(19) DANMARK

(10) DK/EP 3343570 T3

Patent- og Varemærkestyrelsen

(12) Oversættelse af europæisk patentskrift

(51) Int.Cl.: *G 21 G 1/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2019-09-23**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2019-07-03**

(86) Europæisk ansøgning nr.: **16206969.4**

(86) Europæisk indleveringsdag: **2016-12-27**

(87) Den europæiske ansøgnings publiceringsdag: **2018-07-04**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **68GE/68GA-generator**

(56) Fremdragne publikationer:
WO-A1-2008/108311
WO-A1-2011/045019
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KR-B1- 101 646 601

DESCRIPTION

[0001] The present invention relates to a germanium-68/gallium-68 (^{68}Ge/^{68}Ga) generator for a continuous production of a ^{68}Ga daughter nuclide, in accordance with the preamble of claim 1. The invention further relates to the use of at least one oxide of a metal being selected from the group consisting of Vanadium, Niobium and Tantalum in accordance with claim 14.

[0002] ^{68}Ga is a highly attractive positron-emitting radionuclide which meanwhile plays an important role in the use of Positron Emission Tomography (PET). For a brief introduction and summary of the use of ^{68}Ga, and in particular its chelating with DOTATOC, in diagnostics it is referred to applicant's EP 2 439 747 B1.

Background / Prior art technology

[0003] In providing pure radionuclides, element-specific adsorbents are of great interest. This is also true for different fields of the chemical science. However, of special interest is the application of such materials for isolation and production of radionuclides for analytical and medical use.
A key example of the pharmaceutical application of germanium specific materials is a ^{68}Ge/^{68}Ga radionuclide generator system. Such radionuclide generators are e.g. described in EP 2 216 789 A1.

[0004] The ^{68}Ge/^{68}Ga radionuclide generators are based on adsorption of the radionuclide ^{68}Ge on a germanium-specific material. Relatively long-lived ^{68}Ge (T½ = 270.82 d) produces an intermediate short-lived isotope ^{68}Ga (T½ = 67.6 min). While ^{68}Ge is immobilized on a support material continuously formed ^{68}Ga can be repeatedly eluted (produced).

[0005] ^{68}Ga is a positron emitter (β^+ branching = 89 %), which can be used for preparation of radiopharmaceuticals *via* coordinative labelling. During the last years tumour imaging using ^{68}Ga-labelled DOTA-conjugated peptides has become an established approach to diagnose neuroendocrine and other tumours and metastases using PET and PET/CT. A key advantage (cost, logistic advantages) in medical use of ^{68}Ga is its availability *via* ^{68}Ge/^{68}Ga radionuclide generators [1,2].
Essential quality parameters for ^{68}Ge/^{68}Ga radionuclide generators of the prior art are undesired breakthrough of ^{68}Ge, elution yield and elution stability of ^{68}Ga. A limit for ^{68}Ge breakthrough is given in the European Pharmacopoeia monograph [3] along with other parameters to measure the pharmaceutical quality of ^{68}Ga eluate. Elution yield and elution stability of ^{68}Ga are important factors for the efficiency and shelf life of the ^{68}Ge/^{68}Ga

generator. For successful radiolabelling of pharmaceuticals with ^{68}Ga the used ^{68}Ga preparations must satisfy high requirements to chemical and radiochemical quality. ^{68}Ga must be produced in its "ionic" form (i.e., without any complexing agents). ^{68}Ga preparations can be used for coordinative labelling only with low volume and low acidity. The preparation must be free from metallic impurities which are strong competitors for the incorporation of gallium into biomolecules [4-6].

The current $^{68}Ge/^{68}Ga$ radionuclide generator systems available on the global market are based on the application of inorganic ion-exchangers or organic molecules as adsorbents (Table 1). Most commonly used inorganic ion-exchangers are TiO_2 (Cyclotron Company, Russian Federation and Eckert & Ziegler Isotope Products, Germany) and SnO_2 (iThemba Labs, South Africa). Characteristic for these generator types is contamination of ^{68}Ga preparation with the trace of other metals from the used support materials and requirement of high acidity and/or large volume of the eluant. Thus, for the preparation of ^{68}Ga-labelled radiopharmaceuticals utilizing the available metal oxide based radionuclide generator systems of the prior art, pre-processing of the achieved ^{68}Ga eluate is necessary [5-8].

An alternative to inorganic ion-exchangers are organic polymers with introduced single molecules with functional groups that have a high affinity for germanium, as described in EP 2 439 747 B1. Such molecules can be pyrogallol, catechol, etc., which form strong complexes with germanium *via* phenolic hydroxyl groups. The key example is the only metal-free $^{68}Ge/^{68}Ga$ radionuclide generator system on the market (ITG Isotope Technologies Garching GmbH, Germany) which is based on the application of pyrogallol-derivatized SiO_2 as adsorbent [7,9] (Table 1). Such generators are described in detail in applicant's EP 2 439 747 B1. This prior art's $^{68}Ge/^{68}Ga$ radionuclide generator already allows efficient radiolabelling of biomolecules without the need of pre-purification of the ^{68}Ga eluate. However, the organic-based adsorbents applied in radionuclide generator systems are radiolytically unstable when exposed to high doses of radiation. Thus, the advanced chemical stability of the adsorbent plays the important role in developing a $^{68}Ge/^{68}Ga$ generator for advanced performance in higher ^{68}Ge activities.

