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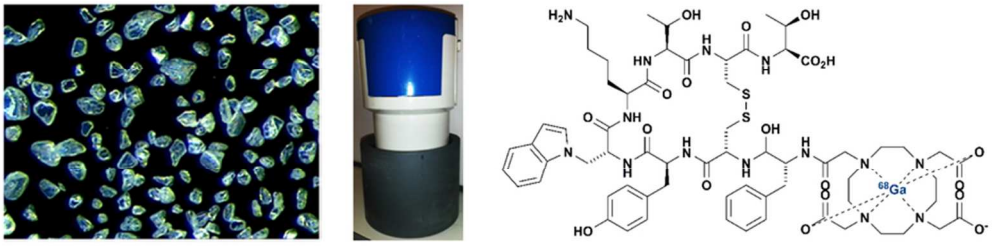
Textual Abstract

Smoothened titania particles for a long-lived radiopharmaceutical grade ^{68}Ge/^{68}Ga generator.



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PAPER

Smoothened titania particles to improve radionuclide separation and their application to the development of a novel [^{68}Ge]/[^{68}Ga] generator

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Gallium-68 has a high potential for clinical positron emission tomography (PET) because of its ^{68}Ge/^{68}Ga generator based production. Unfortunately, during elution of the gallium-68, generators usually display a germanium-68 breakthrough which consequently limits their use in a clinical context. To be more precise, usually used crude anatase presents fragile edges which can split and be co-eluted from the generator during gallium-68 recovery, resulting in metal and germanium-68 contaminations. The addition of a sonication step during the production process of titania induces more resistant smoothened particles which were packed in a quartz glass column to give a novel ^{68}Ge/^{68}Ga generator. The performance of the system (elution profile, elution yield and germanium-68 breakthrough) was determined and followed-up over a period of nine months in terms of reliability and efficiency so as to produce high quality gallium-68 and to radiolabel DOTA-peptides. Elution of gallium-68 from the generator was achieved with a constant yield (≈ 67 ± 5%) and a ^{68}Ge/^{68}Ga ratio typically lower than $2.0.10^{-7}$ which is about 20 fold less than the values observed using crude titania. Moreover, fully automated processes that involved a fractionated elution or a cation exchange preconcentration of gallium-68 were realized. [^{68}Ga]-radiotracers production occurred in less than 20 min with a marked radiochemical purity (> 97%) and yield (80-90%, decay-corrected). We have shown experimentally that smoothened anatase based system generated high quality gallium-68 which was successfully used for the labeling of DOTA-peptides in considerable radiochemical yields and radioactive purity throughout its expected life.

Introduction

In the last five years, gallium-68 has taken an increasingly significant part in the landscape of the diagnostic armamentarium used in positron emission tomography. Undoubtedly, the major impetus for its development has been underpinned by the ready source of gallium-68 produced from a ^{68}Ge/^{68}Ga generator. Moreover, the relatively short half-life of this radioisotope ($T_{1/2}$ = 68 min) and its disintegration characteristics (89% positron emission yield, 1.89 MeV maximum energy) permit acceptable dosimetry for patients during clinical studies.[1,2] As an example, research with this radionuclide led to the [^{68}Ga]-DOTA^0-(Tyr^3)-octreotide ([^{68}Ga]-DOTATOC) which has been proven to be superior to conventional scintigraphy for somatostatin receptor imaging.[3,4] Today, this pioneering approach has furnished two other analogues, the DOTA^0-(Tyr^3-Thr^8)-octreotate (DOTATATE) and the DOTA^0-1-Nal^3-octreotide (DOTANOC), which have high affinities for somatostatin receptor subtypes 2 and subtypes 2, 3 and 5 respectively.[5,6] Recent advances in gallium-68 technology have yielded to new compounds with encouraging results such as the [^{68}Ga]-CPCR4.2 for the PET imaging of solid and haematological tumours which overexpress chemokine receptors type 4 (CXCR4) and the [^{68}Ga]-TRAP(RGD)$_3$ peptide for the imaging of $\alpha_v\beta_3$ integrin which plays a key role in the metastasis of tumour cells.[7] So, the development of the [^{68}Ga]-radiotracers is a valuable contribution to nuclear medicine. Moreover, the chemical reactivity of gallium-68 is similar to gadolinium, yttrium-90 and lutetium-177 which heightens the interest in gallium-68 radiotracers in multimodal diagnoses and therapies. Explicitly, PET/MRI imaging can be carried out with a same ligand, based on the classically used 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) chelating group, but complexed either with gallium-68 or gadolinium and the [^{68}Ga]-radiotracers can be used not only for the detection of a tumour but also to predict the efficacy of treatment by the same compound labeled with β^- emitters such as yttrium-90 and lutetium-177.

