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(54) **Titre :** PROCÉDE DE PURIFICATION DE MACRO-AGREGATS DE SERUMALBUMINE HUMAINE RADIOMARQUES
(54) **Title:** METHOD FOR PURIFICATION OF RADIOLABELED MACROAGGREGATED HUMAN SERUM ALBUMIN

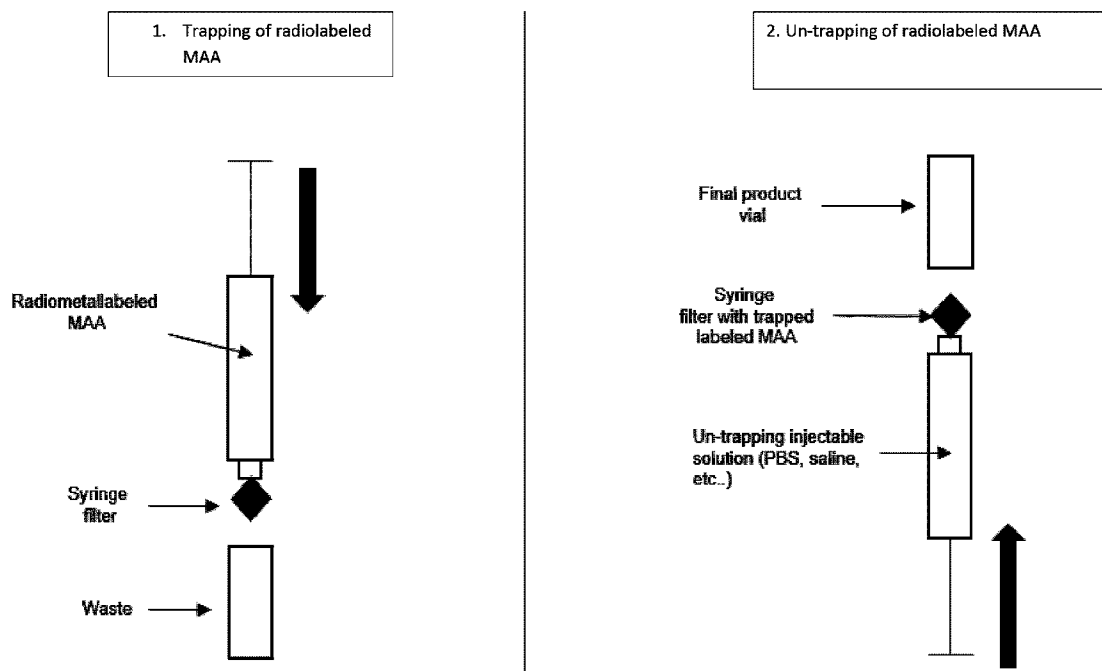


FIG. 1

(57) **Abrégé/Abstract:**

The present invention relates to a method for purifying radiolabelled human serum albumin macroaggregates (MAA) in a solution that can be injected into a patient using a syringe filter, characterized in that the syringe filter used has the property of trapping and releasing the radiolabelled MAA whilst the impurities of the total solution are not retained.

ABSTRACT

**METHOD FOR PURIFICATION OF RADIOLABELED MACROAGGREGATED
HUMAN SERUM ALBUMIN**

5 The present invention relates to a method for the purification of
radiolabeled macroaggregated human serum albumin (MAA) in a solution
injectable to a patient using a syringe filter, wherein the syringe filter used has the
characteristic to trap and untrap the radiolabeled MAA while impurities from the
bulk solution are not retained.

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**METHOD FOR PURIFICATION OF RADIOLABELED MACROAGGREGATED
HUMAN SERUM ALBUMIN**

5 **FIELD OF THE INVENTION**

[0001] The present invention relates to a simplified method for the purification of radiometallabeled macroaggregated human serum albumin (MAA), more simply referred to as radiolabeled herein below. This simplification allows easier automation of such radiotracer syntheses.

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BACKGROUND TECHNOLOGY

Positron emission tomography

[0002] Positron emission tomography (PET) is a medical imaging method for obtaining quantitative molecular and biochemical information of physiological
15 processes in the body. The most common PET radiopharmaceutical in use today is [18F]-fluorodeoxyglucose ([18F]-FDG), a radiolabeled glucose molecule. PET imaging with [18F]-FDG allows to visualize glucose metabolism and has a broad range of clinical indications. Among positron emitters, 18F is the most widely used today in the clinical environment. Due to the increasing regulatory pressure, the
20 radiopharmaceuticals are usually prepared today on single use components assembled in ready-to-use cassettes.

[0003] Besides 18F, radio-metals (e.g. 64Cu, 89Zr, 67Ga, 68Ga, 86Y, 90Y, 177Lu and 99mTc) play a pivotal role in nuclear medicine as therapeutic and imaging agents for radiation therapy and labeling of biologically important low-
25 molecular weight molecules and macromolecules like proteins, peptides and antibodies.