[0006] Taking into consideration the prior art of EP 2 439 747 B1, it is the object of the present invention to provide an improved $^{68}Ge/^{68}Ga$ radionuclide generator which shows a negligible breakthrough of ^{68}Ge during elution of ^{68}Ga, which is stable to radiolysis, particularly when higher ^{68}Ge activities are concerned, and simultaneously providing a high yield of ^{68}Ga and finally, which is essentially of undesired impurities.

[0007] This object is achieved by a $^{68}Ge/^{68}Ga$ generator in accordance with claim 1 and by a use of an oxide of a metal being selected from the group consisting of: Vanadium, Niobium and Tantalum as an inorganic support material for the manufacture of a $^{68}Ge/^{68}Ga$ generator, in accordance with claim 14.

[0008] In particular, the present invention relates to
A $^{68}Ge/^{68}Ga$ generator for a continuous production of a ^{68}Ga daughter nuclide, wherein the ^{68}Ge parent nuclide thereof is specifically adsorbed to an inorganic support material and wherein said ^{68}Ge parent nuclide continuously decays to ^{68}Ga by electron capture at a half-life of 270.82 d,
wherein
the inorganic support material is at least one oxide of a metal being selected from the group consisting of: Vanadium, Niobium and Tantalum.

[0009] The invention further relates to a use of at least one oxide of a metal being selected from the group consisting of: Vanadium, Niobium and Tantalum as an inorganic support material for the manufacture of a $^{68}Ge/^{68}Ga$ generator in accordance with the present invention for a continuous production of a ^{68}Ga daughter nuclide, wherein the ^{68}Ge parent nuclide thereof is specifically adsorbed to an inorganic support material and wherein said ^{68}Ge parent nuclide continuously decays to ^{68}Ga by electron capture at a half-life of 270.82 d.

[0010] A preferred embodiment of the present invention is a $^{68}Ge/^{68}Ga$ generator in which the oxide is an oxide having the general formula (1):

$$M_2O_5 \qquad (1),$$

wherein M represents Vanadium, Niobium or Tantalum.

[0011] The particularly preferred oxide used in the present invention is tantalum pentaoxide (Ta_2O_5), which can be used in its alpha- and/or beta-crystalline form.

[0012] The oxide used as support material in the present invention is obtainable by hydrolyzing a metal halogenide of the general formula (2):

$$MX_5 \qquad (2),$$

wherein M represents Vanadium, Niobium or Tantalum; and X represents chlorine, bromine, or iodine; and converting a metal hydroxide resulting from the hydrolysis to the desired metal oxide by annealing.

[0013] It is a preferred embodiment of the present invention to use $TaCl_5$ as the metal halogenide, the hydrolysis of which resulting in $Ta(OH)_5$.

[0014] Alternatively, in accordance with the present invention, the desired oxide is also obtainable by annealing a metal powder under oxygen atmosphere, wherein said metal is selected from the group consisting of: Vanadium, Niobium and Tantalum, wherein Tantalum is

preferred as metal and the resulting oxide is Ta_2O_5.

[0015] It is a further preferred embodiment of the present invention that the oxide particle size distribution is 5 µm to 300 µm, in particular 10 µm to 200 µm.

[0016] Typically, the ^{68}Ge parent nuclide is adsorbed to the oxide support material in form of $^{68}Ge(IV)$ cations, in particular ^{68}Ge-aquo cations, both of which are easily available.

[0017] In accordance with a further preferred embodiment of the invention, the ^{68}Ga is eluted from the $^{68}Ge/^{68}Ga$ generator with 0,01 M to 0,1 M HCl, in particular with 0,05 M HCl.

[0018] It is a further preferred embodiment of the present invention that the breakthrough of ^{68}Ge is $< 10^{-3}$ %, in particular $< 10^{-6}$ %, preferably $< 10^{-7}$ % at an initial activity of 1000 MBq and $< 4 \times 10^{-7}$ % at an initial activity of 2000 MBq. This is far below the required European Pharmacopoeia [11] values, and far below any $^{68}Ge/^{68}Ga$ generator available on the market (cf. Table 1 below).

[0019] Typical elution yields of ^{68}Ga are more than 65 %.

[0020] The present invention relates to the use of a novel germanium specific adsorbent, i.e. an oxide belonging to the group of metal oxides wherein the metal can be Vanadium, Niobium and Tantalum. Also mixed metal oxides or mixtures of different oxides can be used. Particularly, the pentoxides have proved to be suitable adsorbents for Ge in general and ^{68}Ge, specifically. Although, all of the oxides from the above Vanadium group metals are generally working as specific germanium adsorbents, in practices, it has turned out that tantalum pentoxide (Ta_2O_5) is the most preferred one. The adsorbents in accordance with the present invention can be synthesized via a hydrolysis route from its corresponding pentachlorides, e.g. tantalum pentachloride or via an annealing route from a metal powder of V, Nb, or Ta or a mixture thereof, wherein tantalum powder is preferably used. The oxidations of the metal powders are carried out under normobaric atmospheric conditions. Pharmaceutical use of the adsorbents in accordance with the present invention allows an improved production possibility of medical positron emitting radionuclide ^{68}Ga *via* a novel $^{68}Ge/^{68}Ga$ radionuclide generator. The chemical nature of the adsorbents enable efficient adsorption of ^{68}Ge, efficient and stable desorption of ^{68}Ga, very low breakthrough of ^{68}Ge and high labelling efficiency of biomolecules with ^{68}Ga. Compared to the current systems based on other metal oxide adsorbents of the prior art, e.g. TiO_2 or SnO_2, the desired radionuclide ^{68}Ga can be produced directly (i.e. without any pre-processing) with high chemical and radiochemical purity for preparation of ^{68}Ga-labelled radiopharmaceuticals. Moreover, the adsorbents are chemically inert and stable against radiolysis which allows it to be successfully applied in radionuclide generators of high activities with improved performance.

