Optimized production and quality control of $^{68}$Ga-DOTATATE

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ABSTRACT

Introduction: Optimized production and quality control of $^{68}$Ga-DOTATATE as an efficient and preferable PET radiotracer for somatostatin receptor imaging in neuroendocrine tumors is of great interest. In this study effort has been made to present a fast, efficient, cost-effective and facile protocol for $^{68}$Ga-DOTATATE productions for clinical trials.

Methods: $^{68}$Ga-DOTATATE was prepared using generator-based $[^{68}\text{Ga}]{\text{GaCl}_3}$ and DOTATATE at optimized conditions for time, temperature, ligand amount, gallium content and column cartridge purification followed by proper formulation. The biodistribution of the tracer in rats was studied using tissue counting and PET/CT imaging up to 120 min.

Results: $^{68}$Ga-DOTATATE was prepared at optimized conditions in 7-10 min at 95°C followed by SPE using C$_{18}$ cartridge (radiochemical purity $\approx$99±0.88% ITLC, >99% HPLC, specific activity: 1200-1850 MBq/nM). The biodistribution of the tracer demonstrated high kidney uptake of the tracer in 10-20 min consistent with reported somatostatin receptor mappings.

Conclusion: The entire production and quality control of $^{68}$Ga-DOTATATE is presented including labeling, purification, HPLC analysis, sterilization and LAL test) took 18-20 min with significant specific activity for administration to limited number of patients in a PET center.

Key words: $^{68}$Ga-DOTATATE; Production; Quality control; Optimization; PET/CT
INTRODUCTION

The development of facile, accessible, easy to use preparation and quality control methods for supplying PET radiopharmaceuticals initiated a great interest in developing generator-based PET radiopharmaceuticals including \(^{62}\text{Zn}/^{65}\text{Cu}\) and \(^{68}\text{Ge}/^{68}\text{Ga}\) generators. Thus, the high costs of installation and running a cyclotron in every nuclear medicine center are of less concern especially for large countries. Many Ga-68 generators have been developed by the industries and local vendors based on organic and inorganic solid phases [1-3].

On the other hand, the development of Ga-68 radiopharmaceuticals was parallel to the development of peptide-based radiopharmaceuticals in last 2 decades while the physical half-life of this radionuclide with biological half-life of synthetic peptides was in great accordance typically the most important \(^{68}\text{Ga}\)-peptide radiopharmaceuticals are somatostatin analogs [4]. Starting \(^{68}\text{Ga}\)-DOTATOC applied in the detection of malignancies [5] with high affinities for SS2 and SS3 and lower affinity for SSR5 was shown to be highly accurate in the diagnosis of neuroendocrine tumors, meningiomas, thyroid malignancies, and prostatic cancers as well as many other tumors [6]. However DOTATOC imaging also has limitations showing false positive data for non-tumor tissues in the pancreas, pituitary gland, and in chronic inflammatory conditions [7].

The other developed somatostatin ligand for PET somatostatin receptor imaging is \(^{68}\text{Ga}\)-DOTATE. The recent studies showed while \(^{68}\text{Ga}\)-DOTATOC and \(^{68}\text{Ga}\)-DOTATE considered equally well for staging and patient selection for peptide receptor radionuclide therapy with \(^{177}\text{Lu}\)DOTATE, the slight difference in the healthy organ distribution and excretion may render \(^{68}\text{Ga}\)-DOTATE preferable [8].

In many other studies in neuroendocrine tumors, \(^{68}\text{Ga}\)-DOTATE demonstrated high sensitivity and specificity [9]. Also preliminary results showed that \(^{68}\text{Ga}\)-DOTA-TATE has a higher lesion uptake even in well-differentiated thyroid cancer patients and may have potential advantage over \(^{68}\text{Ga}\)-DOTA-NOC, the other known Ga-68 somatostatin ligand [10].