[0004] In the recent past, a rapid increase has been noted in both clinical and preclinical studies involving 68Ga-labeled radiopharmaceuticals (Velikyan I., *Prospective of 68Ga-radiopharmaceutical development*. Theranostics 2014; 4:47-80; Banerjee S.R., Pomper M.G. *Clinical applications of Gallium-68*. Appl.
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Radiat. Isot. 2013; 76:2-13; Zimmerman B.E. *Current status and future needs for standards of radionuclides used in positron emission tomography*. Appl. Radiat. Isot. 2013; 76:31-37; Smith D.L., Breeman W.A.P., Sims-Mourtada J., *The untapped potential of Gallium-68 PET: The next wave of 68Ga-agents*. Appl. Radiat. Isot. 2013; 76:14-23). This increase can be attributed to the favorable physical characteristics of 68Ga ($E_{\beta_{\max}}$ 1.8 MeV, β^+ 89%, $T_{1/2}$ = 67.7 minutes, against about 6 hours for 99mTc) for imaging various rapidly changing processes (proliferation, apoptosis, angiogenesis) and targets (growth hormones, myocardial and pulmonary perfusion, inflammation and infection), and to some extent, to newer, more reliable production and labeling methods. For example, Gallium-68 labeled somatostatin analogs have already shown their superiority over the existing agent 111In-DTPA-octreotide through enhanced sensitivity, specificity, accuracy and cost effectiveness for the diagnosis of patients with neuroendocrine tumors (Oberberg K., *Gallium-68 somatostatin receptor PET/CT: Is it time to replace 111Indium DTPA octrotide for patients with neuroendocrine tumors?* Endocrine 2012; 42:3-4; Schreiter N.F., Brenner W., Nogami M., Buchert R., Huppertz A., Pape U.F., Prasad V., Hamm B., Maurer M.H., *Cost comparison of 111In-DTPA-octrotide scintigraphy and 68Ga-DOTATOC PET/CT for staging enteropancreatic neuroendocrine tumours*. Eur. J. Nucl. Med. Mol. Imaging 2012; 39: 72-82; Hofman M.S., Kong G., Neels O.C., Eu P., Hong E., Hicks R.J., *High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours*. J. Med. Imaging Radiat. Oncol. 2012; 56:40-47).

[0005] Another reason for the current Gallium-68 infatuation is that it can be produced onsite by widely commercially available 68Ge/68Ga generators. Such 68Ge/68Ga generators are broadly accessible in nuclear medicine facilities not equipped with an on-site cyclotron. The simplicity and lower capital cost of the 68Ge/68Ga generator have made it more popular among the nuclear medicine facilities with relatively lower number of requirements for 68Ga-labeled doses (Rosch F. *Past, present and future of 68Ge/68Ga generators*. Appl. Radiat. Isot. 2013; 76:24-30).

Radiometallabeled macroaggregated human serum albumin (MAA)

[0006] The use of macroaggregated human serum albumin (MAA) as a perfusion agent has been evaluated since 1965 (Furth E.D., Okinaka A.J., Focht E.F., Becker D.V., *The distribution, metabolic fate and radiation dosimetry of ¹³¹I labelled macroaggregated albumin*. J. Nucl. Med. 1965; 6:506-518). In 1974, an instant kit for the preparation of ^{99m}Tc-labeled MAA was evaluated for this purpose using Single Photon Emission Computed Tomography SPECT (Charidra R., Shamoun J., Braunstein P., DuHov O.L., *Clinical evaluation of an instant kit for preparation of ^{99m}Tc MAA for lung scanning*. J. Nucl. Med. 1974; 14-9:702-705). The drug became the standard for lung perfusion studies and still dominates the market (Suga K., Kawakami Y., Zaki M., Yamashita T., Matsumoto T., Matsunaga N., *Pulmonary perfusion assessment with respiratory gated Tc-^{99m} macroaggregated albumin SPECT: preliminary results*. Nucl. Med. Commun. 2004; 25: 183-193). Nowadays, numerous FDA-approved MAA labeling kits for ^{99m}Tc are commercially available (e.g. Pulmocis® (from CisBio), LyoMAA® (from Covidien), HAS-B20® (from Rotop), MAASOL® (from GE), etc.). All those kits are provided under the form of a sterile single use vial that contains ~2.0 mg of MAA particles, ~0.05 mg of SnCl₂ (as a ^{99m}Tc reduction agent) and ~5.0 mg of free albumin.

[0007] Set against the background of the worldwide shortage of ⁹⁹Mo, which decays to form the ^{99m}Tc and is used in about 600,000 medical imaging procedures worldwide every week, it is necessary to think about alternatives in order to be independent of any lack of ^{99m}Tc. The ⁶⁸Ge/⁶⁸Ga generator represents such an attractive alternative. Furthermore, PET/CT delivers images with significantly higher resolution than SPECT. Thus, ⁶⁸Ga-labeled MAA for PET/CT perfusion imaging represents an attractive alternative to ^{99m}Tc-labeled MAA.

