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RESEARCH ARTICLE

Optimization of a Labeling and Kit Preparation Method for Ga-68 Labeled DOTATATE, Using Cation Exchange Resin Purified Ga-68 Eluates Obtained from a Tin Dioxide ^{68}Ge/^{68}Ga Generator

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Abstract

Purpose: The aim of this study was to optimize a radiolabeling method using cationic processed Ga-68 eluates from a SnO_2-based ^{68}Ge/^{68}Ga generator, followed by the development of DOTA-Tyr^3-Thre^8-octreotide (DOTATATE) kits.

Procedures: Diluted generator eluates were adsorbed on a SCX resin and desorbed with acidified 5 M NaCl solution. Optimized labeling conditions were determined by variation of pH, using 35 μg DOTATATE and sodium acetate buffer. DOTATATE kits were developed based on optimized radiolabeling conditions, were labeled, and evaluated.

Results: Optimized labeling conditions resulted in a radiolabeling efficiency of around 99 % and radiochemical yield of almost 85 %. Different kit preparation methods did not significantly influence the radiolabeling results. Kits were found to be stable over 3 months.

Conclusion: A labeling method using SCX-processed Ga-68 eluates was optimized. DOTATATE kits specifically for these SCX-processed Ga-68 eluates were successfully formulated. A post-labeling Sep-Pak C18 purification should be optional.

Key words: DOTATATE, Ga-68 eluate, SnO_2-based ^{68}Ge/^{68}Ga generator, Radiolabeling efficiency, Radiochemical yields, Cation exchange resin, Kits

Introduction

The ^{68}Ge/^{68}Ga generator is the main source of Ga-68 for routine availability. Its advantages include the potential to prepare multiple radiotracer preparations daily and the use of the generator over a long period [1, 2]. DOTA-conjugated peptides can be rapidly and efficiently labeled with Ga-68 at high specific activities [3]. The fractionation method of generator eluates has been used successfully in the radiolabeling process [4] and was found to, among others, reduce large eluate volumes [5–7], but activity loss is problematic.

The use of cationic resin-purified Ga-68 eluates in radiolabeling has become more popular as opposed to fractionation and is well documented [8–11]. The Ga-68 is adsorbed on the resin and desorbed with acetone/HCl mixtures. A major disadvantage of this method is the use of acetone as desorption agent, which has to be eliminated from the final preparation.

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Mueller et al. [12] described an alternative cation exchange concentration/purification method for Ga-68 eluates from TiO_2 generators, using the formation of the anionic and readily elutable $[^{68}GaCl_4]^-$ species during desorption. A labeling method for DOTA peptides was also described [12]. Other investigators adapted the method of Mueller et al. [12] for the automated synthesis of Ga-68-labeled radiopharmaceuticals [13]. Advantages of this method included reduced preparation time largely due to the omission of organic solvents and not requiring C18 purification. Martin et al. [14] investigated purification methods, based on the Mueller principle, using cation exchange cartridges and Ga-68 eluates from a SnO_2-based generator. According to Seemann et al. [15], who compared cation exchange resin-based post-processing methods, using the TiO_2 generator and various radiolabeling model precursors, the acetone- and ethanol-based methods provided greater labeling reproducibility and yields, while the NaCl method resulted in lower yields due to longer labeling times.

The use of kits in radiopharmaceutical preparations is aimed at streamlining labeling procedures for user-friendliness. Various investigators [16–19] developed DOTA-peptide kits that were formulated for use with Ga-68 eluates from TiO_2- or nanoceria-PAN-based generators. Das et al. [18] and Mukherjee et al. [20] developed DOTA-peptide kits for use with cationic resin-purified Ga-68, using the acetone/HCl desorption method. In most previously published reports, DOTA-peptide kits for labeling were based on the use of $^{68}Ge/^{68}Ga$ generators eluted with low HCl concentrations. In the studies by Mukherjee et al. [16, 17], the eluates were directly added to the kits without any pre- or post-processing methods.

