

Installation and Optimization of ^{68}Ga Synthesis Module for Clinical Use: An Institutional Experience

Abstract

Introduction: With advent of gallium-labeling somatostatin analogs and its evaluation under positron emission tomography-computed tomography, there has been a tremendous surge in its application. Gallium 68 can be made available either from onsite cyclotron production or in the form of ready-to-use $^{68}\text{Ge}/^{68}\text{Ga}$ generators. Wherein setting up and running of cyclotron amounts to huge investment and dedicated team, the $^{68}\text{Ge}/^{68}\text{Ga}$ generator has proved to be a better option and viable project. Moreover, due to long half-life of ^{68}Ge , i.e. 271 days, it enables the usage of generator for several months. The preparation of gallium-labeled peptides is much simpler in comparison to ^{18}F radiochemistry, but the radiation exposure has always been an area of concern owing to high-energy annihilation photon of 511 keV. **Materials and Methods:** In this study, we share our experience of self-installation of $^{68}\text{Ge}/^{68}\text{Ga}$ generator during lockdown and the various steps involved in installation of fully automated peptide-labeling system in customized mini hot cell module, synthesis steps, and quality control steps of gallium-based radiopharmaceutical. **Results:** The installation was successfully completed with online assistance during the pandemic situation. The average elution yield met company specification (>80%), and ^{68}Ga -labeled peptides were prepared with high radiochemical purity (>95%). The overall exposure in single batch of production and quality control never exceeded 3 μSv as shielding was well-taken care of with customized mini hot cell. **Conclusion:** With the described experience and validation process, one can easily think of making an installation at his/her center and cater to the needs of society with a new radiopharmaceutical.

Keywords: ^{68}Ga prostate-specific membrane antigen-11, mini hot cell, positron emission tomography-computed tomography, quality control

Introduction

Gallium-68-based radiopharmaceuticals have been established for cancer imaging worldwide. Gallium is available in the form of $^{68}\text{Ge}/^{68}\text{Ga}$ generator and due to long half-life of ^{68}Ge , i.e. 271 days; it enables the usage of the generator for several months. Long shelf-life of generator makes it easily available in any part of the world.^[1] The availability of ^{68}Ga elute at any time and ease of ^{68}Ga -based radiopharmaceutical synthesis gives ^{68}Ga radiopharmaceuticals significant edge over the ^{18}F -based radiopharmaceuticals, which is only available from cyclotron.^[2] The few most important aspects of development of ^{68}Ga radiopharmaceuticals are the versatility of ^{68}Ga chemistry, short half-life of 67.7 min, and development of small tumor-affine peptides.^[3] Notably, the development of targeted somatostatin receptor peptides, i.e., DOTA-TOC,

NOC, and TATE, is one of the major breakthroughs in the development of ^{68}Ga radiopharmaceuticals.^[4] The advent of small peptides and short half-life of ^{68}Ga enables the rapid pharmacokinetics resulting in low radiation burden to the patient.^[5] Among the various peptides available, DOTA peptides and prostate-specific membrane antigen (PSMA)-11 had gained wide popularity. On the one hand, ^{68}Ga DOTA octreotide derivatives were the breakthrough vector molecules and were fundamental for development of present-day ^{68}Ga radiopharmacy and the $^{68}\text{Ge}/^{68}\text{Ga}$ generator;^[6,7] on the other hand, ^{68}Ga -labeled PSMA-11 proved to have a significant impact in management of prostate cancer patients.^[8-10] Although the preparation of gallium-labeled peptides is much simpler in comparison to ^{18}F radiochemistry, the radiation exposure has always been an area of concern owing to high-energy positron of 1.92 MeV with a mean energy of 0.89 MeV and annihilation