[0008] MAA was first successfully labeled with ⁶⁸Ga in 1986 (Maziere B., Loc'h C., Steinling M., Comar D., *Stable labelling of serum albumin microspheres with gallium-68*. Int. J. Radiat. Appl. Instrum. Part A 1986; 37:360-361) and in 1989 (Even G.A., Green M.A., *Gallium-68-labeled macroaggregated human serum albumin, ⁶⁸Ga-MAA*. Int. J. Radiat. Appl. Instr. 1989; 16:319-321) but

never used at that time, probably due to the lack of reliability of the existing $^{68}\text{Ge}/^{68}\text{Ga}$ generators and low availability of PET imaging cameras. Later on, Mathias et al. (Mathias C.J., Green M.A., *A convenient route to [^{68}Ga] Ga -MAA for use as a particulate PET perfusion tracer*. Appl. Radiat. Isot. 2008; 66:1910-1912) successfully labelled MAA with ^{68}Ga as well. Similar results have been reported by using commercially available $^{99\text{m}}\text{Tc}$ -MAA kit systems (Jain A., Subramanian S., Pandey U., Sarma H.D., Ram R., Dash A., *In-house preparation of macroaggregated albumin (MAA) for ^{68}Ga labelling and its comparison with commercially available MAA*. J. Radioanal. Nucl. Chem. 2016 ; 308:817-824 ; Amor-Coarasa A., Milera A., Carvajal D., Gulec S., McGoron A.J., *Lyophilized kit for the preparation of the PET perfusion agent [^{68}Ga]-MAA*. Int. J. Mol. Imaging 2014:1-7; Ament S.J., Maus S., Reber H., Buchholz H.G., Bausbacher N., Brochhausen C., Graf F., Miederer M., Schreckenberger M., *PET lung ventilation/perfusion imaging using ^{68}Ga aerosol (Galligas) and ^{68}Ga -labeled macroaggregated albumin*. Recent Results Cancer Res. 2013; 194:395-423). To remove undesired components like stannous chloride, which is usually used as a reduction component, the lyophilizate of the MAA-kit system was resuspended and washed with 0.9% saline using centrifugation. A pre-conjugation of MAA with the DOTA chelator (Kotzerke J., Andreeff M., Wunderlich G., Wiggermann P., Zphel K., *Ventilation/Perfusion scans using Ga-68 labeled tracers*. Abstracts of invited lectures. World J. Nucl. Med. 2011; 10:26-59) for an efficient ^{68}Ga labelling is not needed in this procedure. After labeling, the ^{68}Ga -MAA were purified using centrifugation, which is time-consuming, decreases significantly the final yield and is not prone to automation. The authors could also show that there was no difference in morphology between unlabeled and labeled MAA particles. Maus et al. (Maus S., Buchholz H.G., Ament S., Brochhausen C., Bausbacher N., Schreckenberger M., *Labelling of commercially available human serum albumin kits with ^{68}Ga as surrogates for $^{99\text{m}}\text{Tc}$ -MAA microspheres*. Appl. Radiat. Isot. 2011; 69:171-175) found similar results and used this method for investigation of the labeling efficiency by using HEPES buffer. A maximum labeling efficiency of 70% has been found and the radiochemical purity after a final Solid Phase Extraction (SPE) purification step (using a C18 SEP-Pack cartridge) was higher than 95%. This SPE final purification was nonetheless shown to dramatically

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reduce the final ^{68}Ga -MAA outcome (> 30% of the labelled MAA remain stuck on the SPE cartridge). All these published reports about the radio-labeling of MAA disclose the use of a crude fraction of the $^{68}\text{Ge}/^{68}\text{Ga}$ generator eluate directly. Because of the use of a crude fraction of the eluate, ^{68}Ge breakthrough of the generator cannot be separated from the final product during the labeling procedure. Furthermore, this method uses only a part of the elutable ^{68}Ga activity. To overcome this drawback, Mueller et al. (Mueller D., Kulkarni H., Baum R.P., Odparlik A., *Rapid synthesis of ^{68}Ga -labeled macroaggregated human serum albumin (MAA) for routine application in perfusion imaging using PET/CT*. 2017; 122:72-77) recently provided a convenient preparation of ^{68}Ga -MAA using a cationic prepurification of the generator eluate. The method allows the use of most of the eluted ^{68}Ga activity from the generator and does not require any purification step of the reaction media as the ^{68}Ge breakthrough is removed during the cationic prepurification. Nonetheless, in the absence of a final purification step, the production can be lost in case of a low-yield labelling. The authors also show that the MAA pre-washing step using centrifugation, to remove the tin chloride, is not necessary to achieve an efficient labelling yield.

[0009] Commercial Gallium-68 ($^{68}\text{Ge}/^{68}\text{Ga}$) generators are widely available. The parent isotope ^{68}Ge has a half-life of 270.95 days and can be easily delivered to hospitals as a generator, where it can be used as the source of Ga-68 for at least 1 year. Short half-life ^{68}Ga can be easily eluted from the generator at any time on the site of application. The ^{68}Ga generator of a chromatographic type is a glass column with a sorbent based on modified TiO_2 . The parent radionuclide ^{68}Ge is fixed on this sorbent. The column is placed into a lead shielding container and provided with eluent and eluate lines. ^{68}Ga , which is generated as a result of ^{68}Ge decay, is eluted from the column for example using a 0.1 M HCl solution. The parent isotope activity is for example between 10mCi (370 MBq) and 100mCi (3700 MBq). ^{68}Ge breakthrough is usually less than 0.005 %.

