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[Continued on next page]

(54) Title: SYSTEM AND METHOD FOR PRODUCING RADIOMEDICAL-GRADE TC-99M

(57) Abstract: The present invention provides systems and methods for producing radiomedical-grade Tc-99m. In particular, the present invention provides systems and methods for producing Tc-99m by proton-irradiation of Mo-100 targets and subsequent separation of the resulting Tc-99m from the irradiated targets.

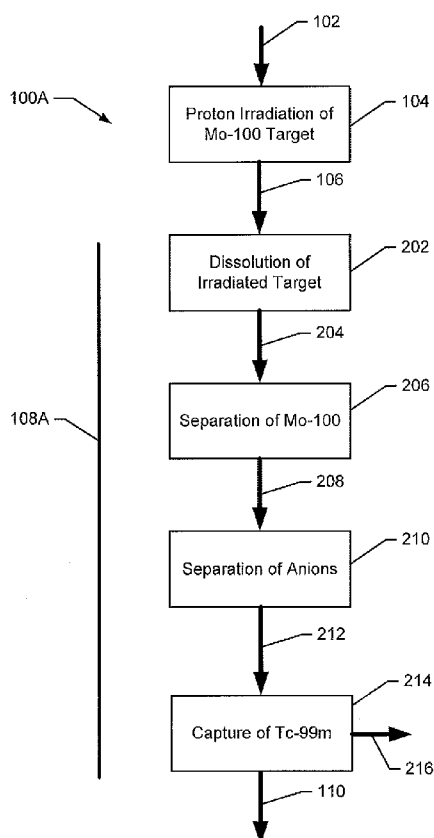


FIG. 2



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SYSTEM AND METHOD FOR PRODUCING RADIOMEDICAL-GRADE TC-99M**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Application No. 61/767,299 filed February 21, 2013, which is incorporated herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to systems and methods for producing radiomedical-grade Tc-99m. In particular, the present invention relates to systems and methods for producing Tc-99m by proton-irradiation of Mo-100 targets and subsequent separation of the resulting Tc-99m from the irradiated targets.

BACKGROUND OF THE INVENTION

[0003] Technetium-99m (Tc-99m) is a widely-used radiometal for medical diagnostic and therapeutic applications. Tc-99m is typically prepared using existing Tc-99m generators which rely upon the decay of an amount of Mo-99. These existing Tc-99m generators include an aqueous solution of Mo-99 loaded onto an adsorbent such as alumina. The Tc-99m resulting from the decay of the parent Mo-99 has a lower affinity for the alumina, allowing the Tc-99m to be eluted from the alumina as needed, using a saline solution as the eluent.

[0004] The Mo-99 parent material used in existing Tc-99m generators is commonly obtained by the neutron-induced fission of a U-235 target. This fission reaction produces Mo-99 as well as a number of unwanted impurities, which may include Cs, Sr, Ru, Zr, Te, Ba, Al, and other alkaline metals and alkaline earth metals. The fission products of the U-235 target are subjected to time-consuming and often expensive purification processes to extract Mo-99 from the various impurities. Existing Mo-99 purification facilities are rarely situated in close proximity to the manufacturing facility that produces the Tc-99m generators, necessitating the shipping of the Mo-99 parent material and further processing at the Mo-99/Tc-99m generator manufacturing facilities. As a result, the overall process of assembling existing Mo-99/Tc-99m generators is relatively complex and particularly sensitive to temporary disruptions in the supply of fission-produced Mo-99, which are known to occur with some regularity.

[0005] An alternative method of producing Tc-99m involves proton irradiation of a Mo-100 target using a device such as a cyclotron. Although the resulting Tc-99m-containing solution does not include the significant impurities present in the reactor output of the uranium fission reaction, the cyclotron process reportedly produces a number of undesired Tc isotopes including Tc-95m, Tc-95, Tc-96, and Tc-97m resulting from the presence of Mo impurities in the Mo-100 target, such as Mo-92, Mo-94, Mo-95, Mo-96, Mo-97 and Mo-98. These impurity levels are reported to be particularly high when using 97% enriched Mo-100 targets; the level of impurities may be greatly reduced by using 100%

enriched Mo-100 targets. However, even if a 100% enriched Mo-100 target is used, there remains the challenge of separating the desired Tc-99m from the irradiated Mo-100 target. At present, existing methods of separating Tc-99m from a proton-irradiated Mo-100 target typically involve elaborate chemical separation techniques that are impractical to implement in a labeling facility such as a radiopharmacy or a hospital.

[0006] A need exists for a system and method of producing Tc-99m that is not reliant upon a supply of fission-produced Mo-99, and further does not require elaborate chemical separation methods that may prevent implementation at a labeling facility. Such a system and method would provide a reliable source of Tc-99m that is less sensitive to fluctuations in the supply of parent material and that may be implemented in a labeling facility using relatively simple chemical techniques.

SUMMARY OF THE INVENTION

[0007] The present invention provides systems and methods for the production of Tc-99m suitable for radiolabeling applications. In particular, the present invention provides systems and methods for producing Tc-99m using proton-irradiation of a Mo-100 target followed by separation of the resulting Tc-99m from the Mo-100 target.

[0008] In one aspect, a process for producing a Tc-99m product is provided that includes irradiating a Mo-100 target with protons produced by a cyclotron to form an irradiated target, dissolving the irradiated target to form an irradiated target solution comprising an amount of Tc-99m dissolved in water, and separating the amount of Tc-99m from the irradiated target solution to form the Tc-99m product.

[0009] This process overcomes many of the shortcomings of existing methods of producing radiomedical-grade Tc-99m. The proton-irradiation may be performed by existing medical or research cyclotrons that are commonly used at labeling facilities in conjunction with other applications such as PET scanning. The use of high purity Mo-100 targets that may be readily obtained commercially result in relatively low concentrations of impurities in the irradiated target. The dissolution of the irradiated target and separation of the Tc-99m from the dissolved target solution may be accomplished entirely within a typical labeling facility using commonly available reagents, materials, and laboratory equipment. This process obviates the reliance upon the fission-produced Mo-99 used in existing Tc-99m generators; this fission-produced Mo-99 is prone to unexpected disruptions in supply at one or more of the facilities involved in its production.

[0010] In another aspect, a process for producing Tc-99m is provided that includes irradiating a Mo-100 target with protons produced by a cyclotron to form an irradiated target and contacting the irradiated target with a solvent to form an irradiated target solution comprising dissolved Mo-100, dissolved Tc-99m, and an amount of dissolved anions. The solvent may be chosen from nitric acid (HNO₃), sulfuric acid (H₂SO₄), and any combination thereof.

[0010] In this aspect, the process may further include contacting the irradiated target solution with a first stationary phase medium to adsorb the dissolved Mo-100 to form a first eluate that contains the dissolved Tc-99m and the amount of dissolved anions. In addition, this process may include contacting the first eluate with a second stationary phase medium to remove the dissolved anions to form a second eluate containing the dissolved Tc-99m. This process may also include contacting the second eluate with a third stationary phase medium to remove the dissolved Tc-99m to form a first Tc-99m product that includes the dissolved Tc-99m adsorbed to the third stationary phase medium.

[0011] Also in this aspect, the process may include contacting the first Tc-99m product with an eluent solvent to desorb the Tc-99m from the third stationary phase medium, forming a second Tc-99m product containing the Tc-99m dissolved in the eluent solvent. The eluent solvent may be chosen from water, saline solution, organic acids, inorganic acids, organic solvents, and any combination thereof.

[0012] In an additional aspect, a system for producing Tc-99m is provided that includes a cyclotron for irradiating a Mo-100 target with protons to form an irradiated target containing the Tc-99m and excess Mo-100. The system also includes a dissolution vessel for dissolving the irradiated target in a solvent to form an irradiated target solution comprising dissolved Tc-99m, dissolved excess Mo-100, and dissolved anions. Also included in this system is a first purification vessel containing a first stationary phase medium to adsorb the dissolved excess Mo-100 from the irradiated target solution to form a first eluate. A second purification vessel containing a second stationary phase medium is also included in the system to adsorb the dissolved anions from the first eluate to form a second eluate. In addition the system includes a capture vessel containing a third stationary phase medium to adsorb the dissolved Tc-99m from the second eluate to form a waste product and a first Tc-99m product containing the dissolved Tc-99m adsorbed to the third stationary phase medium.

[0013] Other features and iterations of the invention are described in more detail below.

DESCRIPTION OF FIGURES

[0014] The following figures illustrate various aspects of the embodiments.

[0015] **FIG. 1** is a flow chart illustrating a method of producing Tc-99m.

[0016] **FIG. 2** is flow chart illustrating a method of producing Tc-99m.

[0017] **FIG. 3** is a schematic illustration of a system for producing Tc-99m.

[0018] Corresponding reference characters and labels indicate corresponding elements among the views of the drawings. The headings used in the figures should not be interpreted to limit the scope of the claims.

DETAILED DESCRIPTION

[0019] In various aspects, methods for producing radiomedical-grade Tc-99m are provided. A flow chart summarizing a method for producing the Tc-99m in one aspect is illustrated in FIG. 1. The method 100 may include irradiating a Mo-100 target 102 with protons at step 104 to produce an irradiated Mo-100 target 106 that includes an amount of Tc-99m as well as excess Mo-100. The radiomedical-grade Tc-99m product 110 may then be separated from the irradiated target 106 at step 108 using relatively simple purification methods. The separation of the Tc-99m product 110 from the irradiated Mo-100 target 106 may be performed in two or more separate purification steps or processes. For example, the Tc-99m product 110 may be separated from the irradiated Mo-100 target 106 by dissolving the irradiated target into a solution and subjecting the solution to a series of chromatography columns to extract the dissolved Tc-99m.

