmol. DOTA-TATE could be labeled with [^{68}Ga]Ga with high radiochemical yield, >99% (ITLC), and a radiochemical purity of >95% (HPLC).
Conclusion: With the here described concentration system and metal purification technique, a low activity containing ^{68}Ga-generator can be used to label DOTA-peptide in preclinical applicable amounts >60 MBq/nmol (40–60 MBq/0.1 mL) and within 20 min.

1. Introduction

^{68}Ga-radiopharmaceuticals are commonly applied in Nuclear Medicine, e.g. to visualize receptor-mediated processes [1–4]. This resulted in an increasing interest of the radiopharmaceutical industry to develop new types of ^{68}Ga-generators, kits and cartridges for radiolabeling which can be clinically applied [1, 5–10]. In contrast to well established relative simple labeling procedures for clinical applications [11], preclinical applications are hampered for reasons like volume restriction, activity concentration (activity per volume, MBq/mL), molar activity (activity per ligand, MBq/nmol), osmolality and metal impurities. High activity concentration is needed to enable sufficient amount of radiopharmaceutical to be injected into small rodents. High molar activity is important when only small amount of radiopharmaceutical can injected and imaging have to be performed.

For preclinical applications of ^{68}Ga-radiopharmaceuticals in mice only low amount of volume can be injected (<200 μL) intravenously (*i.v.*). Therefore, to perform preclinical studies there is a need to use high activity containing ^{68}Ga-generators. Since ^{68}Ga-radiopharmaceuticals are commonly applied into Nuclear Medicine, many departments use a clinical grade ^{68}Ga-generator. These generators can only be used for ~9 month time. The reasons for this are the expiring date of the generator or that the activity is simply too low for labeling a patient dose. The ^{68}Ga-generator eluate only contains <300 MBq (~6 mL) [^{68}Ga]Ga, but this activity is still suitable for

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preclinical use when a concentration technique is applied to increase the activity concentration (i.e. ~500 MBq/mL).

The here described system was investigated by using a clinical grade ^{68}Ga-generator (EZAG), originally with an elution activity of 1110 MBq [^{68}Ga]Ga (now 200–300 MBq). A semi-automatic purification system was developed specifically to concentrate [^{68}Ga]Ga into high volume activities. In contrast to the clinical applied applications in our clinic of ~35 nmol/150 MBq in 9 mL at ~0.3 osmol (~4.2 MBq/nmol) for [^{68}Ga]Ga-DOTA-TATE, specification for *i.v.* injection in mice are 0.2 nmol/5 MBq in ≤0.2 mL at ~0.3 osmol (25 MBq/nmol) [12, 13].

A purification part is necessary, since high radiolabeling efficiencies for ^{68}Ga-radiopharmaceuticals can only be achieved if other trace metals are not or only in low amounts present during the radiolabeling procedure. The reason for this is that the applied peptide model contains the chelator tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) which has the ability to bind also other $M^{2+/3+}$ metals. For our concentration system this is especially relevant since it is based on a cation exchange method. This means that next to [^{68}Ga]Ga, intrinsic cations, e.g. the trace metals Zn, Fe, and Cu, in the eluate could also be concentrated to amounts that influence radiolabeling and thus lower molar activity of the final radiopharmaceutical [14–16]. Therefore, the work was performed as far as possible metal free, additionally, the active removal of metal ions was investigated.

The here described cationic purification method is based on a NaCl technique used for clinical preparation of [^{68}Ga]Ga [17–19]. To desorb [^{68}Ga]Ga from the resin a 5 M NaCl solution is used. Using these conditions for preclinical application, results in a too high osmolality. To lower osmolality, the NaCl purification technique [18] was adapted by decreasing the concentration of NaCl and amount of resin used. To our knowledge there are no publications on these items.

The overall objective of this study was to obtain ^{68}Ga-labeled peptide with a molar activity of 20–30 MBq/nmol within 20 min. The final solution should be isotonic and have a high activity concentration, applicable for preclinical *i.v.* injection in mice (<200 μL).

2. Methods and materials

2.1. Materials

All chemicals and solvents were of analytical or pharmaceutical grade unless otherwise specified and were obtained from Sigma-Aldrich. For [^{68}Ga]Ga, a > 9 month old clinical 1110 MBq grade ^{68}Ga-generator was used (Eckert & Ziegler). DOTA-TATE ([DOTA^0,Tyr^3] octreotate, >95% chemical purity) was purchased from BioSynthema.