The development and evaluation of DOTA-peptide kits, specifically designed for radiolabeling with fractionated Ga-68 eluates obtained from a SnO_2-based $^{68}Ge/^{68}Ga$ generator, was previously reported [21]. There is a need to formulate kits in which cation resin-purified Ga-68, contained in a more acceptable and user-friendly medium, can be used. Based on the existing literature, we identified the SCX/NaCl purification method, originally developed by Mueller et al. [12], as the most promising cationic purification method to meet this requirement. Our first aim was to optimize the labeling method using Ga-68 from a SnO_2 generator that had been purified according to the Mueller et al. [12] principle. DOTATATE was selected as the labeling precursor model. The next aim was to utilize this optimized radiolabeling method in the development of DOTATATE kits, exploring four different kit preparation methods.

Materials and Methods

Elution of the Generator

The Ga-68 was eluted from a SnO_2-based $^{68}Ge/^{68}Ga$ generator (iThemba LABS, Somerset West, South Africa) with 0.6 M HCl. Elution was carried out as follows: in method 1, the generator was eluted with 12 ml 0.6 M HCl and the eluate divided into three 4-ml aliquots (activities ranging from 141 to 185 MBq). In method 2, the generator was eluted with 4 ml 0.6 M HCl (activities ranging from 396 to 415 MBq). All Ga-68 activities were measured in a Capintec Dose Calibrator CRC-55tR (NJ, USA).

Optimization of Labeling Method for the Preparation of [^{68}Ga]DOTATATE

Dilution of the Ga-68 Eluate for SCX Processing The 4-ml Ga-68 aliquot (method 1) or eluate (method 2) was diluted with 4 ml ultrapure pharmaceutical grade water to result in a 0.3 M HCl concentration.

Concentration/Purification of Ga-68 Eluates on the Bond Elut SCX Column A Bond Elut SCX 100 mg (1 ml) column (Agilent Technologies, Santa Clara, USA) was pre-conditioned with 1 ml 5.5 M HCl, followed by 5 ml pharmaceutical grade water. The diluted activity was loaded onto the pre-conditioned cartridge and eluted into a waste vial *Fr1*, followed by a 1 ml water rinse into the same waste vial. The vial was replaced with another vial. Ga-68 was eluted from the cartridge with 0.5 ml of 5 M NaCl and 5.5 M HCl 40:1 (*v*/*v*) (*Fr2*). The activities in both *Fr1* and *Fr2*, as well as the residual activity in the cartridge, were measured.

Determination of the Optimal Quantity of 2.5 M Sodium Acetate (NaOAc) and Radiolabeling of the DOTATATE With Concentrated Eluates and Post-Purification Thereof DOTATATE stock solution (1 mg/ml) was prepared using pharmaceutical grade water and DOTATATE (JPT Peptide Technologies GmbH Berlin, Germany) and 35 µl of the stock solution was added to *Fr2* (0.5 ml). Various 2.5 M NaOAc portions (40–60 µl) were added to the *Fr2*/DOTATATE mixture, 2 ml ultrapure pharmaceutical grade water was added, and the pH was measured, using pH indicator strips (Merck, Darmstadt, Germany). The 2.5 M NaOAc was prepared using sodium acetate trihydrate powder from Sigma-Aldrich (St. Louis, MO, USA). The vial containing the labeling mixture was heated at 95 °C for 15 min. An aliquot was removed for HPLC testing before the reaction mixture was transferred onto a purification unit consisting of a preconditioned 500 mg C18, 3 cm^3, Sep-Pak cartridge, catalog number WAT036815 (Waters, MA, USA). The cartridge was rinsed with 8 ml 0.9 % sodium chloride (NaCl) (Fresenius Kabi, Port Elizabeth, South Africa). The collection vial (*S1*) was removed and replaced with another vial (*S2*). The cartridge was then rinsed with 0.7 ml ethanol:saline (50:50) to desorb the labeled peptide. The cartridge was finally rinsed with 2.25 ml 0.9 % NaCl to displace the retained ethanol:saline from the previous elution step. The activity in *S2* was expressed as the radiochemical yield of labeled peptide.

