

Cyclotron production of $[^{68}\text{Ga}]\text{GaCl}_3$ using solid target and its clinical adaptation through automated purification and GMP-grade production of $[^{68}\text{Ga}]\text{Ga-DOTATATE}$

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Abstract

Background

The clinical demand for [^{68}Ga]Ga-DOTATATE has expanded substantially over the past decade. This is particularly due to its ability to selectively localize the somatostatin receptor expressing lesions in patients with neuroendocrine tumor. The interest in radiometal-based PET imaging is further privileged due to selective targeting of biological markers overexpressed on the tumor cells, and its ability to integrate molecular imaging and targeted radionuclide therapy within a unified theranostic framework. This growing demand has particularly highlighted the supply shortage and production challenges of metal-based PET radiopharmaceuticals, notably the [^{68}Ga]Ga-DOTATATE. The generator-based supply of Ga-68 encounters low activity output issues, transportation or logistical challenges, increasing purchase cost and long procurement times. On other hand the cyclotron-based production is an attractive alternate but currently is restricted to a limited number of specialized facilities.

Methods

Our work demonstrates a practical and transferable approach to cyclotron-based production of Ga-68 through $^{68}\text{Zn}(\text{p},\text{n})^{68}\text{Ga}$ nuclear reaction using the solid target. The work illustrates a complete solid-target-based production workflow including preparation of the target plate(s), cyclotron irradiation, target material dissolution, radionuclide purification, and automation of [^{68}Ga]GaCl₃ and [^{68}Ga]Ga-DOTATATE productions using the NEPTIS radiosynthesis module.

Results

Following the described procedures, we were able to produce 90–110 GBq of [^{68}Ga]GaCl₃ at EOB using an incident proton energy of 12.5 MeV, 40 μA beam current and irradiation time of 2 hrs. The [^{68}Ga]GaCl₃ was obtained in RCY of 51 ± 6 (n.d.c) with > 99% radionuclide purity and molar activity of 137 GBq/ μmol . The produced [^{68}Ga]GaCl₃ was subsequently used in radiosynthesis of [^{68}Ga]Ga-DOTATATE under GMP conditions in RCY of 54 ± 3 with > 98% purity in all aspects for up to 5 hrs at RT.

Conclusion

Rather than proposing an entirely new target design or staying dependent on external supply, the work demonstrates a scalable and self-reliant workflow to Ga-68 production and its subsequent use in radiosynthesis of [^{68}Ga]Ga-DOTATATE. The work also emphasizes the establishment of regional Ga-68 production platform with possible implementation to production of other emerging radio-metals and thus maximizes the use of cyclotron and existing radio pharmacy infrastructure.

Introduction

Positron Emission Tomography (PET) has undergone substantive evolution over the past two to three decades. It was originally famed around a metabolic radiotracer called [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), but has expanded to a growing number of radiolabeled small molecules, peptides, proteins and other biological vectors selectively targeting the cell receptors or disease related biochemical processes (Kelloff et al, 2005; Lin et al, 2022). The basic principle behind PET imaging was based on fundamental characteristic of malignant cells - their tendency to exhibit increased glucose metabolism compared to normal healthy tissues (Pauwels et al, 1998). However, PET has evolved beyond metabolic imaging now, providing complementary information on tumor identification and treatment suitability that in many cases was difficult to achieve through glucose-based imaging (Lin et al., 2022). Additionally, receptor-specific imaging also provides opportunity to integrate molecular imaging and targeted radionuclide therapy within a unified theranostic framework, thus allowing diagnosis and therapy using the same molecular target facilitating seamless transition from diagnosis to treatment (Brandt et al., 2018; Levine et al., 2017; Mikolajczak et al., 2019).

Within this evolving landscape, several radio-metals have been incorporated to tumor specific biomarkers for diagnostic and therapeutic applications. From the diagnostic side, Gallium-68 (Ga-68), Copper-64 (Cu-64) and Zirconium-89 (Zr-89) are widely used PET nuclides each offering a distinct set of physical and chemical properties (Wadas et al. 2010, Brandt et al. 2018). The selection of a radionuclide is closely related to its physical half-life and biological behaviour of the targeting vector. For example, Ga-68 has a short physical half-life ($t_{1/2} = \sim 68$ min) and is therefore well suited for same-day imaging of rapidly clearing peptides or small organic molecules (Zhernosekov et al, 2007). In contrast, Zr-89 with half-life of 78.4 hr is particularly suitable to image kinetically slow or long-circulating biomolecules such as macro peptides, nanomaterials or monoclonal antibodies (Yoon et al, 2020). Hence, matching a radionuclide half-life to pharmacokinetic property of targeting vector is an important consideration in designing the metal-based PET radiotracers.

Out of the several radiometals used in PET imaging, Ga-68 (89% β^+) has been adapted the most in clinical settings, particularly due to its early adaptation and easy access through Germanium-68/Gallium-68 ($^{68}\text{Ge}/^{68}\text{Ga}$) generator (Zhernosekov et al, 2007, Rosch Frank, 2013). The generator-based supply of Ga-68 offers several advantages and is particularly the first choice for any nuclear medicine centre with limited-to-moderate patient load. A major benefit of generator-produced Ga-68 is operational flexibility as radiosynthesis can be performed in any lab equipped with a hot cell and basic radio pharmacy equipment. Also, generator-based Ga-68 supply avoids substantial capital investment on establishing an on-site cyclotron besides its operation, maintenance and post-installation challenges, hence it is comparatively a practical and cost-effective option for centres seeking to initiate Ga-68 PET imaging without major infrastructural investment. Additionally, relatively long half-life of parent radionuclide i.e. Ge-68 ($t_{1/2} = 271$ days) allowing repeated Ga-68 elution's over an extended period makes $^{68}\text{Ge}/^{68}\text{Ga}$ generator a suitable option for efficient utilization of imaging facilities.

However, despite the practical and operational advantages, generator-based access to Ga-68 have several limitations. First, the Ga-68 activity that can be eluted is inherently limited to a generator capacity (Kumar Krishan, 2020; Nelson et al, 2020). Commercially available generators can supply Ga-68 activity in the range of 30–100 mCi, although high activity options are available but demands huge cost and long awaiting times. Also, Ga-68 activity that can be milked from a generator declines as the generator ages. This is particularly relevant for centres with increasing patient load demanding multiple elution's or more than one generator is purchased that ultimately increases the cost and personnel workload. Additionally, a generator is not a single-time investment, recurring procurements are often required every year to maintain continuous and reliable supply of the radionuclide. This was particularly relevant to our hospital where the demand for [^{68}Ga]Ga-DOTATATE and [^{68}Ga]Ga-PSMA-11 was steadily increasing. Although a substantial portion of PSMA imaging has been shifted to ^{18}F -labelled PSMA ligand, but demand for [^{68}Ga]Ga-DOTATATE continue to exceed. Despite the procurement of three 50 mCi $^{68}\text{Ge}/^{68}\text{Ga}$ generators that the hospital purchase almost every year, the Ga-68 supply remains insufficient to accommodate patients load highlighting need for a high throughput cyclotron-based production that can fulfil both the current need and future clinical demand.

