Optimization of the Use of the DOTATATE Kit Manufactured by the Thailand Institute of Nuclear Technology Using a SiO_2-based $^{68}Ge/^{68}Ga$ Generator

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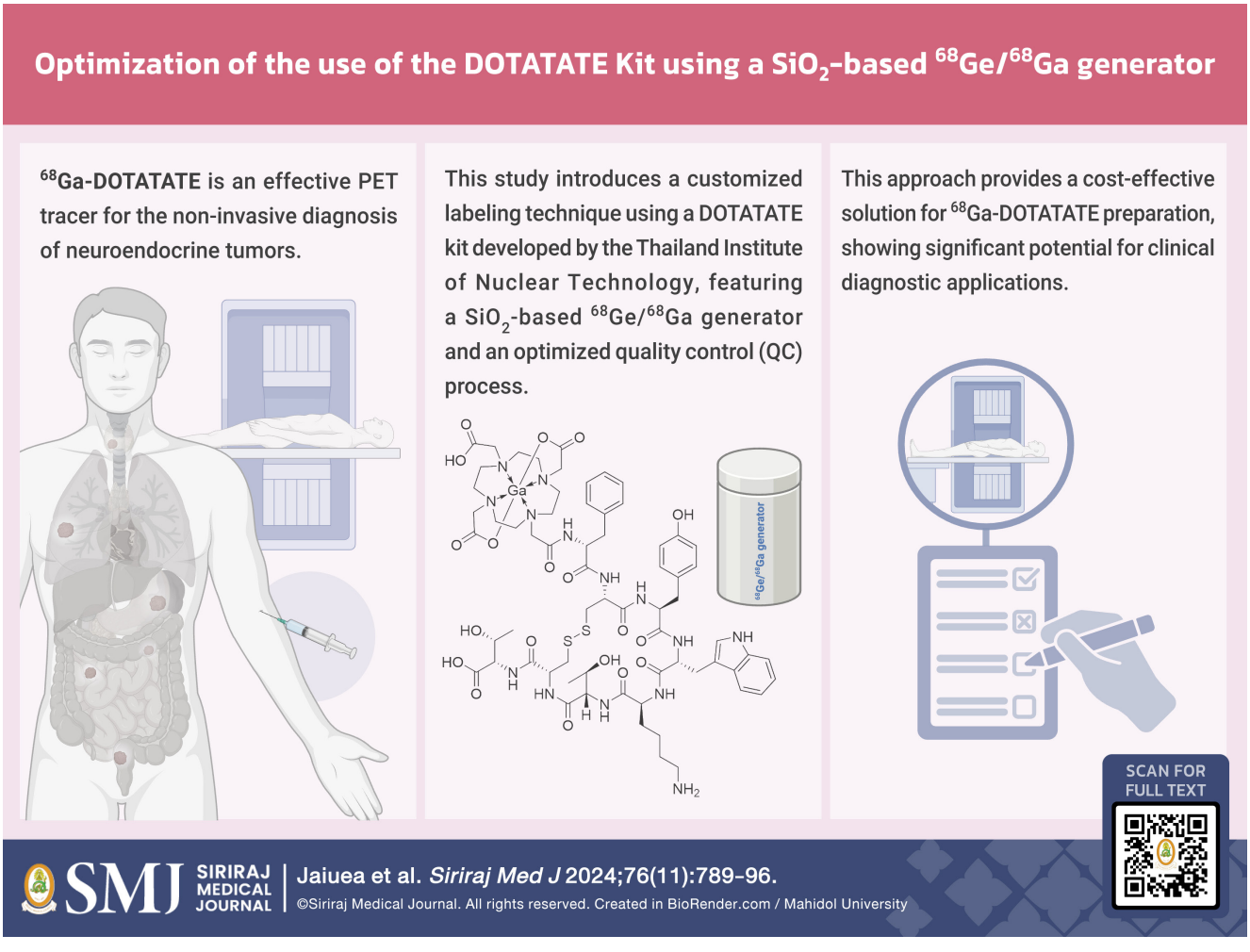