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PROBLEM TO BE SOLVED

5 **[0010]** ^{99m}Tc-labeled-MAA is a widely used established lung perfusion agent using SPECT. Due to the superiority of PET over SPECT and the ⁹⁹Mo upcoming shortage, ⁶⁸Ga-labeled MAA for PET/CT perfusion imaging represents an attractive alternative to ^{99m}Tc-labeled MAA.

10 **[0011]** While the labeling conditions of ⁶⁸Ga with MAA are well defined, there is a lack of an effective, easy to automatize on single use cassette-based system and of time/yield-efficient final purification of labelled ⁶⁸Ga-MAA particles from the bulk reaction media, that would remove the ⁶⁸Ge breakthrough, consistently assure a high radiochemical purity enabling safe patient injection and not impacting the final synthesis yield.

15 **[0012]** Nowadays, such final purification is performed either using centrifugation, which requires extra apparatus, is time consuming, negatively impacts the overall synthesis yield (~20% activity loss) and is unwelcomed from a radioprotection point of view, or using SPE purification, which negatively impacts the yield (> 30% activity loss due to labelled particles stuck on the cartridge). One recent example uses a cationic prepurification of the generator eluate, which is time consuming, without any final purification which is not filled from a regulatory point of view. Alternative synthesis methods with a very effective final purification step are thus highly desirable. The purification method of choice must be effective enough and reliable to ensure a high level of radiochemical purity.

AIM OF THE INVENTION

25 **[0013]** The present invention aims at performing a synthesis of ⁶⁸Ga-labeled MAA particles, which is easily automated on ready-to-use consumables including an efficient final purification of the labelled particles.

SUMMARY OF THE INVENTION

30 **[0014]** The present invention relates to a method for the synthesis and purification of radiolabeled macroaggregated human serum albumin (MAA)

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to form a bulk solution injectable to a patient, wherein the method comprises the following steps of :

- providing a radiometal in a generator, under the form of a generator eluate ;
- 5 - optionally prepurifying the generator eluate on a cationic cartridge and eluting the prepurified generator eluate ;
- synthesizing the radiolabeled MAA in a reactor with MAA particles from a commercially available labeling kit for 99mTc and said generator eluate, prepurified or not ;
- 10 - passing the synthesized radiolabeled MAA particles on a syringe filter membrane which membrane composition, diameter and pore size are chosen so as to trap the radiolabeled MAA particles, while impurities from the bulk solution are not retained, said impurities essentially consisting of free radiometal isotopes, parent radiometal breakthrough and stannous chloride present in said MAA labeling kit for 99mTc ;
- 15 - untrapping said trapped radiolabeled MAA particles from the syringe filter using a saline or buffered solution passing through the syringe filter in the opposite direction of the trapping movement and providing the final bulk solution injectable to a patient into a vial.

20 **[0015]** According to preferred embodiments, the method further comprises one of the following characteristics or a suitable combination thereof :

- radiolabeled MAA particles to be purified are MAA particles labelled with detectable metal ions selected from the group of 99mTc, 94mTc, 48V, 52Fe, 55Co, 64Cu, 68Ga, 67Ga, 111In, 113In, 86Y, 89Zr, 203Pb, 212Bi, 82Rb, 186Re and 81mKr ;
- 25 - radiolabeled MAA particles to be purified are MAA particles labelled with detectable metal ions selected from the group of 99mTc, 68Ga, 86Y, 89Zr and 64Cu ;
- radiolabeled MAA particles to be purified are MAA particles labelled with 99mTc or 68Ga ;
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- the syringe filter membrane pore size is in the range of 0.1 – 10.0 μm ;
- the syringe filter membrane pore size is in the range of 0.1 – 5.0 μm ;
- the syringe filter membrane pore size is in the range of 0.1 – 0.45 μm ;
- the syringe filter membrane diameter is in the range of 10 – 33 mm ;
- 5 - the syringe filter membrane diameter is in the range of 20 – 33 mm ;
- the syringe filter membrane is a low-protein binding hydrophilic membrane selected from the group consisting of PVDF, PES, CA, hydrophilic PTFE, nylon, Glass Fiber, RC, CE, CN and PP ;
- the syringe filter is a single-use filter cartridge possibly having Luer lock fittings ;
- 10 - the syringe filter is attached to a single-use cassette in an automated process ;
- the generator eluate is maintained at room temperature during 2 to 30 minutes or heated at 40-80°C during 2 to 20 minutes before the step of trapping the generator eluate on the syringe filter ;
- 15 - the reactor for synthesizing the radiometallalabeled MAA is an automated synthesizer.

BRIEF DESCRIPTION OF THE DRAWINGS

- 20 **[0016]** FIG. 1 schematically represents radiometallalabeled MAA trapping (left side, the particles are trapped on the filter, while the impurities pass through the filter to the waste) and untrapping (right side, the solution flow untraps the particles) steps.