However, one of the limitations to the use of gallium-68 is the ^{68}Ge/^{68}Ga generator technology, based on the decay of the long-lived germanium-68, which is usually adsorbed on mineral oxides (tin, aluminum or titanium) or organic sorbents.[8-12] This chromatographic system consists in the isolation of a daughter radioisotope from a parent radioisotope by the differences in affinity of the two radionuclides for the sorbent. In this case the germanium-68 has a high affinity for the sorbent whereas

gallium-68 is easily eluted. But, although the generator technology has been investigated for almost 50 years, the sorbents contained in the generator column usually display, during the elution of the gallium-68, fine particles on which traces of the long-lived parent radioisotope were adsorbed. Furthermore, because of the ageing of the material, the contamination can increase over time until the limit for the clinical use of the gallium-68 is reached. Our hypothesis was that a problem associated with the adsorbents used is the presence of fragile edges that could tend to flake off as a powder during elution of the desired daughter radionuclide.[11] This flaking could be one explanation of the presence in the eluate of the long-lived radioisotope which is an impediment for clinical application because it cannot be injected to patient and of the metal contamination which gives a competitive chelation reaction and consequently drastically reduce the radiochemical yield of [^{68}Ga]-radiotracers.

In view of this drawback, a novel ^{68}Ge/^{68}Ga generator was developed, specifically designed to guarantee minimal dissolution of the titania sorbent during gallium-68 elution, resulting in a low and stable germanium-68 breakthrough throughout its life-span. The production and the characterization of the smoothened particles of titanium dioxide were described and the performances of the ^{68}Ge/^{68}Ga generator centered on this adsorbent (elution profile, elution yield and germanium-68 breakthrough) were followed over time to ensure an optimal quality of gallium-68 for the radiolabeling of DOTA-peptides.

Experimental section

Matrix and generator development.

Matrix synthesis: Titanium tetrachloride and ammonium hydroxide were provided by Alpha Aesar (A470-500, USA) and Fisher Scientific (Optima brand, Canada) respectively. Titanium oxide was produced according to described procedure.[13] Briefly, after crystallization, drying and filtration of 10 mL of titanium tetrachloride, titania particles were sonicated in 10 to 15 mL of 0.1 M HCl for 2 h. Then, the material was dried in an open Teflon® bottle in a beaker covered with a watch glass in a furnace at approximately 150°C. The dried material was then transferred into a quartz dish, covered and baked at 500°C for 60 min. The baked material was then sieved using a 38 µm sieve for one min to remove fine particles and produce about 1 g of smoothened anatase titania (38-53 µm) which were analyzed by transmission electron microscopy (TEM) and X-ray diffraction (XRD).

Generator installation: Water (TraceSELECT® Ultra) was obtained from Sigma Aldrich. Hydrochloric acid (HCl, 0.1 M or 1.0 M) was prepared from water and 12 M HCl (Baseline®, Seastar, Canada). Two identical generators designed by Nordion Inc. (Ottawa, Canada) were assembled and loaded in the GIP Cyceron (Caen, France) with initial germanium-68 source ($^{68}GeCl_4$, ≈ 1.18 GBq) obtained in HCl (0.1 M) from iThemba-Labs (South Africa). Generators were composed of a quartz glass column packed with anatase adsorbent and inserted in a lead shielded container. Input/output connections were made with standard Teflon® tubing and connectors. After the germanium-68 source was adsorbed on the titanium oxide sorbent, the generator was washed with hydrochloric acid (0.1 M, 3 × 10 mL) and dried. Two successive elutions (0.1 M HCl, 5 mL) were realized at 24 h and 48 h after the loading. The eluates were measured in a Capintec CRC®-25R dose calibrator (Berthold) and decay-corrected at the end of the elution (EOE) to determine the initial elution yield of the generator, defined as the ratio between experimental and theoretical gallium-68 activities. Consecutively, the gallium-68 activity was measured over time to plot the experimental decay curves and determine the gallium-68 half-life. Then, more than two days after elution, the initial germanium-68 breakthrough was assessed by the detection of a 511 keV γ-ray using γ-ray spectrometry (Wizard^{2}® automatic gamma counter, Perkin Elmer). This measure (decay-corrected at EOE) was realized from an aliquot of the eluate (1 mL) normalized with a fixed standard (CS-6-14, Siemens medical solutions). Then, the metal contamination in eluates was checked by inductively coupled plasma mass spectrometry (ICP-MS, Elan DRC, Sciex instrument, Canada).