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Received 9 July 2024 Revised 29 August 2024 Accepted 7 September 2024
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https://doi.org/10.33192/smj.v76i11.270157

ABSTRACT

Objective: The presence of somatostatin receptors on neuroendocrine tumours enables ^{68}Ga-DOTATATE to precisely detect lesion localization and staging. Thailand Institute of Nuclear Technology (TINT) recently developed a DOTATATE kit for labelling with Ga-68, which is compatible with a TiO_2-based ^{68}Ge/^{68}Ga generator eluted with 0.1 M HCl, but presents a discrepancy with other types of ^{68}Ge/^{68}Ga generators. This research aimed to optimize a radiolabelling method using TINT's kit with a SiO_2-based ^{68}Ge/^{68}Ga generator eluting Ga-68 in 0.05 M HCl. Additionally, a quality control protocol was developed to ensure the formulation's efficacy and reliability in compliance with the 10th edition of the European Pharmacopoeia.

Material and Methods: The SiO_2-based ^{68}Ge/^{68}Ga generator was eluted with 2–4 ml of 0.05 M HCl, added into a lyophilized kit, heated in a dried-block heater at 100 °C for 15 min, cooled down at room temperature, and finally purified using Sep-Pak C18 cartridge. The radiochemical purity was determined by radio thin-layer chromatography and the radioactivity was measured by a gamma well counter. Reproducibility and stability tests were conducted three times.

Results: Employing 4 ml of eluted material, comprising the second and fifth millilitres of $^{68}GaCl_3$, provided a radiochemical purity (RCP) exceeding 95% after purification. Also, ^{68}Ga-DOTATATE remained stable in refrigerator for at least 4 half-lives.

Conclusion: TINT's DOTATATE kit can be successfully labelled with a SiO_2-based ^{68}Ge/^{68}Ga generator, providing ^{68}Ga-DOTATATE with an RCP > 95% for at least 4 half-lives when stored in refrigerator after production. This radiolabelling procedure is suitable for routine clinical application.

Keywords: ^{68}Ga-DOTATATE ; TINT kit ; neuroendocrine tumor, Ga-68 elution ; radiochemical purity (Siriraj Med J 2024; 76: 789-796)

INTRODUCTION

Neuroendocrine tumors (NETs) encompass a diverse group of malignancies arising from neuroendocrine cells, which can be found in various organs throughout the body. As non-functioning tumours, NETs may not cause noticeable symptoms until they grow large enough and metastasize to the liver.[1,2] The global incidence rate of NETs is on the rise, and is currently estimated to affect approximately 4 per 100,000 adults.[3]

Somatostatin receptors (SSTRs), found on the surface of neuroendocrine cells, play critical roles in regulating physiological processes and maintaining homeostasis within the endocrine and nervous systems. SSTRs belong to a family of G protein-coupled receptors with various subtypes, including SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5. Among these SSTRs, SSTR2 stands out as a crucial theranostic target.[4] The SSTR2 RNA yields two splice variants: SSTR2a and SSTR2b, differing in length. The activation of SSTRs occurs through somatostatin (SST), a neuropeptide, which exists in two isoforms known as somatostatin-14 (SST-14) and somatostatin-28 (SST-28), both displaying high affinity for SSTRs.[5,6] The SST-system plays a pivotal role in regulating numerous physiological processes. It operates through multiple pathways activated upon SST binding to SSTRs, leading to either the inhibition of hormone secretion and cell proliferation or the induction of apoptosis.[7,8]

The overexpression of somatostatin receptors (SSTRs) on NET cells surfaces has significant clinical implications as a target for the specific binding of somatostatin analogues, such as octreotide[9], octreotate[10], lanreotide[11], and vapreotide[12], leading to the inhibition of hormone secretion and tumour growth. In addition, these somatostatin analogues can be further conjugated to DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid[13], which can be chelated to trivalent radionuclides in theranostic approaches.[14-16]

On 1 June 2016, the DOTATATE kit (Netspot®, previously Somakit-TATE) was approved by the US Food and Drug Administration (FDA)[17] for preparation of ^{68}Ga-DOTATATE (Fig 1), which is used to detect somatostatin receptor positive NETs in adult and paediatric patients. Various Ga-68 labelling kits are commercially available, predominantly sourced from Europe, notably Germany.[18-23] Recently, the Thailand Institute of Nuclear Technology (TINT) introduced a DOTATATE kit tailored for Ga-68 labelling, showcasing the domestic capability of Thai researchers in cold kit production. This kit formulation aligns with a TiO_2-based ^{68}Ge/^{68}Ga generator eluted with 5 ml of 0.1 M HCl.