25 **DISCLOSURE OF THE INVENTION**

[0017] The method of the present invention allows the purification of ^{68}Ga -labeled MAA particles, prepared using directly the whole generator eluate or alternately including a cationic prepurification of the generator eluate. The

method is furthermore compatible to any commercially available MAA labelling kits for ^{99m}Tc .

[0018] This efficient purification is made by the use of a syringe filter. A syringe filter is a single-use filter cartridge. Syringe filters may have Luer lock fittings, though not universally so. For manual purification, it is attached to the end of a syringe for use. For automated processes, syringe filters can be fixed on single use cassettes. The use of a needle is optional; where desired it may be fitted to the end of the syringe filter. A syringe filter generally consists of a plastic housing with a membrane which serves as a filter. The fluid to be purified may be cleaned by drawing it up through the filter. A syringe filter membrane is characterized by its composition (material and pore size) and its diameter. Common pore sizes available are 0.1, 0.2, 0.22, 0.45, 5 and 10 μm , although intermediate pore sizes are easily available. Membrane diameters of 10, 13, 25, 33 mm are common as well. The syringe filter body may be made of materials such as polypropylene and nylon. The filter membrane may be of polytetrafluoroethylene (PTFE), nylon, cellulose acetate (CA), polyvinylidene fluoride (PVDF), cellulose ester (CE), polyethersulfone (PES), polypropylene (PP), Glass Fiber (GF), regenerated cellulose (RC), cellulose nitrate (CN), etc.

[0019] While passing through the reaction media on the syringe filter membrane, the labelled and unlabelled MAA particles are retained on the filter due to size exclusion, while the ^{68}Ge breakthrough and remaining free $^{68}\text{Ga}^{3+}$ pass through the syringe filter membrane to the waste (FIG. 1, left).

[0020] To untrap the particles from the syringe filter, a solution is passed through the syringe filter membrane, in the opposite (or reverse) direction of the trapping movement, to a final product vial (FIG. 1, right). The untrapping is due to the flow of the untrapping solution. The aforementioned untrapping solution being injectable (e.g. an appropriate phosphate buffer solution or physiological saline, i.e. 0.154 mol/L or 9 g/L NaCl), the resulting tracer solution is readily injectable to a patient.

[0021] It brings several advantages: a reduction of the preparation duration, which results in an increase of the overall yield; a simplification of the automated equipment needed for the synthesis of the radiopharmaceutical; a

purification process which is compatible with any radiolabeled MAA particles, thus which is not limited to ^{68}Ga or $^{99\text{m}}\text{Tc}$; the assurance of a high level radiochemical purity even in case of a low-yield labelling.

[0022] According to the present invention, the purification process is performed by passing the bulk of the synthesis of the radiolabeled MAA particles on a syringe filter, that may be placed on a single-use cassette for automation. This syringe filter has the characteristic to retain the labelled (and unlabelled) MAA products but not the free unlabelled radioisotope (i.e. $^{68}\text{Ga}^{3+}$ in the case of ^{68}Ga -MAA labelling, also the ^{68}Ge breakthrough) assuring a high level of radiochemical purity, and not the tin chloride coming from the original MAA labelling kit either.

[0023] In some embodiments of the present invention, the radiolabeled MAA particles to be purified are MAA particles labelled with a detectable metal ion such as $^{99\text{m}}\text{Tc}$, $^{94\text{m}}\text{Tc}$, ^{48}V , ^{52}Fe , ^{55}Co , ^{64}Cu , ^{68}Ga , ^{67}Ga , ^{111}In , ^{113}In , ^{86}Y , ^{89}Zr , ^{203}Pb , ^{212}Bi , ^{82}Rb , ^{186}Re , ^{81}mKr .

[0024] In some preferred embodiments of the present invention, the radiolabeled MAA particles to be purified are MAA particles labelled with $^{99\text{m}}\text{Tc}$, ^{68}Ga , ^{86}Y , ^{89}Zr or ^{64}Cu .

[0025] In some preferred embodiments of the present invention, the radiolabeled MAA particles to be purified are MAA particles labelled with $^{99\text{m}}\text{Tc}$ or ^{68}Ga .

[0026] In some embodiments, the syringe filter membrane pore size is in the range of $0.1 - 10.0 \mu\text{m}$.

[0027] In some preferred embodiments, the syringe filter membrane pore size is in the range of $0.1 - 5.0 \mu\text{m}$.

[0028] In some preferred embodiments, the syringe filter membrane pore size is in the range of $0.1 - 0.45 \mu\text{m}$.

[0029] In some embodiments, the syringe filter membrane diameter is in the range of $10 - 33 \text{ mm}$.

[0030] In some embodiments, the syringe filter membrane diameter is in the range of $20 - 33 \text{ mm}$.

[0031] In some embodiments, the syringe filter membrane is selected from the group of low-protein binding hydrophilic membranes (PVDF, PES, CA, hydrophilic PTFE, nylon, Glass Fiber, RC, CE, CN, PP).