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photon of 511 keV. Hence, mini hot cell becomes important to reduce radiation burden to professionals. Our hospital is a dedicated cancer hospital and situated in a rural area of western state of India, i.e. Gujarat. We have dedicated nuclear medicine department with one positron emission tomography/computed tomography (PET/CT), one single-photon emission computerized tomography/CT, and high-dose therapy ward. Being a cancer hospital, we were also encouraged by our administration to have ^{68}Ga chemistry laboratory in our department. We placed an order for mini hot cell, $^{68}\text{Ge}/^{68}\text{Ga}$ generator, ^{68}Ga synthesis module, and consumables, which was delivered in the 2nd week of March 2020 amid the pandemic situation of COVID-19. The whole world had almost come to a halt, and the health-care services for oncological patients were also affected, with no exception to nuclear medicine department. Because of shutdown of all transport services, there was a halt to production and supply of the most commonly used ^{18}F -labeled radiopharmaceutical and ^{99}Mo - $^{99\text{m}}\text{Tc}$ generators. On top of this, we were facing a challenge to installation of $^{68}\text{Ge}/^{68}\text{Ga}$ generator with automated synthesis module which had reached just few days before announcement of lockdown. With the passage of each day, the uncertainty of its functioning was piling on, and the buildup of ^{68}Ge along with impurities such as Zn (II) from decay of ^{68}Ga was bound to increase.^[11] The company person who had to come for installation was stuck up due to transportation lockdown, and we were left with no way out. We thought of taking the tasks of installation by ourselves with online assistance from supplier, keeping the instruction manual by our side to come out of this phase of lockdown. We also decided to establish the synthesis and quality control procedure to start operation in our department. In the present study, we have shown the various steps involved in installation of a fully automated peptide-labeling system in a mini hot cell module, synthesis steps, and the quality control step of the gallium-based radiopharmaceutical.

Materials and Methods

Installation of equipment

Installation process was executed locally by us under the online supervision of the installation engineer. We sequentially installed all the components of synthesis module required for routine synthesis of ^{68}Ga radiopharmaceutical for clinical operations.

Installation of mini hot cell

The mini hot cell was specially customized to meet our requirements of shielding. The cell is comprised of three compartments [Figure 1]. The middle compartment shown in Figure 1 was the one which is designed to install the synthesis module with generator, and this compartment has shielding of 45 mm of lead all around. It has power supply required to run the automated synthesis module. We



Figure 1: Hot cell to house ^{68}Ga iQS-TS Synthesis module, ITG, Germany

got this hot cell installed with the help of our local support staff and electrical engineering department.

Installation of Automated synthesis module and $^{68}\text{Ge}/^{68}\text{Ga}$ generator

iQS-TS Synthesis module, ITG, Germany

It is an automated cassette-based synthesis module approved by European agency as Good Manufacturing practice (GMP) certified module. It has capability to synthesis ^{68}Ga -based radiopharmaceuticals by automated process of elution, formulation, and purification of radiopharmaceuticals such as ^{68}Ga -DOTATOC, ^{68}Ga -PSMA-11, ^{68}Ga -exendin, and ^{68}Ga -RGD. The specialized cassette with consumable is required for the synthesis of specific ^{68}Ga -based radiopharmaceuticals.

itG $^{68}\text{Ge}/^{68}\text{Ga}$ Generator, ITG, Germany

This generator has nonmetallic column (silica gel-modified dodecyl gallate) which does not require prepurification steps unlike metallic column $^{68}\text{Ge}/^{68}\text{Ga}$ generator. The column can be eluted by 0.05 M HCl solution. This is a self-shielded generator with lead shielding of 36–50 mm thick.

Installation

We installed itG $^{68}\text{Ge}/^{68}\text{Ga}$ Generator, fully automated iQS-TS Synthesis module, and mini hot cell in our laboratory maintaining hygienic condition and keeping radiation safety in mind. We dressed up with personal protective equipment kit and first examined the parcel containing the $^{68}\text{Ge}/^{68}\text{Ga}$ generator with fully automated synthesis module for any physical damage or sign of leakage visible externally and then disinfected by spraying sanitizer on its outer surface and proceeded for unpacking taking a snapshot of the received material for documenting the quantity and condition of the material on receipt. Two major components, a synthesis module with a laptop and the $^{68}\text{Ge}/^{68}\text{Ga}$ generator, were unpacked. Synthesis module and generator were installed in the hot cell first. After installation of both in hot cells, synthesis cassette was

installed in the synthesis module and the outlet and inlet tube of generator was connected with the respective port of cassette of the synthesis module. All the electric connection of synthesis module and laptop was established and power was switched on.

Testing of equipment postinstallation

After the laptop and synthesis module were switched on, we opened the synthesis module software Isotope Technologies Garching (ITG) Theranostics Synthesizer (iQS-TS) software version 2.30 on the laptop. Software established connection with hardware of synthesis module successfully, and mechanical test was performed automatically and completed successfully. Following the successful installation, we performed rinsing of the generator as described in Figure 2.

Postsuccessful rinsing, we together with online installation engineer accepted this synthesis module for routine operations.