These findings encouraged the initiation of many clinical trials in many countries using \(^{68}\text{Ga}\)-DOTATE. Regarding the use of newly developed generator in the country and the necessity of its evaluation for peptide radiolabeling performance, a detailed, comprehensive study was intended in order to demonstrate the capability of the \(^{68}\text{Ga}\)-labeling of low molar ratios of peptides as is usually described in human being. The need for a fast, small-scale, cost effective production and quality control protocols of this tracer in small radiochemistry labs in these states is also of great interest. The production of this tracer and other peptides using various Ga-68 generators has been reported previously [1-3].

In this work using a small-scale locally-made Ga-68 generator, the most desired Ga-68 tracer for study of somatostatin receptor, i.e. \(^{68}\text{Ga}-\text{DOTATATE}\), for clinicians [11] was developed and passed the quality control tests with reasonable time and costs. Using specific sterile considerations the daily production of the tracer covers 1-2 patients per day with limited irradiation to the personnel.

METHODS

The \(^{68}\text{Ge}/^{68}\text{Ga}\) generator (30 mCi/day activity) was obtained from Pars Isotope Co. Karaj, Iran. Chemicals were purchased from the Aldrich Chemical Co. (Germany). Reverse phase liquid chromatography (RP-HPLC) was performed for radiolabeling and specific activity analyzed of the final product using a KNAUER-D-14163 system, Berlin, Germany using Mobile phase of A: Ultrapure water-TFA 1% (V/V); B: Acetonitrile HPLC Grade using gradient-elution: 0-3 min, A:100%, B: 0%; 3-10 min, A:50%, B: 50%; 10-15 min, A:0%, B:100%; Flow rate:1.5 mL/min; Injection volume: 20 µL. The used was, MZ-Analysentechnik, ODS-H 5µm (100×4.0 mm), Gamma detector: Ray test, Gabi gamma ray detector. Thin layer chromatography (TLC) for DOTATATE quality control was performed on polymer-backed silica gel, F 1500/LS 254, 20 × 20 cm, TLC Ready Foil, Schleicher &Schuell®, (Germany). Normal saline and sodium acetate used for radiolabeling were of high purity and had been filtered through 0.22 µm Cativex filters. Instant thin layer chromatography (ITLC) was performed by counting Whatman No. 2 papers using a thin layer chromatography scanner, Bioscan AR2000, Bioscan Europe Ltd (France). Biodistribution data were acquired by counting normal saline washed tissues after weighting on a Canberra™ high purity germanium (HPGe) detector (model GC1020-7500SL). Radionuclidic purity was checked with the same detector. For activity measurement of the samples a CRC Capintech Radiometer (NJ, USA) was used. Animal studies were performed in accordance with the United Kingdom Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations, 2nd edn. Images were taken in coincidence mode of a Dual-Head SPECT system (SMV, France, Sophia DST-XL).

\(^{68}\text{Ge}/^{68}\text{Ga}\) generator

A prototype 30 mCi \(^{68}\text{Ge}/^{68}\text{Ga}\) generator developed at Pars Isotope Co. Iran, was used in this study [2]. Briefly, metallic gallium powder was melted and...
transferred in niobium capsules and sure sealed. The target was irradiated at 29 MeV energy at a 30 MeV IBA cyclotron (effective 22 MeV protons on the target material). After irradiation the target material was dissolved in 12 M H2SO4 while gently heated and stirred. For increasing the solubility, 30% hydrogen peroxide was added to the mixture followed by the addition of 2 M HCl (30 ml). After completion of the dissolution, carbon tetrachloride (150 ml) was added to the mixture and the organic layer containing 68Ge was extracted from 68Ga containing aqueous solution. 68Ge is then back-extracted into aqueous solution using 0.05 M HCl. The final solution is then used in the manufacture of a SnO2-based generator.

Control of radiochemical purity: Gamma spectroscopy of the final sample was carried out counting in an HPGe detector coupled to a Canberra™ multi-channel analyzer for 1000 seconds. Breakthrough was measured by counting the same sample 48 h after the first test for the detection of small amount of Ge-68 in sample.

Chemical purity control: This step was carried out to ensure that the amounts of Sn, Zn, Fe, germanium and gallium ions resulting from the target material and backing in the final product are acceptable regarding internationally accepted limits. Chemical purity was checked by ICP-OES method. The detection limit of our system was 0.1 ppm for all cations.