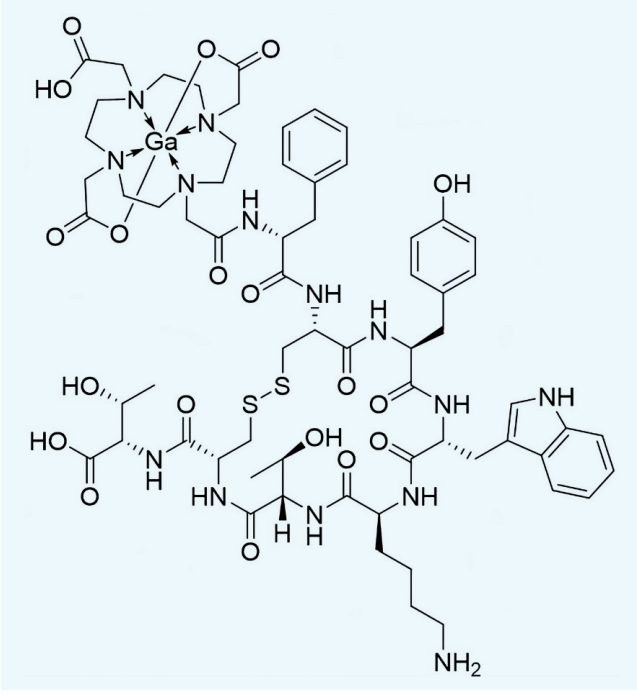

Fig 1. The chemical structure of ^{68}Ga-DOTATATE

However, contemporary commercially available ^{68}Ge/^{68}Ga generators employ solid-phase SiO_2 matrices to yield $^{68}GaCl_3$ through elution with highly diluted HCl, effectively leaving the parent Ge-68 radionuclide on the matrix. This method offers an improved quality of $^{68}GaCl_3$ and superior labelling protocols. This research aims to optimize the radiolabelling process using TINT's DOTATATE kit with a SiO_2-based ^{68}Ge/^{68}Ga generator eluted Ga-68 in 4 ml of 0.05 M HCl. Additionally, a practical quality control protocol was developed to ensure the formulation's efficacy and reliability in compliance with the 10th edition of the European Pharmacopoeia.

MATERIALS AND METHODS

The ^{68}Ge/^{68}Ga generator was purchased from Isotope Technologies München AG (ITM), Medical Isotopes GmbH, Germany. Lyophilized DOTATATE kits were obtained from the Thailand Institute of Nuclear Technology (TINT). All the solvents and reagents were purchased from commercial suppliers and used without further purification. 0.05 M HCl (GMP) was obtained from the pharmacy department at Siriraj Hospital. The Sep-Pak C18 cartridge was purchased from Waters Co., Ltd., USA. The Ga-68 activity was measured with a dose calibrator (CRC25R, Capintec, USA) and measured by gamma-ray spectrometry using a multichannel analyser (MCA), which was integrated with a gamma spectrometer system (Ortec DSPEC jr 2.0) coupled with a high-purity germanium probe (HPGe probe, Ortec Gem20P4-70) for use in the experiments.

Evaluation of Ga-68 elution

The SiO_2-based ^{68}Ge/^{68}Ga generator (ITM, Munich, Germany) was manually eluted with 5.0 ml of 0.05 M HCl with collecting 1.0 ml fractions to determine the Ga-68 activity. The radioactivity of the Ga-68 elution in each fraction was immediately determined in a dose calibrator.