Preparation of DOTATATE Single-Vial Kits DOTATATE stock solution (1 mg/ml) was prepared using pharmaceutical grade water. Single-vial DOTATATE kits were prepared using the following four methods:

DOTATATE Kit A A mass of 15.64 mg of sodium acetate trihydrate salt was weighed into sterile vials and 35 µl of DOTATATE stock solution was pipetted into each vial. The kits were vacuum-dried under sterile conditions in a desiccator connected with a N 726 FT.18 vacuum pump (KNF Neuberger Inc., Trenton, USA) for 3 h at room temperature.

DOTATATE Kit B A volume of 46 µl of 2.5 M NaOAc was pipetted into sterile vials, followed by 35 µl DOTATATE stock solution. The kits were vacuum-dried as above.

DOTATATE Kit C Similar to the procedure for *kit B*, but no drying was applied.

DOTATATE Kit D A volume of 46 µl of 2.5 M NaOAc was pipetted into each sterile vial and 35 µl of DOTATATE stock solution was added to each vial. These kits were frozen with liquid nitrogen and loaded into the freeze-dryer (Edwards, Crawley, UK) with a shelf temperature of − 50 °C for 4 h. The shelf temperature was increased to 35 °C to sublimate the ice and each vial was vacuum-sealed.

The single-vial kits were stored at − 20 °C and removed from the freezer to be brought to room temperature before being used. The quality and stability of the DOTATATE single-vial kits (A, B, C, and D) were evaluated at monthly intervals over a 3-month period.

Radiolabeling of the DOTATATE Kits With Concentrated Eluates and Post-Purification Thereof The 4-ml Ga-68 aliquots (elution method 1) were each diluted and then concentrated/purified on the pre-conditioned SCX column as described previously. The concentrated fraction *Fr2* (0.5 ml) was eluted directly into a kit vial. Pharmaceutical grade water (2 ml) was added to the kit vial; its contents were mixed and the pH was measured, using pH indicator strips. The vial containing the labeling mixture was then heated for 15 min at 95 °C. An aliquot was removed for HPLC and iTLC testing before the reaction mixture was purified on a C18 cartridge (described previously).

Quality Evaluation

Radiolabeling Efficiency and Radiochemical Yield Radiolabeling efficiency (LE) was obtained from the HPLC analysis of an un-purified labeling mixture and describes the amount of labeled DOTA peptide, expressed as a percentage of the total amount of radioactivity species recorded on the HPLC radiochromatogram. Radiochemical purities of Ga-68-labeled DOTATATE before and after Sep-Pak purification were determined by means of HPLC and were also expressed as the percentage of the total radioactivity in the sample. The HPLC equipment consisted of a PerkinElmer Series 200 LC Binary Pump equipped with a Rheodyne Model 7125 injector, a Phenomenex Luna C18 analytical column (250 × 4.6 mm, 5 µm), and a NaI(Tl) radiation flow detector coupled to a high-voltage power supply and ratemeter (Ortec). The mobile phases were 0.1 % (*m*/*v*) trifluoroacetic acid (Sigma-Aldrich, St. Louis, MO, USA) in de-ionized water (A) and acetonitrile (Sigma-Aldrich, St. Louis, MO, USA) (B). Elution was carried out at a flow rate of 1 ml/min, using the following elution program: 0–2 min (100 % A), 2–12 min (70 % B), and 12–15 min (100 % B). Under these conditions, the retention time for free Ga-68 was 2.6–3.7 min; for occasionally present small traces of radiochemical impurities, it was 6.3–9.3 min, while the retention times for [^{68}Ga]DOTATATE was 12.2–12.8 min.

LE values emanating from the use of single-vial kits and cationic-purified Ga-68 eluates were also determined by an iTLC method in order to detect possible colloids (see below).