5 **EXAMPLES**

Example 1

[0032] This example shows the efficiency of using a syringe filter to purify a bulk of ^{68}Ga -MAA. The ^{68}Ga -MAA was synthesized on an automated synthesizer, using a cationic prepurification of the generator eluate: an
10 Eckert & Ziegler $^{68}\text{Ge}/^{68}\text{Ga}$ generator is eluted with 5 mL 0.1 M HCl. The generator eluate is trapped on a PS-H⁺ cationic cartridge that retains the eluted $^{68}\text{Ga}^{3+}$. The activity is then eluted to the reactor using an acidified concentrated NaCl solution. The MAA from a Pulmocis[®] labeling kit, dissolved in an acetate buffer, is added to the reactor. After a heating time of 6 minutes at 60°C, the
15 reaction media is sent to the final product vial and formulated with a phosphate buffer to yield a final pH of 7.0 (final volume is 10 mL). Non-decay corrected (n.d.c.) radiochemical yield is of 75% (111.4 MBq) and the radiochemical purity is of 80%. This final product solution (111.4 MBq) was manually passed through a 25 mm, 5 μm pore size PVDF syringe filter membrane (Millipore Ref.
20 SLSV025LS). The whole labeled ^{68}Ga -MAA particles are retained on the filter (activity on the filter: 88.6 MBq) while the free $^{68}\text{Ga}^{3+}$ passes through the filter (activity in the filtrate: 22.8 MBq). After trapping, 10 mL of physiological saline are passed through the syringe filter, in the opposite direction of the trapping movement, to untrap the labeled particles. An efficient untrapping of 98.2% (2
25 MBq remaining on the filter) is reached. A thin layer chromatography (TLC) analysis showed a radiochemical purity of the untrapped ^{68}Ga -MAA particles of 98.9%.

Example 2

[0033] This example shows the efficiency of using a syringe filter to trap and untrap a bulk of $^{99\text{m}}\text{Tc}$ -MAA. The $^{99\text{m}}\text{Tc}$ -MAA is synthesized using a
30 commercial Pulmocis[®] labeling kit following the routine procedure: the Tc-generator is directly eluted into the Pulmocis[®] labeling kit. After 15 minutes at

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room temperature under a gentle mixing, the ^{99m}Tc -labeled MAA bulk solution was manually passed through a syringe filter (25 mm diameter, 5 μm pore size, PVDF membrane, Millipore Ref. SLSV025LS). The labelled particles are retained on the filter (activity on the filter: 44163 cps/10s). After trapping, 10 mL physiological saline passes through the filter in the opposite direction of the trapping movement. The untrapping efficiency is of 91% (activity remaining on the filter: 4523 cps/10s).

Examples 3-11

[0034] The following examples show the efficiency of using a syringe filter to purify a bulk of ^{68}Ga -MAA. The ^{68}Ga -MAA is synthesized on an automated synthesizer, with no prepurification of the generator eluate (i.e. using the whole generator eluate), but with a final purification on a syringe filter placed on the single-use cassette. An Eckert & Ziegler $^{68}\text{Ge}/^{68}\text{Ga}$ generator is eluted with 5 mL 0.1 M HCl directly to the reactor that contains the MAA particles from a Pulmocis® labeling kit dissolved in 2 mL of a 0.35 M acetate solution. After a heating time of 6 minutes at 60°C , the reaction media is passed through the syringe filter that retains the labeled particles, while the free $^{68}\text{Ga}^{3+}$ and the ^{68}Ge breakthrough pass through the filter to the waste. 10 mL physiological saline are then used to untrap the labelled particles to the final product vial. Synthesis time is of 12 minutes after generator elution. Experiments were repeated varying the filter syringe type (Examples 3 – 11). Table 1 show the non-decay corrected (n. d. c.) radiochemical yield (RCY), the radiochemical purity (RCP) and the ^{68}Ge content (when measured) in the final product vial for Examples 3 - 11.

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Ex. N°	Filter	RCY (%n.d.c.)	RCP (%) at t0	⁶⁸ Ge content(*)
3	25 mm, 5 µm, PVDF Millex Ref. SLSV025LS	46	94.5	/
4	13 mm, 5 µm, CA Steriltech Ref. CA501350	46	99.1	/
5	13 mm, 0.45 µm, PVDF Millex Ref. SLHVX13TL	19	98.7	/
6	25 mm, 0.22 µm, PVDF Millex Ref. SLGV0250S	80	100	< 0.0001%
7	25 mm, 0.22 µm, PVDF Millex Ref. SLGV0250S	82	100	<0.0001%
8	25 mm, 0.22 µm, PVDF Millex Ref. SLGV0250S	83	100	/
9	25 mm, 0.22 µm, PVDF Millex Ref. SLGV0250S	81	100	/
10	25 mm, 0.22 µm, PVDF Millex Ref. SLGV0250S	83	99.5	/
11	25 mm, 0.22 µm, PVDF Millex Ref. SLGV0250S	84	99.7	/

(*) Measured after complete decay of ⁶⁸Ga³⁺. The limit for patient injection is of 0.001% of the initial activity.