Radiochemical purity control: In order to determine the radiochemical purity of the eluted Ga-68 activity, ITLC chromatograms of 68GaCl3 solution in 10% ammonium acetate:methanol on silicagel sheets and in 10 mM DTPA solution (pH- 4) on Whatman No. 1 paper were performed to check the percentage of the colloidal Ga-68 fraction and/or non-cationic gallium species.

Preparation of [68Ga]DOTATATE

The acidic solution of [68Ga]GaCl3 with highest activity from the 3 first 1 mL-elution of the generator (25±2mCi, in 0.6M HCl) was transferred to a 10 ml-borosilicate Reacti-vial containing solid HEPES (530 mg), acetate buffer 20 µL (0.1 M), and DOTATATE solution (33.3, 16.65, 8.32, 4.16 µg in DDH2O) and sealed vial was heated to 80-95°C for 5-10. The mixture put in an ice bath for 2 min followed by the addition of 8 ml of DDH2O. The reaction mixture was then injected into a C18 Sep-Pak Cartridge (Waters) preconditioned with ethanol and water (2:5 ml) according to the vendors protocol. The column was then flushed with air (10 ml) and the amount of the trapped and passed activity was measured. The column was finally washed with ethanol (1ml) and normal saline (9ml) through a 0.22 micron antimicrobial filter into a sterilized vial. The pH of the active solution with acceptable radiochemical purity was adjusted to 5.5.

Quality control of [68Ga]DOTATATE

Radio thin layer chromatography: A 5 µl sample of the final fraction was spotted on a Whatman No.2 paper and SG-TLC stationary phases and methanol: saline mixture (5:1) as well as normal saline were used as mobile phases.

High performance liquid chromatography: HPLC was performed with a flow rate of 1.5 ml/min, pressure: 130 psi for 15 min. HPLC was performed on the final preparation using a gradient of water:acetonitrile(0-100:100-0 % added: 0.1% trifluoroacetic acid) as the eluent by means of reversed phase column chromatography as explained in the experimental section.

Biodistribution in wild-type rats: The distribution of the radiolabeled complex as well as free Ga-68 cation among tissues was determined rats. The total amount of radioactivity injected into each rat was measured by counting the 1-ml syringe before and after injection in a dose calibrator with fixed geometry. The animals were sacrificed by CO2 asphyxiation at selected times after injection (n=5 for each time interval), the tissues (blood, heart, lung, brain, intestine, faeces, skin, stomach, kidneys, liver, muscle and bone) were weighed and rinsed with normal saline and their specific activities were determined with a HPGe detector equipped with a sample holder device as percent of injected dose per gram of tissues.

PET/CT imaging of [68Ga]DOTATATE in wild-type rats

The PET/CT imaging was performed on the Siemens Biograph 6 clinical PET/CT scanner. The rats were placed in supine position and CT scans performed for anatomical reference and attenuation correction (spatial resolution 1.25 mm, 80 kV, 150 mAs) with a total CT scanning time of 20s. Static PET images were acquired for 15 min with 3 sets of emission images starting 45 and 90 min after radiotracer injection for the first rat and after 120 min for the second rat. The SUVmax of the liver, kidneys and bladder with related SUVmax ratios were measured. Reconstruction was performed using the TrueX algorithm with attenuation correction. The reconstruction settings were 2 iterations and 21 subsets to a 336×336 matrix, with a post filtering of 5 mm. Transmission data were reconstructed into a matrix of equal size by means of filtered back-projection, yielding a co-registered image set.
RESULTS

Development and quality control of ⁶⁸Ga generator

Radiochemical separation of Ge-68 from irradiated natural Ga was performed by a two-step extraction in an organic solution followed by back extraction with 96% yield. The presence and absence of ⁶⁸Ga and ⁶⁸Ge was checked at each step using HPGe detector.

Radionuclidic control showed the presence of 511 and 1077 keV all originating from ⁶⁸Ga and showed a radionuclidic purity higher than 99% (E.O.S.).