Generator characterization and follow-up.

Elution profiles: From an equilibrated generator, a fractionated elution was realized with HCl (0.1 M, from 1 to 5 mL) to determine the elution profiles of gallium-68 and germanium-68 respectively.

Gallium-68 recovery test: From an equilibrated generator, two elutions (5 mL, HCl 0.1 M), separated by a time interval varying from Δt = 30 min to 18 h, were realized. The activities contained in the second and in the third elutions were compared with the first elution in order to monitor the gallium-68 recovery over time.

Follow-up of the generator performances: The performances of the generator were evaluated for nine months. From an equilibrated system, one elution (5 mL, HCl 0.1 M) was realized every two weeks to determine the evolution of the ^{68}Ga-elution yield and of the ^{68}Ge/^{68}Ga ratio respectively. Once a month, in addition to this first elution, two other elutions (5 mL, HCl 0.1 M) were performed at Δt = 3h00 and Δt = 5h30 to establish the gallium-68 recovery monitoring.

Radiolabeling probes.

Materials: DOTA^{0}-(Tyr^{3}-Thr^{8})-octreotate (DOTATATE) and DOTA^{0}-1-NaI^{3}-octreotide (DOTANOC) were furnished from Bachem (Research quality) and ABX (Research quality) respectively. Acetone and ethanol (European Pharmacopeia), sodium acetate (trace metal basis), sodium hydroxide (7 M) and acetic acid (TraceSELECT® Ultra) were obtained from Sigma Aldrich. Acetate buffer (pH = 4) was prepared from acetic acid and sodium acetate solutions (0.2 M, 82/18, v/v). HCl (0.05 M)/acetone (2/98, v/v) mixture was realized weekly and stored at - 20°C. Automated processes for radiochemistry were developed on a PC-controlled radiopharmaceutical synthesis device based on a Modular-Lab concept (Eckert & Ziegler Eurotope). Strata™-XC cation exchange columns and tC18 Sep-Pak® cartridges were provided by Phenomenex and Waters respectively.

Automation with cation exchange column purification: Modular-Lab device, computing program and loading procedure were used as commercially available. Briefly, gallium-68 was recovered by elution with HCl (5 mL, 0.1 M). The eluate from the generator was concentrated on a Strata™-XC column and eluted with a solution of HCl (0.05 M) and acetone (2/98, v/v, 800 µL). Free

gallium-68 was introduced into a 10 mL reaction vial containing DOTATATE or DOTANOC (24 nmol) in acetate buffer (2 mL, pH = 4). Complexation was performed at 85°C for 7 min. The reaction vial was then diluted with water (3 mL) and the crude product was adsorbed on a Sep-Pak® tC18 light cartridge. The column was then washed with saline (5 mL). Elution with ethanol/water (50/50, v/v, 1 mL) and dilution with physiological saline (5 mL) gave radiochemically pure [^{68}Ga]-DOTATATE or [^{68}Ga]-DOTANOC (> 97%) in injectable solution. Such automated productions and associated quality control were realized monthly to establish a follow-up of the efficacy of the radiolabeling. Under these conditions, the resulting radiochemical yield (decay-corrected) was 80 ± 6% (n = 5 and n = 9 for generator 1 and 2 respectively).