2.2. Low volume PEEK system

The NaCl based method [18] was implemented in a low volume PEEK system (tubing 0.03 in.) (Fig. 1). A PEEK Bio-Safe column (2.1 × 300 mm) including a 2 μm filter frit with total volume of 173 μL, Triskem) was manually filled with PS-H$^+$ cation exchange resin (CHROMAFIX® PS cartridges, pore size 100 Å, particle size 100 μm, 15–50 mg) and connected to a 6-way manual valve (Inacom instruments). To start purification, the valve was switched to position 2 and the ^{68}Ga-generator was eluted with 6 mL 0.1 M HCl (A). Gallium-68 was trapped by the PS-H$^+$ cation resin on the column. To empty the PEEK tubing and the PS-H$^+$ column, the valve was switched to position 4 and column and tubing were flushed with 10 mL of air (B). The valve was switched to position 3 and the content of the syringe (C), 0.5 mL acidified 5 M NaCl containing 0.05 M HCl, was used to elute [^{68}Ga]Ga from the resin. To determine maximum ^{68}Ga-concentration (MBq/μL), 1 mL of the acidified NaCl was used to elute [^{68}Ga]Ga in fractions (10 × 0.1 mL) from the low volume PEEK system containing the PS-H$^+$ cation resin column. The activity of the obtained eluates was measured in a dose calibrator (VDC 405, Comecer). To precondition the PS-H$^+$ cation resin for the next purification, the valve was switched to position 1 and 6 mL 0.1 M HCl (A) were pushed through the system.

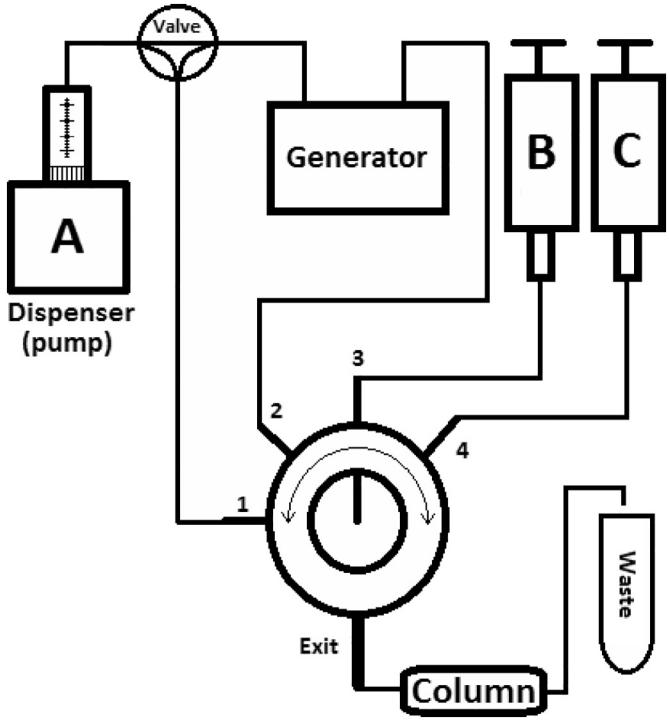

Fig. 1. Scheme of NaCl based purification of ^{68}Ga-generator eluate. A: 6 mL of 0.1 M HCl for eluting generator and preconditioning column. B: 10 mL syringe with air to empty column before elution of [^{68}Ga]Ga. C: 1 mL syringe with acidified 5 M NaCl (containing 0.05 M HCl) for desorption of [^{68}Ga]Ga. Additional valve used to precondition the column without eluting the generator.