For the quality control of the ⁶⁸GaCl₃ solution, a time-activity study performed at the eluted sample after >>10 half-lives of the ⁶⁸Ga in order to check the ⁶⁸Ge breakthrough. The data was recorded up to 8 days after elution. Calculations showed that the ⁶⁸Ge/⁶⁸Ga activity ratio was 1.6600 ×10⁻⁵ at the time of elution.

The concentrations of tin (from generator material), iron (from the sealing parts and acid impurities), zinc (as a decay product) and gallium (as the target material) were determined using inductively coupled plasma (ICP-OES) method (Table 1). The results showed desired chemical purities for all cation impurities during the development generator generations with different particle sizes and packing procedures.

<table>
<thead>
<tr>
<th>Element</th>
<th>Generator 1 (mg/L)</th>
<th>Generator 2 (mg/L)</th>
<th>Generator 3 (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe</td>
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<td>0.432</td>
<td>0.230</td>
</tr>
<tr>
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<td>&lt;0.1</td>
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<tr>
<td>Zn</td>
<td>0.284</td>
<td>0.110</td>
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<tr>
<td>Ge</td>
<td>&lt;0.1</td>
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Table 1: ICP mass data on various prototype generators’ elutions used in this study.

The radiochemical purity of the ⁶⁸GaCl₃ solution was checked in two solvents. In 10 mmol*L⁻¹ DTPAaq. solution (solvent 1), free ⁶⁸Ga⁺⁺ is coordinated to more lipophilic moiety as ⁶⁸Ga(DTPA)²⁻ and migrates to higher Rᵣ. Small radioactive fraction remaining at the origin could be associated to colloids, since in presence of very strong complexing agent (i.e. DTPA), existence of other ionic species than ⁶⁸Ga(DTPA)²⁻ is rare. On the other hand, 10% ammonium acetate: methanol mixture (1:1) (solvent 2) was also used for the determination of radiochemical purity.

The fast eluting species was possibly ⁶⁸Ga and other ionic forms of Ga-68 such as ⁶⁸GaCl₃⁻ (if existed) remained at the origin (Rᵣ0) as well as colloids (not detected).

The differences in the impurity peaks in the two chromatograms could be in part related to the presence of a colloidal impurity which was insignificant. Also insignificant (about <1%) amount of activity can be attributed to other ionic impurities.

Radiolabeling

Many considerations must be taken into account for peptide radionucliding, some influence the radiochemical purity of the complex and some would change the quality of the formulation for human applications [12]. The interaction of all factors is usually crucial for obtaining suitable radiopharmaceutical compounds.

Elution: The elution portfolio of the generator are important since the narrower the activity/volume peak, a sample with higher specific activity is obtained for radiolabeling however using 1M or higher concentration of HCl solutions although usually yield a better radioactivity peak/elution, however the formation of other gallium species not entering the radiolabeling occurred at these concentrations. By the choice of a suitable concentration (0.6-0.7M) most of daily generator eluted activitywas obtained and also the peak of activity ranges for 0.5-1.5 ml of the first elution.

Acidity: It has been shown that the pH of radiolabeling for most of peptide reactions is in the range of 4-5, thus Ga activity elution's using 0.6-0.7 M HCl usually possess low pHS at the range of 1-2 which does not allow the direct use of the elution in the radiolabeling process. Some early investigators reported the evaporation of the of the eluted activity followed by reconstitution in an appropriate buffer, however due to the limited physical half-life of the radionuclide, the addition of calculated amount of solid appropriate base/salt to the elution is proposed as a fast and reliable method.

Time: All considerations are taken into account for minimizing the reaction/purification/formulation process times. Evaporation of the eluent was replaced by the addition of the appropriate base (HEPES) as described above, heating the mixture would shorten the reaction time also should be carefully investigated. The application of solid phase purification method not only minimizes the reaction time and purification but also allows for application extraamounts of Ga activity to get higher yields and specific activities.

Peptide amount: Peptides are highly efficient biological compounds, effective at milli and even microgram scales, leading to side effects if used in higher doses. Usually tracers are used at sub-pharmacological doses in imaging, while these materials are also expensive. The existence of unlabeled peptide in formulations not only blocks the
receptor sites competing the application of radiotracer at molecular level but also will lead to unwanted biological reactions. A series of reactions performed in order to reach the minimal peptide amount needed leading to the application of 8-2 µg of peptide used for a typical labeling.