These practical limitations of $^{68}\text{Ge}/^{68}\text{Ga}$ generator have contributed to growing interest in cyclotron-based production of Ga-68, particularly for the centres experiencing high or consistently growing patient volume. Out of the several cyclotron-based production routes applied to Ga-68 production, $^{68}\text{Zn}(\text{p},\text{n})^{68}\text{Ga}$ nuclear reaction is most convincing route as it involves proton irradiation, and energy is optimal to achieve by many medical cyclotrons (Pandey et al, 2014, Lin et al 2018; Nelson et al, 2020, Rodnick et al, 2020; Thisgaard et al, 2021, Ashhar et al, 2022). Also, the Zinc-68 (Zn-68) used as target material is relatively economic to afford and exceptionally high activity compared to the $^{68}\text{Ge}/^{68}\text{Ga}$ generator can be produced to meet local demand as well as to support near-by PET centres.

The Ga-68 production using $^{68}\text{Zn}(\text{p},\text{n})^{68}\text{Ga}$ can be achieved using either a liquid target where Zn-68 is irradiated in dilute nitric or hydrochloric acid, or through a solid target where Zn-68 is electroplated or pressed on a metallic backing and irradiated using a solid target irradiation station (Pandey et al, 2014, Lin et al 2018; Nelson et al, 2020; Thisgaard et al, 2021). Both production routes proceed through same nuclear reaction and require almost same downstream radiochemical separation, but differs essentially in operational complexity, hardware requirements and amount of activity that can be produced (Ashhar et al, 2022).

A major advantage using a liquid target route is the target hardware is sometimes commercially available, and irradiation solution can be loaded/unloaded through simple capillary tubes already distributed between the cyclotron and hot cell lab. So, operation is relatively simple, but Ga-68 activity that can be produced is constrained due to limitations in the amount of Zn-68 prepared for irradiation, salts deposition leading to precipitation, and pressure buildup in the target body resulting in corrosion and high back pressure (Pandey et al, 2019; Ashhar et al, 2022). Also, the liquid targets cannot be operated at high beam currents as heat dissipation is not as efficient. On other hand the target plate get

direct contact with coolant in the solid target system allowing high beam current(s) and long irradiation times (Nelson et al, 2020; Thisgaard et al, 2021, Becker Kaelyn et al. 2021). Additionally, a solid target plate can contain high quantity of Zn-68 in a compact configuration, and thus high Ga-68 activity (reaching to several Ci's) can be produced which is substantially higher compared to the liquid target-based production (Thisgaard et al, 2021). But major issue with solid target irradiation is; it requires a dedicated irradiation station, and a pneumatically controlled system for loading/unloading of target holder is required which adds complexity to the process. Despite the forementioned challenges, practical benefits of Ga-68 production by cyclotron are so substantial that many production sites are already producing or planning to switch to Ga-68 production by cyclotron. Also, clinical relevance of receptor-specific imaging, particularly [^{68}Ga]Ga-DOTATATE in neuroendocrine tumours and [^{68}Ga]Ga-PSMA-617 or [^{68}Ga]Ga-PSMA-11 in prostate cancer has expanded rapidly, so scalable supply becomes mandatory to fulfil patients demand that cannot be covered through generator(s) or low-throughput production routes.

In view of above benefits, and being a largest producer and supplier of radiopharmaceuticals in the gulf region, the cyclotron and radiopharmaceuticals department (C&RD) at King Faisal Specialist Hospital and Research Centre (KFSH&RC) implemented a scalable route to Ga-68 production and its subsequent use in radiosynthesis of [^{68}Ga]Ga-DOTATATE. Rather than commissioning an entirely new target system, we repurpose an existing solid-target infrastructure that was originally developed for production of Thallium-201 and Iodine-123 radionuclides (Al Jammaz et al, 2007) and successfully validated its use to production of [^{68}Ga]Ga-DOTATATE in clinically useable quality. The work includes electroplating of copper target plates with enriched Zn-68, cyclotron irradiation and dissolution of the target material, post-irradiation purification and complete automation of [^{68}Ga]GaCl₃ purification and [^{68}Ga]Ga-DOTATATE radiosynthesis procedures. Taken together, the work demonstrates high throughput access to Ga-68 with least possible investment or target modifications and thus provides an economically justifiable route to achieve local production of Ga-68 and ^{68}Ga -labelled radiopharmaceuticals.

Materials and Methods

All chemicals and reagents used in experiments were obtained from Merck, Fisher Scientific, or otherwise specified. The concentrated hydrochloric acid (HCl, 37%, trace-metal grade) was purchased from Merck (Merck KGaA, Darmstadt, Germany) and HCl solutions with different molarity were prepared in-house through dilution of the concentrated HCl. Also, molarity of the prepared HCl solutions was verified by quality control (QC) team using acid-base titration against sodium hydroxide (NaOH) solution. Copper sheets used as target support material were purchased from McMaster-Carr (Illinois, USA) and fabricated to required dimensions in cyclotron workshop. The enriched Zn-68 (> 98% enrichment) was obtained from CMR (Centre for Molecular Research; Moscow, Russia) and cartridges used for [^{68}Ga]GaCl₃ purification such as ZR, TK400 and TK200 were purchased from TrisKem (TrisKem International, Bruz, France). The manifold kits used for automation of [^{68}Ga]GaCl₃ purification and

[⁶⁸Ga]Ga-DOTATATE radiosynthesis, and the DOTATATE peptide used as precursor were purchased from ABX (Advanced Biochemical Compounds, GmbH, Germany).

The instant thin-layer chromatography silica gel impregnated strips (iTLC-SG) were obtained from Agilent (Agilent Technologies, California, US) and scanning of the radio-iTLC strips was performed using Bioscan AR2000 radio-TLC scanner (Bioscan, Inc., Washington, USA). The radio-high performance liquid chromatography (radio-HPLC) was performed using Jasco HPLC (Jasco corp. Tokyo, Japan) equipped with a UV detector and a sodium iodide crystal detector from Eckert and Ziegler (Eckert & Ziegler, Berlin, Germany) using Xbridge C18 analytical column (4.6 × 100 mm) purchased from waters (Waters corp. Massachusetts, US). The concentration of residual solvents in final formulation was determined using GC-2010 Plus gas chromatography (Shimadzu corp., Kyoto, Japan) and endotoxins testing was performed using Limulus Amebocyte Lysate (LAL) test kit (Thermo Fisher Scientific, Massachusetts, USA). Radioactivity measurements to determine half-life and radioactivity concentration were performed using Capintec CRC-25R dose calibrator (Mirion Technologies, New Jersey, USA). All QC procedures documented herein were performed using calibrated instruments used in QC testing of routinely produced radiopharmaceuticals.

Preparation of the target plates

The standard copper sheet was machined to required dimensions (120 x 30 x 7 mm; L × W × B) in cyclotron workshop and target plates were thoroughly cleaned to remove surface grease or residual metallic oxides that can interfere with electroplating process. The front surface of each target plate was cleaned with kimwipe soaked in 1 M HCl to remove metal oxides. Following acid cleaning, the plates were rinsed with deionized water and gently scrubbed with shadazzle polish/cleaner to remove grease or remaining surface contaminants. The plates were washed with deionized water afterwards, rinsed with acetone and air-dried. Weight of each target plate was measured at this point using analytical balance, so amount of Zn-68 deposited on each target plate can be determined after electroplating.