[0020] In various other aspects, systems for producing radiomedical-grade Tc-99m using the methods described herein are provided. In an aspect, the system 300 may include a device, such as a cyclotron, to perform the proton irradiation of the Mo-100 target 102. In this aspect, the system may further include one or more components to conduct the separation of the Tc-99m product from the irradiated Mo-100 target using the relatively simple purification methods described herein. Non-limiting examples of the one or more components of the system include vessels, chromatography columns, adsorbent beds, and any combination thereof. In an aspect, the components of the system are operatively connected in series such that the contents exiting each device via a device outlet are delivered to a downstream inlet connected to a corresponding adjacent downstream device.

[0021] The methods and systems described herein overcome at least several limitations of existing methods and systems used to produce Tc-99m in a labeling facility. The Tc-99m produced by the proton irradiation of Mo-100 may be separated from the irradiated target using relatively simple purification steps. By contrast, the Mo-99 used in existing Tc-99m generators, produced by the neutron-induced fission of a U-235 target, requires more elaborate separation techniques to eliminate the impurities. In addition, the system for producing radiomedical-grade Tc-99m using the methods described herein may be designed to be a compact system that is readily housed at most labeling facilities. Using this system, radiomedical-grade Tc-99m, which has a half-life of only six hours, may be produced on-site at a labeling facility and used as soon as it is produced.

[0022] A detailed description of various aspects of the methods and systems used to produce radiomedical-grade Tc-99m are provided herein below.

(I) Method of Producing Tc-99m

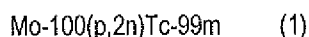
[0023] FIG. 2 is a flowchart illustrating a method of producing radiomedical-grade Tc-99m in one aspect. The Mo-100 target 102 may be irradiated with protons at step 104 to produce the irradiated target 106. The irradiated target 106 may be dissolved at step 202 to produce an

irradiated target solution **204** that may include dissolved Mo-100 and Tc-99m. The Mo-100 within the irradiated target solution **204** may then be separated from the irradiated target solution **204** at step **206** to produce a first eluate **208**, which may include the dissolved Tc-99m as well as other impurities such as anions introduced during step **202** and/or step **206**. The anions may interfere with the separation of the Tc-99m at step **214**, and these anions may be separated from the first eluate **208** at step **210** to produce a second eluate **212** containing the Tc-99m and further containing other impurities. The Tc-99m may be separated from the second eluate **212** at step **214** to produce a waste product **216** as well as the Tc-99m product **110**.

[0024] Each step of the method is described in detail herein below.

a) Proton-Irradiation of Mo-100 Target

[0025] In an aspect, Tc-99m may be produced by proton irradiation of Mo-100 targets according to a reaction described in Eqn. 1:



[0026] Without being limited to any particular theory, the amount and purity of the Tc-99m produced by this reaction depends upon reaction parameters including, but not limited to: the purity or enrichment of the Mo-100 target, the energy of the proton radiation, the thickness of the Mo-100 target, the irradiation time, the magnitude of the proton beam current, and any combination thereof. In general, the combination of reaction parameters may be selected in order to balance the goals of maximizing the yield of Tc-99m and minimizing the production of other unwanted isotopes including, but not limited to, Tc-93, Tc-94m, Tc-95, Tc-95m, Tc-96, and other stable Tc isotopes. In an aspect, the particular combination of reaction parameters may be selected using methods known in the art in order to produce an acceptable yield of Tc-99m of acceptable purity.

[0027] The purity or enrichment of the Mo-100 target may influence the yield and purity of Tc-99m produced by proton irradiation. Non-limiting examples of Mo-100 impurities may include other Mo isotopes. Non-limiting examples of other Mo isotopes include: Mo-92, Mo-94, Mo-95, Mo-96, Mo-97, and Mo-98. Naturally-occurring molybdenum typically contains about 9.63% wt of Mo-100, along with these other Mo isotopes: Mo-92 (14.85% wt), Mo-94 (9.25% wt), Mo-95 (15.92% wt), Mo-96 (16.68% wt), Mo-97 (9.55% wt), and Mo-98 (24.13% wt). These other Mo isotopes may in turn produce unwanted other stable and radioactive Tc isotopes including Tc-93, Tc-93m, Tc-94, Tc-94m, Tc-95, Tc-95m, Tc-96, Tc-96m, Tc-97, Tc-97m, Tc-98, Tc-99, and Tc-99g. The radioactive isotopes are considered to be contaminants because they will add to the radiation dose of the patient; the stable isotopes are also considered to be contaminants because they decrease the specific activity of the material.

[0028] A higher enrichment of the Mo-100 target may be obtained by minimizing the amounts of the other Mo isotopes, thereby reduce the presence of unwanted Tc isotopes produced by

the proton irradiation. In an aspect, the Mo-100 target may be an enriched Mo-100 target containing at least about 95% wt Mo-100. In this aspect, the Mo-100 may be in the form of metallic Mo, or in the form of MoO₃. In other aspects, the Mo-100 target may contain at least about 96% wt Mo-100, at least about 97% wt Mo-100, at least about 98% wt Mo-100, at least about 99% wt Mo-100, at least about 99.5% wt Mo-100, and at least about 99.9% wt Mo-100. In another aspect, enriched Mo-100 targets may be obtained from commercial suppliers at an enrichment of about 95% - 97%+ (Trace Sciences International Inc., Pilot Point, TX, USA) or at an enrichment of 99.54% (Isoflex USA, San Francisco, CA).

[0029] The energy of the protons used to irradiate the Mo-100 target may further impact the yield and purity of the resulting Tc-99m. As is well-known in the art, the proton energy must fall above a reaction threshold in order for the reaction described in Eq (1) to proceed. However, very high proton energies may fall above the reaction threshold of numerous other reactions that produce contaminants. Without being limited to any particular theory, it is well-established that the proton energy must be greater than about 8 MeV. The yield of Tc-99m peaks at a proton energy ranging from about 15 MeV to about 16 MeV and drops about four-fold from the peak yield at a proton energy of about 24 MeV. At proton energies above about 24 MeV, the production of contaminants significantly increases relative to the yield of Tc-99m.

[0030] In another aspect, the proton energy of the irradiated protons may range from about 12 MeV to about 22 MeV. In additional aspects, the proton energy of the irradiated protons may range from about 12 MeV to about 14 MeV, from about 13 MeV to about 15 MeV, from about 14 MeV to about 16 MeV, from about 15 MeV to about 17 MeV, from about 16 MeV to about 18 MeV, from about 17 MeV to about 19 MeV, from about 18 MeV to about 20 MeV, from about 19 MeV to about 21 MeV, and from about 20 MeV to about 22 MeV. In yet another aspect, the proton energy of the irradiated protons may be about 16 MeV.

[0031] The thickness of the Mo-100 target may further influence the yield and purity of Tc-99m produced by proton irradiation. As a proton travels through the material of the target, the energy of the proton may be reduced due to collisions or interactions with the target atoms. As a result, the protons colliding target atoms situated further away from the exposed impact surface of the target may have lower energy compared to the energy of the irradiated protons. As the target thickness increases, this reduction in proton energy across the depth of the target may be enhanced, resulting in the exposure of the target atoms to a wider range of proton energies across the thickness of the target. Put another way, as the thickness of the target increases, the average energy of the protons leaving the target may be decreased. Because the yield and purity of Tc-99m produced by proton irradiation is sensitive to the energy of the irradiated protons, the target thickness may impact the yield and purity of Tc-99m.

[0032] In an additional aspect, the target thickness may be selected so that the average energy of the protons leaving the target is at least about 8 MeV. In other additional aspects,

the target thickness may be selected so that the average energy of the protons leaving the target is at least about 9 MeV, at least about 10 MeV, at least about 11 MeV, at least about 12 MeV, at least about 13 MeV, at least about 14 MeV, and at least about 15 MeV. The target thickness may be influenced by other factors including, but not limited to, the energy of the irradiated protons, the enrichment of the Mo-100 in the target, and any other factor known in the art. In one aspect, the thickness of the Mo-100 target may be governed by the thickness of a single continuous target structure. In another aspect, the thickness of the Mo-100 target may be governed by the net thickness of multiple layers of a Mo-100 foil material forming the target.

[0033] In one aspect, the thickness of the Mo-100 target may range from about 0.05 mm to about 10 mm. In other aspects, the thickness of the Mo-100 target may range from about 0.05 mm to about 0.5 mm, from about 0.25 mm to about 0.75 mm, from about 0.5 mm to about 1.0 mm, from about 0.75 mm to about 1.5 mm, from about 1 mm to about 3 mm, from about 2 mm to about 4 mm, from about 3 mm to about 6 mm, from about 5 mm to about 8 mm, from about 6 mm to about 9 mm, and from about 7 mm to about 10 mm.

[0034] In another aspect, the amount of Mo-100 per surface area of the Mo-100 target may range from about 0.3 g/cm² to about 1 g/cm². In other aspects, the amount of Mo-100 per surface area may range from about 0.3 g/cm² to about 0.5 g/cm², from about 0.4 g/cm² to about 0.6 g/cm², from about 0.5 g/cm² to about 0.7 g/cm², from about 0.6 g/cm² to about 0.8 g/cm², and from about 0.8 g/cm² to about 1 g/cm². In an additional aspect, the amount of Mo-100 per surface area may be about 0.52 g/cm².

[0035] The irradiation time may further impact the yield and purity of the Tc-99m produced using this method. Without being limited to any particular theory, the total amount of Tc-99m produced increases with longer irradiation times, but the production of contaminants, for example Tc-99g, increases at an even higher rate with respect to irradiation time. As a result, the proportion of Tc-99m produced relative to contaminants decreases at higher irradiation times. The irradiation time may be selected in order to produce an amount of Tc-99m above a threshold usable level, while further achieving a level of purity in excess of a usable minimum level. The irradiation time may also be selected based on the size of the cyclotron used and/or the demand for Tc-99m at the particular labeling facility at which the Tc-99m is locally produced.