[0021] Up to date, there exists no literature on the use of metal oxides of the vanadium group of the periodic table of elements, in particular, tantalum pentoxide, as adsorbent in a radiopharmaceutical radionuclide generator of the $^{68}Ge/^{68}Ga$ type. In addition, the synthesis of the metal oxides in accordance with the present invention such as the tantalum pentoxide adsorbent by the below disclosed method is suitable for the purpose of the present invention. The achieved adsorbents underwent a thorough characterization by different solid state techniques, such as x-ray diffraction, scanning electron microscopy, Fourier-transform infrared spectrometry and surface area measurement via Brunauer-Emmet-Teller method. This encompassing analysis has yielded a well-characterized adsorbent with optimized critical parameters elutability of ^{68}Ga, breakthrough of ^{68}Ge, capacity of adsorbent, and labelling properties.

[0022] Table 1 below gives an outline of the $^{68}Ge/^{68}Ga$ generators systems being currently available on the market. The last line of Table 1 shows the $^{68}Ge/^{68}Ga$ generator according to the present invention.

Table 1. Specifications of the $^{68}Ge/^{68}Ga$ generators currently available on the market. The information in table 1 is partly taken from Roesch 2015 [10].

Company	Adsorbent	Eluant	^{68}Ga elution yield	^{68}Ge breakthrough
EZAG (Obninsk)*1	TiO_2	0.1 M HCl	initial: ≈75 % long term: 60 % *2	5 X 10^{-3} %
EZAG (IGG100)	TiO_2	0.1 M HCl	initial: > 65 % long term: > 65 % *2	10^{-3} %
iThemba Labs	SnO_2	0.6 M HCl	initial: > 100 % *3 long term: 75 % *4	< 10^{-2} % *3,5
ITM/ITG (EP 2 439 747B1)	Pyrogallol/silica	0.05 M HCl	≥ 80 % *6	≤ 5 X 10^{-3} % *7
Invention	Ta_2O_5	0.05 M HCl	> 65 %	< 10^{-5} %
Invention	V_2O_5	0.05 M HCl	> 60 %	< 10^{-5} %
Invention	Nb_2O_5	0.05 M HCl	> 60 %	< 10^{-5} %

*1 Provided by Cyclotron Co. Ltd, Obninsk, Russia

*2 After 200 elutions
*3 Expressed as ratio of radioactivities of $^{68}Ge/^{68}Ga$ in the eluate
*4 After 300 days
*5 Values true for daily elutions only
*6 On calibration date in 4 mL 0.05 M HCl
*7 ^{68}Ge content in ^{68}Ga at calibration time

Detailled Description of the invention

[0023] The present invention relates to the use of novel germanium specific adsorbents being selected from the group of vanadium oxide, niobium oxide and tanatalum oxide, particularly tantalum pentoxide (Ta_2O_5) in a $^{68}Ge/^{68}Ga$ radionuclide generator. The chemically inert and stable adsorbents enable efficient adsorption of ^{68}Ge, efficient and stable desorption of ^{68}Ga, very low breakthrough of ^{68}Ge and efficient labelling of biomolecules with ^{68}Ga.

[0024] Further features and advantages of the present invention will become evident from the following description of examples as well as from the drawings:

Fig. 1
is a graphical representation of the percentage of breakthrough of ^{68}Ge as a function of cumulative elution volume of two $^{68}Ge/^{68}Ga$ generators. Comparison between the current ITG GMP generator according to EP 2 439 747 B1 and the Ta_2O_5-based generator according to the present invention shows the significant difference in the levels of breakthrough of ^{68}Ge;

Fig. 2
is a graphical representation of the elution yield of ^{68}Ga as a function of cumulative elution volume of two $^{68}Ge/^{68}Ga$ generators. Comparison between the current ITG GMP generator according to EP 2 439 747 B1 and the Ta_2O_5-based generator of the present invention shows a large difference in the stability of elution yield of ^{68}Ga;

Fig. 3
shows an HPLC chromatogram presenting the results from direct labelling with ^{68}Ga after 90 h of ingrowth time of a 1900 MBq $^{68}Ge/^{68}Ga$ generator. The percentages of free non-labelled ^{68}Ga and labelled ^{68}Ga are 1.73 % and 96.42 %, respectively;

Fig. 4A and Fig. 4B
are images presenting scanning electron microscope (SEM) images of the surface structure of β-Ta_2O_5 (Fig. 4A) and α-Ta_2O_5 (Fig. 4B). From the images one can see the different surface characteristics indicating higher surface area of β-Ta_2O_5 (Fig. 4A) suggesting higher capacity when applied in a $^{68}Ge/^{68}Ga$ generator column; and

Fig. 5

represents an elution profile of ^{68}Ga of a $^{68}Ge/^{68}Ga$ generator applied with Ta_2O_5 adsorbent. Initial ^{68}Ge activity of the generator was 1000 MBq.