Preparation of the electroplating solution

The Zn-68 oxide (1.4 g, isotope enrichment > 98%) was transferred to a clean glass beaker (250 mL) and dissolved using 6 M HCl (~ 10 mL) while stirring at room temperature (RT). The solution was heated to 70–80°C for additional 5–10 minutes to allow complete dissolution of Zn-68 in HCl solution. Once Zn-68 is completely dissolved, the beaker was removed from heating and allowed to cool to RT. Thereafter, 2–3 mL of hydrazine monohydrate was added in portions while stirring to allow formation of white precipitates. The solution was left to stir for additional 10 minutes and concentrated HCl (37%, trace-metal grade) was added afterwards in portions till the white precipitates are redissolved and clear/transparent solution is obtained. The resulting solution was then diluted with Milli-Q water to get final volume of 200–220 mL (enough to cover the target plates in electroplating chamber), and pH of electroplating solution was confirmed (should be around 1–2).

Zn-68 electroplating of copper target plates

The prepared electroplating solution was used to electroplate four target plates that will be used for four individual Ga-68 productions. Since our electroplating chamber is set to accommodate two target plates per run, the four target plates were electroplated in two rounds. The clean and pre-weighed copper plates were carefully mounted on electroplating chamber (shown in Fig. 1) and connected to negative terminal of the power supply (GPS-3030D, GW Instek, Taipei, Taiwan). A platinum wire serving as anode positioned at centre of the electroplating chamber was connected to positive terminal of power supply. After confirming the electrical connections, electroplating solution was added to the chamber and 700 mA current (corresponding to 350 mA per target plate) was applied. A stirring rod positioned above was inserted to electroplating chamber to keep the solution homogeneous and to ensure uniform deposition of Zn-68 on the target plates.

The electroplating process was continued like this for 1 hr. Upon completion, the power supply was turned off, and solution was drained from the electroplating chamber. The Zn-68 plated target plates were carefully removed and washed with milliQ water to remove residual electrolyte solution. The plates were rinsed with acetone afterwards, air-dried and weighted to determine amount of Zn-68 electrodeposited on each plate. The process was repeated to electroplate the remaining two plates in the second round.

Cyclotron irradiation

The Zn-68 plated target plate was transferred to hot cell connected to the cyclotron vault via a pneumatically controlled target-transfer system. The target plate was carefully mounted onto the target holder and fastened using screws as shown in Fig. 2. A graphite degrader with 0.5 μm thickness (calculated through SRIM calculations) was positioned at entrance of the target holder to reduce proton energy from 15.5 MeV to incident energy of 12.5 MeV. Once the target plate is assembled on target holder, it was pneumatically transferred to cyclotron for irradiation. Once correct positioning of the target holder is confirmed and required vacuum conditions are met, Zn-68 deposited on the target plate was irradiated using Cyclone 30 MeV cyclotron (Ion Beam Applications (IBA), Louvain-la-Neuve, Belgium) with proton energy of 15.5 MeV (corresponding to 12.5 MeV on target plate) using 36–40 μA beam current for 1.5-2 hours. The target holder was transferred back to same hot cell on completion of irradiation time, and target plate was carefully detached from the holder using a custom designed semi-automatic screwdriver.

Dissolution of target material

The target plate was transferred to purification hot cell using an automated conveyor belt for target material dissolution and purification of produced Ga-68. Once the target plate is received in purification hot cell, it was securely mounted on to the dissolution holder so the surface containing Zn-68 is exposed

for dissolution as shown in Fig. 3. The target material was dissolved using 6 M HCl (7–8 ml) in two rounds, using 3–4 ml in each round. The HCl solution was allowed to stay in contact with target material for approximately 2 minute and collected to a clean V-bottom glass vial using a vacuum line. The second round of dissolution was performed the same way and complete target dissolution volume (6–8 mL) was collected into a V-bottom glass vial for subsequent purification.

Purification of Ga-68 as $[^{68}\text{Ga}]\text{GaCl}_3$ and automation of the purification process

The target dissolution volume collected in the V-shaped glass vial contains cyclotron produced Ga-68, enriched Zn-68, and other metallic and radionuclide impurities generated during irradiation or target dissolution process. Therefore, purification of dissolution volume was performed to separate Ga-68 from unwanted metallic or radionuclide impurities. Initially, the Ga-68 purification was performed manually to finalize the purification conditions, and thereafter the process was automated to facilitate its translation to large-scale production.

Several solid-phase extraction (SPE) resins have been reported to selectively isolate the Ga-68 from bulk dissolution volume in high radiochemical yield and are routinely applied to $[^{68}\text{Ga}]\text{GaCl}_3$ production at many production sites (Lin et al 2018; Nelson et al, 2020, Rodnick et al, 2020; Thisgaard et al, 2021, Ashhar et al, 2022), so little effort to optimize the purification conditions was required in our case. Our focus here was to validate a purification process that is simple/reproducible to allow automation, and $[^{68}\text{Ga}]\text{GaCl}_3$ obtained after purification is qualified for subsequent use in $[^{68}\text{Ga}]\text{Ga-DOTATATE}$ radiosynthesis. Out of the three SPE cartridge-based purification that we evaluated (details are given in discussion part), most robust purification was achieved using a combination of ZR (a hydroxamate-based resin, 2 mL) and TK200 (a tri-octylphosphine oxide-based resin, 2 mL) cartridges as also reported by Rodnick et al, 2020, Thisgaard et al, 2021 and Svedjehed et al, 2022. Apart from the target dissolution that was performed through a semi-automated way, complete purification and formulation of Ga-68 as $[^{68}\text{Ga}]\text{GaCl}_3$ was performed using the NEPTIS radiosynthesis module following the sequence given in Fig. 4.

The radiosynthesis module was prepared using the appropriate cassette and required reagents were installed on to the manifold at designated positions. The ZR cartridge was conditioned with 6 mL of 1.5 M HCl, and TK200 cartridge was conditioned with 6 mL of water for injection (WFI) followed by 6 mL of 1.5 M HCl. Following conditioning, the cartridges were installed at the designated positions, and automation script was loaded. All automation preparations were completed prior to transfer of target dissolution volume to purification hot cell, and once the target dissolution volume arrives the purification hot cell, inlet line of the manifold was connected to V-shaped vial containing target dissolution volume and automation was started.

The target dissolution volume (6–8 mL) was loaded on ZR cartridge, where the Ga-68 was retained on the cartridge while eluate was collected into a clean glass vial. The ZR cartridge was subsequently washed with 20 mL of 6 M HCl, and complete volume was collected into the same glass vial to recover enriched Zn-68 afterwards. The Ga-68 retained on ZR cartridge was eluted using 5 mL of 0.75 M HCl and loaded directly to TK200 cartridge for further purification. The TK200 cartridge was washed with 3.5 mL of 0.15 M HCl containing 2M NaCl to reduce acid concentration and to remove remaining unwanted impurities. The Ga-68 retained on the TK200 was finally eluted as $[^{68}\text{Ga}]\text{GaCl}_3$ into a clean sterile glass vial using 5 mL of 0.05 M HCl. The entire $[^{68}\text{Ga}]\text{GaCl}_3$ purification was achieved in 22 minutes.