Table 1 – Results of Examples 3-11

- 5 **[0035]** Table 1 shows the high efficiency of using syringe filters for the purification of radiolabeled MAA. High-level radiochemical yield is almost always achieved, even in cases of low labeling yield and of low untrapping yield. The procedure is also time-effective, as the synthesis time, including the final purification and dispensing to the final product vial, is of 12 minutes after the
- 10 generator elution.

CLAIMS

1. A method for the synthesis and purification of radiolabeled macroaggregated human serum albumin (MAA) to form a bulk solution injectable to a patient, wherein the method comprises the following steps of :

- 5 - providing a radiometal in a generator, under the form of a generator eluate ;
- optionally prepurifying the generator eluate on a cationic cartridge and eluting the prepurified generator eluate ;
- synthesizing the radiolabeled MAA in a reactor with MAA particles from a commercially available labeling kit for 99mTc and said generator eluate, prepurified or not ;
- 10 - passing the synthesized radiolabeled MAA particles on a syringe filter membrane which membrane composition, diameter and pore size are chosen so as to trap the radiolabeled MAA particles, while impurities from the bulk solution are not retained, said impurities essentially consisting of free radioactive metal isotopes, parent radioactive metal breakthrough and stannous chloride present in said MAA labeling kit for 99mTc ;
- 15 - untrapping said trapped radiolabeled MAA particles from the syringe filter using a saline or buffered solution passing through the syringe filter in the opposite direction of the trapping movement and providing the final bulk solution injectable to a patient into a vial.
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2. The method according to claim 1, wherein radiolabeled MAA particles to be purified are MAA particles labelled with detectable metal ions selected from the group of 99mTc, 94mTc, 48V, 52Fe, 55Co, 64Cu, 68Ga, 67Ga, 111In, 113In, 86Y, 89Zr, 203Pb, 212Bi, 82Rb, 186Re and 81mKr.

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3. The method according to claim 1, wherein radiolabeled MAA particles to be purified are MAA particles labelled with detectable metal ions selected from the group of 99mTc, 68Ga, 86Y, 89Zr and 64Cu.

4. The method according to claim 1, wherein radiolabeled MAA particles to be purified are MAA particles labelled with 99mTc or 68Ga.

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5. The method according to any one of claims 1 to 4, wherein the syringe filter membrane pore size is in the range of 0.1 – 10.0 μm .
6. The method according to claim 5, wherein the syringe filter membrane pore size is in the range of 0.1 – 5.0 μm .
- 5 7. The method according to claim 6, wherein the syringe filter membrane pore size is in the range of 0.1 – 0.45 μm .
8. The method according to any one of claims 5 to 7, wherein the syringe filter membrane diameter is in the range of 10 – 33 mm.
9. The method according to claim 8, wherein the syringe filter
10 membrane diameter is in the range of 20 – 33 mm.
10. The method according to claim 8 or 9, wherein the syringe filter membrane is a low-protein binding hydrophilic membrane selected from the group consisting of PVDF, PES, CA, hydrophilic PTFE, nylon, Glass Fiber, RC, CE, CN and PP.
- 15 11. The method according to claim 1, wherein the syringe filter is a single-use filter cartridge possibly having Luer lock fittings.
12. The method according to claim 1, wherein the syringe filter is attached to a single-use cassette in an automated process.
13. The method according to claim 1, wherein the generator
20 eluate is maintained at room temperature during 2 to 30 minutes or heated at 40-80°C during 2 to 20 minutes before the step of trapping the generator eluate on the syringe filter.
14. The method according to claim 1, wherein the reactor for synthesizing the radiolabeled MAA is an automated synthesizer.