**Metal content:** The presence of metal impurities affect complexation reaction due to the presence of impurities at ppm levels compared to the existence of Ga-68 cation at ppb or even less amounts. Usually the radiolabeling yield decreases with the competition of other cations esp. ferric cation in the radiolabeling reaction, leading not only to lower specific activity, but also competition at the receptor level. This is why the amount of cation release from a generator should be checked so often not only in the beginning of the generator application in any center but also routinely. Long term radioysis reaction occurring in the matrix of the generator is a major concern. Also the interaction of Zn, Ga with DOTA moiety is reported leading to the unwanted reaction with conjugated peptide. The routine daily or twice a week elution of the generator even if not used for the radiolabeling, would help the removal of unwanted cold cation presence in the radiolabeling eluent.

**Solid-phase extraction:** In order to get the best specific activity using the minimum peptide amount, usually the best partition eluted from the generator with highest activity is used in radiolabeling which usually lead to the presence of extra amount of unreacted Ga content. The removal of the excess gallium cation from the reaction mixture is easily performed using a Light C_{18} Cartridge available. During the optimization of radiolabeling procedure for using a new generator, the exact determination of injected radioactivity, flow through activity, eluted activity (using the final eluent) and also retained activity on the C_{18} column is of great importance. In many cases when the activity is not absorbed on the column and is just passed through, denotes the presence of the Ga ionic species than Ga^{3+} usually formed while high concentration HCl. On the other hand in cases where the activity is retained on the column usually the formation of colloids is suspected. These findings usually can be refrained by radiochemical purity control of the generator eluent. In a normal run with optimized conditions usually high radiochemical purity (>99%) with 60-75% of radiochemical yield is obtained (Figure 1). Figure 2 shows the HPLC chromatogram of an optimized radiotracers production on a reverse phase column using a gradient of water to acetonitrile.

The high polarity of the starting eluting mobile phase (H_{2}O 100%) would let to the fast removal of any free cation from the column with retention time of 0.7-1 min, while with increasing the amount of acetonitrile content in the mobile phase mixture the radiolabeled complex is washed out (9-10 min). Usually for better reproducibility the column is washed for 20 minutes followed by washing by water again.

Fig. 1. ITLC of {\textsuperscript{68}}GaCl\textsubscript{3} (left) and {\textsuperscript{68}}Ga-DOTATATE (right) in methanol: saline (5:1) mixture as mobile phase on Whatman No.2 paper.

**Biodistribution**

Biodistribution studies were performed for \textsuperscript{68}Ga-DOTATATE and free Ga\textsuperscript{3+}. As reported previously, \textsuperscript{68}Ga is excreted majorly from gastrointestinal tract (GIT) with high blood content due to transferrin binding at early time intervals, as well as significant colon, bone and stomach activity content is observed, kidney is not a significant accumulation site (not shown). As a radiolabeled peptide complex is rapidly washed out from the blood circulation into receptor rich organs with very low uptake in the liver. As an inhibitory hormone, somatostatin has activity in stomach reducing the emptying rate as well as relaxing smooth muscles in gastrointestinal system (Figure 3).
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Fig 3. Biodistribution of $^{68}$Ga-DOTATATE (37 MBq, 100μCi) in wild-type rats 15-120 min after iv injection via tail vein (%ID/g: percentage of injected dose per gram of tissue calculated based on the area under curve of 511 keV peak in gamma spectrum) (n=5).

Imaging studies

As shown in Figure 4, the MIP (Maximum Intensity Projection) images of injected rats clearly show the significant activity concentration of $^{68}$Ga-DOTATATE in kidneys. The low levels of uptake in other organs were clearly seen.