Examples

[0025] The following synthesis method is described by way of example for the manufacture of tantalum pentoxide as the most preferred metal oxide in accordance with the present invention. However, those having average skill in the art will understand that the present synthesis method easily can be applied to the manufacture of the other preferred embodiments of the present invention, namely vanadium pentoxide and niobium pentoxide, particularly due to their close chemical properties.

Synthesis of Ta_2O_5

[0026] A synthesis method for the Ta_2O_5 adsorbent was developed by the applicant using two primary synthesis routes: hydrolysis route using tantalum pentachloride ($TaCl_5$) as a starting material and annealing route using tantalum powder (Ta powder) as a starting material.

Hydrolysis route

[0027] Hydrolysis of $TaCl_5$ was performed in water using controlled water/$TaCl_5$ ratio. Temperature of water during the hydrolysis process was adjusted and kept stable in order to control the particle size of the final product Ta_2O_5. Annealing temperature of the tantalum hydroxide ($Ta(OH)_5$) was chosen based on the solid phase investigations in order to find the best performance for the adsorbent applied in a $^{68}Ge/^{68}Ga$ radionuclide generator.

Annealing route

[0028] Oxidation of Ta powder was performed with starting material with selected particle size distribution. Annealing temperature of the Ta powder was chosen based on the solid phase investigations in order to find the best performance for the adsorbent applied in a $^{68}Ge/^{68}Ga$ radionuclide generator.

Specifications of synthesized Ta_2O_5

[0029] The specifications of the synthesized Ta_2O_5 applied in the radiopharmaceutical $^{68}Ge/^{68}Ga$ generator include the following criteria: annealing temperature, particle size distribution, distribution factor between ^{68}Ge and adsorbent (K_D), and desorption (elutability) of ^{68}Ga. The criteria are summarized in Table 2 below.

Table 2. Specifications of synthesized Ta_2O_5.

Specification	Criterium
Annealing temperature	800 - 1350 °C
Distribution factor (K_D)	2000 - 20000 mL/g
Elutability of ^{68}Ga	≥ 65 %
Particle size distribution	10 - 200 µm

Characterization of Ta_2O_5 adsorbent

[0030] During the development of synthesis of the tantalum pentoxide adsorbent different parameters correlating to adsorption and desorption properties of ^{68}Ge and ^{68}Ga, respectively, were investigated (Table 3). These parameters included crystal structure and surface morphology of the Ta_2O_5, surface area and particle size distribution. The results obtained by radiochemical analysis for ^{68}Ge (distribution factor (K_D) and capacity) and for ^{68}Ga (elutability) were correlated by the observations and results obtained by analytical techniques such as x-ray diffraction (XRD) applied for crystal structure analysis, scanning electron microscopy (SEM) (Figure 4) applied for surface morphology investigations, surface area determination (Brunauer-Emmet-Teller (BET)) and determination of particle size distribution.

Table 3. Correlation between the different specifications of the synthesized Ta_2O_5 adsorbent material.

Adsorbent	Annealing temperature (°C)	Particle size distribution (µm)	K_D for ^{68}Ge (mL/g)	Elutability of ^{68}Ga
β-Ta_2O_5	800 – 1350	10 – 200	137992 – 240964	7.2 %
			101219 – 140377	37 %
			18691 – 19522	47 %
			7878 – 8905 *1	69 % *1
α-Ta_2O_5	1500	10 – 200	779 – 870	67 %
			567 – 615	68 %

*1 Particles of < 8 µm diameter separated

[0031] Tetravalent germanium exists in generator-relevant solution pH (0.05 M HCl) and Ge concentrations ([Ge_{total}] < 0.005 M) in the form of germanic acid ($Ge(OH)_4$) [12,13]. In these conditions germanium binds with hydroxyl groups on the surface of tantalum pentoxide [14]. Experiments have indicated a clear positive correlation between small particle size and high surface area to efficient adsorption of ^{68}Ge. On the other hand, small particle size has a negative effect on the efficiency of elutability of ^{68}Ga. That is why the main goals in the development of the synthesis method for Ta_2O_5 have been to minimize the formation of small particles (< 10 µm), and to increase the surface area of Ta_2O_5 particles. In the Figure 4 one can see the difference in the surfaces of the two crystalline forms of Ta_2O_5: the particles formed of β-Ta_2O_5 (Fig. 4A) have surface covered with caves and formations formed during the aggressive chemical conditions of hydrolysis; thus providing higher surface area and higher K_D and capacity for ^{68}Ge compared to the particles of α-Ta_2O_5 (Fig. 4B) where these morphological structures have "melted" due to high annealing temperature. On the other hand, the glossy surface characteristics of the α-Ta_2O_5 effects provide better elutability properties for ^{68}Ga.

[0032] In conclusion: the aim has been to develop a method of synthesis for Ta_2O_5 adsorbent with the ideal equilibrium between efficient adsorption of ^{68}Ge (shelf life) and efficient elutability of ^{68}Ga (elution yield).

[0033] A batch of germanium specific adsorbent was synthesised by following the hydrolysis route:
Tantalum pentachloride ($TaCl_5$) was mixed with hot water (80 °C, solid/liquid ratio 20 g/L) to produce tantalum hydroxide ($Ta(OH)_5$), which was annealed under 900 °C over 24 h in order to form crystalline tantalum oxide (Ta_2O_5). After isolation of particles with a size range of 10 µm - 200 µm the final material was used as an adsorbent for the $^{68}Ge/^{68}Ga$ generators.

