Comprehensive Quality Control of the ITG Ge-68/Ga-68 Generator and Synthesis of Ga-68 DOTATOC and Ga-68 PSMA-HBED-CC for Clinical Imaging.

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Abstract

Objectives A GMP Ge-68/Ga-68 generator that utilizes modified Dodecyl-3,4,5-trihydroxybenzoate hydrophobically bound to a Octadecyl silica resin (C-18) as an adsorbent has been developed that allows for very dilute HCl (0.05 N) to efficiently elute metal impurity free $^{68}$Ga$^{3+}$ ready for peptide labeling. We characterized the performance of this generator system over a year in conjunction with the production of $^{68}$Ga labeled DOTATOC and PSMA-HBED-CC intended for clinical studies and established protocols for batch release.

Methods A 2040 MBq self-shielded ITG $^{68}$Ge/$^{68}$Ga generator provided metal-free $^{68}$GaCl$_3$ ready for peptide labeling in the iQS Fluidic Labeling Module following elution with 4 mL of 0.05N HCl. The compact system was readily housed in a laminar flow cabinet allowing an ISO class-5 environment. $^{68}$Ga labeling of peptides using GMP kits was performed in 15-20 min and the total production time was 45-50 min. Batch release quality control specifications were established to meet IND submission and IRB approval standards.

Results Over a period of 12 months, $^{68}$Ga elution yields from the generator averaged 80% (range 72.0%-95.1%) and $^{68}$Ge breakthrough was <0.006% initially decreasing with time to 0.001% (expressed as % of $^{68}$Ge activity present in the generator at the time of elution), a unique characteristic of this generator. The radiochemical purity of both $^{68}$Ga-DOTATOC and $^{68}$Ga-PSMA-HBED-CC determined by HPLC analysis was >98% with a minimum specific activity of 12.6 GBq/µmole and 42 GBq/µmole respectively. The radionuclidic ($^{68}$Ge) impurity was ≤0.00001% (under the detection limit). Final sterile, pyrogen-free formulation was provided in physiological saline with 5-7% ethanol.

Conclusions The GMP certified ITG $^{68}$Ge/$^{68}$Ga generator system was studied for a year. The generator system is contained within the iQS Fluidic Labeling Module and it is compact, self-shielded and easy to operate using simple manual techniques. The system provides radiolabeled peptides with high (>98%) radiochemical purity and greater than 80% radiochemical yield. The $^{68}$Ge levels in the final drug products were under the detection limits at all times. $^{68}$Ga-DOTATOC and $^{68}$Ga-PSMA-HBED-CC investigational radiopharmaceuticals are currently being studied clinically under INDs submitted to the U.S. FDA.

Key words: Ga-68 generator, $^{68}$Ga-PSMA-HBED-CC, $^{68}$Ga-DOTATOC, quality control


**Introduction**

With the broad success of \(^{18}\text{F}-\text{FDG}\) it is hard to imagine that Gallium-68 (\(^{68}\text{Ga}\)) was the first short lived, high specific activity positron emitter used for clinical investigation. \(^{68}\text{Ga}\)-EDTA was used for brain tumor annihiscopy (1), a coincidence based detection system used long before the advent of positron emission tomography (PET) cameras. \(^{68}\text{Ga}\) use for clinical applications was only preceded by the long-lived \(^{74}\text{As}\) (17.5 d) and the carrier added \(^{64}\text{Cu}\) (12.8 h, produced as \(^{64}\text{Cu}(n,γ)^{64}\text{Cu}\)) (2). This first attempt of producing \(^{68}\text{Ga}\) (and specifically \(^{68}\text{Ga}\)-EDTA) was based in a liquid-liquid extraction, evidently not the most practical procedure (2). Follow up was provided by Greene and Tucker in 1961, producing the first adsorbent-based \(^{68}\text{Ge}/^{68}\text{Ga}\) generator, using a neutral alumina bed to retain the \(^{68}\text{Ge}\) while eluting the \(^{68}\text{Ga}\) as a 0.005 M EDTA complex in 25 ml solution (pH=7) (3). While an improvement over the solvent extraction system, the radionuclide was eluted in a large volume necessitating pre-concentration before use. The elution volume was reduced in a subsequent design by Yano and Anger in 1964, optimizing the original Greene and Tucker generator while eluting the \(^{68}\text{Ga}\) generator as \(^{68}\text{Ga}\)-EDTA (4). In some ways it can be said that the \(^{68}\text{Ge}/^{68}\text{Ga}\) generator is as old as its SPECT analogue \(^{99}\text{Mo}/^{99m}\text{Tc}\) (5).