[0036] In an aspect, the irradiation time may range from about 3 hours to about 24 hours. In another aspect, the irradiation time may range from about 3 hours to about 18 hours, from about 3 hours to about 12 hours, from about 3 hours to about 9 hours, and from about 3 hours to about 6 hours. In other aspects, the irradiation time may be about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, and about 10 hours. In yet another aspect, the irradiation time may be about 3 hours. In still another aspect, if higher amounts of Tc-99m are desired, the method may include several cycles of irradiation of several Mo-100 targets using an irradiation time of about 3 hours, with replacement of the irradiated Mo-100 target with a new Mo-100

target between irradiation cycles. In one aspect, the irradiation time may be about 6 hours or less at an irradiation current of about 25 μA . For example, irradiation at 25 μA for about 6 hours may achieve a batch yield of about 40GBq Tc-99m; longer irradiation times may produce quantities of Tc-99m in excess of the demand of the labeling facility.

[0037] The magnitude of the proton beam current may further impact the yield of Tc-99m using this method. This magnitude, typically measured in units of amperes, quantifies the overall rate at which protons are irradiated at the target. Without being limited to any particular theory, a higher proton beam current results in a higher yield of Tc-99m without impacting purity, all other factors being equal. The magnitude of the proton beam is typically limited by the capacity of the cyclotron or other device used to irradiate the sample. In one aspect, the proton beam current may range up to about 1.2 mA, the maximum proton beam current commonly achievable using existing devices. In other aspects, the proton beam current may range from about 25 μA to about 600 μA , the typical range of existing medical cyclotrons. In other aspects, the proton beam current may range from about 25 μA to about 75 μA , from about 50 μA to about 100 μA , from about 75 μA to about 150 μA , from about 125 μA to about 200 μA , from about 150 μA to about 250 μA , from about 200 μA to about 400 μA , from about 300 μA to about 500 μA , and from about 400 μA to about 600 μA . A more detailed description of cyclotrons and other devices used to irradiate the sample are provided herein below.

b) Dissolution of Irradiated Target

[0038] In an aspect, the irradiated target, which may contain Tc-99m, unused Mo-100, and other contaminants as described herein above, may be dissolved to form an irradiated target solution. The transformation of the irradiated target from a solid state to the irradiated target solution may facilitate the subsequent removal of contaminants and ultimate capture of the Tc-99m formed during the proton irradiation of the target. In a dissolved state, the irradiated target solution may be subjected to relatively simple and commonly used purification techniques including, but not limited to, chromatographic separation techniques such as liquid chromatography.

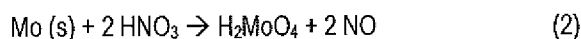
[0039] The irradiated target may be dissolved in a solvent to form the irradiated target solution in an aspect. In other aspects, two or more Mo-100 targets may be proton-irradiated separately and all of the irradiated targets may be dissolved in a solvent to form a single batch of irradiated target solution. Any known solvent capable of dissolving molybdenum may be selected for use as the solvent. Non-limiting examples of suitable solvents include nitric acid (HNO_3), sulfuric acid (H_2SO_4), aqua regia, hydrogen peroxide (H_2O_2), and ammonium hydroxide (NH_4OH). The solvent used to dissolve the irradiated target may be selected based upon one or more factors including, but not limited to: solubility of Mo and/or Tc isotopes in the solvent; compatibility of the solvent with subsequent separation processes such as liquid chromatographic separation; ease of working with the selected solvent with respect to safety, availability of supply, and storage; the generation of caustic or toxic fumes during the formation of the irradiated target solution; the need for other associated conditions to

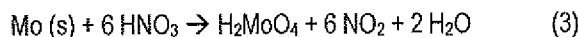
perform the dissolution with the solvent such as heating, cooling, or stirring; and the non-reactivity of the solvent and irradiated target solution with the materials used in the construction of the components included in various aspects of the system. The volume of solvent used to dissolve the irradiated target may be selected to ensure complete dissolution of the irradiated target, based on factors including, but not limited to, the solubility and the saturation concentration of the irradiated target within the solvent. In one aspect, the amount of solvent used in relation to the irradiated target may be selected in order to provide reactant compounds in an amount at least 20% higher than the stoichiometric amount of reactant compounds needed to dissolve the target.

[0040] In one aspect, the solvent may be sulfuric acid. In this aspect, the irradiated target may be contacted with the sulfuric acid with a strength ranging from about 1M to about 6M; the strength of the sulfuric acid may influence the amount of time needed to completely dissolve the irradiated target. In other aspects, the solvent may be sulfuric acid with a strength ranging from about 1M to about 2M, from about 1.5M to about 2.5M, from about 2M to about 3M, from about 2.5M to about 3.5M, from about 3M to about 4M, from about 3.5M to about 4.5M, from about 4M to about 5M, from about 4.5M to about 5.5M, and from about 5M to about 6M. In another aspect, the sulfuric acid may be heated to facilitate and/or accelerate the dissolution of the irradiated target into the sulfuric acid. In one aspect, the temperature of the sulfuric acid may range from about 30°C to about 50°C.

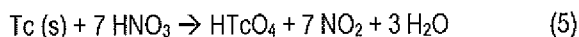
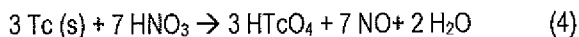
[0041] In another aspect, the solvent may be nitric acid. Because nitric acid is relatively non-reactive with stainless steel materials commonly used in liquid chromatography columns, tubing, and fittings, nitric acid may be compatible with most components of the system for producing Tc-99m in various aspects. The irradiated target may be contacted with the nitric acid having a strength ranging from about 1M to about 6M in this aspect; the strength of the nitric acid may influence the amount of time needed to completely dissolve the irradiated target. In other aspects, the solvent may be nitric acid with a strength ranging from about 1M to about 2M, from about 1.5M to about 2.5M, from about 2M to about 3M, from about 2.5M to about 3.5M, from about 3M to about 4M, from about 3.5M to about 4.5M, from about 4M to about 5M, from about 4.5M to about 5.5M, and from about 5M to about 6M. In another aspect, the nitric acid may be combined with sulfuric acid having a strength as described herein previously. In yet another aspect, the nitric acid may be heated to facilitate and/or accelerate the dissolution of the irradiated target. In one aspect, the temperature of the nitric acid may range from about 30°C to about 50°C.

[0042] The resulting irradiated target solution may contain dissolved ions of irradiated target isotopes or compounds containing the irradiated target isotopes, as well as other ions and compounds associated with the solvent or the dissolution reactions of the irradiated target within the solvent. For example, if the solvent is nitric acid, the Mo within the irradiated target may undergo dissolution reactions as described in Eqn. (2) and Eqn. (3):



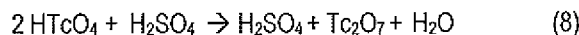
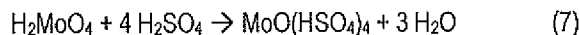
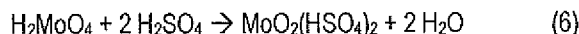


In addition, the Tc within the irradiated target may undergo dissolution reactions as described in Eqn. (4) and Eqn. (5):



[0043] In this example, the H_2MoO_4 and HTcO_4 compounds in solution are dissociated into hydrogen ions ($[\text{H}]^+$), molybdate ions ($[\text{MoO}_4]^{2-}$) and pertechnetate ions ($[\text{TcO}_4]^-$). In addition, the irradiated target solution may include other ions including, but not limited to, nitrate ions ($[\text{NO}_3]^-$) resulting from nitric acid used as a solvent in this example.

[0044] By way of a second example, if the solvent used is a mixture of nitric acid and sulfuric acid, in addition to the reactions described in Eqns. (2) – (5), the Mo and Tc may undergo additional reactions as described in Eqns. (6) – (8):



[0045] In additional aspects, any known method for dissolving Mo and Tc metals into an acid solution may be used including, but not limited to, electrochemical methods, or any other suitable method known in the art.

c) Separation of Mo-100

[0046] In another aspect, the method of producing Tc-99m may further include separating the dissolved Mo-100 from the irradiated target solution. Any known method of selectively removing a dissolved compound from a solution containing other compounds may be used including, but not limited to: liquid-liquid or solvent extraction methods, precipitation and filtration methods, chromatography methods, and any other separation, purification, and/or extraction methods known in the art. Non-limiting examples of chromatography methods suitable for removing the Mo-100 from the irradiated target solution include gas chromatography, liquid chromatography, ion exchange chromatography, reversed-phase chromatography, and any other suitable chromatography method.

[0047] In one aspect, the dissolved Mo-100 may be separated from the irradiated target solution using a liquid chromatography method. In this aspect, the irradiated target solution may be contacted with a first stationary phase medium having a high affinity for the dissolved Mo-100 relative to the dissolved Tc-99m in the irradiated target solution. Upon contact with the first stationary phase medium, the dissolved Mo-100 may be preferentially adsorbed to the surface of the first stationary phase medium, leaving a first eluate that includes the irradiated target solution less the dissolved Mo-100.

[0048] The composition of the first stationary phase medium may be selected based on factors including, but not limited to: the selective affinity of the first stationary phase medium surface for binding Mo-100, the compatibility of the first stationary phase medium surface chemistry with the pH of the irradiated target solution, the compatibility of the first stationary phase medium surface chemistry with additional anions and/or cations resulting from the formation of the irradiated target solution, and any combination thereof. In an aspect, any known stationary phase media may be contacted with the irradiated target solution to remove the dissolved Mo-100 from the solution to form the first eluate. Non-limiting examples of suitable first stationary media include alumina (Al_2O_3), zirconia (ZrO_2), titania (TiO_2), zirconia-titania composite ($\text{TiO}_2/\text{ZrO}_2$), silica (SiO_2), ceria (CeO_2), ion exchange resins, and manganese dioxide (MnO_2). The surface of the first stationary phase medium may be modified to enhance the affinity of the adsorbent material for the Mo-100 in the irradiated target solution. Non-limiting examples of surface-modified adsorbent materials include sulfated alumina composite materials and alumina-sulfated zirconia composite materials. In another aspect, the first stationary phase medium is manganese dioxide (MnO_2).