2.3. Radiolabeling

To obtain high radiolabeling yield, the pH should be around 3.5 [20, 21]. To determine accurately how much buffer is needed, aliquots of 100 μL ^{68}Ga-eluate (acidified 5 M NaCl) were collected by using the described low volume PEEK system. After decay, pH titration curves were performed using sodium acetate, sodium formate, or HEPES as buffer, all were 1.5 M with a pH of 5.0 [22]. For the labeling, aliquots of 100 μL of ^{68}Ga-eluate (acidified 5 M NaCl) were adjusted to a final pH of 3.5 by adding the desired buffer solution. Using 15 or 50 mg of PS-H$^+$ cation resin and HEPES as buffer, 125 μL and 50 μL are required, respectively. For sodium acetate and sodium formate only 50 mg of cation PS-H$^+$ resin was applied and 60 μL and 125 μL were needed, respectively, to obtain a pH of 3.5. DOTA-TATE was used as peptide model. Radiolabeling was started after addition of DOTA-TATE (up to ~25 MBq/nmol) by heating for 5 min at 80° C [23]. I.e. for a 24 h ^{68}Ga-eluate (120–180 MBq), 4.8–7.2 μL of DOTA-TATE (1 μmol/mL) was added. After cooling to room temperature, quality control of [^{68}Ga]Ga-DOTA-TATE was performed. Quality control included radiochemical yield (RCY) of ^{68}Ga as measured by ITLC-SG [20, 21] and radiochemical purity (RCP) of [^{68}Ga]Ga-DOTA-TATE as measured by HPLC [24, 25]. RCP is here defined as % of radiotracer that is present in the desired chemical form. [^{68}Ga]Ga-DOTA-TATE was analyzed with a HPLC system (Alliance, Waters), containing a UV-detector (W2487 Waters Dual λ Absorbance Detector). UV absorption was measured at 278 nm. A Symmetry C_{18} column (5 mm × 4.6 mm × 250 mm, Waters) was used with a gradient profile as described earlier [23], mobile phase 0.1% TFA (A) and methanol (B). Radioactivity was monitored with a

system including a NaI detector, digital multichannel analyzer and dedicated software (MetorX B·V), connected to the HPLC system.

2.4. Osmolality

If 5 M NaCl solution was used to desorb [^{68}Ga]Ga from the PS-H$^+$ cation resin, after radiolabeling, the reaction mixture had to be diluted to physiological conditions to achieve the required conditions (200 pmol/5 MBq [^{68}Ga]Ga-DOTA-TATE in ≤0.2 mL ~0.3 osmol) which are suitable for *i.v.* mice injection. To lower the osmolality we studied the effect of reducing the NaCl concentration and investigated whether this affects the ^{68}Ga-desorption yields. 2–5 M acidified NaCl (1 mL) was used to desorb [^{68}Ga]Ga from PS-H$^+$ resin. Additionally, the influence of the amount of PS-H$^+$ resin (15–50 mg) on the osmolality was studied.

2.5. Trace metal quantification

To reduce metal ions ($M^{2+/3+}$), all buffers and additives were mixed with Chelex (1 g/~50 mL) for >144 h, which was removed by filtration (Millipore, 0.22 μm filter) before use.

Samples of buffer solutions, 0.1 M HCl solution, and acidified NaCl, which was used to eluate [^{68}Ga]Ga, were collected, and trace metals were quantified ($n = 3$). Labeling of DOTA-TATE was performed with addition of [^{175}Lu]Lu ICP standard with additionally small aliquots (50 μL) of collected samples. [^{175}Lu]Lu ICP standard was added to determine whether labeling conditions were optimal to obtain incorporation of $M^{2+/3+}$ metals. After labeling these samples were analyzed by UHPLC (Acquity H-Class, Waters) ($n = 3$) as described Breeman et al. (for a typical example see Fig. 2) [26]. Labeling without addition of an aliquot of sample as described above was considered as reference.

To investigate the influence of trace metals derived from the described low volume PEEK system (Fig. 1.), the PS-H$^+$ resin was rinsed with >3 M HCl. Trace metal content was determined before and after rinsing the system by collecting NaCl fractions. Aliquots of collected NaCl fractions (50 μL) were added and metals were quantified as described above.

3. Results

3.1. Low volume PEEK system

After eluting the low volume PEEK system with fractions of in total 1 mL acidified NaCl, it became clear that only 0.5 mL 5 M acidified NaCl was required to desorb [^{68}Ga]Ga. Due to the dead volume of the system only ~0.3 mL was recovered containing ~60% of the ^{68}Ga-activity. Purification of the eluate resulted in a high activity concentration (400–600 MBq/mL). All The retained volume (dead volume) was discarded by rinsing the system with 0.1 M HCl. Another reason for rinsing the system with 0.1 M HCl was preconditioning of the resin for the next elution of the ^{68}Ga-generator. Calculations of concentrations of [^{68}Ga]Ga and Zn, but also osmolality are based on the 0.3 mL of eluate. All elution steps were performed with a flowrate between 1 and 2 mL/min, higher flowrate will result in lower RCY and a to high pressure within our system.