Synthesis of radiopharmaceuticals

Preparation of reagents

The stock peptide, 500 μg of PSMA-11, was dissolved in 3 mL of ultrapure water, and 30 aliquots of 100 μL each were dispensed in 1 mL Eppendorf tube aseptically, closed and stored at -20°C . Similarly, the stock peptide, 1000 μg of DOTATOC, was dissolved in 3 mL of ultrapure water, and 30 aliquots of 100 μL each were dispensed in 1 mL Eppendorf tube aseptically and stored at -20°C . On the day of synthesis, one Eppendorf containing peptide (PSMA-11/DOTATOC) was taken out and allowed to attain room temperature before use.

Radiopharmaceutical synthesis process in iQS-TS Synthesis module is an automated process which involves several steps. The entire synthesis process can be divided into four sections, mechanical testing, presynthesis steps, radiopharmaceutical synthesis, and filter integrity test. Entire process is summarized in Figure 3.

Synthesis module and laptop connected to it were switched on, and iQS-TS software is switched on. Software

automatically establishes connection with the synthesis module and starts mechanical test.

Mechanical test

The mechanical test involves test for syringe actuator, rotary valves, inbuilt radioactive detectors, and heater functionality. After the successful completion of mechanical test, software prompts to place the sterile cassette on iQS-TS automated Synthesis module.

Presynthesis steps

Cassette is removed from its package, and all the connections are assured for mechanical integrity and attached to the dedicated slots available for attachment. After installation of cassette, all the consumables such as HCl, saline, and ethanol bottles are attached to the respective port on the cassette. The product and waste vials are also attached to the respective places to the cassette. Finally, generator's output port is attached with the cassette, and peptide PSMA-11/DOTATOC is inserted in the reaction vial from peptide port (red connector). Here end the presynthesis steps.

Radiopharmaceutical synthesis

After the presynthesis steps, synthesis has to be initiated on the software and entire process of synthesis takes around 17 min. The synthesis process involves multiple steps described in Figure 3. Process starts with automated elution of 4.15 ml of 0.05 M HCl into the reactor vial containing reconstituted peptide (PSMA-11/DOTATOC) in 1 ml Na-acetate buffer. Meanwhile, the inbuilt heater used for heating the reaction vial mixture achieves the ambient temperature for labeling (95°C), and C18-cartridge conditioning is prompted automatically. The C-18 cartridge is conditioned with 50% ethanol and purged with saline to get activated. The mixture in the reaction vial is heated for 5 min for successful labeling peptide (PSMA-11/DOTATOC) with ^{68}Ga . After the labeling, the content of the reactor vial is passed over reversed-phase C18 cartridge, wherein the labeled peptide is trapped in the C18 ion exchange cartridge and the remaining unbound