[0049] The irradiated target solution may be contacted with the first stationary phase medium in any known configuration including, but not limited to, a fluidized bed and a column. In one aspect, the first stationary phase medium may be included in a chromatography column. The amount of first stationary phase medium included in the chromatography column may be selected based on: the amount of irradiated target solution to be treated, the desired size of the system to produce Tc-99m, the composition of the first stationary phase medium, and any combination thereof.

[0050] In one aspect, if the first stationary phase medium is MnO_2 , the amount of first stationary phase medium may range from about 1g to about 50g in a chromatography column. In other aspects, the amount of MnO_2 stationary phase medium may range from about 1g to about 2g, from about 1.5g to about 3g, from about 2g to about 4g, from about 3g to about 5g, from about 6g to about 10g, from about 7.5g to about 15g, from about 10g to about 20g, from about 20g to about 30g, from about 30g to about 40g, and about 40g to about 50g.

[0051] Prior to contacting the irradiated target solution and the first stationary phase medium, additional compounds may be added to the irradiated target solution to modify the chemical properties of the irradiated target solution including, but not limited to, the solution's pH, and the ionic species in solution. Non-limiting examples of additional compounds that may be added to the irradiated

target solution include sodium hydroxide, ammonium hydroxide, nitric acid, sulfuric acid, organic solvents, and any other additional compound known in the art. In one aspect, the additional compound may be added to enhance the affinity of the first stationary phase medium for the Mo-100 in the irradiated target solution. In addition, if the irradiated target solution was heated to enhance the dissolution of the irradiated target within the solvent as described herein above, the irradiated target solution may be cooled prior to contacting the irradiated target solution with the first stationary phase medium.

d) Separation of Anions

[0052] In an aspect, the first eluate may include additional compounds resulting from the process of dissolving the irradiated target to form the irradiated target solution as well as the process of removing the dissolved Mo-100 from the irradiated target solution to form the first eluate. For example, if the irradiated target was dissolved in nitric acid, the first eluate may contain nitrate anions ($[\text{NO}_3^-]$). As a second example, if a MnO_2 stationary phase medium was used to remove the Mo from the irradiated target solution, the first eluate may further include manganese ($[\text{Mn}^{2+}]$) cations.

[0053] Without being limited to any particular theory, these additional ionic compounds may interfere with the processes used to isolate the desired Tc-99m radioisotope product from the irradiated target solution. For example, the process used to isolate the Tc-99m from the irradiated target solution may involve column chromatography processes that are known in the art to be sensitive to the ionic milieu in which the desired analyte is to be adsorbed to a stationary phase medium. Because the chromatographic adsorption process may involve the ionic attraction of the Tc-99m in the form of pertechnetate ($[\text{TcO}_4^-]$) anions to the adsorbent material, any other dissolved anions may compete with the pertechnetate ions to interact with the surface of the adsorbent material, thereby interfering with the selective adsorption of Tc-99m.

[0054] In one aspect, the process may include the removal of dissolved anions from the first eluate to produce a second eluate. Non-limiting examples of dissolved anions that may be removed from the first eluate include nitrate anions ($[\text{NO}_3^-]$), sulfate anions ($[\text{SO}_4]^{2-}$), and hydroxide anions ($[\text{OH}^-]$). The dissolved anions may be selectively removed by any known separation, purification, and/or extraction method. Non-limiting examples of suitable methods for removing dissolved anions from the first eluate include liquid-liquid or solvent extraction methods, precipitation and filtration methods, and chromatography methods. Non-limiting examples of chromatography methods suitable for removing dissolved anions from the first eluate include gas chromatography, liquid chromatography, ion exchange chromatography, reversed-phase chromatography, and any other suitable chromatography method.

[0055] In an additional aspect, the dissolved anions may be separated from the first eluate using a liquid chromatography method. In this aspect, the first eluate may be contacted with a second stationary phase medium having a high affinity for the dissolved anions relative to the dissolved

Tc-99m in the first eluate. Upon contact with the second stationary phase medium, the dissolved anions may be preferentially adsorbed to the surface of the second stationary phase medium, leaving a second eluate that includes the first eluate less the dissolved anions.

[0056] The composition of the second stationary phase medium may be selected based on: the selective affinity of the second stationary phase medium surface for binding dissolved anions, the compatibility of the second stationary phase medium surface chemistry with the pH of the first eluate, the compatibility of the second stationary phase medium surface chemistry with the additional anions and/or cations resulting from the formation of the irradiated target solution and first eluate, and any combination thereof. In an aspect, any known stationary phase medium may be contacted with the first eluate to remove the dissolved anions to form the second eluate. Non-limiting examples of suitable second stationary phase media include alumina (Al_2O_3), zirconia (ZrO_2), silica (SiO_2), ceria (CeO_2), titanium dioxide (TiO_2), manganese dioxide (MnO_2), zeolites, tin dioxide (SnO_2), and ion exchange resins. The surface of the second stationary phase medium may be modified to enhance the affinity of the adsorbent material for the dissolved anions in the first eluate.

[0057] In another aspect, the second stationary phase medium is an anion exchange material, also known as an anionic exchanger. Non-limiting examples of suitable anionic exchangers include any material comprising quaternary ammonium on styrene divinylbenzene copolymers as well as commercially available anionic exchangers such as AG-1 and AGMP1 (BioRad Laboratories, USA), Amberjet 4200 Cl and 440 Cl (Rohm and Haas Company, USA), and Dowex-1 (Dow Chemical Company, USA). In one particular aspect, the second stationary phase medium is AG-1 anionic exchanger.

[0058] The first eluate may be contacted with the second stationary phase medium in any known configuration including, but not limited to, a fluidized bed and a column. In one aspect the second stationary phase medium may be included in a chromatography column. The amount of the second stationary phase medium included in the chromatography column may be selected based on: the amount of first eluate to be treated, the desired size of the system to produce Tc-99m, the composition of the second stationary phase medium, and any combination thereof.

[0059] In one aspect, if the second stationary phase medium is the AG-1 anionic exchanger, the amount of second stationary phase medium may range from about 1g to about 50g in the chromatography column. In other aspects, the amount of AG-1 anionic exchanger may range from about 1g to about 2g, from about 1.5g to about 3g, from about 2g to about 4g, from about 3g to about 5g, from about 6g to about 10g, from about 7.5g to about 15g, from about 10g to about 20g, from about 20g to about 30g, from about 30g to about 40g, and from about 40g to about 50g.

[0060] Prior to contacting the first eluate and the second stationary phase medium, additional compounds may be added to the first eluate to modify the chemical properties of the first eluate including, but not limited to, the first eluate's pH, and the ionic species in solution. Non-limiting examples of additional compounds that may be added to the first eluate include sodium hydroxide,

ammonium hydroxide, nitric acid, sulfuric acid, organic solvents, and any other additional compound known in the art. In one aspect, the one or more additional compounds may be added to enhance the affinity of the second stationary phase medium for the anions in the first eluate.

e) Capture of Tc-99m

[0061] In an aspect, the process for producing Tc-99m may include isolating the Tc-99m from the second eluate to produce a Tc-99m product. The Tc-99m, which may be in the form of pertechnetate anions ($[\text{TcO}_4^-]$) within the second eluate, may be selectively removed by any known separation, purification, and/or extraction method. Non-limiting examples of suitable methods for removing the dissolved pertechnetate anions from the second eluate include liquid-liquid or solvent extraction methods, precipitation and filtration methods, and chromatography methods. Non-limiting examples of chromatography methods suitable for removing dissolved pertechnetate anions from the second eluate include gas chromatography, liquid chromatography, ion exchange chromatography, reversed-phase chromatography, and any other suitable chromatography method.

[0062] In an additional aspect, the dissolved Tc-99m may be separated from the second eluate using a liquid chromatography method. In this aspect, the second eluate may be contacted with a third stationary phase medium having a high affinity for the dissolved Tc-99m relative to any other dissolved ions within the second eluate. Upon contact with the third stationary phase medium, the dissolved Tc-99m may be preferentially adsorbed to the surface of the third stationary phase medium, leaving a third eluate that may be typically discarded or otherwise treated for recycling or disposal using known methods.

[0063] The composition of the third stationary phase medium may be selected based on: the selective affinity of the third stationary phase medium surface for binding dissolved Tc-99m, the compatibility of the third stationary phase medium surface chemistry with the pH and other chemical properties of the second eluate, and the compatibility of the third stationary phase medium surface chemistry with any additional anions and/or cations resulting from the formation of the irradiated target solution, the first eluate, and the second eluate. In an aspect, any known stationary phase medium may be contacted with the second eluate to isolate the dissolved Tc-99m anions to form the Tc-99m product. Non-limiting examples of suitable third stationary phase media include alumina (Al_2O_3), zirconia (ZrO_2), silica (SiO_2), ceria (CeO_2), titanium dioxide (TiO_2), manganese dioxide (MnO_2), zeolites, tin dioxide (SnO_2), and ion exchange resins. The surface of the third stationary phase medium may be modified to enhance the affinity of the adsorbent material for the dissolved Tc-99m anions in the second eluate. In various embodiments, the third stationary phase medium may be alumina, tin dioxide or DOWEX-1 (Dow Water & Process Solutions, USA). In another aspect, the third stationary phase medium comprises alumina including, but not limited to, acidic alumina.

[0064] The second eluate may be contacted with the third stationary phase medium in any known configuration including, but not limited to, a fluidized bed and a column. In one aspect, the

third stationary phase medium may be situated within a chromatography column. The amount of the third stationary phase medium situated within the chromatography column may be selected based on: the amount of second eluate to be treated, the desired size of the system to produce Tc-99m, the composition of the third stationary phase medium, and any combination thereof.

