Development of the Purification Process of Gallium-68 Eluted from Germanium-68/Gallium-68 Generator

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ABSTRACT

Objective: ^{68}Ga has a half-life of 68 minutes, with 89% of its decay is through positron emission. It is available from generator systems and possesses suitable property for labeling radioligands. These aspects make ^{68}Ga a promising tracer for positron emission tomography (PET) imaging. This study aims to develop the purification process of the ^{68}Ga eluates from ^{68}Ge/^{68}Ga generator after its recommended shelf-life and ensuring the quality through the radiolabeling process.

Materials and Methods: In this study, we explored the development of a purification method for ^{68}Ga eluted from a ^{68}Ge/^{68}Ga generator before radiolabeling was investigated. Cation and anion exchange chromatography techniques were combined to remove trace amounts of competing metal ion impurities. Post-purification, the eluate's metal contents were analyzed using inductively coupled plasma atomic emission spectroscopy (ICP-AES). Breakthrough of ^{68}Ge was measured using a multi-channel analyzer (MCA) spectrometer with high-purity germanium (HPGe) radiation detectors. Additionally, the radiochemical purity of ^{68}Ga-NOTA-RGD was analyzed by high-performance liquid chromatography (HPLC).

Results: Metal impurities including Fe(II), Zn(II) and Al(III) were reduced by 61%, 38% and 44% respectively. The ^{68}Ge breakthrough was approximately ~10^{-3}%. The labeling efficiency with NOTA-RGD, a tracer for angiogenesis imaging, resulted in an average yield of ^{68}Ga-NOTA-RGD (not corrected for decay) of around 50%, with a radiochemical purity by HPLC of approximately 98%–99%.

Conclusion: Cation exchange in combination with anion exchange chromatography was thus proven to be an efficient method for purification of the ^{68}Ga eluate from a ^{68}Ge/^{68}Ga generator prior to labeling the ^{68}Ga PET radiotracer.

Keywords: ^{68}Ge/^{68}Ga generator; purification; radiolabeling; ion exchange purification; PET (Siriraj Med J 2024; 76: 90-96)

INTRODUCTION

The use of positron emission tomography (PET) has widely expanded in recent years. With its excellent resolution, high sensitivity, and potential for precise quantitative analysis, PET imaging is one of the most effective diagnostic tools in nuclear medicine today. The majority of radiopharmaceuticals used in PET are short-lived positron-emitting compounds. The four-basic cyclotron-produced radionuclides most widely employed are: ^{18}F ^{11}C, ^{15}O, and ^{13}N. It is also possible to obtain radionuclides that emit positrons from generator systems, with some examples being ^{82}Rb from ^{82}Sr and ^{68}Ga from ^{68}Ge. While standard PET radionuclides and non-standard PET radionuclides are usually just made up of four basic radionuclides, such as ^{68}Ga, the range

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has expanded in recent years in both preclinical and clinical studies.[1]

As ^{68}Ga decays, 89% of it is decayed through positron emission. In addition, the ^{68}Ge parent material decays with a half-life of 270.8 days through electron capture. Currently, ^{68}Ga is usually available from an in-house ^{68}Ge/^{68}Ga generator that most users will have on site but independent of an on-site cyclotron. ^{68}Ge with a long physical half-life is ideal for clinical settings with its suitable lifespan. However, if used for more than a year, the eluting of ^{68}Ga usually requires a hydrochloric acid solution containing $^{68}GaCl_3$ as its chemical form.[2,3]

The use of radiolabeled peptides in nuclear oncology is increasing. In particular, positron-emitting peptides have now been developed. ^{68}Ga-labeled compounds are becoming increasingly popular in clinical PET.[4] ^{68}Ga-labeled DOTA-peptides are the most generally used radiotracers for PET imaging, especially ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-TATE in the diagnosis of neuroendocrine tumors.[5,6] More recently, NOTA a commonly used bifunctional chelator, has been shown to possess a superior ^{68}Ga-binding ability, and so ^{68}Ga-NOTA-RGD was developed as a radiotracer for the visualization of angiogenesis.[7]

During the past few years, gallium has seen a change in its role in infection imaging. While ^{67}Ga-citrate has been extensively used for the past four decades but with limitations, now ^{68}Ga citrate and $^{68}GaCl_3$ are usually used for infection imaging.[8]