[0034] Two generator columns were filled with a known amount of the adsorbent (8 g). The columns were loaded with a known amount of ^{68}Ge (1000 MBq, 2000 MBq) and stable Ge (total mass of Ge = 80 µg). The radionuclide generators were produced under GMP-conditions.

[0035] The $^{68}Ge/^{68}Ga$ generators were subjected to an elution programme and the critical parameters were followed. At the current stage of the elution programme the following values related to the critical parameters are valid:

- Current total cumulative elution volume: 700 mL (1000 MBq), 400 mL (2000 MBq)
- Elution yield of ^{68}Ga: > 65 %, stable
    - Currently: 70 % (1000 MBq), 73 % (2000 MBq) (Figure 2)
- Elution volume: 6 mL (Figure 6)

- Breakthrough of ^{68}Ge: < 10^{-6} % (level of Ph. Eur.: 10^{-3} %)
    - Currently: 10^{-7} % (1000 MBq), 4 x 10^{-7} % (2000 MBq) (Figure 1)
- Labelling efficiency: > 96 % after 90 h of ingrowth period *via* direct elution (^{68}Ga-DOTA-TOC) (Figure 3).

Critical quality parameters: breakthrough of ^{68}Ge and elution yield of ^{68}Ga

[0036] In general, some factors related to the properties of the adsorbent of $^{68}Ge/^{68}Ga$ generator affect on the critical quality parameters of ^{68}Ga eluate. Low chemical stability of adsorbent increases the breakthrough of ^{68}Ge in the conditions of high radiolytical stress. Moreover, during the shelf life of a generator ^{68}Ge activity zone moves *via* elutions along the adsorbent column making germanium prone to be partly diffused inside the crystal lattice defects of metal oxides or the network of carbon chains of pyrogallol-derivatives and silica. These diffusion phenomena are likely to be factors which cause the decrease of elution yield of ^{68}Ga *via* elutions being typical for the prior art $^{68}Ge/^{68}Ga$ generators on the market.

[0037] Tantalum pentoxide was originally chosen to be used as adsorbent for two main reasons: It is chemically inert and stable material, which makes it suitable to be applied in conditions of high radiolysis and surprisingly yielding low breakthrough of ^{68}Ge (Figure 1). Moreover, the fact that the tantalum cation is (primarily) in pentavalent oxidation state was regarded to be beneficial for the ^{68}Ga elution yield stability and preventative against the diffusion of tetravalent germanium into the crystal lattice of the Ta_2O_5 (Figure 2). Evidence of these properties, i.e., chemical stability and nature can be seen in the Figures 1 and 2 presenting the behaviour of breakthrough of ^{68}Ge and elution yield of ^{68}Ga in the GMP generator and Ta_2O_5 generator in function of cumulative elution volume, respectively.

Critical quality parameter: labelling properties of generator

[0038] Labelling properties of a radiopharmaceutical $^{68}Ge/^{68}Ga$ generator applied with synthesized Ta_2O_5 adsorbent were tested by a method based on the monograph of European Pharmacopoeia [11]. The test was performed for ^{68}Ga eluate eluted from a generator with the nominal ^{68}Ge activity of 1900 MBq and ingrowth time (time of no elutions) of 90 hours. The aim of the test was to demonstrate the stability of the Ta_2O_5 adsorbent against radiolysis even during a longer period of time of no elutions. The results obtained by high-pressure liquid chromatography (HPLC) from the direct labelling were over 96 % yield of labelled product. This

clearly demonstrates the extensive stability of the Ta_2O_5 adsorbent used in a $^{68}Ge/^{68}Ga$ generator, and indicates that no rinsing after weekends is necessary in order to yield a fully functional generator for the use of radiolabelling (Figure 3).

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[0039]

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Patentkrav

1. $^{68}Ge/^{68}Ga$-generator til kontinuerlig produktion af et ^{68}Ga-datter-nuklid, hvor ^{68}Ge-moder-nuklidet deraf er specifikt adsorberet på et uorganisk bærermateriale, og hvor ^{68}Ge-moder-nuklidet kontinuerligt nedbrydes til ^{68}Ga ved en elektronindfangning med en halveringstid på 270,82 dage,
kendetegnet ved, at
det uorganiske bærermateriale er mindst et oxid af et metal, der er udvalgt fra gruppen bestående af: Vanadium, Niobium og Tantal.

2. Generator ifølge krav 1, **kendetegnet ved, at** oxidet er et oxid med den almene formel (1):

$$M_2O_5 \qquad (1),$$

hvor M repræsenterer Vanadium, Niobium eller Tantal.

3. Generator ifølge krav 1 eller 2, **kendetegnet ved, at** oxidet er tantal-pentaoxid (Ta_2O_5).

4. Generator ifølge krav 3, **kendetegnet ved, at** Ta_2O_5 foreligger i sin alpha- og/eller beta-krystallinske form.

5. Generator ifølge et af de foregående krav, **kendetegnet ved, at** oxidet kan opnås ved at hydrolysere et metalhalogenid med den almene formel (2):

$$MX_5 \qquad (2),$$

hvor M repræsenterer Vanadium, Niobium eller Tantal; og X repræsenterer chlor, brom eller iod; og at omdanne et metalhydroxid, der resulterer af hydrolysen, til det ønskede metaloxid ved udglødning.