Optimization of the labelling method for the preparation of 68Ga-DOTATATE

General labelling procedure: the ^{68}Ge/^{68}Ga generator was eluted with 2–4 ml of 0.05 M HCl for labelling. It was ensured that an elution had been conducted at least 24 hours in advance. The fraction of $^{68}GaCl_3$ solution was collected and added into a lyophilized cold kit of DOTATATE, then heated in a dried-block heater at 100 °C for 15 min and cooled down at room temperature for 5 min.

In experiment 1, the fraction of $^{68}GaCl_3$ solution comprising the 2nd to 3rd millilitre (2 ml) of the overall volume was collected. No further purification was performed.

In experiment 2, the fraction of $^{68}GaCl_3$ solution comprising the 1st to 4th millilitre (4 ml) of the overall volume was collected. No further purification was performed.

In experiment 3, the fraction of $^{68}GaCl_3$ solution comprising the 2nd to 4th millilitre (3 ml) of the overall volume was collected. No further purification was performed.

In experiment 4, the fraction of $^{68}GaCl_3$ solution comprising the 2nd to 5th millilitre (4 ml) of the overall volume was collected. No further purification was performed.

In experiment 5, the fraction of $^{68}GaCl_3$ solution comprising the 2nd to 5th millilitre (4 ml) of the overall volume was collected. The labelled product was purified using pre-treatment with the Sep-Pak C18 cartridge eluting ethanol (EtOH) 2.0 ml and later washed with 2 ml of normal saline solution. The Sep-Pak C18 cartridge was then eluted with EtOH:H_2O (1:1) 2 ml. The RCP was determined by radio thin-layer chromatography (RTLC) using 1 M NH_4OAc:MeOH (1:1) and the radioactivity was measured by a gamma well counter. The pH of ^{68}Ga-DOTATATE was also measured using a pH meter.

Radiochemical purity analyses

Radiochemical purity (RCP) analyses were conducted using radio thin-layer chromatography (RTLC) with silica paper strips as the stationary phase. The mobile phase consisted of 1 M NH_4OAc:MeOH (1:1), and the radioactivity was measured using a gamma well counter.

Reproducibility and stability test

To assess the reproducibility and consistency of

the labelling method in experiment 5, the experiment was replicated 4 times. At regular time points, a 2 µl sample was taken for RTLC analysis. The stability of ^{68}Ga-DOTATATE was evaluated by incubating at 4 °C in a refrigerator for 4 half-lives and monitored by RTLC every half-life, which was approximately 68 min.

RESULTS AND DISCUSSION

Ga-68 elution profile

The ITM ^{68}Ge/^{68}Ga generator, utilizing modified dodecyl-3,4,5 trihydroxybenzoate hydrophobically bound to an octadecyl silica resin (C-18) as an adsorbent, was developed in GMP-grade tailored for effectively eluting $^{68}GaCl_3$ solution without metal impurities in highly diluted HCl (0.05 M). The Ga-68 eluate does not require further pre-concentration and pre-purification, making it ready for radiolabelling. The elution profiles of each eluate are shown in Fig 2. The majority of the Ga-68 activity was found in fractions 2 to 4. Fraction 1 contained a trace amount of Ga-68 activity, while fraction 5 provided approximately 5% of the overall Ga-68 activity. During the period studied, the elution profile of Ga-68 remained unchanged. This Ga-68 elution pattern aligns with the findings from our prior study.[24] Moreover, the pH of each fraction fell within the range of 1.7–1.9, which is suitable for labelling with DOTA.[25,26]

Optimization of the labelling method for the preparation of ^{68}Ga-DOTATATE

The TINT kits contained 20 µg DOTATATE, 34 mg NaOAc, and 1 mg ascorbic acid. These components were dissolved in sterile water, and the solution was adjusted pH to 6.5 with NaOH. After filtering through a 0.22 µm membrane, each 1 ml of the filtered solution was dispensed into a 10-ml vial. All the vials were then frozen at -40 °C for 3 h and subsequently lyophilized at -20 °C overnight in a vacuum freeze-dryer. There was no further optimization of the DOTATATE content, as that had already been done in the formulation. Instead, this systematic approach aimed to develop an optimum labelling method.