In several ^{68}Ge/^{68}Ga generator systems, ^{68}Ge is adsorbed on a wide range of solid supports, including metal oxides, such as SnO_2, TiO_2, and Al_2O_3; organic materials, e.g., pyrogallol-formaldehyde resins; and inorganic materials, e.g., silica.[9-11] The main drawback of these systems is that the ^{68}Ga eluate is usually contaminated with long-life ^{68}Ge and trace metallic impurities, which could potentially compete with the ^{68}Ga ion when labeled with nanomole levels of conjugated peptides/biomolecules or other carrier ligands. In addition, the eluate from ^{68}Ge/^{68}Ga generators usually has a relatively large volume and high HCl concentration from 0.1–1N, which causes problems in the labeling process. Therefore, dedicated procedures to purify and concentrate ^{68}Ga before labeling are needed.[12]

There has been a recent report describing a method of purifying ^{68}Ga for performing ^{68}Ga-labeled radiopharmaceuticals from ^{68}Ge/^{68}Ga generator eluates eluted with HCl/acetone mixtures on a micro-cation exchange column.[13-15] In other studies, several approaches for purification and concentration have been reported. An effective post-processing technique for ^{68}Ge/^{68}Ga generators using cation and anion exchange chromatography was developed to provide high ^{68}Ga recovery, ^{68}Ge removal, the removal of metallic impurities, lower acidity, and minimized volumes, which would all be useful for direct radiolabeling reactions with a high labeling efficiency of ^{68}Ga-NOTA-RGD.

The aim of this study was to develop a purification method that makes use of both cation exchange and anion exchange processes to purify ^{68}Ga eluates with a high radiochemical purity (RCP) and short purification times. The system should also provide a ^{68}Ga eluate that can be directly used for labeling with a high radiolabeling yield and the highest radionuclidic purity.

MATERIALS AND METHODS

Purification process of the ^{68}Ga eluate

The ^{68}Ge/^{68}Ga generator was purchased from iThemba LABS (Somerset West, South Africa) and had been previously checked for metallic impurities. The elution was done using sterilized 0.6N HCl[12] prepared from ultra-purified hydrochloric acid and tri-distilled water. In order to elute the generator, 6 mL HCl 0.6N was used, and the eluate was divided into five equal portions of 1.2 mL each. The first portion was the non-purified eluate. The second through fifth portions were used for eluate purification by loading the eluate on the top of the cation exchange column. The column was pre-conditioned with 0.5 mL of 98% acetone/0.05 N HCl. The eluate in each column was eluted using 2 mL of 97.6% acetone with different concentrations of HCl (0.05N, 0.10N, 0.15N, and 0.2N). Each eluate from 50 mg of the cation exchange resin, which by now was in the form of $[^{68}GaCl_4]$-, was passed down to 50 mg of the anion exchange resin. The trapped $[^{68}GaCl_4]$- in the anion exchange resin was eluted with 1 mL ultra-purified water. After the purification process, the purity of the eluate in aqueous solution was investigated by inductively coupled plasma atomic emission spectrometry (ICP-AES).

Study of the metal impurities by ICP-AES

Metal impurities in the eluate were analyzed using a Spectro Arcos 165 ICP-AES system equipped with a Cetac ASX-520 autosampler. The measurements were performed using an ICP-AES spectrometer to investigate the metal ions, whereby the most prominent atomic and ionic analytical lines were chosen, including Fe at 238.104 nm, Zn at 206.2 nm, Ge at 265.118 nm, and Al at 396.153 nm. The concentrations of the following metal ions were determined by comparing them to 50, 100, 200, and 400 ppb solutions prepared from the 1000 ppb standard solution.

Germanium-68 breakthrough

Germanium-68 breakthrough was calculated by comparing the daughter radionuclide (^{68}Ga) to the parent radionuclide (^{68}Ge). Germanium-68 breakthrough was measured after complete ^{68}Ga decay (<48 h) by a multi-channel analyzer (MCA) equipped with a high-purity germanium (HPGe) detector.

Radiolabeling of ^{68}Ga-NOTA-RGD

Purified ^{68}Ga (111 MBq in 1 mL of tri-distilled sterile water) was added to a 20 µg lyophilized NOTA-RGD kit (supplied by Jae Min Jeong Seoul National University, Jongro-gu, Seoul, Korea)[16], and the pH was adjusted to 5.0 with 0.1M ammonium acetate buffer. The pH of the mixture was checked with a pH indicator strip and then the mixture was heated in a water bath at 100 °C for 15 min. After cooling, the labeled product ^{68}Ga-NOTA-RGD was sterilized by 0.22 µm Millipore filtration.