Despite the early endeavors in \(^{68}\text{Ge}/^{68}\text{Ga}\) generator production, the surge faded because of the lack of a cationic gallium elution system that would allow for diverse drug development and the absence of a clinically viable positron imaging system. At the same time the advent of the Anger Camera in the 1960s (6) together with the reliable \(^{99}\text{Mo}/^{99m}\text{Tc}\) generator system (5) jumpstarted the use of \(^{99m}\text{Tc}\) in nuclear imaging, increasing to this day. The invention of the first Positron Emission Tomography (PET) systems in the early 1970s combined with the successful labeling of glucose as \(^{18}\text{F}-\text{Fluorodeoxyglucose}\) (\(^{18}\text{F}-\text{FDG}\)) by Al Wolf and Joanna Fowler at Brookhaven National laboratories in 1978 drew attention further away from \(^{68}\text{Ga}\) (7).

The first reliable, durable, commercially available \(^{68}\text{Ge}/^{68}\text{Ga}\) generator was produced by New England Nuclear and it was based on a β-SnO\(_2\) inorganic separation resin matrix, eluting ionic gallium and first described by Loch in 1980 (8). It was followed nearly 20 years later by the Obinsk \(^{68}\text{Ge}/^{68}\text{Ga}\) generator (Russia) and it conveniently coincided with the surge of PET cameras for \(^{18}\text{F}-\text{FDG}\) metabolic imaging in the early 2000s (9). The Obinsk generator delivered cationic gallium in 5 ml 0.1 N HCl, which could be easily buffered for chelation (9). The Obink’s technology was further developed by Eckert and Ziegler into the first Chemical Grade \(^{68}\text{Ge}/^{68}\text{Ga}\) generator (IGG100), which recently received marketing authorization in the EU/EEA countries. This generator is based on a TiO\(_2\) matrix, which could potentially introduce metallic competitors during \(^{68}\text{Ga}\) chelation. Some pre-purification of the \(^{68}\text{Ga}\) is necessary before labeling when high specific activity is required (10). The IGG100 specification sheet assures 65% \(^{68}\text{Ga}\) elution yield and a \(^{68}\text{Ge}\) breakthrough of 0.00003 % when new to 0.001 % after 200 elutions (expressed as % of \(^{68}\text{Ge}\) activity present in the generator at the time of elution).

The iThemba Labs \(^{68}\text{Ge}/^{68}\text{Ga}\) generator was also introduced into the market in the 2000s and it is an improved version of the one originally sold in the 1980s by New England Nuclear, also based in a β-SnO\(_2\) inorganic separation resin (8). Similarly to the IGG-100 (TiO\(_2\) based) the \(^{68}\text{Ge}\) breakthrough and minor metallic impurities (Zn, Fe, Sn, Ti, Cu and Al) represent a potential problem because they can compete with \(^{68}\text{Ga}\) during complex formation (11,12). Stability studies of this generator showed 0.003% of \(^{68}\text{Ge}\) in
the elution, increasing to 0.08% after 100 days (13). $^{68}$Ge did not pose a patient risk because it was completely eliminated after the DOTA precursor labeling by reverse phase Sep-Pak purification (0-11 Bq in the final composition). However, for practical purposes $^{68}$Ge should be kept below 0.01%, so that high volumes of long-lived liquid waste is not generated. The reported DOTA precursor labeling was also lower (60-90% in 15 minutes at 95°C) than those obtained when using the TiO$_2$ based IGG-100 (>95% in 10-15 minutes at 95°C) (11).