Based on the formulation, the manufacturer suggested using a 5 ml solution of 0.1 M HCl eluting into a TiO_2-based ^{68}Ge/^{68}Ga generator at an approximate flow rate of 1–2 ml/min. The second and third millilitres (2 ml) of the eluted $^{68}GaCl_3$ solution were collected and added to a lyophilized DOTATATE cold kit. For these optimization experiments, we used the same amount of $^{68}GaCl_3$ solution, specifically the second and third millilitres (2 ml) as a reference collected from the ITM ^{68}Ge/^{68}Ga generator, added to the TINT's lyophilized DOTATATE kit. The labelling was conducted in a dry-block heater at 100 °C for 15 min and then cooled to room temperature for 5 min. The manufacturer did not advise any purification step.

The radiochemical purity (RCP) in the first experiment was 13.72%. The low RCP might be due to the high concentration of Ga-68 eluate from the SiO_2-based ^{68}Ge/^{68}Ga generator, which could cause significant impurities. By increasing the amount of $^{68}GaCl_3$ solution to 3 ml, specifically collected from the second to fourth millilitres, the impurity levels were found to be significantly reduced, resulting in an increased RCP of 58.27%. This improvement can be attributed to the larger amount of $^{68}GaCl_3$ collected.

Based on the results of experiment 2, the volume

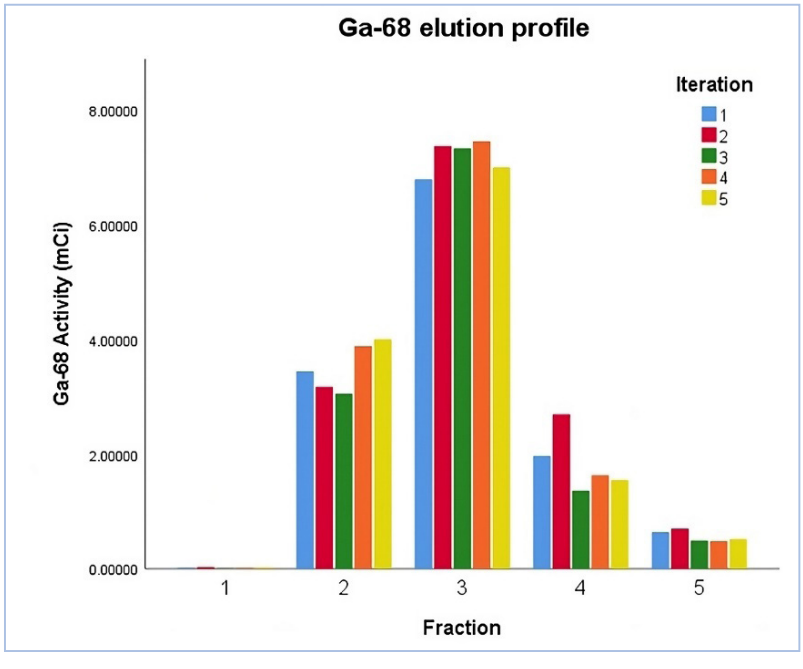

Fig 2. The Ga-68 elution profile

of Ga-68 eluate was increased to 4 ml in subsequent experiments. In experiment 3, the eluate was collected from the first to the fourth millilitre, resulting in an RCP of 13.06%, whereas in experiment 4, the eluate was collected from the second to the fifth millilitre, resulting in an RCP of 29.75%. Due to the greater amount of Ga-68 in the fifth fraction compared to the first fraction, there was more Ga-68 available to chelate with DOTATATE in experiment 4. However, both experiments still showed higher levels of unbound Ga-68 compared to in experiment 2.

According to the standard labelling procedure recommended by ITM, the suitable amount of Ga-68 is 4 ml. In experiment 5, to achieve a higher RCP, the second to fifth millilitres (4 ml) of $^{68}GaCl_3$ were used. Additionally, a purification step using a Sep-Pak C18 cartridge was incorporated into the method. Consequently, the RCP in experiment 5 was measured at 95.08% (Table 1), a result that was corroborated by the RTLC scanner (Fig 3).