Quality control of ^{68}Ga-NOTA-RGD

The labeling efficiencies and radiochemical purities of the purified ^{68}Ga-NOTA-RGD were determined by high-performance liquid chromatography (HPLC) (Agilent Tech., Series 1200) with a Phenomenex Jupiter column C-18, 5 µm, 4.6 × 250 mm. The solvents were 0.1% (m/v) trifluoroacetic acid (TFA) in deionized water (A) and 100% acetonitrile (B). Elution was carried out at a flow rate of 1 mL/min, under UV–visible illumination (200, 280 nm) with a gamma-ray detector (Raytest Gabi Star), using the elution program in Table 1.

As a result, the peak for free ^{68}Ga appeared at 3.5 to 4 min, whereas peaks for small particles of the radiochemical impurities appeared at 3.0 to 3.5 min, while ^{68}Ga-NOTA-RGD showed an earlier retention time of 9.0 to 9.5 min.

RESULTS

The small amounts of Fe(III), Zn(II), Ge(IV), and Al(III) were found in the eluate. The concentration of Ge(IV) was less than 1 ppb while all the other metals were less than 1 ppm. After the purification process, Fe(II), Zn(II), and Al(III) were reduced by 61%, 38%, and 44%, respectively, compared to the initial non-purified evaluation (Table 2).

The ^{68}Ga eluted from the ^{68}Ge/^{68}Ga generator usually contains small amounts of metallic impurities that represent metals that can compete with ^{68}Ga(III) in the radiopharmaceutical labeling process, thereby adversely affecting both the ^{68}Ga labeling yields and the specific activity of the labeled compound. These metal impurities, especially Fe(III), and the ^{68}Ge breakthrough need to be effectively removed. Here, the concentrations of metallic ions before and after purification are shown in Table 2.

TABLE 1. HPLC gradient for the elution of ^{68}Ga-NOTA-RGD

Time (min)	0.1% Trifluoroacetic acid (TFA) in deionized water (A)	Acetonitrile (ACN) (B)
0–4	90%	10%
4–10	30%	70%
10–13	10%	90%

TABLE 2. Metal impurities concentrations in ^{68}Ga eluates eluted with different acetone / hydrochloric acid mixtures.

Metal	Non-purified	98% Acetone/ 0.05N HCl	98% Acetone/ 0.1N HCl	98% Acetone/ 0.15N HCl	98% Acetone/ 0.2N HCl
Al(III)	1.46E-04	5.16E-05	2.88E-04	6.31E-05	8.17E-05
Fe(III)	6.36E-04	6.52E-04	5.18E-04	4.50E-04	2.48E-04
Zn(II)	1.73E-04	7.59E-05	1.14E-04	2.78E-04	1.06E-04
Ge(IV)	7.97E-06	2.04E-06	1.11E-06	1.23E-06	4.08E-07

^{68}Ge breakthrough

The ^{68}Ge breakthrough in 12 samples using a SnO_2-based ^{68}Ge/^{68}Ga generator. After the complete decay of ^{68}Ga (> 48 h), the quantitative measurement of ^{68}Ge breakthrough was performed using a calibrated gamma spectrometer equipped with a coaxial (HPGe) detector. The ^{68}Ge breakthrough from the generator was found to be approximately 10^{-3}% of the eluted ^{68}Ga activity after purification. This is in accord with many publications that have reported breakthrough of the ^{68}Ge parent radionuclide as usually less than 0.001%

Elution efficiency after purification and the labeling of RGD peptide with ^{68}Ga

The entire purification process, including two purification steps, cation exchange and anion exchange chromatography, was completed within 30 min. The mean activity at the first elution was 2.89 ± 0.11 mCi. The radioactivity levels of ^{68}Ga at the first elution and after passing through the cation and anion exchange columns and labeling with NOTA-RGD peptide are shown in Table 3. Without correction for the decay, the mean activities after the two purification steps and labeling were 2.00 ± 0.10, 1.74 ± 0.10, and 1.44 ± 0.10 mCi, respectively. In this study, the elution efficiencies after the purification steps were found to range between 50% to 70%. The elution efficiency decreased to about 69.02 ± 2.88% after the first purification step, 60.03 ± 2.54% after the second step, and 49.89 ± 2.49% after the labeling, see Table 3. In this study, it was approximately 70% over a processing time of not more than 30 minutes. However, the labeling efficiency was 99% and only a small amount of free ^{68}Ga was detected when labeling NOTA-RGD peptide with the purified ^{68}Ga, see Table 4.