The activities in the collected fractions (*S1* and *S2*), as well as the remaining activities in the reaction vial and on the C18 cartridge, were measured in a dose calibrator. The radiochemical yield (RY) was calculated by expressing the decay-corrected activity in the C18 fraction *S2* as a percentage of the initial activity.

Colloid Determination of the Pre-Sep-Pak Un-Purified Ga-68-Labeled DOTA Peptides The iTLC mobile phase consisted of a mixture of 1 M ammonium acetate:methanol (1:1) according to the method of Mukherjee et al. [17]. The iTLC-SG strips were prepared as follows: 9 cm long, 1.5 cm wide and the spot with activity (approximately 0.37 MBq) was placed at 1.5 cm from the bottom of the strip. The iTLC strip was then inserted in a chromatography tank containing 10 ml of the mobile phase and allowed to develop. Development time was approximately 10 min. The strip was removed from the tank and allowed to air dry before it was scanned using an Omni-rad EZ Scan (Carroll & Ramsey Associates, CA, USA), coupled to a Chromatopac C-R8A integrator (Shimadzu, Kyoto, Japan). The LE was obtained directly from the integrated values on the iTLC chromatogram. It was expressed as the amount of labeled DOTA peptide with R_f value = 0.9, expressed as a percentage of the total amount of radioactivity species recorded on the iTLC radiochromatogram.

Microbiological Evaluation of DOTATATE Cold Kits Sterility testing on the formulated DOTATATE cold kits was performed according to the methods prescribed in the European Pharmacopeia. A total of 12 samples of the

DOTATATE single-vial kits (three of each kit type) were tested. These DOTATATE single-vial kits were each dissolved in (up to 0.5 ml) in a mixture of 5 M NaCl and 5.5 M HCl 40:1 (*v*/*v*) and then analyzed for bacterial growth. The sterile 5 M NaCl and 5.5 M HCl 40:1 (*v*/*v*) was used to closely represent the Ga-68 eluate that would be added to the kit but avoid false negative results that may occur due to the presence of the Ga-68.

Endotoxin testing was performed on 12 DOTATATE cold single-vial kits (three of each kit type) dissolved in up to 1.0 ml sterile saline. The testing was performed according to the European Pharmacopeia using the chromogenic method. A Lonza LAL Test Chromogenic Kit (Basel, Switzerland) was used.

Testing for Ge-68 in Radiolabeled Preparations The ^{68}Ge breakthrough was determined at least 24 h after preparation of the labeled product in order to allow all Ga-68 in the initial sample to decay, so that any Ga-68 present was due to the decay of Ge-68. A Canberra gamma spectrometer with a germanium detector and Genie 2000 software was used. The breakthrough (%) was defined as the ratio of activity of Ge-68 divided by the initial Ga-68 activity.

Results

Determination of the Optimal Volume of 2.5 M NaOAc (pH)

The results in Table 1 present data on the influence of the volume of NaOAc on radiolabeling and C18 purification results of [^{68}Ga]DOTATATE, using 35 μg DOTATATE and SCX-processed Ga-68 eluates.

The addition of 40–50 μl NaOAc (labeling mixture pH 2.0–3.5) resulted in a consistent increase in the average LE of 93 to 99 %, but there was a decrease of 79 to 70 % when 55–60 μl (pH 4.0–4.5) of NaOAc were added. The average RY (*S2*) remained constant (81–84 %) with the addition of 40–48 μl NaOAc but decreased significantly (64–20 %) when 50–60 μl (pH 3.5–4.5) NaOAc were added. The average activity remaining on the vial was 2–8 % for the addition of 40–48 μl (pH 2.0–3.0) NaOAc, but increased dramatically thereafter with as much as around 55 % when volumes of 55–60 μl (pH 4.0–4.5) of NaOAc were added.

Radiolabeling Efficiency and Radiochemical Yield Results Under Optimized Conditions

Under optimized conditions, the LE ranged from 95 to 99 % and the RY (*S2*) ranged from 83 to 89 %. The remaining activity on vial (*S3*) was fairly consistent between 5 and 6 %, and the activity remaining on the C18 cartridge (*S4*) was 3–10 %.