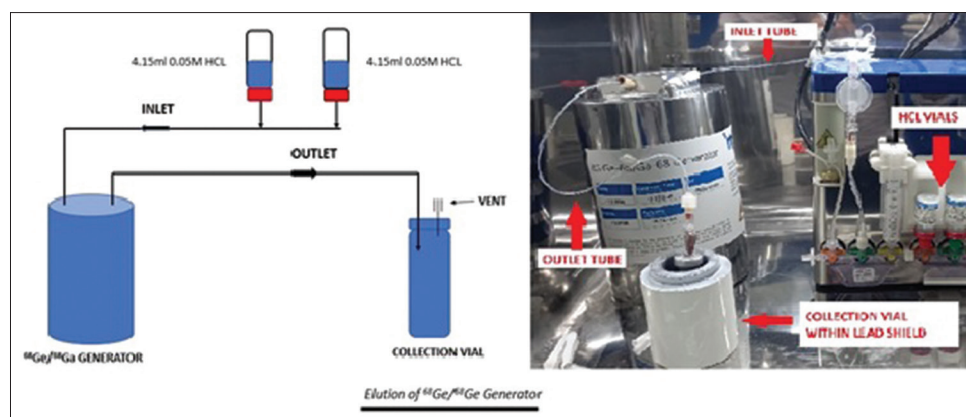


Figure 2: Elution of $^{68}\text{Ge}/^{68}\text{Ga}$ generator

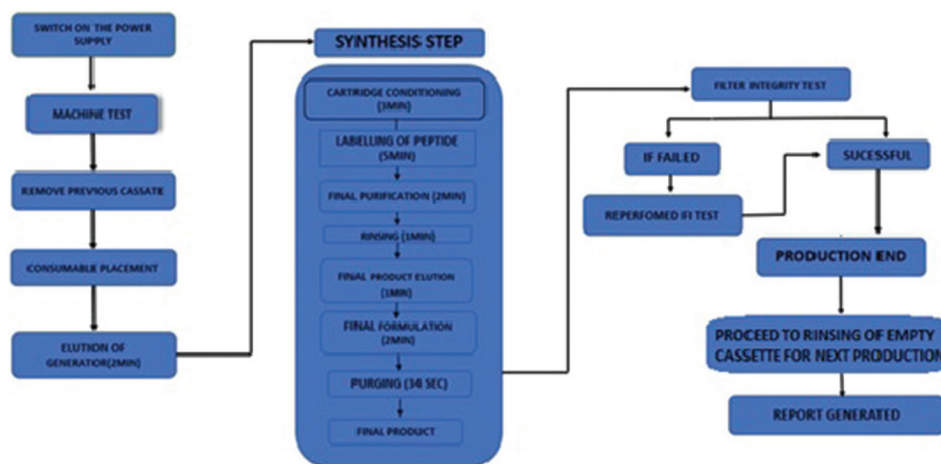


Figure 3: ^{68}Ga radiopharmaceutical synthesis sequence in iQS-TS Synthesis module, ITG, Germany

content in reaction solution is transferred to the waste vial. Subsequently, the reactor is rinsed again for any remaining activity and passed over C18 ion exchange cartridge. Final elution and formulation of the product with 50% ethanol and saline, respectively, are done via a 0.22 μm Millipore filter. A schematic flowchart of the above-mentioned steps can be seen, as mentioned in Figure 3. The synthesis module with cassette installed is shown in Figure 4.

Filter integrity and rinsing

The filter integrity of 0.22 μm filter requires one-time operator intervention in removal of product tubing having 0.22 μm filter and attached needle from the product vial and putting it into the waste vial for performing the test. It is performed by subjecting the filter to 2.37 bar (237 kPa) pressure. Pass/fail of integrity test is displayed as a popup screen. If integrity test passes, the product is free of microbes; second, if integrity test fails, it is re-performed; and if it fails twice, we need to filter the product again using Millipore filter.

Analysis and quality control of the radiopharmaceutical was evaluated as follows:

- pH: pH test of product was performed using pH paper after every synthesis
- Half-life of the radionuclide: The half-life of the radionuclide was calculated by decay method using calibrated dose calibrator CRC®-25PET Dose Calibrator, Capintec Inc., NY, USA. Eluted activity was measured eight times from 0 min to 70 min at 10-min interval and plotted on semi-log paper, and half-life was calculated
- Gamma-ray spectra: It was acquired under a calibrated multichannel analyzer (CAPRAC-t, Capintec, Inc.) using a point source of the product. The sample was also evaluated at 24 and 48 h after production to determine the ^{68}Ge breakthrough
- Radiochemical purity: Radiochemical purity was performed using Sillica Gel – Instant Thin Layer



Figure 4: Fully automated PC controlled synthesis module (cassette installed)

Chromatography (SG-ITLC) strip of 8 cm \times 1 cm and 0.5 M sodium citrate buffer as solid and mobile phases, respectively. A drop of final product was spotted on the SG-ITLS strip at point of spotting (PS), and chromatogram was developed up to solvent front (SF). ^{68}Ga -labeled radiopharmaceuticals remain at PS, and unlabeled fraction of ^{68}Ga moves to SF. Counting was performed in well counter (gamma-ray spectrometer), and Radiochemical Purity (RCP) was calculated as shown in Equation 1 below.

$$\%RCP = \frac{Cnt(PS) \times 100}{Cnt(PS) + Cnt(SF)} \quad \text{Equation 1}$$

Where

%RCP = Percentage radiochemical purity

Cnt (PS) = Count at PS

Cnt (SF) = Count at SF

Synthesis yield

Synthesis yield was calculated to know the efficiency of the synthesis. Synthesis yield was calculated by using Equation 2.

$$\% \text{Yield} = \frac{\text{Acti}(\text{GaRP}) \times 100}{\text{Acti}(\text{Ge})} \quad \text{Equation 2}$$

Where

%Yield = Percentage synthesis yield

Acti (GaRP) = Measured activity of ⁶⁸Ga radiopharmaceutical just after synthesis

Acti (Ge) = Theoretically calculated activity of ⁶⁸Ge

Sterility test

The small amount of prepared radiopharmaceutical from every batch was stored in the airtight sterile vial, and after 5 syntheses, it was sent for sterility test in microbiology laboratory.

Radiation monitoring

Radiation survey was performed using Radiation Alert Ranger-05805 of SE International during the synthesis. Radiation exposure to the radiochemist was measured using pocket dosimeter, Polimaster PM-1610.