Quality Control of $[\text{Ga}]\text{GaCl}$

The $[^{68}\text{Ga}]\text{GaCl}_3$ was qualified against defined parameters given in European Pharmacopeia (Ph. Eur.) monograph to confirm its suitability for subsequent use in radiolabelling. Briefly, the radionuclide purity was assessed by gamma spectrometry using high-purity germanium (HpGe) detector. 2 μL of $[^{68}\text{Ga}]\text{GaCl}_3$ was analysed using Canberra HPGe detector (Mirion Technologies, USA) and resulting gamma-energy spectrum was evaluated using Genie 2000 spectroscopy software to confirm radionuclide identity. The radiochemical purity was evaluated by radio-iTLC using 1 μL of $[^{68}\text{Ga}]\text{GaCl}_3$ on iTLC-SG strip and iTLC was developed using 1 M citrate buffer as mobile phase. The iTLC strip was then analysed using Bioscan AR-2000 scanner to evaluate percent radiochemical purity (RCP) by distribution of radioactivity at application point and solvent front. To determine physical half-life, 100 μL of $[^{68}\text{Ga}]\text{GaCl}_3$ was taken in an eppendorf tube and radioactivity decay was measured at three different time points. The measured activity was subsequently plotted against theoretical decay of Ga-68 to confirm half-life. Also, the concentration of relevant cold metals, i.e. Iron (Fe), Copper (Cu), and Zinc (Zn) in $[^{68}\text{Ga}]\text{GaCl}_3$ bulk solution was determined using colorimetric analysis where 100 μL of $[^{68}\text{Ga}]\text{GaCl}_3$ sample was compared against 100 μL of 5 and 15 $\mu\text{g/mL}$ reference standards, and colour intensity of $[^{68}\text{Ga}]\text{GaCl}_3$ sample was visually compared against reference standards to estimate concentration of metals in $[^{68}\text{Ga}]\text{GaCl}_3$ bulk. Additionally, the apparent molar activity (AMA) of purified $[^{68}\text{Ga}]\text{GaCl}_3$ was determined by DOTA-chelator titration using DOTATATE peptide at five different concentrations (0.5, 1.0, 1.5, 2.0, and 2.5 nmol). The peptide concentrations were prepared in 1 M sodium acetate buffer (pH 4–5) that was pre-treated with Chelex-100 and mixed with ~ 150 MBq of $[^{68}\text{Ga}]\text{GaCl}_3$ in final volume of 0.5 mL. pH of the reaction mixture was confirmed (should be close to 4) and vials were set to heat at 95°C for 10 min. Thereafter, 2 μL from each vial was spotted on iTLC-SG strips and %RCY was determined using methanol:1 M ammonium acetate buffer (1:1, v/v) as mobile phase and apparent molar activity was calculated based on the DOTATATE peptide amount required to achieve 50% labelling.

Radiosynthesis and automation of $[\text{Ga}]\text{Ga}$ -DOTATATE

The purified [^{68}Ga]GaCl₃ was subsequently used in radiosynthesis of [^{68}Ga]Ga-DOTATATE using the second NEPTIS radiosynthesis module. The cassette for radiosynthesis of [^{68}Ga]Ga-DOTATATE was installed on the module along with required reagents and consumables. A strong cation-exchange (SCX) cartridge was used to concentrate [^{68}Ga]GaCl₃ before labelling, and a C18 cartridge was used to purify final radiolabelled product. The SCX cartridge was conditioned with 10 mL of WFI, while C18 cartridge was conditioned with 5 mL of ethanol followed by 10 mL of WFI. Also, the reaction vessel of the cassette was preloaded with 3 mL of 5 M HEPES buffer (pH 7) and 300–500 µg of DOTATATE peptide (depending on the starting activity). A 0.22 µm sterile filter was attached to outlet of the cassette and connected to a clean sterile glass vial for product collection. Following the mandatory preparations, inlet of the radiosynthesis module was connected to the vial containing [^{68}Ga]GaCl₃ solution and automation of [^{68}Ga]Ga-DOTATATE was achieved following the scheme given in Fig. 5.

The [^{68}Ga]GaCl₃ solution was loaded on SCX cartridge to concentrate the Ga-68 activity, and eluent from the cartridge was directed to waste bottle. The SCX cartridge was washed with 10 mL of WFI, and retained Ga-68 was eluted directly into the reactor using 1.5 mL of 5 M NaCl solution. As the reactor was preloaded with HEPES buffer and the DOTATATE peptide, the total reaction mixture (~ 5 mL) was heated to 110°C for 10 minutes. After the labelling time is completed, the reaction mixture was loaded on C18 cartridge. 10 mL of WFI was added to the reactor vial and loaded to C18 as a subsequent step. The [^{68}Ga]Ga-DOTATATE was eluted from C18 using 2.5 mL of ethanol/water (1:1, v/v) into the final product vial. Thereafter, 12 mL of phosphate-buffered saline (PBS) containing 100 mg of sodium ascorbate (approximately 7 mg/mL in final formulation) was passed through the 0.22 µm filter and added to the product vial yielding final formulation volume of 15 mL. The synthesis of [^{68}Ga]Ga-DOTATATE including formulation was achieved in 24 minutes.

Quality Control of [^{68}Ga]Ga-DOTATATE

The [^{68}Ga]Ga-DOTATATE was evaluated against defined quality specifications given in the Ph. Eur. monograph and United States Pharmacopeia (USP) including pH, radionuclide purity, radiochemical/chemical purity, half-life confirmation, residual solvent content, bacterial endotoxins, osmolality and sterility. Briefly, the radionuclide purity was determined using HpGe gamma spectrometry as described for [^{68}Ga]GaCl₃. Radiochemical and chemical purity was assessed by radio-iTLC and radio-HPLC analysis. For radio-iTLC, 1 µL of [^{68}Ga]Ga-DOTATATE was applied on an iTLC-SG strip, and developed using methanol:1 M sodium acetate buffer mixture (1:1, v/v) as mobile phase. Radio-HPLC analysis was performed by Jasco radio-HPLC system using waters Xbridge analytical column (4.1 x 100 mm) as stationary phase and 0.1% trifluoroacetic acid (TFA) in water (solvent A) and 0.1% TFA in acetonitrile (solvent B) using a gradient elution of 10–90%B in 12 minutes at flow rate of 1 mL/min. The concentration of residual solvents was determined by GC-2010 Plus gas chromatography equipped with optima-WAX capillary column (0.25 µm film thickness) using helium as carrier gas. Osmolality of final product was determined using fiske one-ten osmometer (Fiske Advanced Instruments, Massachusetts,

USA) and bacterial endotoxin testing was performed using LAL test kit. Sterility was performed by incubating 200 μL of [^{68}Ga]Ga-DOTATATE (after decay) with commercially available tubes of tryptic soy broth and thioglycolate medium and incubated at 25°C and 32°C respectively to monitor evidence of microbial growth for up to 14 days.