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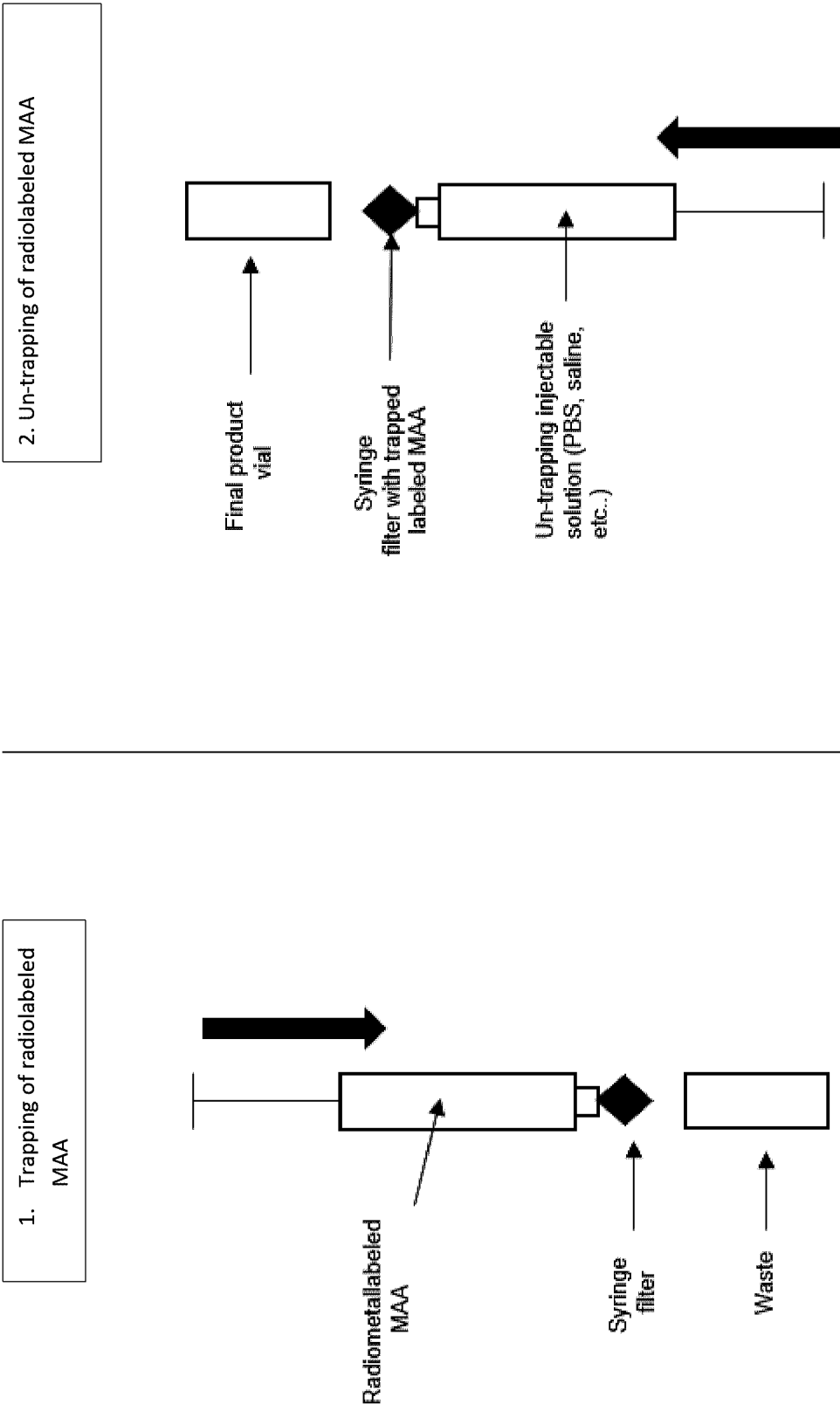
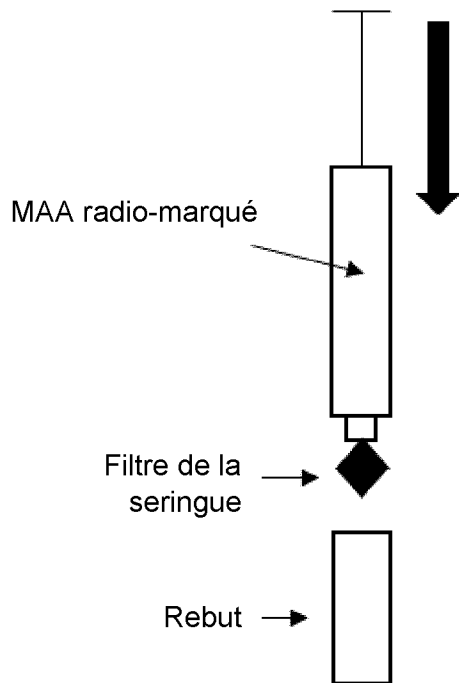


FIG. 1

2. Piégeage du MAA radio-marqué



1. Libération du MAA radio-marqué

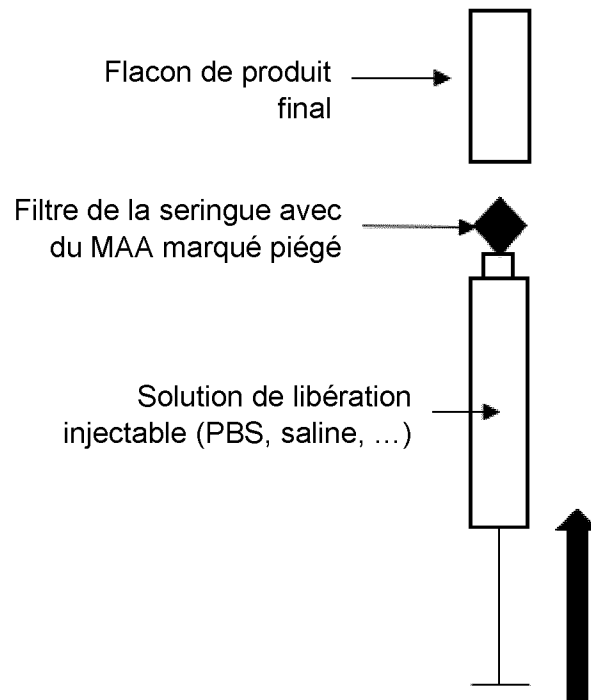


FIG. 1