6. Generator ifølge krav 5, **kendetegnet ved, at** metalhalogenidet er $TaCl_5$, og det resulterende hydroxid er $Ta(OH)_5$.

7. Generator ifølge krav 1 til 4, **kendetegnet ved, at** oxidet kan opnås ved udglødning af et metalpulver under oxygenatmosfære, hvor metallet er udvalgt fra gruppen bestående af: Vanadium, Niobium og Tantal.

8. Generator ifølge krav 7, **kendetegnet ved, at** metallet er Tantal, og det resulterende oxid er Ta_2O_5.

9. Generator ifølge et af de foregående krav, **kendetegnet ved, at** oxid-partikelstørrelsesfordelingen er 5 µm til 300 µm, især 10 µm til 200 µm.

10. Generator ifølge et af de foregående krav, **kendetegnet ved, at** ^{68}Ge-modernuklidet er adsorberet på oxid-bærermaterialet i form af ^{68}Ge(IV)-kationer, især ^{68}Ge-aquo-kationer.

11. Generator ifølge et af de foregående krav, **kendetegnet ved, at** ^{68}Ga elueres fra generatoren med 0,01 til 0,1 M HCl, især med 0,05 M HCl.

12. Generator ifølge krav 11, **kendetegnet ved, at** gennembruddet af ^{68}Ge er $< 10^{-3}$ %, især $< 10^{-6}$ %, fortrinsvis $< 10^{-7}$ % ved en startaktivitet på 1000 MBq og $< 4 \times 10^{-7}$ % ved en startaktivitet på 2000 MBq.

13. Generator ifølge krav 11, **kendetegnet ved, at** elutionsudbyttet af ^{68}Ga er > 65 %.

14. Anvendelse af mindst et oxid af et metal, der er udvalgt fra gruppen bestående af: Vanadium, Niobium og Tantal som et uorganisk bærermateriale til fremstilling af en ^{68}Ge/^{68}Ga-generator i overensstemmelse med krav 1 til 13, til en kontinuerlig produktion af et ^{68}Ga-datter-nuklid, hvor ^{68}Ge-moder-nuklidet deraf er specifikt adsorberet på et uorganisk bærermateriale, og hvor ^{68}Ge-moder-nuklidet kontinuerligt nedbrydes til ^{68}Ga ved elektronindfangning ved en halveringstid på 270,82 dage.

15. Anvendelse ifølge krav 14, **kendetegnet ved, at** der anvendes et oxid med den almene formel (1):

M_2O_5 (1),

hvor M repræsenterer Vanadium, Niobium eller Tantal.