Recovery of enriched Zn-68 after irradiation

The collected Zn-68 sample from 5 individual irradiation experiments were combined into a 250 ml beaker and set to heat at 100°C to reduce total volume to ~ 50 mL. Following volume reduction, 5 M NaOH solution was added in portions under stirring to increase pH and to promote formation of Zn-68 hydroxide ($^{68}\text{Zn}(\text{OH})_2$) as white precipitates. 2 g of sodium cyanide (NaCN) was added in to the solution afterwards and stirred for additional 10–15 min to dissolve the precipitates obtained in the previous step. After a clear solution is obtained, 5 M sodium meta-bisulphite solution was added while stirring for 15–20 minutes and solution was left overnight to allow sedimentation of the precipitates.

The following morning, supernatant was carefully decanted and zinc sulphite precipitates together with small amount of residual solution was transferred to a 30 mL eppendorf tube and centrifuged at 5000 rpm for 5 minutes. After centrifugation, the supernatant was removed completely and resulting solid residue was redissolved in 6 M HCl (~ 20 mL) and transferred to a beaker to heat at 100°C to evaporate residual sulphur/sulphite along with HCl fumes. Once half of the HCl volume is left, the beaker was shifted to RT and 5 M NaOH solution was added again to get Zn-68 as hydroxide precipitates. The resulting white precipitates were separated by centrifugation, overnight dried in oven and measured to estimate Zn-68 recovery based on difference in starting and collected amount at end of the process. The $^{68}\text{Zn}(\text{OH})_2$ was subsequently reused in preparation of new target plates following the procedure described earlier.

Results and Discussion

Most of the literature on Ga-68 production using solid target even some referenced in this article use a circular metallic disk as target backing support. The circular discs are relatively straightforward to integrate with commercially available target holders and also shape of the plated target surface is more compatible with irradiation beam radius, however, in our case implementing a circular or disc shaped target would require number of modifications in the existing infrastructure including target-holder design, electroplating setup, change in target dissolution apparatus and most importantly commissioning of the entire process requiring a lot of time and experiments. Therefore, the existing solid-target station was proposed to implement Ga-68 production and was subsequently validated to avoid considerable capital investment that would have to spend on development of a new target system.

The amount of Zn-68 electrodeposited on each target plate was determined by difference in weight of the target plate before and after electroplating. On average 235 ± 20 mg of Zn-68 was electrodeposited on each target plate using the provided conditions. Thickness of the Zn-68 electroplated layer was calculated based on the deposited mass, surface area of the target plate, and density of the target

material, and thickness of 24 μm was obtained. Also, the percent yield of electroplating (efficiency) was determined by calculating the theoretical yield based on applied current and electroplating time using Faraday equation and compared with actual amount of Zn-68 obtained on the target plate and electroplating efficiency of 54% was acquired.

For irradiation, an incident proton energy of 12.5 MeV was selected based on thickness of the target material following the SRIM simulation. Since the solid-target irradiation station in our facility is integrated with Cyclone 30 cyclotron and minimum proton energy that can be achieved through this machine is 15.5 MeV, hence a 0.5 μm graphite degrader was incorporated in front of beamline to reduce proton energy to 12.5 MeV at the target surface. Also, the initial irradiation experiments were performed using beam current of 60 μA , yielding up to 5 Ci (185 GBq) of Ga-68 activity at EOB within 2 hr of irradiation, however, a fine hole in the graphite degrader was observed after couple of irradiations, so maximum beam current was set to 40 μA and all further experiments were performed using 12.5 MeV incident energy with beam current of 36–40 μA .

Table 1

Performance of different SPE cartridges evaluated for purification of [^{68}Ga]GaCl₃ and quality assessment of purified [^{68}Ga]GaCl₃ through subsequent use in radiosynthesis of [^{68}Ga]Ga-DOTATATE. All activity measurements reported in the table are n.d.c.

Experiment details	TK400 alone			TK400 and TK200			ZR and TK200		
Ga-68 activity used for purification (mCi)	398	138	300	414	133	372	255	383	260
[^{68}Ga]GaCl ₃ collected after purification (mCi)	253	94.7	182.5	231	67.3	176	145.7	185.8	138
[^{68}Ga]GaCl ₃ purification yield	63.5	68.6	60.8	55.7	50.6	47.3	57.1	48.5	53.0
Radionuclide purity (Gamma spectrometry)	> 99			> 99			> 99		
Radiochemical purity (Radio-iTLC)	95–98			95–98			97–98		
	> 15µg/mL (Zn ⁺² - turbidity in solution)			< 5µg/mL (Zn ⁺²)			< 5µg/mL (Zn ⁺²)		
	< 5µg/mL (Fe ⁺² and Cu ²⁺)			< 5µg/mL (Fe ⁺² and Cu ²⁺)			< 5µg/mL (Fe ⁺² and Cu ²⁺)		
[^{68}Ga]GaCl ₃ used for DOTATATE labeling (mCi)	148	72	125	152	31	125.3	113	140	90
[^{68}Ga]Ga-DOTATATE in final formulation (mCi)	23.5	17.7	24	72.6	13	57	63.1	73.4	46.2
%Yield of radiosynthesis	15.8	24.5	19.2	47.7	41.9	45.5	55.8	52.4	51.3
Radio-iTLC [^{68}Ga]Ga-DOTATATE	67.3	74.8	58.8	96.4	94.7	96.8	> 98	> 98	> 98
Radio-HPLC [^{68}Ga]Ga-DOTATATE	> 98			> 98			> 99		

We also evaluated the target dissolution conditions with addition of hydrogen peroxide (H₂O₂, 5–10% V/V) in 6 M HCl and heating of the target plate to 70–80°C during dissolution process as reported by Thisgaard et al, 2021 and Svedjehed et al, 2022. We were willing to investigate if more Ga-68 activity can be collected from the target plate with H₂O₂ addition or through heating, but no big difference in Ga-68 activity was observed. In fact, slight yellowish coloration of target dissolution volume was observed for

samples having H_2O_2 . Also, we are using copper as backing target material, we were concerned extensive target dissolution may leach copper from the target backing and could potentially compromise the quality of produced Ga-68, so we decided not to use severe target dissolution conditions. Additionally, we decided to use two dissolution rounds (using 3–4 mL of 6M HCl in each cycle) as we were able to recover 80% of the produced activity in two rounds. Although it was possible to recover 5–10% additional activity using the third round but considering the possible co-extraction of non-radioactive metallic impurities affecting overall quality of purified $[\text{}^{68}\text{Ga}]\text{GaCl}_3$, the third fraction was excluded from the product stream.