[0065] In one aspect, if the third stationary phase medium is acidic alumina, the amount of third stationary phase medium may range from about 1g to about 50g in the chromatography column. In other aspects, the amount of acidic alumina may range from about 1g to about 2g, from about 1.5g to about 3g, from about 2g to about 4g, from about 3g to about 5g, from about 6g to about 10g, from about 7.5g to about 15g, from about 10g to about 20g, and from about 15g to about 25g, and from about 20g to about 30g, and from about 25g to about 35g, and from about 30g to about 40g, from about 35g to about 45g, and from about 40g to about 50g.

[0066] Prior to contacting the second eluate and the third stationary phase medium, additional compounds may be added to the second eluate to modify the chemical properties of the second eluate including, but not limited to, the second eluate's pH or other chemical properties such as the ionic species in solution. Non-limiting examples of additional compounds that may be added to the second eluate include sodium hydroxide, ammonium hydroxide, nitric acid, sulfuric acid, organic solvents, and any other additional compound known in the art. In one aspect, the one or more additional compounds may be added to enhance the affinity of the third stationary phase medium for the anions in the first eluate.

[0067] In one embodiment, the Tc-99m product may be the Tc-99m adsorbed to the third stationary phase medium. In this embodiment, the Tc-99m product may be removed from the container within which the second eluate was contacted with the third stationary phase medium and use in the desired radiomedical application. In another embodiment, the Tc-99m product may be formed by contacting the third stationary phase medium with an eluent, as described in detail below.

f) Elution of Tc-99m

[0068] In an embodiment, the process further comprises forming a Tc-99m product by eluting the adsorbed Tc-99m by contacting the third adsorbent with an eluent. In this embodiment, the eluted Tc-99m mixture may be maintained in solution within the eluent for use in the desired radiomedical application, or the eluted Tc-99m mixture may be formed into a dried particulate product by removing the solvent from the eluted Tc-99m mixture using known methods including, but not limited to, evaporation.

[0069] The eluent may be selected based on: the ability of the eluent to desorb the Tc-99m from the third stationary phase medium used in the process; biocompatibility of the eluent; compatibility of the eluent with the radiomedical applications including, but not limited to, the production of radiolabels and radiopharmaceutical compositions; and the compatibility of the eluent with solvent removal techniques including, but not limited to, evaporation. Non-limiting examples of suitable eluents

include: water; saline solution; organic acids; inorganic acids; and organic solvents such as hexane, pentane, cyclohexane, benzene, dichloromethane, chloroform, ether, ethyl acetate, acetone and alkanols including ethanol and methanol. In one aspect, a sterile, physiological saline solution may be used as the eluent. The physiological saline solution may comprise a 0.9% w/v solution of sodium chloride in sterile water. When physiological saline solution is used as the eluent, the eluted Tc-99m mixture may be used directly for radiopharmaceutical applications.

(II) Device for Producing Tc-99m from Mo-100 Target

[0070] In various other aspects, systems for producing radiomedical-grade Tc-99m using the methods described herein are provided. FIG. 3 is a schematic diagram illustrating the relationship of various components of the system 300 in an aspect. The system 300 may include a cyclotron 302 to irradiate the Mo-100 target 102 with protons to produce the irradiated target 106. The system 300 may further contain a dissolution vessel 304 to dissolve the irradiated target 106, a first purification vessel 306 to separate the dissolved Mo-100 from the irradiated target solution 204, a second purification vessel 308 to separate the anions from the first eluate 208, and a capture vessel 310 to separate the Tc-99m product 110A from the second eluate 212 and to produce the waste product 216. The system 300 may further include a waste vessel 312 to capture and/or store the waste product 216.

[0071] In another aspect, described in further detail herein previously, the Tc-99m product 110A may be produced in the form of Tc-99m adsorbed to a third stationary phase medium such as alumina. In another aspect, the Tc-99m may be separated from the third stationary phase adsorbent by contacting the Tc-99m product with an eluent 316 such as a saline solution. In this aspect, the system 300 may further include an eluent source 314 to introduce the eluent 316 into the capture vessel 310 to produce a Tc-99m mixture 318 containing the Tc-99m dissolved in the eluent 316, and a Tc-99m vessel 320 to store the Tc-99m mixture 318. Depending on the choice of eluent 316, the Tc-99m mixture 318 may be used without further modification for labeling diagnostic imaging compounds and other radiopharmaceutical and radiomedical applications.

[0072] The components of the system 300 may be interconnected to facilitate the transfer of a first product produced with a first component into the second component in one embodiment. For example, the first purification vessel 306 may include a first purification vessel inlet (not shown) connected to a dissolution vessel outlet (not shown) to facilitate the transfer of the irradiated target solution 204 into the first purification vessel 306. Similarly, the second purification vessel 308 may be connected downstream of the first purification vessel 306, the capture vessel 310 may be connected downstream of the second purification vessel 308, and so on. In another embodiment, one or more of the components of the system 300 may be stand-alone devices, and a product produced by a first component may be removed to a separate container and transferred to a second component of the system for further processing. For example, the irradiated target solution 204 may be removed from

the dissolution vessel **304** into a separate container and subsequently introduced into the first purification vessel **306** from the separate container.

[0073] The various components of the system **300** are described in further detail herein below.

a) Cyclotron

[0074] In an aspect, the system **300** may include a cyclotron **302** to perform the proton irradiation of the Mo-100 target **102** to produce the irradiated target **106**. Any known cyclotron device may be used in the various aspects of the method, so long as the selected cyclotron device is capable of delivering a proton beam within the operational parameters suitable for producing Tc-99m as described herein above. For example, the cyclotron may produce a beam of protons having an energy ranging from about 8 MeV and about 24 MeV in various aspects, or the cyclotron may produce a proton beam having an energy ranging from about 15 MeV and about 16 MeV in various other aspects. In another example, the cyclotron may produce a proton beam with a current up to about 1.2 mA, or ranging from about 100 μ A to about 600 μ A.

[0075] In addition to these operational characteristics, the cyclotron may be selected to be compact in size so that the cyclotron may be housed and operated in a wide variety of radiolabeling and radiomedical facilities. In an aspect, the cyclotron used to perform the proton irradiation of the Mo-100 target may be any known research or medical cyclotron device. The cyclotron may be a commercially available cyclotron device, or the cyclotron may be custom-built for use in an aspect of the system **300**. In one aspect, the cyclotron may be a medium-energy, high current medical cyclotron, such as a PET cyclotron used to produce PET or SPECT isotopes; in this aspect, the medical cyclotron may produce a proton beam energy from about 15 MeV to about 24 MeV, and a beam current of up to at least 300 μ A. In an aspect, the research or medical cyclotron has the capability to produce proton beams at any energy within a continuous range to facilitate the optimization of the proton irradiation of the Mo-100 target for enhanced Tc-99m yield. Commercially available cyclotrons and associated inner shielding may be housed in a room as small as about 7m x 7m, although larger commercially available cyclotrons may also be sufficiently compact to be housed and operated on-site within a hospital or other radiomedical facility.

b) Dissolution Vessel

[0076] In an aspect, the system **300** may include a dissolution vessel **304** for dissolving the irradiated target to produce the irradiated target solution. The dissolution vessel **304** may be any container known in the art capable of dissolving the irradiated target into the solvent to form the irradiated target solution. The dissolution vessel **304** may be operatively connected to the cyclotron **302** such that the irradiated target **106** may be transferred directly from the cyclotron **302** into the dissolution vessel **304**. The dissolution vessel **304** may include an opening (not shown) into which the irradiated target **102** and the solvent may be introduced; this opening may be reversibly sealed by any method

known in the art including but not limited to a threaded cap, a locked hatch, a sealable access port, and any other known sealable opening.

[0077] The solvent may be introduced into the dissolution vessel **304** through the reversibly sealed opening. Alternatively, the dissolution vessel **304** may include a solvent inlet (not shown) operatively connected to a solvent reservoir (not shown) containing an amount of solvent to be transferred into the dissolution vessel via the solvent inlet. The solvent inlet may further include a means of controlling the flow of solvent into the dissolution vessel **304** including but not limited to a stopcock, a manual valve, a remotely-controlled valve, or any other known flow control device.

[0078] The dissolution vessel **304** may further include additional features to facilitate the formation of the irradiated target solution **204**. The dissolution vessel **304** may include heating and/or cooling components to control the temperature of the mixture of irradiated target **106** and the solvent as the irradiated target solution **204** is formed. For example, if the dissolution reaction of the irradiated target **106** and the solvent is exothermic or endothermic, heating or cooling of the dissolution vessel **304** may maintain the reacting mixture at a temperature suitable for the reaction to proceed. In another example, the reaction mixture may be heated or cooled in order to maintain a reaction temperature that reduces the time needed to form the irradiated target solution **204** or results in the complete dissolution of the irradiated target **106** in the solvent. The dissolution vessel **304** may further be pressurized or evacuated to provide a controlled reaction pressure within the dissolution vessel **304** including but not limited to movable pistons, vacuum lines, pressurized gas lines, and any other known pressure control devices.

[0079] The dissolution vessel **304** may further include features for mixing the reaction mixture within the dissolution vessel **304** to facilitate the formation of the irradiated target solution **204**. Any known methods of mixing the contents within a reaction vessel may be incorporated into the dissolution vessel **304** including, but not limited to: magnetic stirring rods, mixing paddles, introduction of inert gas bubbles, shaking or vibration of the dissolution vessel **304**, and any other known mixing method.