Determination of Kit Composition Parameters and Preparation of Single-Vial Kits

Based on previous work by the same authors [21] where fractionated Ga-68 eluates were used, 35 μg of DOTA-peptide was used for all the radiolabeling experiments. The results of the optimized labeling experiments, emanating from the use of SCX-processed Ga-68 eluates, were used to calculate the required quantity of NaOAc for the kits. The inclusion of 15.64 mg of sodium acetate trihydrate salt (in kit A) or 46 μl of 2.5 M NaOAc (in kits B, C, and D) as buffer in the kit formulation ensured a radiolabeling mixture with a consistent pH of 3.0.

Quality Evaluation of the DOTA-Peptide Kits

Radiolabeling Efficiency (HPLC) and Radiochemical Yield Table 2 presents data on the LE of [^{68}Ga]DOTATATE, using SCX-processed Ga-68 eluates and single-vial kits containing 35 μg DOTATATE, stored for various periods at − 20 °C. Over the 12-week storage period, LE results obtained from all four the DOTATATE single-vial kit types were consistently above 98 %. The RY obtained with the single-vial DOTATATE single-vial kit types ranged from 75 to 89 %. No obvious decline in the RY was observed over this period. The radiochemical purity post-C18 purification was always in the order of 100 % (not tabulated).

Colloid Determination of the Pre-Sep-Pak Un-Purified [^{68}Ga]DOTATATE, Using an iTLC Method The R_f results of Mukherjee et al. [17], whose iTLC method was used in this investigation, served as a guideline to identify the location of the various radioactive species. The R_f value of the labeled peptide was given as 0.9–1, while the R_f of free Ga-68 as well as colloidal Ga-68 was given as 0–0.1. Under those iTLC conditions, no detectable quantities of colloids were present in the un-purified Ga-68-labeled DOTATATE, as indicated in Table 3. Over the 12-week storage period, LE (iTLC) results on pre-purified Ga-68-labeled DOTATATE were consistently above 99 %, with the exception of DOTATATE single-vial kit D.

Microbiological Evaluation of DOTATATE Cold Kits All the samples were found to be sterile. The average endotoxin contents of the single-vial kits were all below 2 IU/ml (see Table 3) and met the European Pharmacopeia specification for bacterial endotoxins which is less than 175 IU in the total administered volume.

pH The pH values of the DOTATATE radiolabeling solutions (for kits A, B, C, and D) were all consistently 3.0 over the 3-month period.

Table 1. Influence of volume of sodium acetate on radiolabelling results of [^{68}Ga]DOTATATE, using SCX-processed Ga-68 eluates

Vol. 2.5 M NaOAc (µl)	pH range of labelling mixture	Labelling efficiency (%)[a]	S1 (%)	S2 (%)	S3 (%)	S4 (%)
40 ($n = 4$)	2.0–2.5	93 ± 6	6 ± 3	82 ± 4	2 ± 0.5	11 ± 2
42 ($n = 4$)	2.5–3.0	96 ± 4	3 ± 2	83 ± 2	2 ± 0	12 ± 2
44 ($n = 4$)	2.5–3.0	98 ± 1	2 ± 0	83 ± 3	3 ± 1	12 ± 3
46 ($n = 12$)	3.0	99 ± 1	2 ± 0.4	84 ± 3	7 ± 4	7 ± 4
46 ($n = 4$)[b]	3.0	97 ± 2	3 ± 0.5	81 ± 2	5 ± 1	12 ± 3
48 ($n = 4$)	3.0	98 ± 0.5	3 ± 1	82 ± 2	8 ± 2	7 ± 3
50 ($n = 3$)	3.5	99 ± 1	3 ± 1	64 ± 6	24 ± 4	9 ± 1
55 ($n = 1$)	4.0	79	10	24	55	12
60 ($n = 1$)	4.5	70	12	20	54	14