For $[\text{}^{68}\text{Ga}]\text{GaCl}_3$ purification, three different SPE resins were tested to isolate Ga-68 from Zn-68 and other radionuclide/metallic impurities. As presence of metal contaminants can adversely affect radiolabelling efficiency, the quality of $[\text{}^{68}\text{Ga}]\text{GaCl}_3$ purified from each procedure was assessed through $[\text{}^{68}\text{Ga}]\text{Ga-DOTATATE}$ radiolabelling. The simplest of the three purification procedures was using a single cartridge, TK400 (an octanol-based resin, 2mL) as reported by Tieu et al, 2019. Considering the operational simplicity and limited number of steps leading to short processing time and easy automation, we were willing to evaluate single cartridge purification method first. Although the best $[\text{}^{68}\text{Ga}]\text{GaCl}_3$ purification yield out of the three purification procedures was achieved using TK400 cartridge (as shown in data given in Table 1), but we were not able to produce $[\text{}^{68}\text{Ga}]\text{Ga-DOTATATE}$ in satisfactory radiochemical purity (analysed by radio-iTLC) using TK400 alone. Our first thought here was the lower pH of the radiolabelling reaction as $[\text{}^{68}\text{Ga}]\text{GaCl}_3$ from TK400 is eluted straight after Zn recovery step (with no additional step/cartridge to adjust HCl molarity), but after additional radiolabelling experiments with careful control on labelling parameters including reaction pH (adjusted using 2M NaOH solution), temperature, and peptide concentration, the radiochemical purity of resulting $[\text{}^{68}\text{Ga}]\text{Ga-DOTATATE}$ (analysed by iTLC) was below 80%. The bad radiolabelling of $[\text{}^{68}\text{Ga}]\text{Ga-DOTATATE}$ could also be due to excess of Zn-68 co-eluting with $[\text{}^{68}\text{Ga}]\text{GaCl}_3$ as we could see turbidity/precipitation in Zn^{+2} metal testing purified by TK400 alone. But since our primary objective was to establish a reliable purification method capable of producing $[\text{}^{68}\text{Ga}]\text{GaCl}_3$ in adequate quality for subsequent use in $[\text{}^{68}\text{Ga}]\text{Ga-DOTATATE}$ radiosynthesis, further optimization using the single-cartridge method was not pursued.

The two-cartridge purification including a combination of TK400/TK200 and ZR/TK200 cartridges was evaluated later according to published procedures (Thisgaard et al, 2021 and Svedjehed et al, 2022). The overall workflow using both set of cartridges was quite similar, except for minor differences in HCl molarity used for cartridge conditioning or activity loading/unloading, hence it was possible to implement same automation script using any of the purification method. Thisgaard et al. used an additional cartridge, LN (containing an acidic alkylphosphorus resin, 2mL) to selectively trap iron and remaining impurities before Ga-68 was loaded to TK200 cartridge. Likewise, Svedjehed et al. used an A8 cartridge (an anion exchange resin, BioRad) before loading Ga-68 to TK200. As separation of Ga-68 from Zn-68 is primarily achieved through TK400 or ZN cartridge, and TK200 is used to extract remaining radionuclide impurities being produced during irradiation/target dissolution or to lower acid molarity in

final [^{68}Ga] GaCl_3 sample, so we performed purification without LN or A8 cartridge. Also, having fewer purification steps without compromising quality of [^{68}Ga] GaCl_3 could be beneficial considering ease automation and especially the short half-life of Ga-68 involved in the process, so [^{68}Ga] GaCl_3 purification was evaluated using TK400/TK200 and ZR/TK200 set only.

The comparable [^{68}Ga] GaCl_3 purification yields were obtained using either ZR/TK200 or TK400/TK200 combination as given in Table 1, but ZR/TK200 set was selected for further development because slightly higher %RCY for [^{68}Ga] GaDOTATATE was obtained using [^{68}Ga] GaCl_3 purified using ZR/TK200 cartridges. Most importantly radio-iTLC of [^{68}Ga] GaDOTATATE using the ZR/TK200 purified [^{68}Ga] GaCl_3 was always > 98, even after 5 hours of EOP, whereas radio-iTLC of [^{68}Ga] GaDOTATATE using [^{68}Ga] GaCl_3 purified by TK400/TK200 was at borderline (96–98%) at EOP, and %RCY could be risked further considering couple of hours of product stability need for transportation and late-schedule patients. Importantly, the purified [^{68}Ga] GaCl_3 collected using ZR/TK200 was consistently suitable for [^{68}Ga] GaDOTATATE radiolabelling demonstrating effective removal of Ga-68 from Zn-68 or other metallic/radionuclide impurities that were probably interfering with [^{68}Ga] GaDOTATATE radiolabelling using TK400/TK200 or a single-cartridge method.

Table 2

Validation results of [^{68}Ga]Ga-DOTATATE radiosynthesis using ZR/TK200 purified [^{68}Ga]GaCl₃ and corresponding QC results demonstrating compliance with defined quality specifications for clinical use

Experiment details	V-01	V-02	V-03
Ga-68 activity used for purification (mCi)	2160	1565	1071
[^{68}Ga]GaCl ₃ collected after purification (mCi)	1190	885	539
[^{68}Ga]GaCl ₃ purification yield	55	56.5	50.3
Radionuclide Purity (Gamma spectrometry)	99.89	99.92	99.74
Radiochemical Purity (Radio-iTLC)	99.17	98.76	98.31
Half-life confirmation (CRC-25R)	67 minutes	70 minutes	69 minutes
Metals (Zn ⁺² , Fe ⁺² , Cu ⁺²)	0.3 µg/GBq of Ga-68	0.7 µg/GBq of Ga-68	0.9 µg/GBq of Ga-68
[^{68}Ga]GaCl ₃ used for [^{68}Ga]Ga-DOTATATE production (mCi)	680	572	428
Amount of DOTATATE peptide used for labeling (µL)	500	450	350
[^{68}Ga]Ga-DOTATATE activity collected in final formulation (mCi)	389	323	231
%Yield of [^{68}Ga]Ga-DOTATATE	57.2	56.4	53.9
Chemical/Radiochemical purity (Radio-TLC)	98.99	98.21	98.06
Radiochemical purity (Radio-HPLC)	> 99	> 99	> 99
pH of [^{68}Ga]Ga-DOTATATE formulation	7.3	6.8	7.5
Residual solvents (%Ethanol)	8.1	5.7	6.2
Osmolality (mOsm/Kg)	1854	1643	1471
Endotoxin testing (LAL)	< 5 Eu/mL	< 5 Eu/mL	< 5 Eu/mL
Sterility	Pass	Pass	Pass

After optimizing the [^{68}Ga]GaCl₃ purification and ensuring the [^{68}Ga]GaCl₃ quality is adequate to provide consistent [^{68}Ga]Ga-DOTATATE radiolabelling with > 98% purity in all aspects (as shown in Table 2), automation of [^{68}Ga]GaCl₃ purification and [^{68}Ga]Ga-DOTATATE radiosynthesis was performed using the NEPTIS radiosynthesis modules. Although automation of procedures was done on NEPTIS synthesizers, but overall process is simple and can easily be adopted to other radio synthesis modules. Since we were

willing to evaluate quality of each [^{68}Ga] GaCl_3 purification batch during validated runs, [^{68}Ga] GaCl_3 purification and radiosynthesis of [^{68}Ga] Ga -DOTATATE was performed using two NEPTIS modules placed in two separate hot cells, but for future work we are planning to shift production to Trasis AllinOne synthesizer to accomplish automation using one hot cell or move both NEPTIS radio synthesizer module in one hot cell where [^{68}Ga] GaCl_3 (after purification) will be taken directly by the second synthesizer for [^{68}Ga] Ga -DOTATATE radiosynthesis.