[0080] The dissolution vessel **304** may be constructed from any material capable of forming the walls of the dissolution vessel **304** and maintaining the structural integrity of the container walls under all combinations of temperature and pressure conditions experienced during the formation of the irradiated target solution **204**. In addition the material of the dissolution vessel may be selected to be inert or resistant to degradation by the solvent and/or irradiated target **106**. Non-limiting examples of suitable vessel materials include stainless steel and other metals, glass, plastics, and any other container material known in the art. The particular choice of materials may depend on any one or more of at least several factors including, but not limited to the selected temperature and pressure conditions within the dissolution vessel and the chemical properties of the selected solvent. For example, if the selected solvent is nitric acid, the vessel material may be selected to be stainless steel because this material is known to be non-reactive with nitric acid. The dissolution vessel **304** may be constructed

using a single material or using a composite material formed from a combination of at least two different materials. For example, the dissolution vessel 304 may be formed from a metal with an inner lining formed from glass, plastic, or any other suitable vessel lining material known in the art.

[0081] The dissolution vessel 304 may contain one or more inlets and/or outlets to facilitate the introduction of the irradiated target 106 and/or solvent into the dissolution vessel 304, and the removal of the irradiated target solution 204 from the dissolution vessel 304. As described herein previously, the dissolution vessel 304 may include a reversibly-sealed opening and/or a solvent inlet. The dissolution vessel may further include a dissolution vessel outlet (not shown) to remove the irradiated target solution 204 from the dissolution vessel 304. The dissolution vessel outlet may further include a valve, stopcock, or any other known flow control devices to implement the removal of the irradiated target solution 204 from the dissolution vessel 304. The dissolution vessel outlet may transfer the irradiated target solution 204 into a separate transfer vessel, or the dissolution vessel outlet may be operatively connected to the inlet of a first purification vessel 306 to facilitate the direct transfer of the irradiated target solution 204 from the dissolution vessel 304 into the first purification vessel 306.

b) First Purification Vessel

[0082] In an aspect, the system 300 may include a first purification vessel 306 for separating the dissolved Mo-100 from the irradiated target solution 204. The first purification vessel 306 may contain the first stationary phase medium described herein above and may be provided in a variety of known configurations including, but not limited to, a fluidized bed and a column. In an aspect, the first purification vessel 306 may be a chromatography column containing the first stationary phase medium. Non-limiting examples of suitable chromatography columns include: high-performance liquid chromatography (HPLC) columns, normal-phase chromatography columns, reversed phase chromatography columns, displacement chromatography columns, ion-exchange chromatography columns, and flash column chromatography columns. The size of the chromatography column in this aspect provides sufficient volume to contain the desired amount of first stationary phase medium as described above; typically, the amount of first stationary phase medium may range from about 1g to about 20g as described herein above.

[0083] In this aspect, the chromatography column may be any length and diameter suitable for performing the removal of the dissolved Mo-100 from the irradiated target solution 204. The length and diameter of the chromatography column used as the first purification vessel 306 may be selected depending on: the composition of the first stationary phase medium, the composition of the irradiated target solution 204, the method of chromatographic separation to be performed, and any combination thereof.

[0084] The first purification vessel 306 may be constructed using any suitable vessel material known in the art. The selection of the vessel material may be based on: non-reactivity of the material to the compounds in the irradiated target solution 204, non-interference with the material

with the function of the first stationary phase medium in adsorbing the dissolved Mo-100 in the irradiated target solution **204**, ability of the material to maintain structural integrity under the temperature, pressure and other process conditions associated with the separation of the dissolved Mo-100 from the irradiated target solution **204**, and any combination thereof. Non-limiting examples of suitable vessel materials include stainless steel and other metals, glass, plastics, and any other vessel material known in the art. For example, if the selected solvent within the irradiated target solution **204** is nitric acid, the vessel material may be selected to be stainless steel because this material is non-reactive with nitric acid. The first purification vessel **306** may be constructed using a single material or using a composite material formed from a combination of at least two different materials. For example, the first purification vessel **306** may be formed from a metal with an inner lining formed from glass, plastic, or any other suitable vessel lining material known in the art.

[0085] The first purification vessel **306** may operate as a stand-alone vessel, or the first purification vessel **306** may be operatively connected to the dissolution vessel **304** in order to receive the irradiated target solution **204** directly from the dissolution vessel **304**. In an aspect, the first purification vessel **306** may include one or more inlets and/or outlets to facilitate the introduction of the irradiated target solution **204** into the first purification vessel **306**, and the removal of the first eluate **208** from the first purification vessel **306**. The first purification vessel inlet (not shown) may be operatively connected to the dissolution vessel outlet to facilitate the transfer of the irradiated target solution **204** in one aspect. In another aspect, the first purification vessel **306** may further include one or more additional inlets to introduce one or more additional compounds to modify the chemical properties of the irradiated target solution **204** prior to introduction into the first purification vessel **306** as described previously herein above; the one or more additional inlets may be operatively connected to one or more sources containing the one or more additional compounds. In yet another aspect, the first purification vessel **306** may further include a first purification vessel outlet (not shown) to facilitate the transfer of the first eluate **208** from the first purification vessel **306** to the second purification vessel **308**. Any one or more of the additional inlets and/or outlet may further include valves, stopcocks, or any other known flow control devices to implement the controlled movement of materials through the additional inlets and/or outlet.

b) Second Purification Vessel

[0086] In an aspect, the system **300** may further include a second purification vessel **308** for separating the dissolved anions from the first eluate **208**. The second purification vessel **308** may contain the second stationary phase medium described herein above and may be provided in a variety of known configurations including, but not limited to, a fluidized bed and a column. In an aspect, the second purification vessel **308** may be a chromatography column containing the second stationary phase medium. Non-limiting examples of suitable chromatography columns include: high-performance liquid chromatography (HPLC) columns, normal-phase chromatography columns, reversed

phase chromatography columns, displacement chromatography columns, ion-exchange chromatography columns, and flash column chromatography columns. The size of the chromatography column in this aspect provides sufficient volume to contain the desired amount of second stationary phase medium as described above; typically, the amount of second stationary phase medium may range from about 1 g to about 20g as described herein above.

[0087] In this aspect, the chromatography column may be any length and diameter suitable for performing the removal of the dissolved anions from the first eluate **208**. The length and diameter of the chromatography column used as the second purification vessel **306** may be selected depending: the composition of the second stationary phase medium, the composition of the first eluate **208**, the method of chromatographic separation to be performed, and any combination thereof.

[0088] The second purification vessel **306** may be constructed using any suitable vessel material known in the art. The selection of this vessel material may be based on: non-reactivity of the material to the compounds in the first eluate **208**, non-interference with the function of the second stationary phase medium in adsorbing the dissolved anions in the first eluate **208**, ability of the material to maintain structural integrity under the temperature, pressure and other process conditions associated with the separation of the dissolved anions from the first eluate **208**, and any combination thereof. Non-limiting examples of suitable vessel materials include stainless steel and other metals, glass, plastics, and any other vessel material known in the art. The second purification vessel **308** may be constructed using a single material or using a composite material formed from a combination of at least two different vessel materials. For example, the second purification vessel **308** may be formed from a metal with an inner lining formed from glass, plastic, or any other suitable vessel lining material known in the art.

[0089] The second purification vessel **308** may operate as a stand-alone vessel, or the second purification vessel **308** may be operatively connected to the first purification vessel **306** in order to receive the first eluate **208** directly from the first purification vessel **306**. In an aspect, the second purification vessel **308** may include one or more inlets and/or outlets to facilitate the introduction of the first eluate **208** into the second purification vessel **308**, and the removal of the second eluate **212** from the second purification vessel **308**. The second purification vessel inlet (not shown) may be operatively connected to the first purification vessel outlet to facilitate the transfer of the first eluate **208** in one aspect. In another aspect, the second purification vessel **308** may further include one or more additional inlets to introduce one or more additional compounds to modify the chemical properties of the first eluate **208** prior to introduction into the second purification vessel **308** as described previously herein above; the one or more additional inlets may be operatively connected to one or more sources containing the one or more additional compounds. In yet another aspect, the second purification vessel **308** may further include a second purification vessel outlet (not shown) to facilitate the transfer of the second eluate **212** from the second purification vessel **308** to the capture vessel **310**. Any one or more of the additional inlets and/or outlet may further include valves, stopcocks, or any other known flow

control devices to implement the controlled movement of materials through the additional inlets and/or outlet.

b) Capture Vessel

[0090] In an aspect, the system 300 may further include a capture vessel 310 for isolating the dissolved Tc-99m from the second eluate 212. The capture vessel 310 may contain the third stationary phase medium described herein above and may be provided in a variety of known configurations including, but not limited to, a fluidized bed and a column. In an aspect, the capture vessel 310 may be a chromatography column containing the third stationary phase medium. Non-limiting examples of suitable chromatography columns include: high-performance liquid chromatography (HPLC) columns, normal-phase chromatography columns, reversed phase chromatography columns, displacement chromatography columns, ion-exchange chromatography columns, and flash column chromatography columns. The size of the chromatography column in this aspect provides sufficient volume to contain the desired amount of third stationary phase medium as described above; typically, the amount of third stationary phase medium may range from about 1 g to about 20g as described herein above.

[0091] In this aspect, the chromatography column may be any length and diameter suitable for performing the isolation of the dissolved Tc-99m from the second eluate 212. The length and diameter of the chromatography column used as the second purification vessel 306 may be selected depending on any one or more of at least several factors including the composition of the third stationary phase medium, the composition of the second eluate 212, and the method of chromatographic separation to be performed.

[0092] The second purification vessel 306 may be constructed using any suitable vessel material known in the art. The selection of this vessel material may be based on: non-reactivity of the material to the compounds in the second eluate 212, non-interference with the function of the third stationary phase medium in adsorbing the dissolved Tc-99m in the second eluate 212, ability of the material to maintain structural integrity under the temperature, pressure and other process conditions associated with the separation of the dissolved Tc-99m from the second eluate 212, and any combination thereof. Non-limiting examples of suitable vessel materials include stainless steel and other metals, glass, plastics, and any other vessel material known in the art. The capture vessel 310 may be constructed using a single material or using a composite material formed from a combination of at least two different vessel materials. For example, the capture vessel 310 may be formed from a metal with an inner lining formed from glass, plastic, or any other suitable vessel lining material known in the art.