In both examples described above, pre-purification of the eluent is needed to obtain high $^{68}$Ga labeling yields (>90%). A metal free GMP generator was recently introduced into the market by ITG: The ITG $^{68}$Ge/$^{68}$Ga Generator, which is based on a modified Dodecyl-3,4,5-trihydroxybenzoate hydrophobically bounded to an Octadecyl modified silica resin (C-18 resin) (Fig 1). The generator is eluted with 0.05 M HCl and can be easily buffered for labeling. No pre-purification of $^{68}$Ga is needed due to the metal free column matrix, however it is recommended to elute 24 hours before labeling to eliminate excess $^{68}$Zn from $^{68}$Ga decay.

Introducing an organic chelating group to retain the parent nuclide, $^{68}$Ge, in a long-lived generator poses potential radiolysis issues, thus, the generator was exhaustively tested. This paper describes the characteristics of an ITG $^{68}$Ge/$^{68}$Ga Generator for a period of one year in routine use.

**Materials and Methods:**

All reagents were at least metal-trace grade. The ITG $^{68}$Ge/$^{68}$Ga Generator (GMP) was obtained from Isotopen Technologies Garching GmbH (ITG GmbH). Hydrochloric acid (Sigma-Aldrich, USA) 99.999% trace metals basis (100 ml) was used to elute the ITG $^{68}$Ge/$^{68}$Ga Generator. MilliQ (18.2 MΩ) water was obtained from a Direct Q$^+$ system (Millipore, USA). DOTATOC (GMP) and DKFZ-PSMA-11 (GMP) were obtained from ABX pharmaceuticals (Radeberg, Germany). Ultrapure anhydrous sodium acetate (NaOAc) was used to buffer the generator elution (Sigma-Aldrich, USA). Labeling kits were obtained directly from ITG GmbH (Munich, Germany) as well as fluidic cassettes.

The $^{68}$Ge/$^{68}$Ga generator was eluted with 4 mL 0.05 M HCl for labeling. For testing, the generator was eluted with 6 ml 0.05M HCl collecting 1 ml fractions to determine $^{68}$Ga activity (CRC-15 PET, Capintec, USA), elution yield and profile. The dose calibrator setting was verified with a $^{68}$Ge/$^{68}$Ga NIST traceable volumetric source. Fractions were saved for over 24 hours and tested for $^{68}$Ge content (Wallac Wizard 3” 1480, Perkin-Elmer, USA). A NIST traceable $^{68}$Ge/$^{68}$Ga 12x75 mm (1 ml bottom) source containing 4.54 kBq (122.72 nCi, Bench/Mark, USA) at calibration (07/25/2014) was used to determine well counter detection efficiency and quantify the total $^{68}$Ge activity in the eluent. The dose calibrator accuracy was tested using another NIST traceable volumetric (syringe and vial geometry) containing 20.017 MBq (0.541 mCi, Bench/Mark) at the time of calibration (07/25/2014).

The metallic content of the generator eluent was determined by ICP-MS (7700x ICP-MS, Agilent Technologies). Metallic impurities might interfere with Ga-68 during the labeling process and thus lower the radiochemical yield. Trace metals of interest were Fe, Ni, Cu, Zn, Nb and Pb. To determine the content of these metals, calibration standards containing these elements in the following concentration were prepared to obtain a calibration curve: 10 µg/L, 20 µg/L, 30 µg/L, 40 µg/L, 50 µg/L and 100 µg/L.
The generator eluent was diluted by a factor of 10 with 0.05 M HCl. The 0.05 M HCl was further measured as the blank sample.