3.2. Radiolabeling

Aliquots (100 μL) of desorbed [^{68}Ga]Ga in acidified NaCl were used to test 3 different buffers. To increase pH to 3.5 only 60 μL of sodium acetate or 125 μL of sodium formate and HEPES were required (see Fig. 3.)

Labeling performed with a standard molar activity of 25 MBq/nmol with sodium acetate and sodium formate as buffer resulted in low RCY (<86%). Best labeling results (>99%) with high reproducibility (see Fig. 5) were obtained with HEPES as buffer.

4. Osmolality

4.1. NaCl concentration

Reducing NaCl concentration from 5 M down to 2 M resulted in a decreased desorption of [^{68}Ga]Ga (Fig. 4A). Since reduced NaCl concentration results in a reduced osmolality of the final solution, 3 M acidified NaCl, which gave the best desorption results for the less

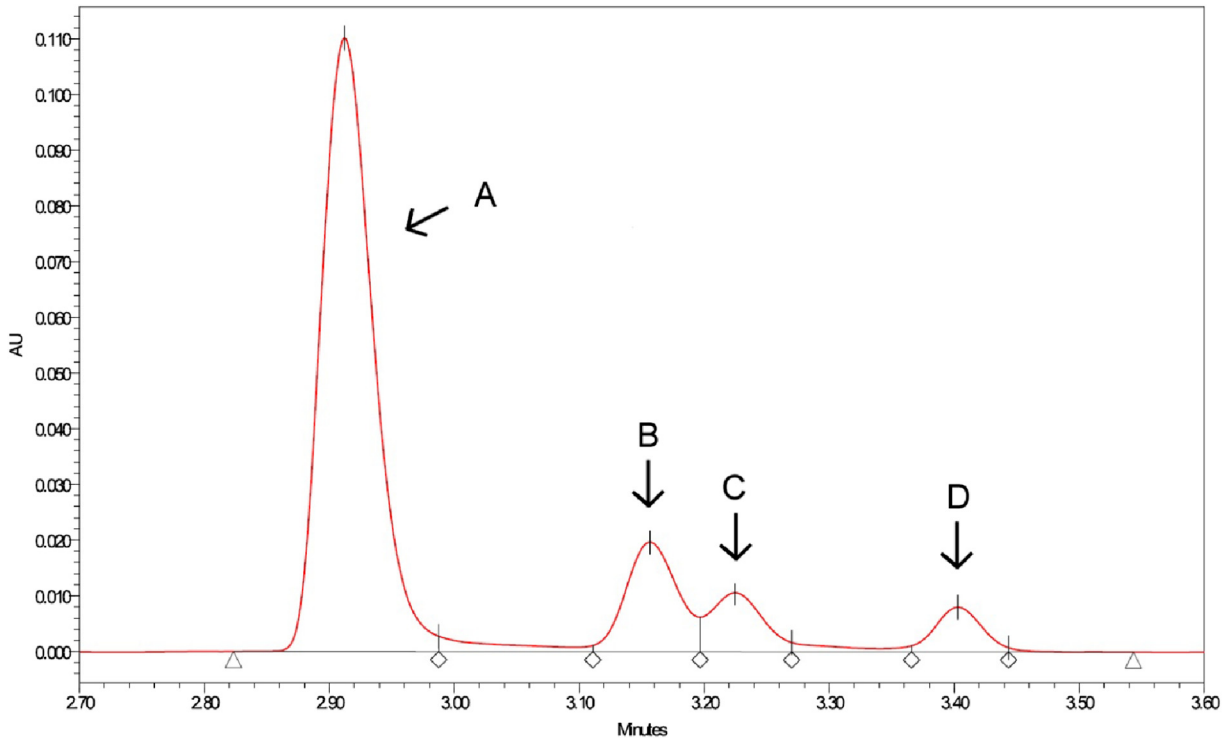

Fig. 2. UV (278 nm) UHPLC chromatogram of: DOTA-TATE (A) labeled with (B): Zn, (C): Fe or (D): Cu. Described method was used to quantify present trace metals [26].