Results

We were able to perform installation of the synthesis module and were successfully done and certified by installation engineer after successful run of rinsing sequence. We carried out 20 times radiopharmaceutical synthesis (7 times ⁶⁸Ga-DOTATOC and 13 times ⁶⁸Ga-PSMA-11) using this synthesis module till now. All the synthesis was completed successfully including filter integrity test. In all the synthesis, final product (⁶⁸Ga-DOTATOC/⁶⁸Ga-PSMA-11) was clear colorless solution free from particulate matter, and pH was in the range of 4–6. The average half-life calculated from the graph plotted was 68 min, and there were a prominent peak at 511 keV and a small peak at 1022 keV (summation peak) under gamma-ray spectrometer at all the occasions, as shown in Figure 5. The ⁶⁸Ge breakthrough was <0.0001%. The average % synthesis yield and average % radiochemical purity obtained over all the synthesis were 62.6 (±2.3) and 99.1 (±0.2) %, respectively [Table 1]. We performed sterility test three times, and all the three times, it was free from microbes.

Radiation monitoring

Radiation exposure outside the hot cell was found to be at background level. The average whole-body radiation exposure during the synthesis and quality control per

batch was in range from 1 μSv to 3 μSv. Major portion of radiation exposure was received during dose calibration and quality control.

Discussion

The average yield of ⁶⁸Ga from our generator was 84.76% which was quite good in comparison to the value indicated by the manufacturer, claiming it to be not <80%. In the 10 productions of gallium-labeled peptides, we recorded the radiochemical yield to be always greater than the reported value with improved reproducibility, as has been observed by Milos Petrik *et al.*^[12] In a study reported by Aslani *et al.*,^[13] it clearly highlighted the reduction in ⁶⁸Ge breakthrough, which was in consensus to the germanium-68 breakthrough observed at our Institute. It was always below the recommended level of 0.001% of the total radioactivity. Second, the exposure dose range to the radiochemist during the entire production and quality control was between 1 μSv to 3 μSv, wherein an average of 1 μSv was registered during the automated synthesis under the customized mini hot cell and the extra radiation was generally recorded/received while carrying out the quality control parameters. The same has also been observed by Nanabala *et al.* wherein the radiation dose measured with pocket dosimeter never exceeded 3 μSv in a production batch.

Finally, there are multiple inbuilt sensors such as thermocouples, pressure detector, flow meters and activity detectors, which help in better analysis of the situation/process undergoing during the various steps of synthesis along with a real-time report being generated from the fully automated system which helps us in documentation of the radiopharmaceutical preparation. Moreover, with the single use of sterile cassettes, there is no wastage of time for intense cleaning and sanitation

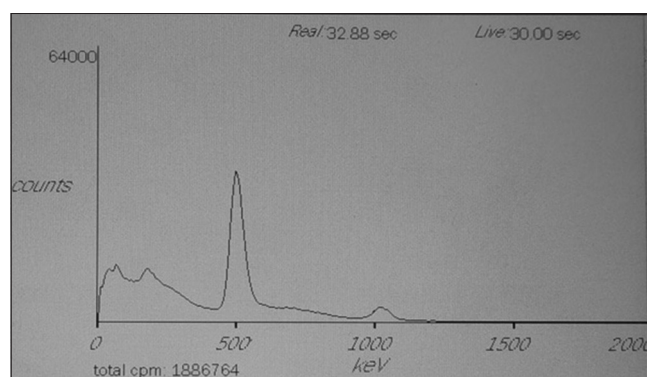


Figure 5: Spectrum of ⁶⁸Ga elute in multichannel analyzer

Table 1: Percentage synthesis yield, pH, and percentage radiochemical purity over all the synthesis

	Number of syntheses	Percentage synthesis yield (average over all the synthesis)	pH (across all the synthesis)	Percentage RCP (average over all the synthesis)
⁶⁸ Ga DOTATOC	7	62.6±2.3	4-6	99.1±0.2
⁶⁸ Ga PSMA-11	13	63.4±2.2	4-6	99.3±0.2

RCP: Radiochemical purity, PSMA: Prostate-specific membrane antigen, DOTATOC: (DOTA0-Phe1-Tyr3) octreotide

process; second, by simply changing the cassette, multiple syntheses can be easily carried out for various tracers and with a different radionuclide. The major one-time cost is the cost of generator, otherwise the routine consumables used for radiosynthesis of various peptides are low enough to make it viable after installation. Indeed, the experience of radiolabeling peptides under a fully automated system is advantageous.

Conclusion

iQS-TS Synthesis module is easy to install, and a qualified radiochemist can install it under the supervision of installation engineer. Our study shows that the synthesis yield and radiochemical purity of the product were at par with published literature with very little radiation exposure to the radiochemist and maintaining sterility of the product.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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