Labeling was performed using the ITG’s iQS ⁶⁸Ga Fluidic Labeling Module and the ITG ⁶⁸Ga Peptide Radiolabeling KIT (ITG, Germany) at 95°C for 5 minutes for both ⁶⁸Ga-DOTATOC and ⁶⁸Ga-PSMA-HBED-CC (14). For ⁶⁸Ga-DOTATOC labeling 100 µl of a 250 µg/ml solution (25 µg) of DOTATOC (GMP) was predissolved in 1 ml buffer solution (part of the labeling kit), while only 5 µl of a 1 mg/ml PSMA-HBED-CC (5 µg) solution was used in similar fashion. The labeled molecule was purified in-line with the labeling module using a reverse phase C-18 Sep-Pak Lite (Waters, USA) and filtered through a Cathivex®-GV 0.22 µm filter (Merck Millipore, USA) for sterilization. Radiochemical purity was assessed by HPLC using a Waters NovaPak C18 4.6 x 150 mm column in a Varian binary solvent dual UV system (Agilent, USA) and radiodetector (Eckert & Ziegler, Germany). All preparations were compared to known stable Ga-DOTATOC and Ga-PSMA-HBED-CC standards (ABX, Germany). Radionuclidic purity was evaluated using a multichannel analyzer (Canberra, USA) and in a high efficiency, low background well counter after ⁶⁸Ga decay (> 24 hours after labeling). Sterility was tested by aliquoting 0.1 ml of the drug product into trypticase soy broth and thioglycollate medium and incubated for 15 days to assess bacterial growth. Endotoxin content was measured using an automated Endosafe system (Charles Rivers, USA). Filter integrity (0.22 µm filter used for sterilization) was tested at 50 psi with a bubble point method. Ethanol content of the final product was confirmed to be under the 10% limit using Gas Chromatography (SRI Instruments, USA).

Results and Discussion:

The GMP ITG ⁶⁸Ge/⁶⁸Ga Generator contained 2040 MBq (55.14 mCi) ⁶⁸Ge at calibration date. Elution yield of the ITG ⁶⁸Ge/⁶⁸Ga Generator during a one year period was an average of 80% and never went below 70%. The highest yield obtained was 95.1% at day 26th post-calibration, while the lowest obtained was 72.0% on day 328th post-calibration. The elution yield decreased with a linear trend (R²=0.957, Fig 2) over the period studied. This behavior was also described during the characterization of the IGG-100 and the iThemba labs ⁶⁸Ge/⁶⁸Ga generators. In the case of the IGG-100 the decrease was attributed to rearrangements that take place in the matrix where suspension/precipitation of the TiO₂ resin forms layers that cover the adsorbed ⁶⁸Ge and once it decays the resulting ⁶⁸Ga is no longer accessible for elution because of physical trapping. No feasible theory was provided for this effect during the iThemba Labs generator characterization but it can be safely assumed that a similar process is very likely to occur as well for both the iThemba and the ITG generator.

Most of the ⁶⁸Ga eluted activity (>95%) was eluted within the first 3 ml of 0.05M HCl elution within the first 200 days of use. However the elution profile changed (Fig 2, elution profiles) after this period, eluting only 85% of the total eluted activity in the first 3 ml and 10-12% in the last ml. In contrast, the same ⁶⁸Ge concentration was found in every fraction, making the total eluted activity dependent on the total elution volume. The initial eluted ⁶⁸Ge activity was just under 120 kBq (=3 µCi), or 0.006% of the ⁶⁸Ge activity present in the generator at the time of elution (Fig 3).
In contrast with previous results obtained while testing the IGG-100 and the IThemba Labs generators, the amounts of $^{68}$Ge in the eluent decrease to 10.4 kBq (0.3 µCi) after 340 days for the ITG Generator. The decrease is not only observed for the absolute activity, but also in the $^{68}$Ge percentage (down to 0.0012%). This characteristic is unique for the ITG generator and could be attributed to the overall decrease in radiolysis and activity concentration with the decrease of total activity, nevertheless no controlled experiment have been design to date to test these conditions. In any case there was no evidence of significant radiolysis since no UV absorbent chemical impurities were found in any of the chromatograms (given that trihydroxybenzoate will absorb in the same wavelengths used for the drug QC, 220 and 280 nm) performed during the quality control. The metallic content of the eluate was found to be extremely low and is given in table 1.