For quantitative uptake behavior, maximum standard uptake values (SUVmax) were measured for liver, kidney and bladder in all imaging studies. In Figure 4-A, the SUVmax were 1.37, 1.06, 0.37 and 0.27 for right kidney, left kidney, bladder and liver 45 minutes after $^{68}$Ga-DOTATATE injection in the first rat. PET/CT imaging, 90 minutes after injection, shows the reduction of the aforementioned values to 1.23, 0.94, 0.27 and 0.18 for right kidney, left kidney, bladder and liver, respectively. The kidney uptake was more pronounced when comparing the SUVmax values of kidneys to liver. The activity content in organs in 60-120 minutes post injection is almost the same as what was observed in 30 min, showing the receptor binding of the tracer in all images.

DISCUSSION

As a radiolabeling source for Ga-68 based radiopharmaceuticals specially ligands with very low molarities (including peptides), the chemical purity is crucial and usually this chemical purity suffice the...
procedure. Thus the presence of metal impurities is comparable or even better than other commercial generators eluents.

Fig 5. PET/CT fused images of [68Ga]DOTATATE in two rats; A) Static PET/CT scans of the first rat, 45 and 90 minutes after injection, show significant accumulation of [68Ga]DOTATATE in kidneys. B) PET/CT fused image of the second rat, 120 minutes after injection. The injected doses were 4.4MBq for both rats.

One important issue in the eluted activity was the determination of Ga-68 radiochemical form. In highly acidic elutions the formation of other ionic complexes from the generator was possible including $^{68}$GaCl$_4^-$. In many cases this species present in the solution did not participate in complexation process. Dilution and/or pH changes also were not possible due to the formation of volatile species and/or high ionic strength of the solution not recommended for radiopharmaceuticals.

Recent studies have shown that in addition to brain, gut and neuroendocrine localizations, somatostatin receptors are expressed in most lymphatic tissues, (including gut-associated lymphatic tissue), spleen and thymus; in the cortical and medullary area of the kidney; in the stroma of the prostate and in the epithelial cells of the thyroid [13].

In our study however due to the systemic injection of the tracer blood brain barrier penetration was not observed leading to low accumulation in brain. In case of spleen a significant uptake observed 30 min post injection. Stomach is the major accumulation site which has been shown repeatedly by many reports.

Also kidneys are another major site of accumulation not only due to the urinary excretion of the hydrophilic peptide but also the presence of high concentrated somatostatin receptor (SSTR) in the cortical and medullary area of the kidney.

The integration of the ligand in receptor rich organ cells is a major cause of stable accumulation of the tracer in all time intervals [14], which has also led to the development of therapeutic radiolabeled DOTATATE complexes including $^{177}$Lu-DOTATATE and $^{90}$Y-DOTATATE [15].

At optimized conditions, 5-10 micrograms of the peptide was used for the preparation of $^{68}$Ga-DOTATATE using 20-25 mCi (1-1.5 ml) of freshly eluted Ga-68 in 7-10 min at 95°C followed by SPE using C$_{18}$ cartridge leading to the radiochemical purity of >99% using HPLC and specific activity of 1200-1850 MBq/nM. These findings are far better than the reported peptide used in the automated, semi-automated methods using other generators, (1-3), possibly due to the better performance of the solid phase used in terms of minimum possible metal impurities and solid phase particle size and exact use of buffering agent.

CONCLUSION

$^{68}$Ga-DOTATATE complex was prepared in high radiochemical purity (>99%, ITLC, HPLC) and specific activity of 1200-1850 MBq/nM. The time, temperatures, buffer content, and solid phase purification factors were all optimized for developing a clinical batch under sterile conditions. A 25-30 mCi eluted Ga activity from the generator was radiolabeled at 95°C using 2-8 micrograms of the starting commercial peptide in 6 minutes followed by purification and formulation of the tracer for injection. An 8-10 min quality control time for simultaneous RTLC and HPLC was also needed. The biodistribution of the tracer demonstrated intestine, spleen and medullary kidney uptake all in accordance with the reported somatostatin receptor distribution in rat and other mammals. This study can be used as an optimized protocol for production and quality control of $^{68}$Ga-DOTATATE and possibly other radiolabeled Ga-68 peptides for clinical applications in nuclear medicine centers far from a cyclotron facility by using a Ga-68 generator.

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