Automation with fractionated elution: Modular-Lab device and computing program were modified from commercially available process to remove the Strata™-XC column. Gallium-68 was recovered by elution with HCl (1 mL, 0.1 M). The eluate from the generator was introduced into a 10 mL reaction vial containing the DOTATATE (24 nmol) in acetate buffer (1 mL) and sodium hydroxide (10 µL, 7 M) to obtain a mixture buffered at pH = 4. Complexation was performed at 85°C for 7 min and the formulation was realized as described above to afford radiochemically pure (> 97%) [^{68}Ga]-DOTATATE in injectable solution. The associated radiochemical yield (decay-corrected) was 90 ± 1% (n = 3 for generator 2).

Quality Control: Radiochemical purity was determined by analytical high-pressure liquid chromatography (HPLC). HPLC was performed with a L6200 intelligent pump and a L4250 UV-Vis detector at λ = 254 nm (Merck) coupled with a NaI radioactive detector (Saint Gobain Crystals) and the data were acquired and analyzed by a Galaxy Workstation software (Agilent Technologies). All HPLC analyses were conducted by injection of an aliquot of the final solution on C18 reverse phase µBondapak™ column (10 µm, 125 Å, 3.9 x 300 mm) provided by Waters. Isocratic elution technique was adopted and the flow rate was maintained at 1 mL/min. [^{68}Ga]-DOTATATE (t_R = 13.6 min) or [^{68}Ga]-DOTANOC (t_R = 13.7 min) were analyzed using aqueous mobile phase containing 25% or 30% acetonitrile respectively and 0.1% trifluoroacetic acid.

Then, after the radiochemically pure product was allowed to decay for more than two days, the germanium-68 breakthrough was assessed by γ-ray spectrometry as described previously.

Results and discussion

Matrix and generator development, characterization and follow-up.

In order to develop a robust sorbent, we developed smoothened particles removing the edges of the crude anatase. We supposed that such modification in the physical profile of the particles could significantly improve the performance of the sorbent in comparison with commercial generator matrix. To reach this aim, we first take care of the purity of the reagents and materials used for the preparation of titania. The amount of metal contaminants must be kept as low as possible to ensure optimal performances of the sorbent.

Then, we adopted a standard crystallization technique from titanium chloride to obtain crude anatase which structure was ensured by 500°C baking and checked by XRD. This crude product was sonicated in order to smooth the fragile edges initially present without denaturation of the crystal particles which adequate sizing was ensured by a sieving (Fig. 1).

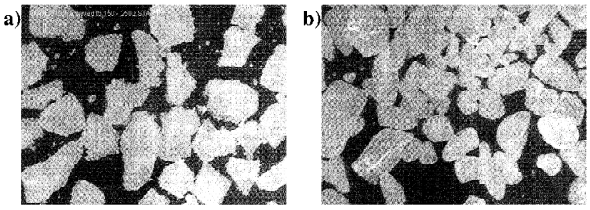

Fig. 1 Anatase electron micrograph (a) before sonication; (b) after treatment.

In the view of testing the potential of our sorbent to separate gallium-68 from germanium-68, we packed the treated titania in the quartz glass column. After the novel generator was installed and washed, its initial characteristics were evaluated. Firstly, gallium-68 identification was realized by half-life measurement ($T_{1/2}$ = 67.4 ± 0.5 min) which is in accordance with theoretical gallium-68 half-life ($T_{1/2}$ = 68 min) (see supporting information). Secondly, the elution profiles were studied. It is evident from the data that about 80% of the gallium-68 activity is contained in 1 mL of HCl (0.1 M) and that more than 95% of the gallium-68 can be eluted with a very small volume (2 mL) (Fig. 2a). These characteristics are similar to most of the described systems for which 1 mL contained 75 to 90% of the gallium-68 activity (Table 1). Concerning the germanium-68 breakthrough, a very low ^{68}Ge/^{68}Ga ratio was observed in 1 mL ($0.4.10^{-7}$). This ratio increased with the elution volume to reach $1.6.10^{-7}$ with 5 mL (Fig. 2b). So, two procedures can be considered for further investigations, either an elution with 1 mL of HCl (0.1 M) which permits about 80 % of the gallium-68 recovery with a reasonable volume and a low germanium-68 breakthrough or an elution with 5 mL of HCl (0.1 M) which maximizes the amount of gallium-68 eluted but in a larger volume.