Radiolabeling of $^{68}$Ga-DOTATOC and $^{68}$Ga-PSMA-HBED-CC was performed using the same standard operating procedure (See Supplementary Materials). The HBED chelate is capable of complexing gallium at room temperature (25ºC), however the labeling was performed at 95ºC for 5 minutes and the higher temperature provided consistency and better mixing, and did not diminish the radiochemical purity of the final product. Having the same procedure and the same labeling set up for both imaging agents ($^{68}$Ga-DOTATOC and $^{68}$Ga-PSMA-HBED-CC) of clinical interest simplifies the overall operation. The contents of the product vial, waste vial, C-18 Sep-Pack and 0.22 µm filter were measured in a dose calibrator to assess labeling yield and efficiency of trapping/elution (Fig 4).

Higher radiochemical yield and smaller variability was found for the labeling of $^{68}$Ga-PSMA-HBED-CC (91.3±1.3 %) compared to that of $^{68}$Ga-DOTATOC (84.1±10.1%). Nevertheless, the main variability was found during the elution from the C-18 Sep-Pack, while the activity in the waste vial (presumably free $^{68}$Ga) was under 5% (1.7±0.6 and 4.1±2.5% respectively). Around 5% percent of the produced $^{68}$Ga-PSMA-HBED-CC activity (4.5±1.2%) was retained in the filter while only 2.5±1.3% of the labeled $^{68}$Ga-DOTATOC did. These results evidence the high $^{68}$Ga labeling yields (≥95%) obtained in short labeling times (5 min) while using the ITG $^{68}$Ge/$^{68}$Ga generator eluate, presumably because of the absence of metal impurities in the eluent. Invariably the eluted $^{68}$Ge radionuclidic impurity was successfully eliminated during the C-18 purification stage, since it was only found in the waste vial while the product vial contained amount bellow the detection limit (0.00001% of the $^{68}$Ge activity present at the time of elution). High product radiochemical purity (>98%) was found for all preparations (See Supplementary Materials) quantified by radio-HPLC. The release criteria for $^{68}$Ga-DOTATOC and $^{68}$Ga-PSMA-HBED-CC we established has been established for routine production using the methods described above (Table 2).

**Conclusions**

The GMP certified ITG $^{68}$Ge/$^{68}$Ga Generator system was studied for a year. An average 80% $^{68}$Ga elution yield was found, and always over 70% yield. The generator system is contained within the iQS-Fluidic Labeling Module and it is compact, self-shielded and easy to operate using simple manual techniques. The system provides radiolabeled peptides with high (>98%) radiochemical purity and greater than 80% non-corrected radiochemical yield. The amounts of $^{68}$Ge present in the generator elution decreases with time of use, a unique characteristic of this generator. The $^{68}$Ge levels in the drug products were under the detection limits at all times.
Currently at our institution, clinical studies using these radiopharmaceuticals have been initiated for imaging neuroendocrine tumors ($^{68}$Ga-DOTATOC) and prostate cancer ($^{68}$Ga-PSMA-HBED-CC) under separate INDs submitted to the U.S. FDA. The institutional review board of our institution has approved these studies and all subjects have signed a written informed consent. The ability to successfully prepare high purity pharmaceutically acceptable injectable solutions of $^{68}$Ga-DOTATOC and $^{68}$Ga-PSMA-HBED-CC on a routine basis has facilitated the introduction of these important imaging agents into the clinic.
References:

Figure 1. Active $^{68}$Ge trapping group in the ITG $^{68}$Ge/$^{68}$Ga generator.
Figure 2. ITG $^{68}$Ge/$^{68}$Ga Generator long term elution yield (A) (linear fit provided for reference) and elution profile study (365 days) (B).
Figure 3. ITG generator’s $^{68}$Ge breakthrough as neat eluted activity (A) and % of eluted germanium with respect to the total $^{68}$Ge activity present at the time of elution (B). Linear fit provided for reference.
Fig 4. Percent of activity measured of A: $^{68}$Ga-DOTATOC and $^{68}$Ga-PSMA-HBED-CC in product vial, waste vial, C-18 Sep-Pak and 0.22 µm filter; and B: $^{68}$Ge in product and waste vial after 24 hours (as percent of $^{68}$Ge activity in the generator at time of elution).
Table 1. Concentration of the metallic impurities of the ITG Ge-68/Ga-68 Generator in 4 mL of the eluate at the time of the first elution (1850 MBq of $^{68}$Ga).

<table>
<thead>
<tr>
<th>Trace Metal</th>
<th>ITG Ge-68/Ga-68 Silica Based Generator</th>
<th>Obninsk Ge-68/Ga-68 TiO$_2$ Based Generator [11]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ppm (µg/ml)</td>
<td>ppm (µg/ml)</td>
</tr>
<tr>
<td>Fe</td>
<td>0.146</td>
<td>2,100±1,300</td>
</tr>
<tr>
<td>Ni</td>
<td>0.006</td>
<td>0.254±0.124</td>
</tr>
<tr>
<td>Cu</td>
<td>≤ 0.001</td>
<td>0.014±0.006</td>
</tr>
<tr>
<td>Zn</td>
<td>0.030</td>
<td>5.050±0.147</td>
</tr>
<tr>
<td>Nb</td>
<td>≤ 0.001</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Pb</td>
<td>0.016</td>
<td>0.008±0.005</td>
</tr>
</tbody>
</table>
Table 2. Release Criteria for $^{68}$Ga-DOTATOC and $^{68}$Ga-PSMA-HBED-CC

<table>
<thead>
<tr>
<th>TEST</th>
<th>$^{68}$Ga-DOTATOC</th>
<th>$^{68}$Ga-PSMA-HBED-CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Colorless, no particles</td>
<td>Colorless, no particles</td>
</tr>
<tr>
<td>Radionuclidian Identity</td>
<td>62-74 min</td>
<td>62-74 min</td>
</tr>
<tr>
<td>Radionuclidian Purity</td>
<td>99.5% 511 KeV</td>
<td>99.5% 511 KeV</td>
</tr>
<tr>
<td>Radiochemical Identity</td>
<td>RT = 7.5 ± 0.7 min</td>
<td>RT = 7.1 ± 0.7 min</td>
</tr>
<tr>
<td>Radiochemical Purity</td>
<td>≥96%</td>
<td>≥96%</td>
</tr>
<tr>
<td>Chemical Purity</td>
<td>≥90%</td>
<td>≥90%</td>
</tr>
<tr>
<td>Assay (mCi/ml)</td>
<td>1.0 - 8.0</td>
<td>1.0 - 8.0</td>
</tr>
<tr>
<td>Specific Activity (mCi/μmol)</td>
<td>340-2730</td>
<td>340-2730</td>
</tr>
<tr>
<td>$^{68}$Ge Impurity (@ 24h)</td>
<td>≤0.001%</td>
<td>≤0.001%</td>
</tr>
<tr>
<td>pH</td>
<td>4.0 - 8.0</td>
<td>4.0 - 8.0</td>
</tr>
<tr>
<td>Filter Bubble Test ($P_t$)</td>
<td>$P_t$ ≥ 50 psi</td>
<td>$P_t$ ≥ 50 psi</td>
</tr>
<tr>
<td>LAL Test</td>
<td>&lt; 29 EU/ml</td>
<td>&lt; 29 EU/ml</td>
</tr>
</tbody>
</table>
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