16. Anvendelse ifølge krav 14 eller 15, **kendetegnet ved, at** der anvendes tantal-pentaoxid (Ta_2O_5) som oxid.

DRAWINGS

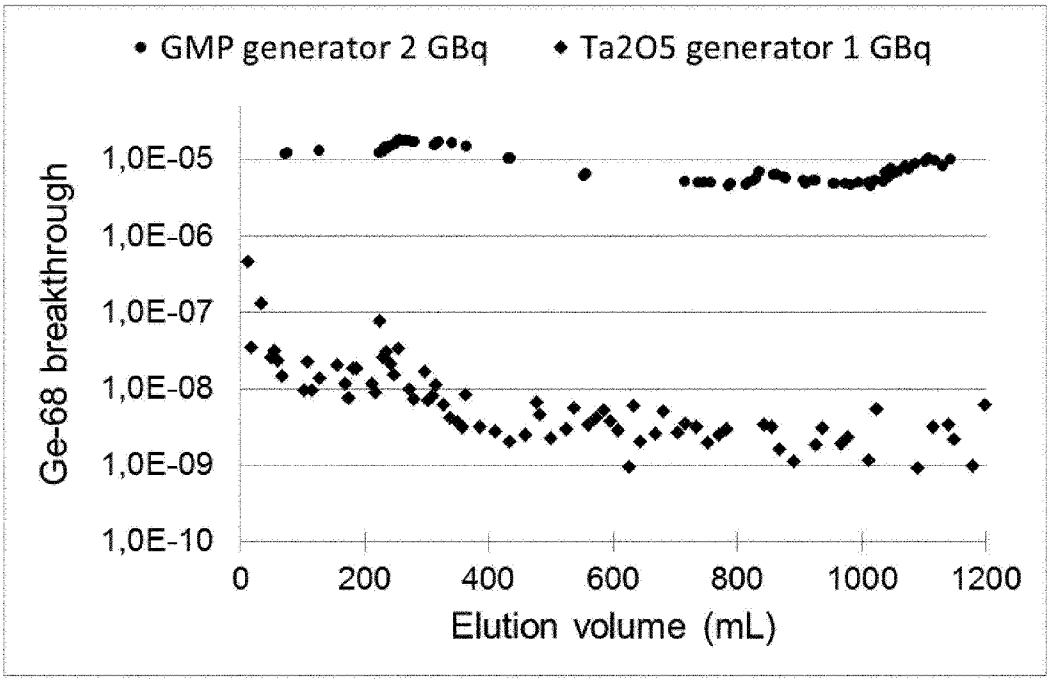

Fig. 1

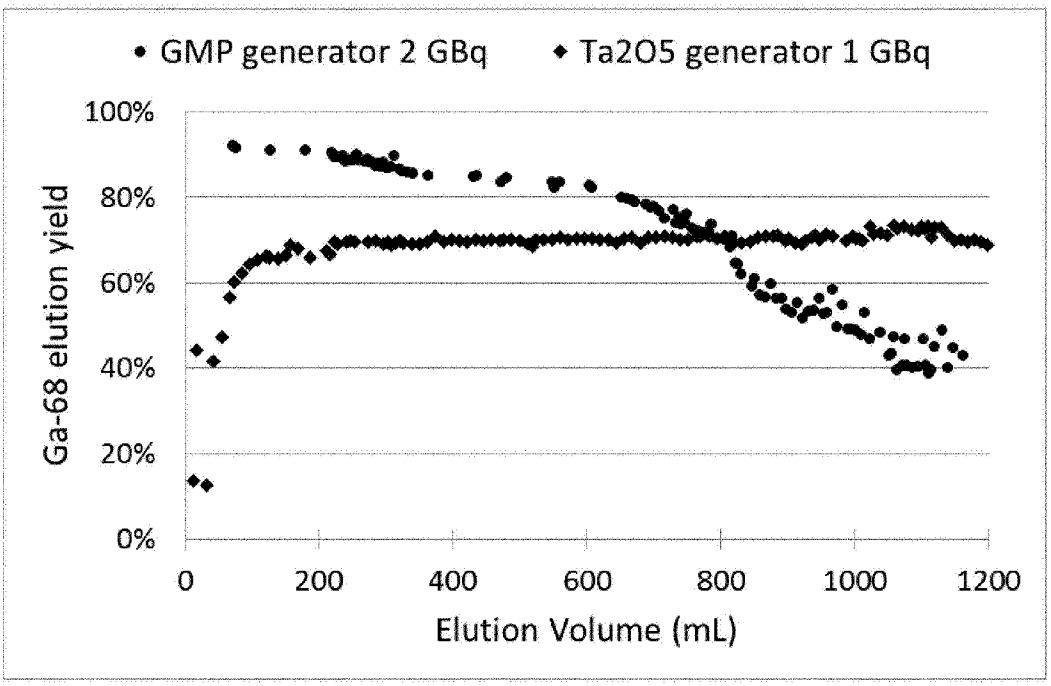

Fig. 2

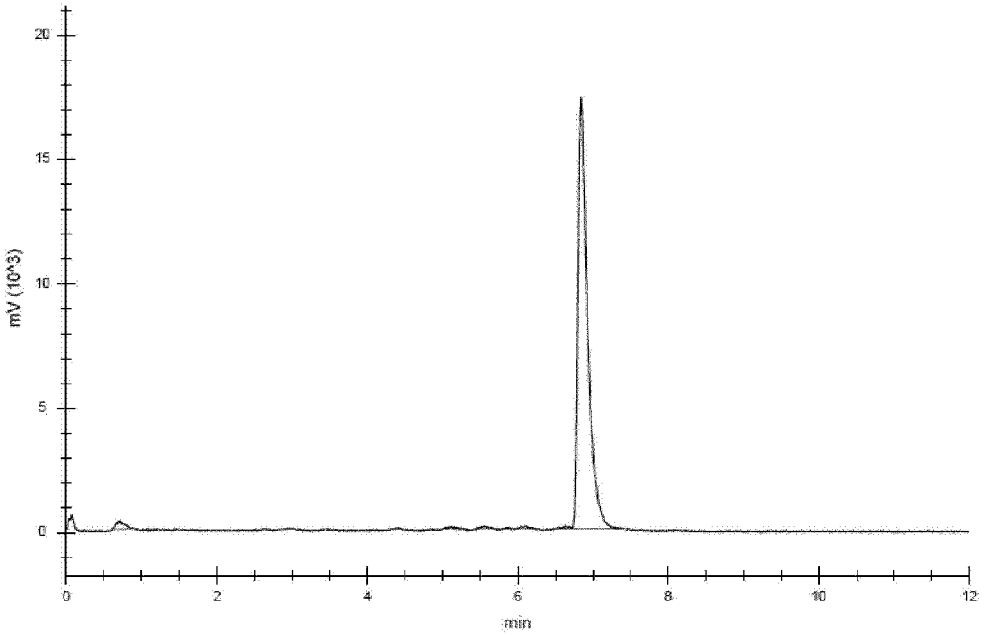

Table of Results:

Calculation Method: Percent

No.	Peak-Start (min)	Peak-End (min)	Ret. Time (min)	Area	Height (mV)	Percent	Name	Response
1	0.617	0.867	0.700	2756000.0	333.33	1.725		
2	4.333	4.467	4.433	158000.0	46.00	0.099		
3	5.025	5.258	5.125	620000.0	88.00	0.388		
4	5.467	5.658	5.550	697000.0	109.22	0.436		
5	5.825	5.900	5.850	69000.0	25.33	0.043		
6	6.017	6.225	6.042	730000.0	116.96	0.457		
7	6.500	6.700	6.625	687702.9	108.59	0.430		
8	6.700	7.342	6.850	154067300.0	16985.66	96.422		