The complexation yield of Ga-NOTA-RGD was validated by HPLC studies. Fig 1 shows the typical HPLC pattern of ^{68}Ga-NOTA-RGD. The ^{68}Ga-NOTA-RGD peak was collected at a retention time of 9.0–9.5 min, while free ^{68}Ga peak appeared at 3.5–4 min, and small traces of radiochemical impurities at 3.0–3.5 min.

The efficacy of ^{68}Ga for the preparation of radiopharmaceuticals for PET imaging was confirmed by radiolabeling NOTA-RGD with a very high complexation yield. The radiochemical purity (RCP) of ^{68}Ga-NOTA-RGD was higher than 99%. The process of labeling was completed within 30 minutes. The mean labeling efficiency was 99.31 ± 0.32%, while the unlabeled ^{68}Ga was 0.69 ± 0.32%, as shown in Table 4.

TABLE 3. Radioactivity in mCi of ^{68}Ga at the first elution, and after the two purification steps and labeling (The percentage reduction of radioactivity is in parenthesis).

	Radioactivity of ^{68}Ga in mCi and the percentage reduction (%)						
Test no	First elution	After purification by cation exchange		After purification by anion exchange		After labeling	
1	2.93	2.05	(69.97)	1.75	(59.73)	1.48	(50.51)
2	2.82	1.95	(69.15)	1.69	(59.939)	1.43	(50.71)
3	2.94	1.99	(67.69)	1.73	(58.84)	1.44	(48.98)
4	3.02	1.95	(64.57)	1.72	(56.95)	1.41	(46.69)
5	2.95	2.11	(71.53)	1.84	(62.37)	1.53	(51.86)
6	2.77	1.83	(66.06)	1.63	(58.843)	1.39	(50.18)
7	2.62	1.94	(74.05)	1.65	(62.98)	1.40	(53.44)
8	2.90	2.02	(69.66)	1.72	(59.31)	1.46	(50.34)
9	2.98	2.12	(71.14)	1.92	(64.43)	1.61	(54.03)
10	3.01	2.14	(71.10)	1.89	(62.79)	1.44	(47.84)
11	2.91	1.88	(64.60)	1.67	(57.393)	1.34	(46.05)
12	2.85	1.96	(68.77)	1.62	(56.84)	1.37	(48.07)
Mean	2.89	2.33	(69.02)	2.24	(60.03)	2.06	(49.89)
S.D.	0.11	0.11	(2.88)	0.13	(2.54)	0.10	(2.49)

TABLE 4. Analysis of ^{68}Ga-NOTA-RGD and unlabeled ^{68}Ga by HPLC.

Test no	Area count (cps)			% Area	
	Region 1	Region 2	Total count	Region 1	Region 2
1	80.11	18020.06	18706.17	0.43	99.57
2	100.45	17896.08	17996.53	0.56	99.44
3	77.45	18223.69	18301.14	0.42	99.58
4	256.22	17745.32	18001.54	1.42	98.58
5	59.91	19304.39	19364.30	0.31	99.69
6	147.25	17593.25	17740.50	0.83	99.17
7	201.43	17620.13	17821.56	1.13	98.87
8	81.11	18375.34	18465.45	0.44	99.56
9	154.6	20362.14	20516.74	0.75	99.25
10	145.64	18122.65	18268.29	0.80	99.20
11	93.01	16934.67	17027.68	0.55	99.45
12	105.56	17291.59	17397.15	0.61	99.39
Mean ± SD				0.69 ± 0.32	99.3 ± 0.32