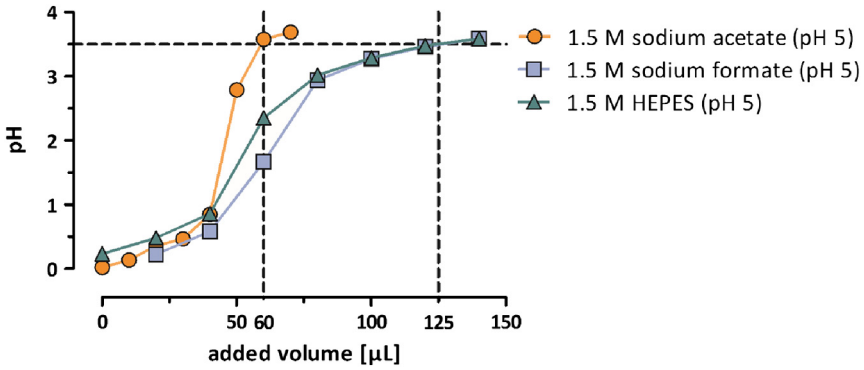

Fig. 3. ^{68}Ga-eluate (acidified 5 M NaCl) was titrated with sodium acetate, sodium formate and HEPES, respectively. Choice of buffers was based on Bauwens et al. [22].

concentrated solutions, was used for further investigation. 60% of ^{68}Ga-activity could be collected in only 0.3 mL (Fig. 4.B).

4.2. Amount of PS-H$^+$ resin

The RCY decreased by 7% when the amount of PS-H$^+$ cation resin was reduced by 70%. In addition, the reduction in amount of resin resulted in a reduction of required HEPES buffer to obtain a pH of 3.5. When reducing the amount of resin from 50 mg to 15 mg the amount of HEPES buffer was reduced from 125 µL to 50 µL (Fig. 5). This resulted in a decreased osmolality and a final volume reduction of 37%. Radiolabeling performed with 3 M acidified NaCl using 15 mg of PS-H$^+$ resin resulted in robust labeling with RCY's of >99% (see Fig. 6.).

Overall, osmolality of the final labeling solution using 3 M NaCl for ^{68}Ga-desorption was 4.5 osmol, to obtain isotonic conditions (0.3 osmol), a 15× dilution with MilliQ water was required. After dilution ~5 MBq/0.2 nmol in 200 µL [^{68}Ga]Ga-DOTA-TATE could be injected.

5. Trace metal quantification

After Chelex 100 treatment of buffers and other additives, trace metals were reduced from >10 nmol/mL to <1 nmol/mL. DOTA-TATE could be labeled with [^{68}Ga]Ga at high RCY, >99% (ITLC), and RCP, >95% (HPLC) (Fig. 5.). After rinsing buffers and additives with Chelex 100, the labeling mixture as described above resulted in a total amount of <1.5 nmol trace metal per labeling.

6. Discussion

6.1. Application of low volume PEEK system

When using an 1850 MBq ^{68}Ga-generator, (Eckert & Ziegler, ~60% RCY) results in 1110 MBq final eluate (t = 0). This result, after radiolabeling and release (1 h), in a maximum activity of ~600 MBq/6 mL. This means that even with a new ^{68}Ga-generator, the activity concentration is too low for direct preclinical use. To have a continuous access to applicable preclinical amounts, the here described low volume PEEK system is required.

As described in the introduction, in contrast to the clinical applied specifications for [^{68}Ga]Ga-DOTA-TATE: 150 MBq ^{68}Ga[Ga] labeled to ~35 nmol of DOTA-TATE in 9 mL at ~0.3 osmol (molar activity: ~4.2 MBq/nmol), specifications for *i.v.* injection in mice are: 5 MBq ^{68}Ga[Ga] labeled to 0.2 nmol DOTA-TATE in ≤0.2 mL ~0.3 osmol (molar activity 25 MBq/nmol). Since uptake of DOTA-TATE is based on a receptor mediated binding process, a much lower amount (<0.2 nmol) of DOTA-TATE is required to prevent saturation of the receptor [12, 27, 28]. Therefore, the clinically applied [^{68}Ga]Ga-DOTA-TATE procedure could only be used for preclinical application if the final activity is >900 MBq.