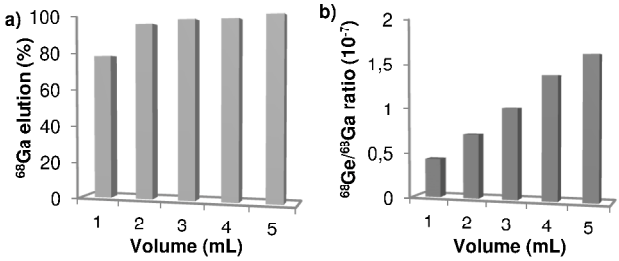

Fig. 2 Fractionated elution (a) ^{68}Ga elution profile; (b) ^{68}Ge/^{68}Ga ratio.

Then, we monitored the initial restoration rate of the gallium-68 after a first elution with 5 mL of HCl (0.1 M) in order to prove the ability of our system to generate gallium-68 quickly. From a first elution, the gallium-68 activity on the column will increase over time to the equilibrium between parent and daughter radioisotope decays as shown in Fig. 3.[18] Experimentally, no limitation for eluting the generator at least three times per day was observed, initially and during all the life of the generator, with a gallium-68 restoration of 85 ± 3% in the second elution at Δt = 3h00 and 82 ± 4% in the third elution at Δt = 5h30 (see

Table 1 Comparison between generator characteristics.

Generator (Column Material)	Fractionated elution	5 mL elution			
	Percentage of gallium-68 activity contained in 1 mL [b]	^{68}Ga elution yield (%)		^{68}Ge/^{68}Ga ratio ($\times 10^{-7}$)	
		Initial	Long term (days)	Initial	Long term (days)
EZAG, Germany, Obninsk (TiO_2)[a,14,15]	80	75	60 [c] (ND)	< 500	< 500 (300)
EZAG, Germany, IGG-100 (TiO_2) [a,14]	80	>65	>65 (ND) [c]	<3	500 (300)
iThemba LABS, South Africa (SnO_2) [a,14]	80	ND	75 (300)	200	n/a
ITG Germany, (Silica) [a,14]	75	>80	>80 (ND) [d]	< 500	n/a
Bhabha Atomic Research Centre, India, NanoCeria-PAN (Ce^{IV}) [16]	50	82 ± 5	82 ± 5 (210)	<100	< 100 (210)
Bhabha Atomic Research Centre, India, Nano-Zirconia (Zr^{IV}) [17]	> 90	>80	>80 (350)	<100	< 100 (350)
Nordion, Canada, and Cyceron, France (smoothened TiO_2)	80	65 ± 1	67 ± 5 (280) [c]	2.0 [e]	< 1.0 (280) [c, f] ≈ 100 (280) [g,h]

[a] commercial source, [b] based on 100% gallium-68 activity in 5 mL elution, [c] 200 elutions, [d] throughout shelf-life of 4-6 months, [e] at equilibrium, [f] undamaged generator 1, [g] 150 elutions, [h] damaged generator 2.

supporting information).

The next parameter studied to ensure the long time robustness of the generator is the estimation of its ageing over a period of 9 months. Three of the key signs of a degradation of the sorbent are the variation of the elution yield, the increase of the elution time induced by a partial plugging of the column tip, and the increase of contaminant amounts co-eluted with gallium-68. Experimentally, the fast elution (2 mL/min) during all of the study, evoked no plugging and guaranteed minimal decay losses during elution procedure. Then, the elution yield was calculated from the value of the germanium-68 source loaded on the generator column and the experimental gallium-68 amount eluted. This parameter is nearly constant (67 ± 5%) and supposed no degradation of the chromatographic properties of the sorbent during all of its shelf-life (see supporting information). When comparing to other published generators, the elution yield was one of the lowest but stable over time and comparable to IGG-100 (Table 1). Next, as our system was especially designed to guarantee a low amount of germanium-68 during gallium-68

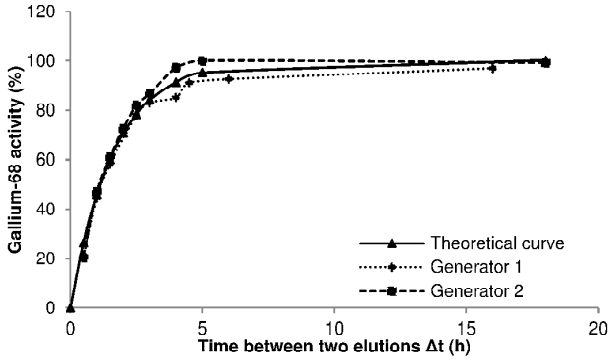

Fig. 3 Gallium-68 recovery over time.