Conclusion

The main objective of this work is adaptation of an existing solid-target infrastructure to scalable production of [^{68}Ga] GaCl_3 and its subsequent use in radiosynthesis of [^{68}Ga] Ga -DOTATATE for clinical use. The work was particularly driven due to shortage of Ga-68 supply from $^{68}\text{Ge}/^{68}\text{Ga}$ generators, and growing clinical demand of ^{68}Ga -labeled radiopharmaceuticals notably the [^{68}Ga] Ga -DOTATATE. Even with purchase of three 50 mCi $^{68}\text{Ge}/^{68}\text{Ga}$ generators that are procured annually, the shortage of [^{68}Ga] Ga -DOTATATE was persistent resulting in patient rescheduling or delays in treatment planning, highlighting the urgency for a scalable and high throughput route to Ga-68 supply.

The proposed work provides a practical and cost-effective route to production sites already possessing a solid-target irradiation station and seek to establish local production of ^{68}Ga -labeled radiopharmaceuticals. Although, the study highlights production of Ga-68 only, but platform can surely be implemented to production of other clinically relevant radiometals as we are pursuing to adopt similar path to Cu-64 production as a subsequent step. Hence, the presented work does not only address the Ga-68 supply shortage but facilitates development of a local radionuclide production platform and thus maximizes the utilization of existing cyclotron and radio pharmacy infrastructure. Overall, the work reduces reliance on generator-based supply or continuing on expensive purchase of Ga-68 and demonstrates how strategic adaptation of an existing target infrastructure can overcome supply limitations and supports transition from dependence to scalable production of Ga-68 and possibly the other metal-based PET radiopharmaceuticals.

Abbreviations

DOTA

1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid

DOTATATE

DOTA-(Tyr³)-octreotate

Ga-68

Gallium-68

[^{68}Ga]-DOTATATE

^{68}Ga -labeled DOTA-(Tyr³)-octreotate

PET

Positron Emission Tomography
[⁶⁸Ga]GaCl₃
Gallium-68 chloride/trichloride
GBq
Gigabecquerel
MBq
Megabecquerel
Ci
Curie
mCi
Millicurie
Th-201
Thallium-201
I-123
Iodine-123
MeV
Million electron volts
μA
Microampere
μmol
Micromoles
EOB
End-of-bombardment
RCY
Radiochemical Yield
GMP
Good manufacturing practices
Eu. Pharm.
European Pharmacopeia
[¹⁸F]FDG
[¹⁸F]fluorodeoxyglucose
SSTR
Somatostatin targeting receptor
PSMA
Prostate-specific membrane antigen
t_{1/2}
Half-life
⁶⁸Ge/⁶⁸Ga
Germanium-68/Gallium-68

C&RD
Cyclotron and Radiopharmaceuticals Department
HCl
Hydrochloric acid
HNO₃
Nitric acid
M
Molar
KFSH&RC
King Faisal Specialist Hospital and Research Centre
Zn-68
Zinc-68
CMR
Centre for Molecular Research
SPE
Solid-phase extraction
ZR
Hydroxamate-based resin
TK400
Octanol-based resin TK200:tri-octylphosphine oxide-based resin
WFI
Water for injection
pH
potential of hydrogen
HpGe
High-purity germanium detector
iTLC
instant thin-layer chromatography
iTLC-SG
Instant thin-layer chromatography silica gel impregnated strips
APA
Apparent molar activity
HEPES
4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
TFA
Trifluoroacetic acid
ICP-MS
Inductively coupled plasma-mass spectrometry
SCX
Strong cation-exchanger

C18
Octadecyl-carbon resin
 $\text{Zn}(\text{OH})_2$
Zinc hydroxide
NaCN
Sodium cyanide
NaOH
Sodium hydroxide
 H_2O_2
Hydrogen peroxide
HPLC
High performance liquid chromatography
GC
Gas chromatography
NaI
Sodium iodide
LAL
Limulus Amebocyte Lysate.

Declarations

Ethical approval and consent to participate

Not applicable; this study did not involve human participants or human-derived data.

Consent for publication

Not applicable

Conflict of interest

The authors declare that they have no competing interests.

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Authors Contribution.

WR was responsible for overall planning and supervision of this study. He designed the experimental work, carried out the electroplating experiments, and performed optimization of target dissolution and [^{68}Ga] GaCl_3 purification procedures. Also, WR compiled the experimental data, interpreted the results, and prepared the manuscript for submission. SN assisted WR with radionuclide purification and particularly contributed to automation of [^{68}Ga] GaCl_3 purification and [^{68}Ga] Ga -DOTATATE radiosynthesis procedures. YY performed all quality control work for both [^{68}Ga] GaCl_3 and [^{68}Ga] Ga -DOTATATE including endotoxin and sterility testing. HA assisted WR with electroplating experiments and recovery of Ga-68 after irradiation experiments. AH assisted with SRIM simulation and computational aspects of the study. All authors have read and approved the final version of the manuscript.

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Availability of the data

and materials:

The supporting data is provided as supplementary info and can be downloaded from xxxxx.

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Figures

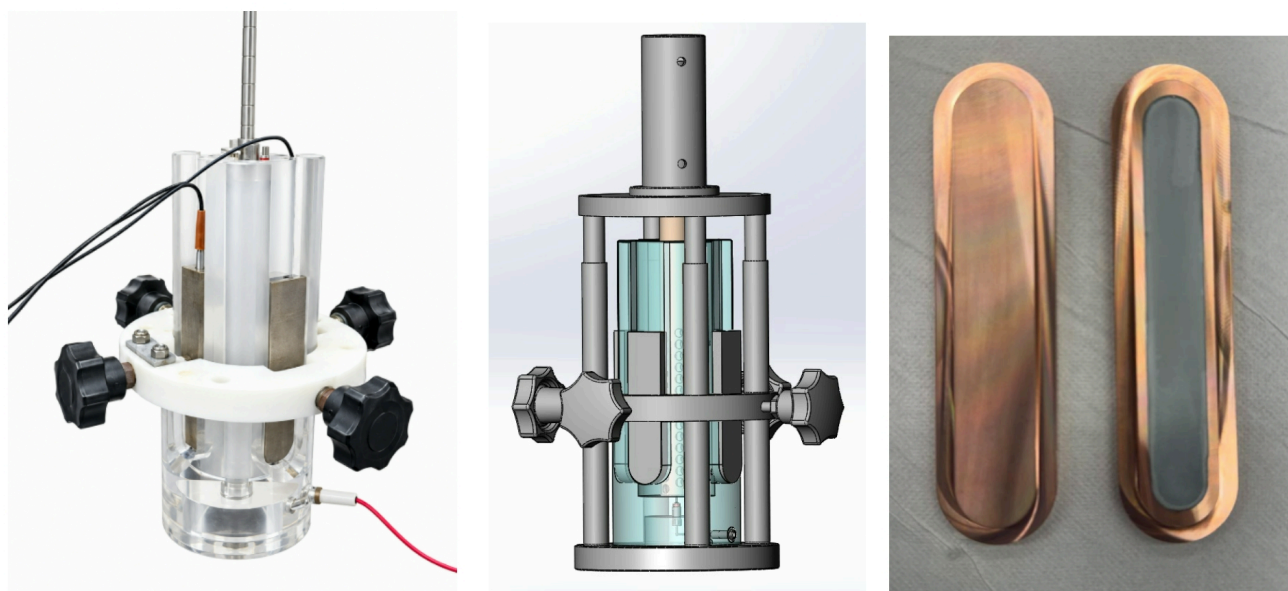


Figure 1

Electroplating chamber in its original shape (left) and schematic representation (middle) showing stirring rod in the middle, anode as red, and two black wires as cathode that are connected to copper target plates. Also, the target plates before and after Zn-68 electroplating are shown (right).