[0093] The capture vessel 310 may operate as a stand-alone vessel, or the capture vessel 310 may be operatively connected to the second purification vessel 308 in order to receive the second eluate 212 directly from the second purification vessel 308. In an aspect, the capture vessel

310 may include one or more inlets and/or outlets to facilitate the introduction of the second eluate **212** into the capture vessel **310**, and the removal of the waste product **216** from the capture vessel **310**. A capture vessel inlet (not shown) may be operatively connected to the second purification vessel outlet to facilitate the transfer of the second eluate **212** in one aspect. In another aspect, the capture vessel **310** may further include one or more additional inlets to introduce one or more additional compounds to modify the chemical properties of the second eluate **212** prior to introduction into the capture vessel **310** as described previously herein above; the one or more additional inlets may be operatively connected to one or more sources containing the one or more additional compounds. In yet another aspect, the capture vessel **310** may further include a waste outlet (not shown) to facilitate the transfer of the waste product **216** from the capture vessel **310** to the waste vessel **312**.

[0094] As described herein above, the desired Tc-99m product produced by the system **300** may be the Tc-99m adsorbed to a third stationary phase medium such as alumina in one aspect. In this aspect, the capture vessel **310** may further include a product outlet to facilitate the removal of the Tc-99m product **110A** from the capture vessel **310**. In this aspect, the product outlet may be reversibly sealed by any method known in the art including but not limited to a threaded cap, a locked hatch, a sealable access port, and any other known sealable opening.

[0095] In another aspect described herein above, the Tc-99m may be eluted from the third stationary phase medium by contacting the third stationary phase medium with adsorbed Tc-99m with an eluent solvent such as sterile saline solution. To this end, the capture vessel **310** may further include an eluent solvent inlet (not shown) to transfer the eluent **316** into the capture vessel **310**. The eluent solvent inlet may be operatively connected to an eluent source **314** to provide a steady supply of eluent **316** to the capture vessel **310** as needed. In addition, the capture vessel **310** may further include a Tc-99m solution outlet (not shown) to facilitate the transfer of the eluted Tc-99m mixture **318** into a Tc-99m vessel **320**.

[0096] Any one or more of the additional inlets and/or outlets described in association with the various aspects of the capture vessel **310** may further include valves, stopcocks, or any other known flow control devices to implement the controlled movement of materials through the additional inlets and/or outlet. For example, the capture vessel **310** may further include a valve operatively attached to the waste outlet and the Tc-99m solution outlet to implement the delivery of fluid leaving the capture vessel to either the waste vessel **312** or the Tc-99m vessel **320** as appropriate in an additional aspect. In this additional aspect, the valve may be configured to deliver the exiting fluid to the waste vessel **312** while the second eluate **212** is delivered to the capture vessel **310**. In addition, the valve may be configured to deliver the exiting fluid to the Tc-99m vessel **320** while the eluent solvent **316** is delivered to the capture vessel **310**.

DEFINITIONS

[0100] The term "eluent", as used herein, refers to the liquid that is introduced into the stationary phase after the stationary phase has contacted the feed solution, resulting in the elution of components of the feed solution.

[0101] The term "stationary phase", as used herein, refers to the media or material that adsorbs components of the feed solution in a chromatography column.

[0102] When introducing elements of the present invention or the preferred embodiments(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[0103] Having described the invention in detail, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims. Those of skill in the art should, however, in light of the present disclosure, appreciate that many changes could be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention, therefore all matter set forth herein is to be interpreted as illustrative and not in a limiting sense.

CLAIMS

What is claimed is:

1. A process for producing a Tc-99m product, comprising:
irradiating a Mo-100 target with protons produced by a cyclotron to form an irradiated target;
dissolving the irradiated target to form an irradiated target solution comprising an amount of Tc-99m dissolved in water; and
separating the amount of Tc-99m from the irradiated target solution to form the Tc-99m product.
2. The process of claim 1, wherein the Tc-99m product comprises the amount of Tc-99m adsorbed to a stationary phase medium.
3. The process of claim 1, wherein the Tc-99m product comprises Tc-99m dissolved in an amount of sterile saline solution.
4. The process of claim 1, wherein the irradiated target is dissolved by contacting the irradiated target with an amount of a solvent chosen from nitric acid (HNO_3), sulfuric acid (H_2SO_4), aqua regia, hydrogen peroxide (H_2O_2), and ammonium hydroxide (NH_4OH) to form the irradiated target solution.
5. The process of claim 4, wherein the solvent is nitric acid (HNO_3).
6. The process of claim 1, further comprising contacting the irradiated target solution with at least two different stationary phase media in sequential order to form the Tc-99m product, wherein the at least two stationary phase media are chosen from alumina (Al_2O_3), zirconia (ZrO_2), silica (SiO_2), ceria (CeO_2), titanium dioxide (TiO_2), manganese dioxide (MnO_2), zeolites, tin dioxide (SnO_2), and ion exchange resins.
7. The process of claim 6, wherein the irradiated target solution is contacted with manganese dioxide (MnO_2), an ion exchange resin, and alumina (Al_2O_3) in sequential order to form the Tc-99m product.
8. The process of claim 7, further comprising contacting the alumina (Al_2O_3) with an amount of sterile saline solution to form a second Tc-99m product comprising the amount of Tc-99m dissolved in the amount of sterile saline solution.

9. A process for producing Tc-99m, comprising:
 - irradiating a Mo-100 target with protons produced by a cyclotron to form an irradiated target;
 - contacting the irradiated target with a solvent to form an irradiated target solution comprising dissolved Mo-100, dissolved Tc-99m, and an amount of dissolved anions wherein the solvent is chosen from nitric acid (HNO_3), sulfuric acid (H_2SO_4), and any combination thereof;
 - contacting the irradiated target solution with a first stationary phase medium to adsorb the dissolved Mo-100 to form a first eluate comprising the dissolved Tc-99m and the amount of dissolved anions;
 - contacting the first eluate with a second stationary phase medium to remove the dissolved anions to form a second eluate comprising the dissolved Tc-99m; and
 - contacting the second eluate with a third stationary phase medium to remove the dissolved Tc-99m to form a first Tc-99m product comprising the dissolved Tc-99m adsorbed to the third stationary phase medium; and
 - contacting the first Tc-99m product with an eluent to desorb the Tc-99m from the third stationary phase medium, forming a second Tc-99m product comprising the Tc-99m dissolved in the eluent, wherein the eluent is chosen from water, saline solution, an organic acids, an inorganic acid, an organic solvent, and any combination thereof.
10. The process of claim 9, wherein the Mo-100 target comprises Mo-100 in the form of either metallic Mo, MoO_3 , or any combination thereof.
11. The process of claim 10, wherein the Mo-100 target comprises at least 95% wt of Mo-100.
12. The process of claim 11, wherein the protons have a proton energy ranging from about 15 MeV to about 16 MeV.
13. The process of claim 12, wherein the solvent is nitric acid.
14. The process of claim 13, wherein the dissolved Mo-100 is in the form of molybdate ions ($[\text{MoO}_4]^{2-}$), the dissolved Tc-99m is in the form of pertechnetate ions ($[\text{TcO}_4]^-$), and the dissolved anions are nitrate anions ($[\text{NO}_3]^-$).
15. The process of claim 14, wherein the first stationary phase medium is manganese dioxide (MnO_2).
16. The process of claim 15, wherein the second stationary phase medium is an anionic exchanger comprising a styrene divinylbenzene copolymer functionalized with a quaternary ammonium moiety.
17. The process of claim 16, wherein the third stationary phase medium is acidic alumina.
18. The process of claim 17, wherein the eluent is saline solution.

19. A system for producing Tc-99m comprising:
- a cyclotron for irradiating a Mo-100 target with protons to form an irradiated target comprising the Tc-99m and excess Mo-100;
 - a dissolution vessel for dissolving the irradiated target in a solvent to form an irradiated target solution comprising dissolved Tc-99m, dissolved excess Mo-100, and dissolved anions;
 - a first purification vessel containing a first stationary phase medium to adsorb the dissolved excess Mo-100 from the irradiated target solution to form a first eluate;
 - a second purification vessel containing a second stationary phase medium to adsorb the dissolved anions from the first eluate to form a second eluate;
 - a capture vessel containing a third stationary phase medium to adsorb the dissolved Tc-99m from the second eluate to form a waste product and a first Tc-99m product comprising the dissolved Tc-99m adsorbed to the third stationary phase medium.
20. The system of claim 19, wherein the dissolution vessel, the first purification vessel, the second purification vessel, and the capture vessel are constructed from a vessel material selected from the group consisting of stainless steel and other metals, glass, plastics, and any combination thereof.
21. The system of claim 19, wherein the first purification vessel is a chromatography column and the first stationary phase medium is manganese dioxide (MnO_2).
22. The system of claim 19, wherein the second purification vessel is a chromatography column and the second stationary phase medium is an anionic exchanger comprising a styrene divinylbenzene copolymer functionalized with a quaternary ammonium moiety.
23. The system of claim 19, wherein the capture vessel is a chromatography column and the third stationary phase medium is acidic alumina.
24. The system of claim 19, wherein:
- the first purification vessel further comprises a first purification vessel inlet operatively connected to a dissolution vessel outlet of the dissolution vessel to transfer the irradiated target solution to the first purification vessel;
 - the second purification vessel further comprises a second purification vessel inlet operatively connected to a first purification vessel outlet of the first purification vessel to transfer the first eluate to the second purification vessel;
 - the capture vessel further comprises a capture vessel inlet operatively connected to a second purification vessel outlet of the second purification vessel to transfer the second eluate to the second purification vessel; and
 - the capture vessel further comprises a capture vessel outlet to transfer the waste product out of the capture vessel.