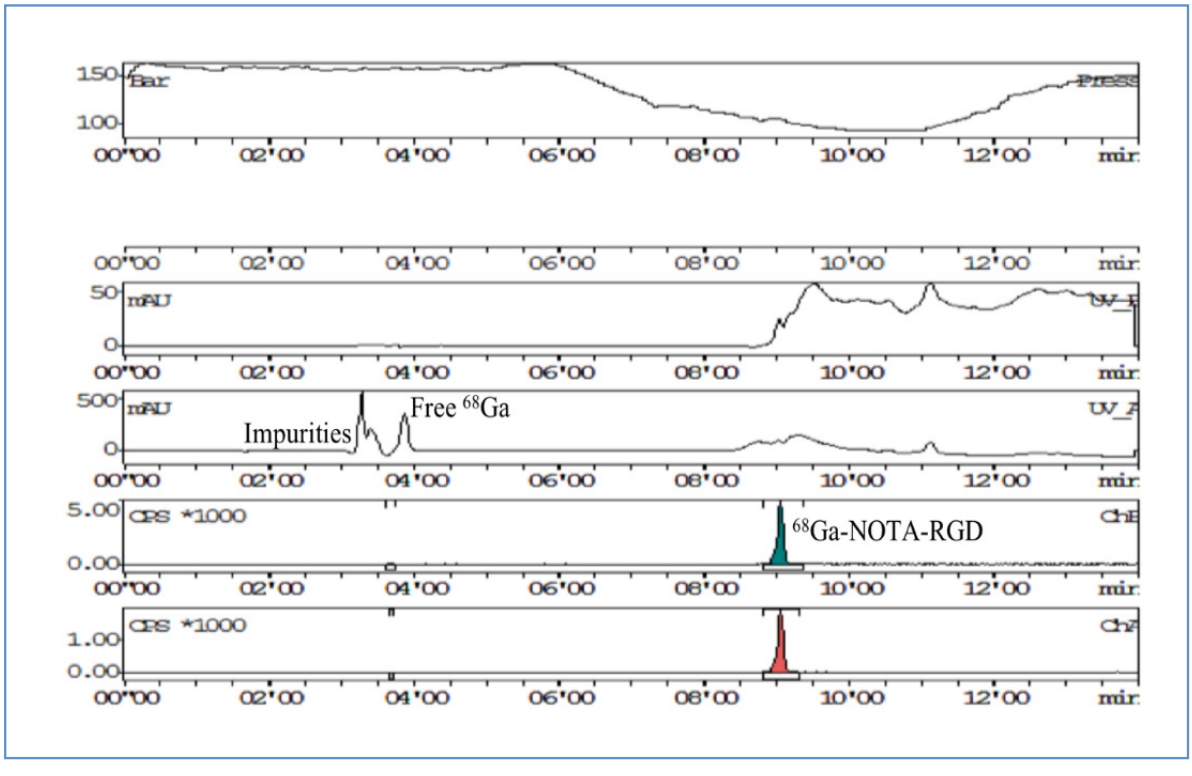

Fig 1. HPLC chromatogram patterns of ^{68}Ga-NOTA-RGD.

CONCLUSION AND DISCUSSION

The $^{68}Ge/^{68}Ga$ generator used in this study was a SnO_2-based generator. By measuring the metallic impurities by ICP-AES, it was verified that metallic impurities were present that could interfere with the formation of Ga(III) complexes. Therefore, before the radiolabeling of peptides, the ^{68}Ga eluate would need to be purified using a cationic exchange column, an anionic exchange column, or both. In this study, ^{68}Ga solutions were purified on both cation and anion exchange columns. We eluted the ^{68}Ga eluate using different concentrations of acetone/hydrochloric acid mixtures after each transfer. Schultz et al.[17] used different sets of chromatographic columns, 50W X8 cation, and UTEVA resin, and eluted with 0.1M HCl. Metal analysis by ICP-AES demonstrated that the stable metals were reduced to less than 0.2 ppm, but Fe(III) could not be removed, while the breakthrough of ^{68}Ge was less than 0.02% of the ^{68}Ga activity.