Reproducibility and stability

Based on the optimized outcomes (Table 1), the labelling process in experiment 5 was replicated three times to ensure reproducibility. The RCP was observed to fall within the range of 98.36%–99.22% (Table 2). The obtained RCPs through the RTLC indicated the presence of minute colloidal traces. The use of the post-labelling Sep-Pak C18 purification suggested that Ge-68 breakthrough was not detected in any of the ^{68}Ga-DOTATATE preparations. These findings collectively

TABLE 1. Optimization of labelling method

Experiment	1	2	3	4	5
Ga-68 fraction	2 - 3	2 - 4	1 - 4	2 - 5	2 - 5
Ga-68 volume (mL)	2	3	4	4	4
Ga-68 activity (mCi)	12.06	13.67	12.74	11.15	12.81
pH before labelling	1.35	1.37	1.34	1.29	1.21
Purification	No	No	No	No	Yes
RCP (%)	13.72	58.27	13.06	29.25	95.08

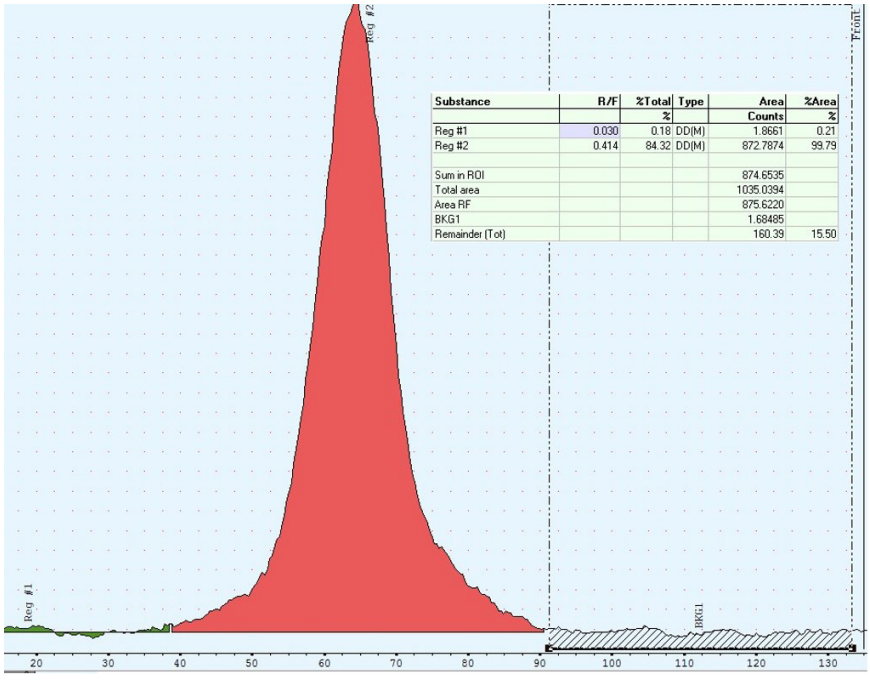

Fig 3. RTLC chromatogram of ^{68}Ga-DOTATATE

TABLE 2. Reproducibility and stability.

Iteration	5.1	5.2	5.3	Mean± SD.
Ga-68 activity (mCi)	13.50	13.18	13.55	13.41+0.20
^{68}Ga-DOTATATE activity (mCi)	9.65	9.57	9.63	9.62+0.04
RCP of final product (%)	98.36	98.94	99.22	98.84+0.44
RCP after 1st half-life (%)	98.46	99.10	98.87	98.81+0.32
RCP after 2nd half-life (%)	98.44	99.12	99.22	98.93+0.42
RCP after 3rd half-life (%)	98.42	98.84	99.09	98.78+0.34
RCP after 4th half-life (%)	98.37	99.15	98.62	98.71+0.40

imply that the quality of ^{68}Ga-DOTATATE prepared under these conditions aligned with the standards outlined for ^{68}Ga-DOTATOC in the 10th edition of the European Pharmacopoeia.[27]

Additionally, conducting a basic RTLC analysis can identify impurities before the preparation is diluted for injection, offering a significant advantage in terms of the procedure's duration and consequently the overall radiochemical yield. Here, when the final product of ^{68}Ga-DOTATATE was stored in a refrigerator at 4–8 °C, the RCP remained stable, with less than 5% label loss for at least 4 half-lives.