elution, we focused its evaluation on the radionuclide purity of the eluates and, especially on the quantification of the long-lived parent radioisotope. Unfortunately, because of germanium-68 decay to gallium-68 solely by electron capture, this long-lived radioisotope could not be directly estimated. After more than two days of decaying, the long-lived contamination of the eluate is measured by γ-ray spectrometry of the residual gallium-68 activity (511 keV γ-emission) in secular equilibrium with the germanium-68 breakthrough. Experimentally, the ^{68}Ge/^{68}Ga ratio (< $2.0.10^{-7}$) was constant during all the study, about 20 fold less than the values observed using the same generator that included untreated titania,[13] and was clearly lower than the recommended one for a clinical use (^{68}Ge/^{68}Ga ratio < 10^{-5}).[19] This characteristic proved that the radionuclidic purity of the gallium-68 is suitable for radiopharmaceutical development. Moreover, as the germanium-68 contamination is associated to the release of sorbent particles, we supposed no degradation of the titanium oxide, i.e. less than 1 ppm of titanium per milliliter of eluate as determined initially by ICP-MS. So, as a result of the use of sonicated particles, the performances of the ^{68}Ge/^{68}Ga generator were improved with the increase of the robustness of the crystal sorbent. A noticeable difference with the other generators is that this novel system did not show an ageing with a ^{68}Ge/^{68}Ga ratio lower than $1.0.10^{-7}$ after 9 months of a regular use (Table 1).

But, what happens if the generator is not eluted regularly? After a short time without elution of the ^{68}Ge/^{68}Ga generator (from 2 to 14 days) we observed in the first elution a spike in ^{68}Ge/^{68}Ga ratio of ≈ $40.0.10^{-7}$ which easily fell at the second elution realized 24 h after the first one (< $5.0.10^{-7}$) (data not shown). This phenomenon could be attributed to the accumulation of radiolysis degradation of the titanium oxide resulting in a higher co-elution of fine titania particles and gallium-68 in the first elution.[13] Most of the time, in a clinical context, this washing elution is discarded to ensure no germanium-68 contamination in the products and consequently has negligible impact on routine use of the generator in a hospital. But, we supposed that if it is stopped for a long time, the radiolysis can drastically damage the sorbent. Experimentally, the results showed a breaking point for a period without using the generator comprised between 2 and 2.5 months (Fig. 4). Explicitly, after a long period without use, a strong spike in ^{68}Ge/^{68}Ga ratio was observed (≈ $80.0.10^{-7}$) but whereas it easily decreased to the initial level of $2.0.10^{-7}$ when the generator was stopped for 2 months, this value was maintained superior to $10.0.10^{-7}$ after a stop of 2.5 months.

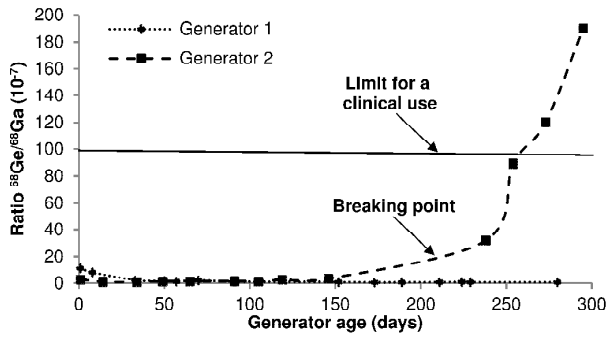

Fig. 4 Germanium-68 breakthrough follow-up: generator 1 stopped 2 months (day 90 - 152); generator 2 stopped 2.5 months (day 159 - 237).

After damaging, its performances were irrevocably affected with a continuous increase of the germanium-68 breakthrough, and the clinical limit was overtaken after only 15 elutions. Regarding these results, we recommend that a long time break should not exceed 2 months.