Number of experiments given within brackets
S1 first Sep-Pak fraction collected with 8 ml saline, *S2* (radiochemical yield) = second Sep-Pak fraction collected with 0.7 ml ethanol:saline [50:50] + 2.25 ml saline, *S3* remaining activity in vial, *S4* remaining activity in Sep-Pak after collecting S2
[a]Determined by means of HPLC
[b]Influence of volume of sodium acetate (pH) on radiolabelling and Sep-Pak C18 purification results of [^{68}Ga]DOTATATE, using 35 µg DOTATATE and SCX-processed Ga-68 eluates showing mean values of decay-corrected activities in various fractions, expressed as percentages of the starting activity (141–185 MBq or higher activity concentrations 396–415 MBq)

Ge-68 in Radiolabeled Preparations No Ge-68 was found in the Ga-68-labeled product.

A summary of the quality control results between DOTATATE single-vial kits A, B, C, and D after a 12-week storage period at − 20 °C is given in Table 3.

Discussion

A radiolabeling method of DOTA peptides was described in literature [12], using SCX-processed Ga-68. Labeling was conducted in a relatively large volume (3.7–3.9 ml), using ammonium acetate buffer. Our labeling method was based on using NaOAc buffer, smaller reaction volumes (2.5–2.6 ml), and improved pH control. The NaOAc was used because it ensured a radiolabeling mixture with a consistent pH throughout the labeling process and was successfully used in previously published work [5–7, 16–18, 22–24]. The selected amount of DOTA peptide (35 µg) was based on that used in a previous study [21]. Under the current conditions, the DOTATATE molar concentration was 9.4–9.7 µM. We also focused our investigations on the search for an optimum pH range for labeling, with the aim to improve radiolabeling yields and to reduce losses of activity during post-labeling purification.

The radiolabeling of DOTA peptides is highly pH dependent [5, 25]. Breeman et al. [5] found that pH 3.5–4.0 was the optimal pH for incorporation of Ga^{3+} in the labeling process. Velikyan et al. [26, 27] performed labeling of DOTA peptides at a pH of about 4.6. Meyer et al. [28] found the optimal pH range for the radiolabeling to be 4.3–5.0. However, in our study, at pH 3.5, although the LE was 99 %, the RY (*S2*) dropped below 65 % with almost 25 % of the activity remaining on the vial. At pH 4.0–4.5, these figures dropped even further. This may be due to the less acidic conditions causing hydrolysis of the Ga-68. These discrepancies between LE and actual RY illustrate that under certain non-optimal labeling conditions, LE on its own could not be a true reflection of RY. The optimal pH for the radiolabeling process in this study was found to be 3.0. Where individual LE and C18 purification results at pH 3 after addition of 46 µl 2.5 M NaOAc are given, the average activity remaining on the vial (*S3*) under optimized labeling conditions was 6 ± 0.6 %.

Both generator elution methods resulted in similar labeling results. The first elution method was predominantly used in this study in order to increase the number of labeling experiments that could be performed with a single elution. In a routine clinical setup, when higher activity is required, eluates with higher activity concentration can be introduced into labeling mixtures, using eluates obtained from elution method 2.

Once labeling conditions, using resin-purified eluates, had been optimized, we embarked on the formulation of kits. The pre-determined amount of sodium acetate required for the DOTA-peptide kits was based on the quantity of buffer required to adjust the pH of the solution to a pH of 3.0. Based on the results, the different methods of kit preparation do not have a significant influence on the radiolabeling

Table 2. HPLC pre-Sep-Pak purification radiolabelling efficiency results of [^{68}Ga]DOTATATE, using SCX-processed Ga-68 eluates and single vial kits

Kit storage period at − 20 °C	Radiolabelling efficiency (%)			
	Kit A	Kit B	Kit C	Kit D
1 week ($n = 3$)	99.7 ± 1	99.0 ± 1	99.0 ± 1	–
4 weeks ($n = 3$)	99.3 ± 1	99.0 ± 1	99.0 ± 2	99.0 ± 0
8 weeks ($n = 3$)	99.3 ± 1	98.7 ± 2	99.3 ± 1	99.0 ± 0
12 weeks ($n = 3$)	98.3 ± 1	98.7 ± 2	99.7 ± 1	99.0 ± 1