This study reveals successful radiolabelling of ^{68}Ga-DOTATATE using TINT's kit and $^{68}GaCl_3$ eluted from a SiO_2-based ^{68}Ge/^{68}Ga generator, with a focus on ensuring compliance with the 10th edition of the European Pharmacopoeia. The targeted binding of ^{68}Ga-DOTATATE to somatostatin receptors (SSTRs) enables highly sensitive and specific imaging, which is essential for the precise localization of both primary and metastatic NETs. This precision plays a critical role in accurate staging, guiding treatment decisions, and monitoring the response to therapy. Additionally, the identification of SSTRs expression on NETs through ^{68}Ga-DOTATATE PET/CT scans not only aids in visualization but also has therapeutic implications. Patients with SSTR-positive tumors may be candidates for peptide receptor radionuclide therapy (PRRT) using agents like ^{177}Lu-DOTATATE or ^{225}Ac-DOTATATE. This form of therapy delivers targeted radiation directly to tumor cells, minimizing damage to normal tissues and potentially leading to improved patient outcomes. The use of ^{68}Ga-DOTATATE in this way represents a significant advancement in both diagnostic imaging and targeted radionuclide therapy, offering a comprehensive approach to managing neuroendocrine tumors.

CONCLUSION

The optimized radiolabelling method of ^{68}Ga-DOTATATE using the TINT kit with the SiO_2-based ^{68}Ge/^{68}Ga generator was successful. In clinical practice, an injection dose of approximately 5 mCi of ^{68}Ga-DOTATATE is recommended for the diagnosis of NET. In this study, the activity of ^{68}Ga-DOTATATE in the final product was 9.14 ± 0.96 mCi, which is sufficient to administer to one patient per production batch. ^{68}Ga-DOTATATE was stable with a radiochemical purity of more than 95% for at least 4 half-lives in the refrigerator after production, in accordance with the 10th edition of the European Pharmacopoeia.

Thus, the DOTATATE cold kit manufactured by TINT can be effectively and reliably labelled with a SiO_2-based ^{68}Ge/^{68}Ga generator-eluted Ga-68 in 4 ml of 0.05 M HCl, suitable for routine clinical application. It is expected that widespread utilization of the TINT kit with this radiolabelling method will have a beneficial impact on ^{68}Ga-DOTATATE preparation at a reasonable expense. The utility of ^{68}Ga-DOTATATE in clinical practice significantly enhances the precision of lesion localization and improves diagnostic accuracy. By providing detailed and specific imaging of NETs, it plays a critical role in informing personalized treatment planning. This imaging technique also serves as a foundation for targeted therapies such as PRRT and offers insights that can directly influence patient outcomes. The ability

to precisely identify and target tumor cells with ^{68}Ga-DOTATATE not only supports more effective treatment strategies but also contributes to improved prognoses for patients with SSTR-positive NETs.

ACKNOWLEDGEMENTS

This research project was supported by the Faculty of Medicine Siriraj Hospital, Mahidol University, Grant Number (IO) R016632023. The authors gratefully acknowledge Ms. Phattaranan Phawaphutanon for the project execution; and Ms. Dollaporn Polyeam, Mr. Karnchana Sae-jang, and Mr. Yuti Jirawattanapalin for support with the statistical analyses.

DECLARETION

Grants and Funding Information

This project is not funded by any external sources.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

Conceptualization and methodology, P.J., S.K., K.L., T.D. and S.S.; Formulation and Kit manufacture, K.L., T.D.; Formal analysis, S.K. and S.S.; Visualization and writing – original darft, P.J.; Writing – review and editing, S.K. and S.S.; Funding acquisition, S.S.; Supervision, S.S. All authors have read and agreed to the final version of the manuscript.

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