To conclude, according to germanium-68 breakthrough, this generator gave the lowest contamination compared to previously described generators, based on SnO_2 or TiO_2 columns where degrading performances were observed over time (Table 1).[20-22] This high stability can easily be attributed to the increased robustness of smoothed particles.

Radiolabeling probes.

Most of the time, post-elution purification by ion exchange column (IEX) is used to promote higher quality of gallium-68 in a smaller volume of solvent. This technique allows the elimination of most of the metallic impurities which can interfere in the complexation step such as the stable zinc ions (from the decay of the gallium-68) or iron.[9,23] Even if ICP-MS of gallium-68 eluates showed initially no metal contamination (less than 1 ppm per milliliter of titanium and zinc and no relevant values for other metals during elution of gallium-68), IEX columns can reduce germanium-68 breakthrough. Tests realized with Strata^{TM}-XC columns showed that the $^{68}Ge/^{68}Ga$ ratio decreased from $1.5.10^{-7}$ to an undetectable value ($< 0.1.10^{-7}$). From this result, an automated production of DOTA-peptide on Modular-Lab device with IEX pre-purification of gallium-68 was realized in 20 min (see supporting information). Such procedure was realized monthly during all the life of the generator to follow the ability of the gallium-68 to label DOTATATE or DOTANOC with efficient and reproducible gallium-68 incorporation in the molecules (96 ± 4%) and radiochemical yield (80 ± 6%) (see supporting information). The excellent performances of this method ensure potential production of germanium-68-free ($< 0.1.10^{-7}$) DOTA-peptides in a clinical context.

Last step of the study was to determine the ability of the crude gallium-68 to produce DOTA-peptides. According to the elution profile of the generator, we can elute it with 1 mL of HCl (0.1 M) in order to keep the highest gallium-68 concentration with limited germanium-68 contamination. We realized this study beyond the damaged generator shelf-life which guaranteed the presence of germanium-68 ($^{68}Ge/^{68}Ga$ ratio $\approx 1.6.10^{-4}$) and metal ion contaminations. The complete procedure of the fractionated elution was conducted in 18 min and we observed that the incorporation of gallium-68 was similar (> 95%) to the previous procedure using a Strata^{TM}-XC column, even if we used the first elution after a short period corresponding to a week-end without using the generator. These results suggest that the metal contamination and more precisely the amount of zinc or titanium ions contained in the gallium-68 eluates was kept so low that it did not interfere in the complexation reaction. Nevertheless, we noticed higher radiochemical yields for fractionated elution method (90 ± 1%) compared with Strata^{TM}-XC protocol (80 ± 6%) essentially because of the absence of pre-purification step with IEX columns which induced some losses. Although the two approaches exhibit similar results and germanium-68-free products, a pre-purification with an IEX cartridge guarantees a safe use of gallium-68 with total elimination of the long-lived parent radioisotope during Strata^{TM}-XC purification and so, is more relevant for the clinical use of such radiopharmaceuticals.

Conclusions

Our study highlighted the characteristics of the smoothened particle-based generator which afforded, during all the study, constant elution yields, a high quality gallium-68 and the ability to perform at least three elutions a day. Analyses of the eluates indicated that the $^{68}Ge/^{68}Ga$ ratio still remained lower than the limit fixed for a clinical use, even after 9 months of use, if the generator was not stopped for more than 2 months.

The ability to use fractionated elution for radiolabeling supposed that the metal impurity accumulation was always kept very low even when the generator was old. Moreover, the follow-up of the radiolabeling by cation-exchange purification confirmed the high reliability of the generator and the ability of the process to furnish high quality of DOTA-peptides in a short-time synthesis.

Notes and references

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† Electronic Supplementary Information (ESI) available: Gallium-68 half-life determination (Fig. S1), gallium-68 recovery at Δt = 3h00 and 5h30 in function of generator age (Table S1), gallium-68 elution yield throughout generator life-span (Fig. S2), illustration of Modular-Lab device (Fig. S3), reagents and materials for the device (Table S2), analytical HPLC analysis of [^{68}Ga]-DOTATATE and [^{68}Ga]-DOTANOC (Fig. S4), [^{68}Ga]-DOTATATE radiolabeling for generator 1 and 2 respectively (Table S3). See DOI: 10.1039/b000000x/

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