Fig. 3

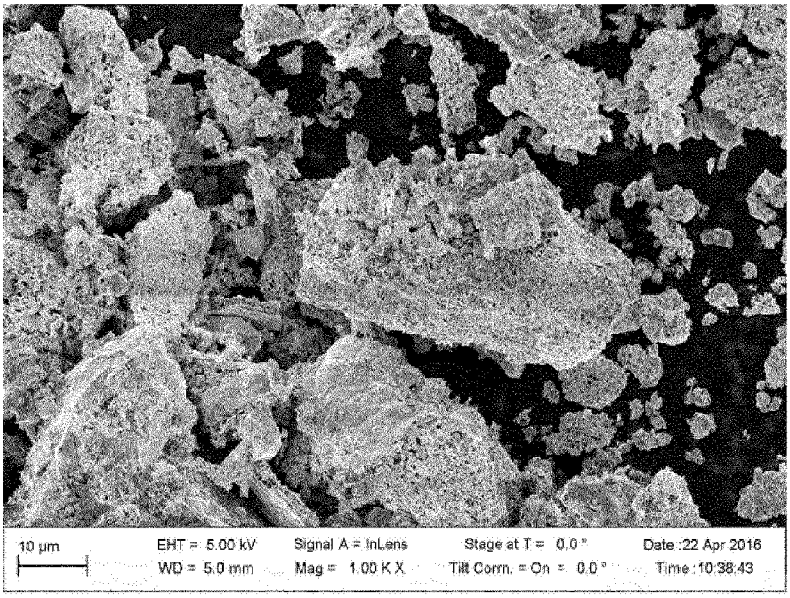
10 µm
EHT = 5.00 kV
WD = 5.0 mm
Signal A = InLens
Mag = 1.00 K X
Stage at T = 0.0 °
Tilt Corrn. = On = 0.0 °
Date :22 Apr 2016
Time :10:38:43

Fig. 4A

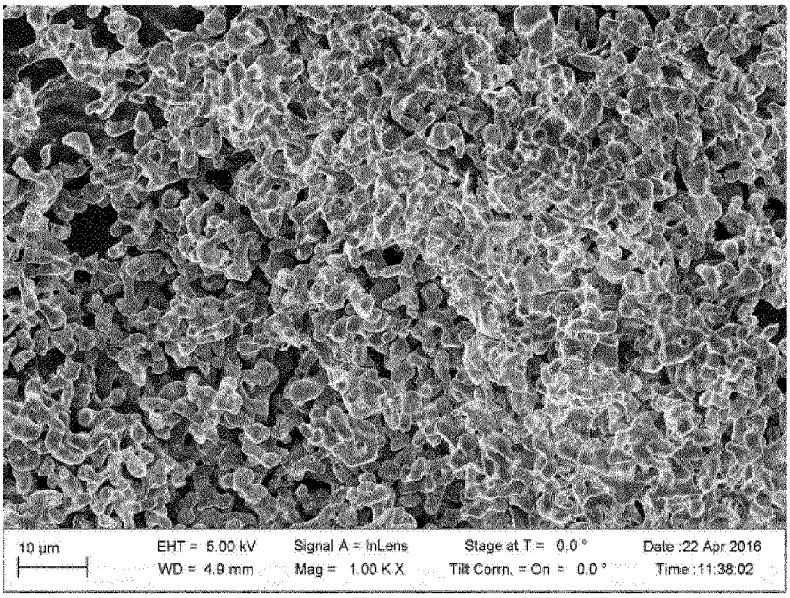
10 µm
EHT = 5.00 kV
WD = 4.9 mm
Signal A = InLens
Mag = 1.00 K X
Stage at T = 0.0 °
Tilt Corrn. = On = 0.0 °
Date :22 Apr 2016
Time :11:38:02

Fig. 4B

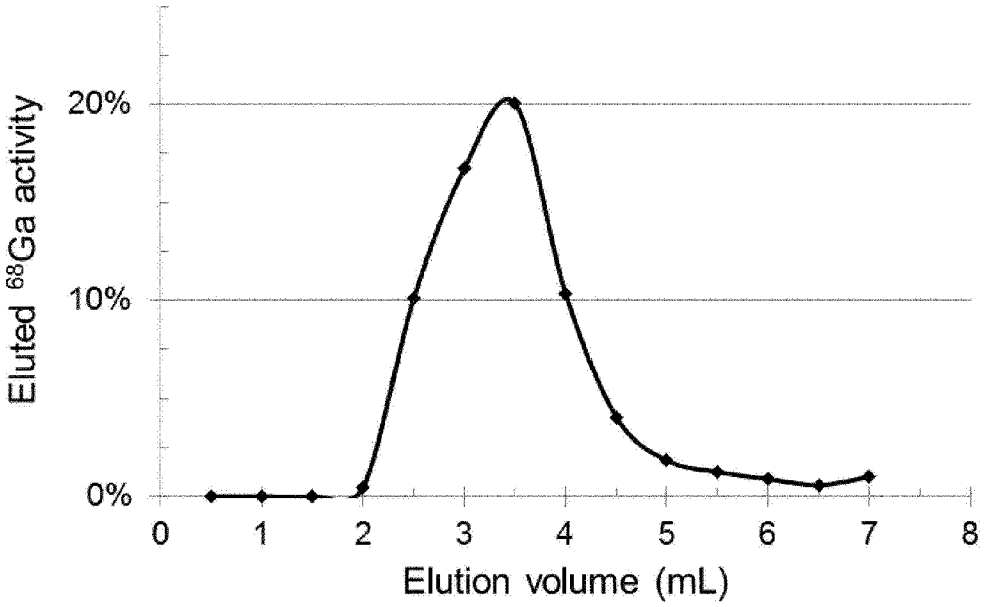

Fig. 5