Germanium-68 is strongly absorbed by metal oxides or organic materials, making ^{68}Ge breakthrough highly unlikely. However, the metal impurities from ^{68}Ge breakthrough in the eluate are lesser problems compared to patient exposure to radiation when used for the radiolabeling of peptides or other biomolecules. As a minimum, the radionuclidic purity of ^{68}Ga chloride solution should be limited to 99.9% of the total radioactivity, whereas ^{68}Ge should not exceed 0.001% (EU Pharm). Some have even reported values less than 10^{-4}% to 10^{-5}%. Konstantin et al.[18] reported that the initial amount of $^{68}Ge(IV)$ was decreased by a factor of 10^4 when using a TiO_2-based generator. Roesch[20] reported that ^{68}Ge breakthrough levels ranged from 0.01% to 0.001% for fresh generators, but they increase with extended use. Since the ^{68}Ge breakthrough has been shown to increase over the lifetime of the generator and our generator had been used for more than 18 months, our presented result of 10^{-3}% of the eluted ^{68}Ga activity is considered an acceptable result. This means our generator also fulfills the requirement of the European Pharmacopeia (EU) concerning the radionuclide purity for ^{68}Ga of 99.9%. Concerning the radiation absorbed dose, a recent publication reported that ^{68}Ge is rapidly excreted in the urine, which greatly diminishes the potential radiation absorbed dose. Lin M et al.[21] demonstrated that the elution of ^{68}Ge from a commercial titanium-dioxide-based $^{68}Ge/^{68}Ga$ generator resulted in markedly low ^{68}Ge breakthrough, in the order of 14 to 25 nCi. When labeled with DOTATOC, spectroscopic analysis of the synthesis components demonstrated that the ^{68}Ge breakthrough in the final products was quantitatively removed. Sudbrock et al.[22] reported that the content of long-lived ^{68}Ge breakthrough increased to more than 100 ppm over the entire period of use of the generator, while the chelator DOTA eliminated ^{68}Ge efficiently during labeling. The maximum ^{68}Ge activity found in the labeled product (below 10 Bq) and the effective doses received by the patient from ^{68}Ge in the ^{68}Ga-DOTATATE final product were lower than 0.1 μSv, meaning practically insignificant for patients.

After the elution of ^{68}Ga, the activity of ^{68}Ga was measured immediately using a calibrated ionization chamber to determine the elution efficiency. The ^{68}Ga elution yields dropped with increasing its usage frequency or shelf-life. In this study, the elution yield of our generator was found to be lower than 50% because it has been used for almost 18 months. Roesch[23] reported that the ^{68}Ga-eluted yields range from about 70% to 80% for fresh generators, but these decrease over time. The initial yield of the generator has been reported to range from 75% to 100% and the long-term yield from 60% to more than 80%. Patrascu et al.[24] reported an elution efficiency of 80% and Konstantin et al.[18] reported an initial activity of more than 97% from a TiO_2-based generator.

The time spent processing the generator eluate, synthesizing the labeled product, and purifying it reduced the production yield. In this study without correction for the decay, the final yield of ^{68}Ga-NOTA-RGD peptide was less than 50% (49.89 ± 2.49%). A final yield of 46 ± 5% for the ^{68}Ga-labeled DOTA-conjugated octreotide was reported by Roesch and Filosofov.[25] Further, the decay-corrected yields of ^{68}Ga radiopharmaceuticals did not exceed 60% to 70%.

For the clinical application of ^{68}Ga produced by $^{68}Ge/^{68}Ga$ generators, it is important to obtain ^{68}Ga in a purified chemical form, maximize the elution yield of ^{68}Ga, and reduce the elution volume while maintaining a permissible level of ^{68}Ge impurity in the eluate. There is a possibility of regularly eluting $^{68}Ge/^{68}Ga$ from the generator in a way that provides an acceptable radioactive concentration, yield, and purity. It was reported by Asti et al.[19] that the concentration of ^{68}Ge breakthrough increased with time, with approximately a 15% increase per month, ranging from 1.1×10^{-2}% to 2.6×10^{-2}% of the ^{68}Ga activity within their 7 months of evaluation. Moreover, the elution yields of ^{68}Ga from these generators decreased from 82% to 69% when elution was repeated, i.e., 100 times, over the period of 7 months.[19]

The RCP of the ^{68}Ga-labeled product should be greater than 99%, which would result in a high efficiency of radiolabeling with a small volume and low acidity. In the present study, the efficacy of ^{68}Ga for the preparation of radiopharmaceuticals for PET imaging was confirmed by radiolabeling NOTA-RGD with a very high yield.

At present, an automatic synthesis module to produce ^{68}Ga-NOTA-RGD may be used. The module was connected to a line elution ^{68}Ge/^{68}Ga generator with a purification part and controlled by a personal computer program for easy production and to make it suitable for routine work. However, a variety of post-processing methods, such as anionic exchange and cationic exchange purification, are required to purify the eluate. It is also of particular importance for the labeled products to have high specific activities.

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