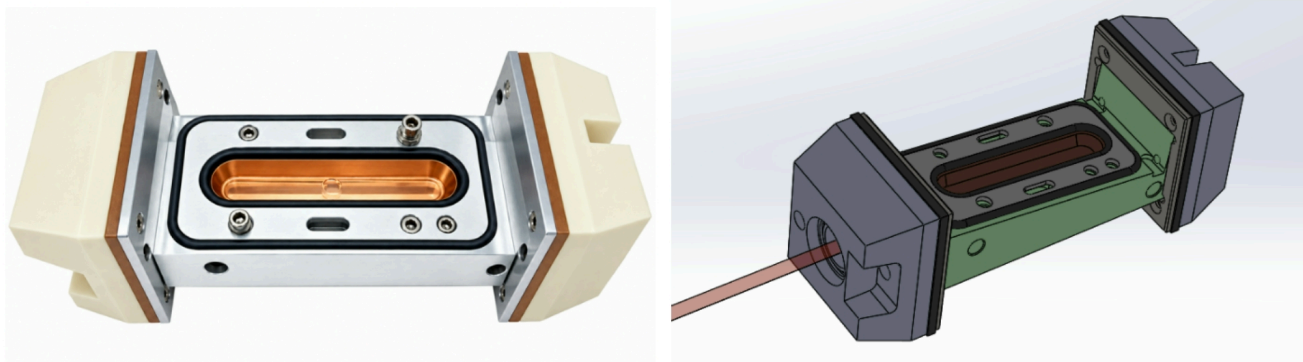


Figure 2

Target holder with Zn-68 plated target plate (upside down) in its original configuration (left) and schematic representation of incident proton beam hitting on the target material (right)



Figure 3

Target plate holder used for dissolution of the target material in open (left) and closed (right) shape. The cable supply visible in the picture is connected to an integrated heater, so (if required) dissolution can be performed while heating the target plate.

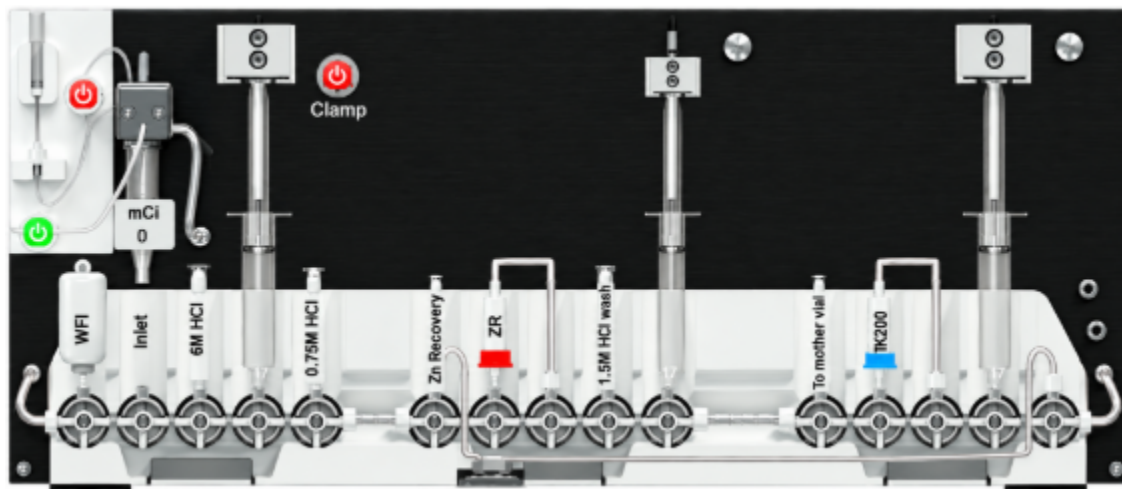


Figure 4

The automation script used for purification of $[^{68}\text{Ga}]\text{GaCl}_3$ using the NEPTIS radiosynthesis module.

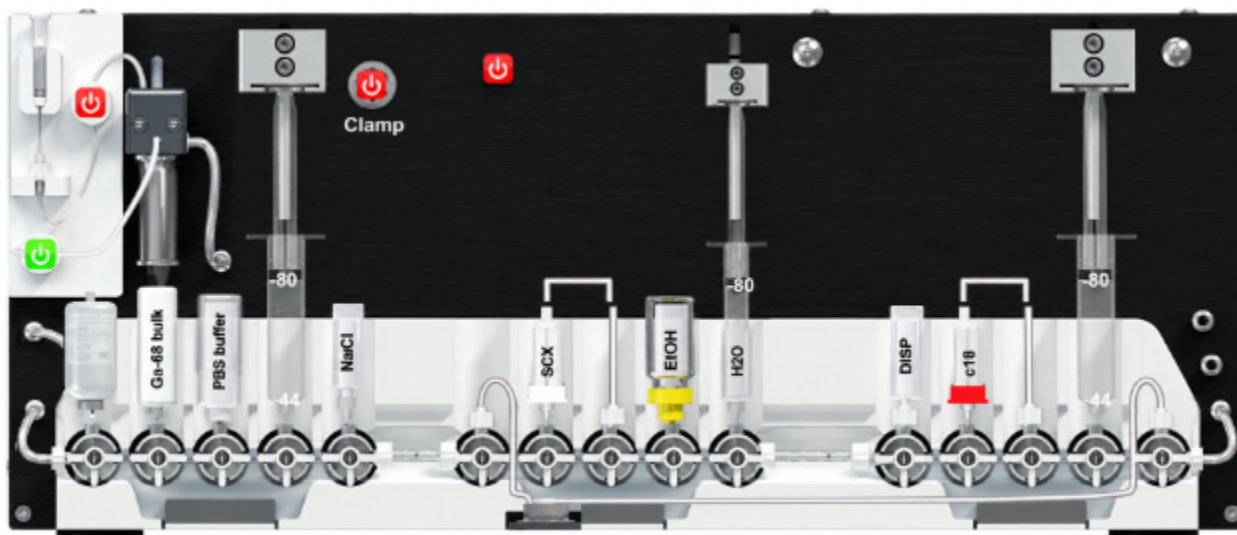


Figure 5

The automation script used for radiosynthesis of $[^{68}\text{Ga}]\text{Ga-DOTATATE}$ using the NEPTIS radiosynthesis module.

Supplementary Files

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