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Introduced the $^{68}Ge/^{68}Ga$ generator with highest produced ^{68}Ga activity

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Abstract

Interest in using ^{68}Ga is rapidly increasing for clinical PET applications due to its favorable imaging characteristics and increased accessibility. Focus of this present was to provide our evaluation of the TiO_2-SnO_2 -based $^{68}Ge/^{68}Ga$ generator. The introduced generator has highest ^{68}Ga activity compared to other commercial $^{68}Ge/^{68}Ga$ generators.

This generator from Pars Isotope company with a nominal activity of 70 mCi showed a stable ^{68}Ga elution profile. The obtained results will be useful in standardizing the evaluation of $^{68}Ge/^{68}Ga$ generator for clinical use.

Keywords: $^{68}Ga/^{68}Ga$ generator, ^{68}Ga, Gallium-68, PARS-GalluGEN

Introduction

^{68}Galium (^{68}Ga) is one of the radionuclides that is widely used for diagnostic purposes in Nuclear Medicine. In contrast to the more frequently used PET nuclides ^{18}F or ^{11}C, there is no need for an on-site cyclotron. At the same time, more detailed good manufacturing practice (GMP) standards for production of radiopharmaceuticals in Europe call for robust and reproducible production routines for ^{68}Ga radiopharmaceuticals [1].

The $^{68}Ge/^{68}Ga$ generator has emerged as a convenient source to provide 68Ga in a hospital radiopharmacy for the synthesis of ^{68}Ga-labeled radiopharmaceuticals and represents a developmental milestone in the field of PET-based molecular imaging. As a metallic radionuclide, ^{68}Ga has great capability to be used for radiolabeling molecular tumor targeting vectors, such as peptides or proteins (monoclonal antibodies or fragments thereof), through a bifunctional chelator link[2,3]. Over the years, a variety of $^{68}Ge/^{68}Ga$ generators have been developed using a gamut of sorbents such as Al_2O_3, CeO_2, SnO_2, TiO_2, ZrO_2, and organic matrices [1].

Common commercially available generators are Cyclotron Co. Ltd. (Obninsk, Russian Federation; TiO_2-based), Eckert & Ziegler GalliaPharm (Germany; TiO_2-based), iThemba LABORATORIES (Republic of South Africa; SnO_2-based), ITG Isotope Technologies Garching GmbH (Munchen, Germany; silicabased), Galli Eo (from IRE EliT, Fleurus, Belgium;
unspecified resin) and PARS Isotope PARS-GalluGEN (Tehran, Iran; SnO_2/TiO_2 based) [4].

To date, the commercially available 68Ge/68Ga generators do not exceed the capacity of 1.85GBq (50mCi) and recently itG produced new 68Ge/68Ga generator with a nominal activity of 4.04 GBq (109 mCi) and elution efficiency about 60% [4].

In this context, we report the new $^{68}Ge/^{68}Ga$ generator of PARS Isotope as PARS-GalluGEN (Fig 1) which nominally provided 70 mCi ^{68}Ga (120 mCi loaded ^{68}Ge). The eluated ^{68}Ge have low metallic impurities and exhibited low ^{68}Ge breakthrough and suitability of the ^{68}Ge for the preparation of ^{68}Ge-labeled radiotracers.

Figure 1. 70 mCi *$^{68}Ge/^{68}Ga$ generator*

Experimental

Preparation of the materials

PARS–GalluGEN generator eluted with 3 mL of 0.1 M HCl a flow rate of 3 mL/min. The generator elution profiles were studied by collecting the eluates from different generators as 0.5 mL aliquots, and the activity of each fraction was determined by measuring the activity in a dose calibrator.

After an elution of the PARS–GalluGEN generator the ^{68}Ga will be built up by the continuous decay of the parent ^{68}Ge. The generator requires at least 7 hours to achieve almost full yield after being eluted, but in practice it is also possible to elute the generator after 4 hours. The output will decrease due to decay of the ^{68}Ge parent over time. For example, after 9 months' decay (39 weeks), the ^{68}Ge will be reduced by 50 %.

The breakthrough refers to the actual ^{68}Ge content of the eluate, and is reported as the ^{68}Ge activity in the eluate relative to that on the generator column. The European Pharmacopoeia 8 specifies that gallium (^{68}Ga) chloride solution shall not contain more than 10 µg of Fe and Zn per GBq of 68Ga in eluate that is used for radiolabelling and that no more than 0.001% of 68Ge should be present in the 68Ga eluate. Each generator was eluted at least once in a day and the elution yield was determined using the following equation:

$$Elution\ \ yield(\%) = \frac{As(t)}{A_1^0(1-e^{-\lambda_2 t})} \times 100$$

Results and discussion

The most commonly available commercial ^{68}Ge/^{68}Ga generator systems are based on TiO_2 or SnO_2 as sorbents, from which ionic ^{68}Ga $^{3+}$ is eluted in 0.1–1M HCl. Comparison of these data and our experimental lead us to choose the mixed resin as sorbent [5].
A small amount of ^{68}Ge is eluted from the column with each elution. ^{68}Ge breakthrough is expressed as a percentage of total ^{68}Ge eluted from the column to loaded ^{68}Ge with decay correction factor. The ^{68}Ge breakthrough for this generator is not more than 0.001 % of the eluted ^{68}Ge activity and typically begins as low as 0.0005 % at the point of release and may rise slightly with the number of elution.

	^{68}Ge	^{68}Ga
Half-live	270.95 days	67.71 minutes
Type of decay	Electron capture	Positron emission
X-rays	9.225 (13.1 %) 9.252 (25.7 %) 10.26 (1.64 %) 10.264 (3.2 %) 10.366 (0.03 %)	8.616 (1.37 %) 8.639 (2.69 %) 9.57 (0.55 %)
gammas		511 keV (178.28 %), 578.55 keV (0.03 %) 805.83 keV (0.09 %), 1077.34 keV (3.22 %) 1260.97 keV (0.09 %) 1883.16 keV (0.14 %)
beta+		Energy max. Energy 352.60 keV 821.71 keV (1.20 %) 836.00 keV 1899.01 keV (87.94 %)

Table 1: Physical characteristics of mother and daughter

All development batches were produced using drug substance Gallium Chloride ($^{68}GaCl_3$) obtain by decay of adsorbed ^{68}Ge on tin dioxide and titanium dioxide column physical and chemical test were performed to characterize the radionuclide. Physical characteristics of both mother and daughter are summarized in Table 1.

Conclusions

PARS-GalluGEN Generators are delivered with a given amount of elutable ^{68}Ga activity at calibration time and eluted with 0.1 M HCl and solution suitable for the subsequent labelling.. Elution yield with 3 ml of 0.1 M HCl is 62-52% of the loaded ^{68}Ge on the column. Elution profile of the generator show that more than 90% of the elutable activity is collected in the middle 2ml of the eluate. Only a low percentage of activity (< 10%) was eluted in the first and final 0.5 mL fractions

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