Table 3. Radiolabelling and microbiological quality control results, using SCX-processed Ga-68 eluates and single vial kits containing 35 μg DOTATATE, after storage for 3 months at − 20 °C

Quality control parameters	Kit A	Kit B	Kit C	Kit D
Radiolabelling efficiency (%) (HPLC)[a]	98.3 ± 1	98.7 ± 2	99.7 ± 1	99.0 ± 1
Radiolabelling efficiency (%) (iTLC)[a]	99.5 ± 1	100 ± 0	100 ± 0	98.7 ± 1
Radiochemical yield (%) (Sep-Pak)[a]	80 ± 6	84 ± 5	84 ± 4	87 ± 1
Activity lost in reaction vial (%)	6 ± 2	3 ± 0.6	3 ± 0.6	5 ± 1.5
Endotoxin count (of cold kit) (IU/ml)[a]	1.8 ± 0.2	1.4 ± 0.1	1.1 ± 0.2	1.6 ± 0.1
Sterility (of cold kit)[a]	Sterile	Sterile	Sterile	Sterile
pH[a]	3.0	3.0	3.0	3.0

[a] $n = 3$

results. This implies that any one of the four methods can be used to prepare the kits depending on the convenience and available infrastructure. The labeling yields obtained from kit C were the most consistent over the entire 12-week period. The ultimate use of this kit preparation method might therefore be the most advantageous, also in terms of ease and user-friendliness, as it requires no extra weighing of ingredients or drying of the kit.

The LE results obtained from the iTLC method imply the absence of colloids. No ^{68}Ge was found in any of the Ga-68-labeled DOTATATE preparations due to the SCX-processing (results were not reported above). These two results suggest that there might be no need for the post-labeling purification of the Ga-68-labeled peptide when labeling is done under these conditions. In a radiopharmacy setup, a simple iTLC analysis may be performed to detect colloids or free Ga-68, before the preparation can be diluted for injection. The absence of a need for post-labeling purification would have a big advantage in terms of the length of the whole procedure and therefore the overall radiochemical yield.

Based on the microbiological evaluation results, the radiolabeled DOTA-peptide kits were found to be sterile and microbiologically suitable for clinical intravenous application.

The consistent pH values of the labeling reaction mixtures emanating from the DOTA-peptide kits fall within the acceptable pH range required for the DOTA-peptide labeling.

The preceding SCX purification step ensured the removal of all traces of Ge-68 breakthrough.

The use of these DOTATATE kits reduces the labeling process. Their stability allows for storage periods of at least up to 3 months. Additional investigation of the DOTA-peptide kits over longer storage periods may even extend this period further.

This study is a first, according to the best of the authors' knowledge, which describes the use of Ga-68 eluates, obtained from a SnO_2 generator and purified with the acidified NaCl/SCX cationic resin technology, in DOTA-peptide kit labeling.

Conclusion

The successful development of a labeling method using pre-concentrated Ga-68 eluates from a Bond Elut SCX (100 mg) cation exchange resin was achieved. The method produced a high LE of around 99 % and high radiochemical yield of almost 85 %. The labeling results for DOTA-peptide labeling at a pH of 3 were found to be superior to those at a higher pH.

The objective of formulating user-friendly stable DOTATATE kits specifically for SCX-processed Ga-68 eluates has been achieved. The single-vial kits containing DOTATATE and NaOAc buffer may be prepared in four relatively simple ways. The kits can be radiolabeled with Ga-68 reliably and consistently in a clinical environment. Results showed that post-labeling Sep-Pak C18 purification might not be required and should be optional, as no significant quantities of free or colloidal Ga-68 were detected in the labeling experiments. No Ge-68 was present due to the SCX purification step.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

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