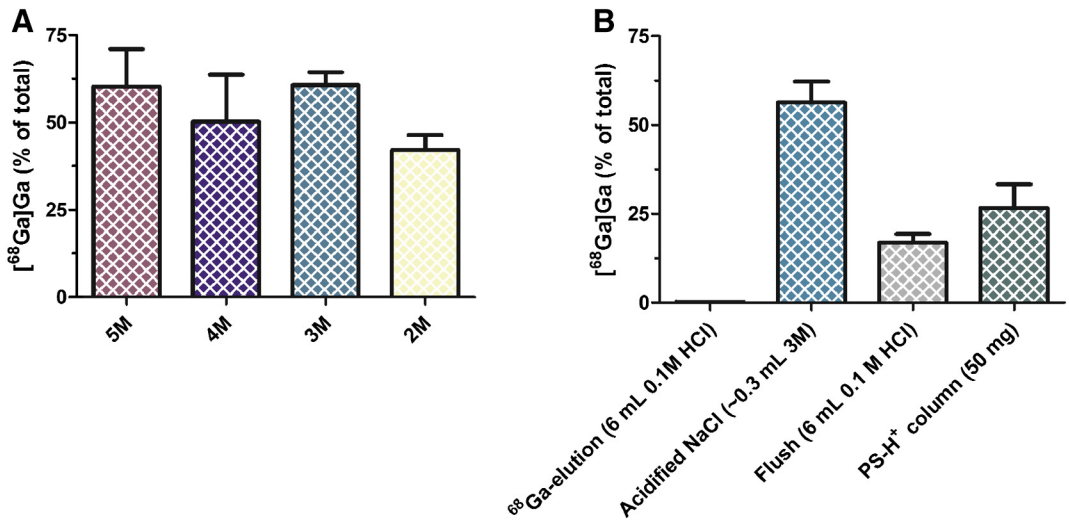

Fig. 4. A-B: To investigate maximum ^{68}Ga-concentration (MBq/mL), 0.05 M HCl acidified NaCl with increasing molarity (2-5 M) was used to desorb [^{68}Ga]Ga from PS-H$^+$ resin. Due to the dead volume of the system (~0.2 mL), [^{68}Ga]Ga was collected in ~0.3 mL. A: Desorbed [^{68}Ga]Ga in % (50 mg of PS-H$^+$) was plotted as f[NaCl]. B: ^{68}Ga-activity profile when using the low volume PEEK system.

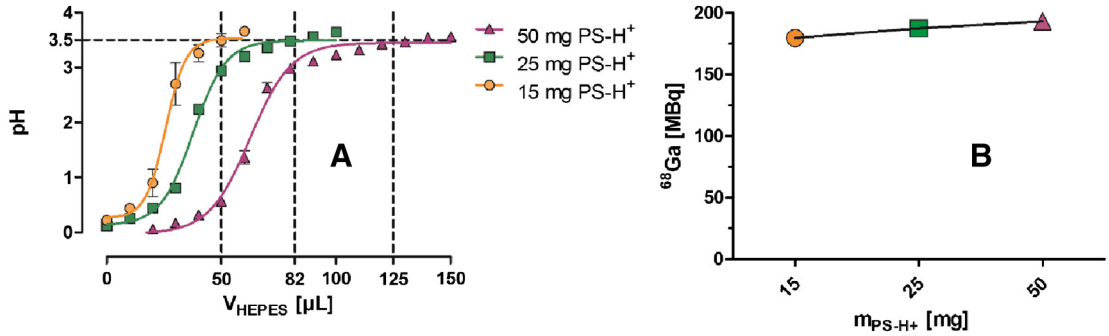

Fig. 5. A-B The effect of the amount of PS-H^+ (15–50 mg) on the pH of the eluate. A: HEPES-buffer was used to determine the volume required to buffer the eluate to the desired pH (pH: 3.5). B: The effect of the amount of PS-H^+ on the RCY of activity in ^{68}Ga-eluate.

The low volume PEEK system is an easy to use system where PS-H^+ resin can be reused multiple times. After intensive use of the resin (>30 purifications) lower RCY of the labeling were observed. Therefore, the PS-H^+ resin had to be cleaned by flushing the system with higher concentrated HCl (>3 M) or by renewing the resin.

6.2. NaCl concentration/amount of PS-H^+ resin

In comparison to Bauwens et al. [22] only small volumes of buffer are needed to obtain a pH of 3.5. The reasons for this are lower volumes of eluate and higher concentrations of buffers. Since Bauwens used an anion purification is used it is also likely that small amounts of HCl end up in final solution and influence the amount of required buffer. To lower osmolality, the NaCl purification technique [18] was adapted by decreasing the concentration of NaCl and the amount of PS-H^+ cation resin. To our knowledge there are no other publications on these items. For clinical cationic purification methods using other types of cation resins, 50–100 mg of resin are regularly used resulting also in high RCY of [^{68}Ga]Ga [11, 18].

6.3. Trace metal quantification

To minimize addition of trace metal derived from vials or chemicals, ultra-pure metal free vials, solutions and buffers must be used. A potential source for intrinsic metals is HCl. Since relative high volumes of 0.1 M HCl are used to elute the ^{68}Ga-generator and metals ($M^{2+/3+}$) are expected to be concentrated on the PS-H^+ resin as well, significant amounts of metals can be expected in the final labeling solution. This underlines the importance to use ultra-pure metal free HCl solutions. Labeling for preclinical use based on receptor mediated processes requires high molar activity and therefore only nanomoles of molecules/peptides are used. Under these conditions even small amounts of trace metals could already influence radiolabeling. i.e. here performed labeling with a molar activity of 30 MBq/nmol, starting with a ^{68}Ga-activity of 90 MBq only 3 nmol of peptide is added and 1.5 nmol of trace metal could already influence RCY. As shown these conditions resulted in high RCY. For ^{68}Ga-labeling, Oehlke et al. stated that if metals occupy <80% of the present molecules to be labeled, no influence on RCY is expected [15]. Additionally, labeling kinetics, volume of final labeling mixture could also play a role in achieving high RCY. Moreover, more research on the resin is required to obtain more information on metal selectivity.

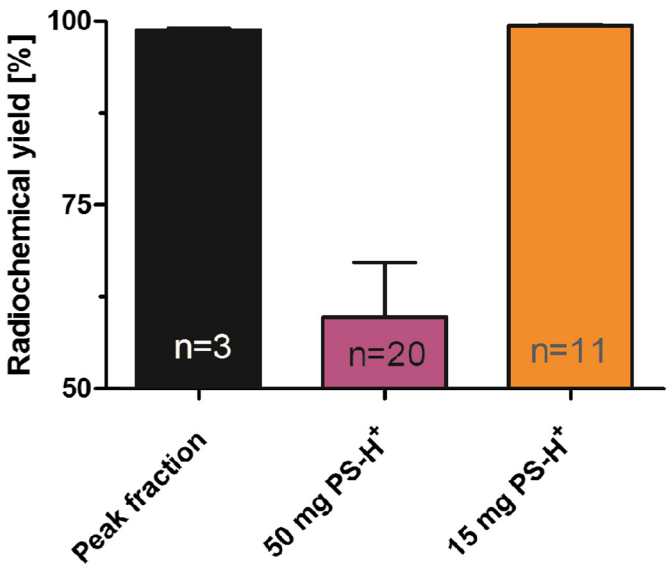

Fig. 6. Gallium-68 labeling with high molar activity (20–30 MBq/nmol) was performed with ^{68}Ga-eluate obtain with either direct elution of the ^{68}Ga-generator or using described semi-automated system with 50 or 15 mg of PS-H^+ resin. Labeling of all three conditions was performed within 20 min.

7. Conclusions

With the here described system and metal purification technique, a low activity containing ^{68}Ga-generator can be used to label DOTA-peptide at 60 MBq/nmol within 20 min. Optimal conditions to achieve these results are: Elution of ^{68}Ga-generator and other eluent with a flowrate of 1–2 mL/min, using 15 mg PS-H^+ cation resin to absorb [^{68}Ga]Ga and 3 M of NaCl to desorp [^{68}Ga]Ga and 1.5 M HEPES (pH 5) as buffer for radiolabelling. DOTA-TATE can be labeled with [^{68}Ga]Ga at high RCY, >99% (ITLC) and RCP >95% (HPLC). Concentration resulted in high activity concentration (400–600 MBq/mL). Labeled peptide (40–60 MBq/0.1 mL) could be diluted with MilliQ water to isotonic conditions (0.3 osmol) in preclinical applicable amounts (~200 µL/mouse).

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