25. The system of claim 24, further comprising a mobile phase source to introduce a mobile phase into the capture vessel containing the first Tc-99m product to produce a second Tc-99m product comprising the Tc-99m dissolved in the mobile phase, wherein the mobile phase source comprises a mobile phase outlet operatively connected to the capture vessel inlet.

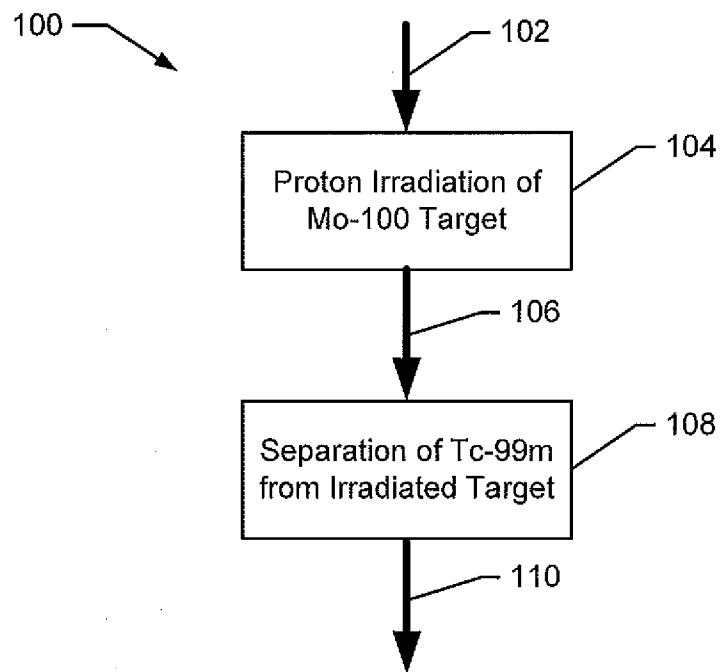


FIG. 1

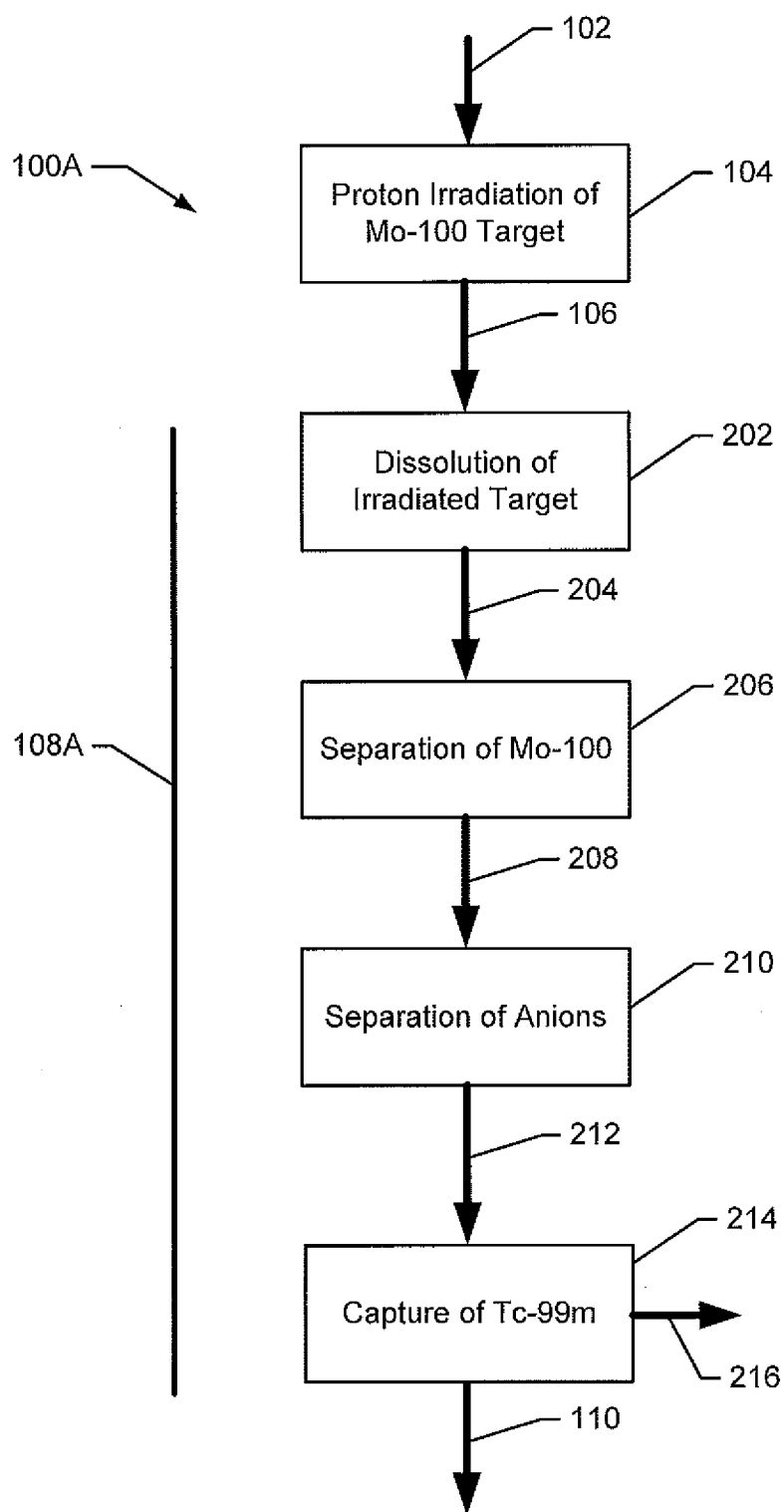


FIG. 2

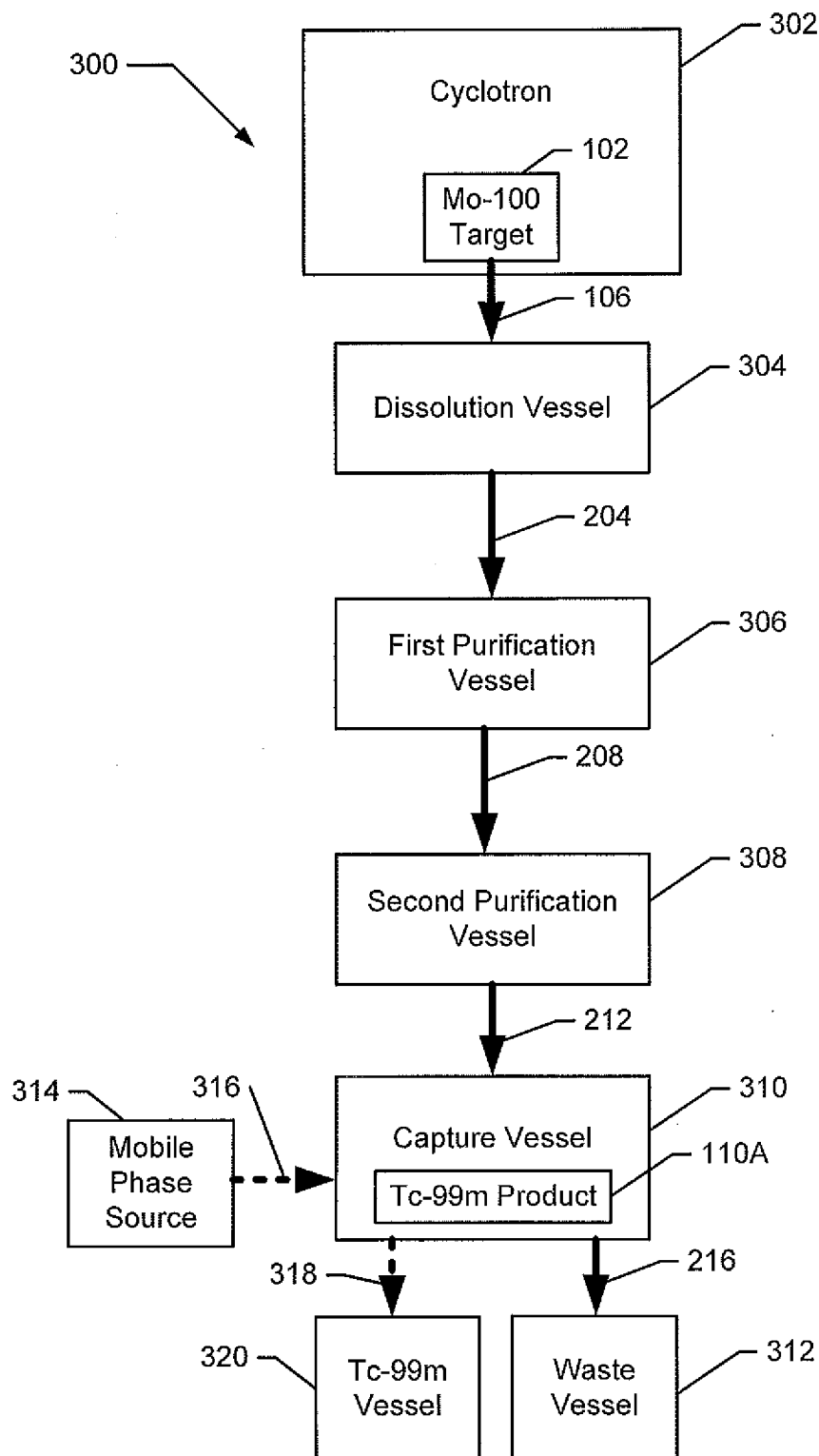


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/016661

A. CLASSIFICATION OF SUBJECT MATTER
INV. G21G1/00
ADD. G21G1/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G21G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/139220 A1 (UNIV ALBERTA [CA]; WILSON JOHN [CA]; GAGNON KATHERINE [CA]; MCQUARRIE) 18 October 2012 (2012-10-18) paragraphs [0022], [0044], [0057], [0058], [0049], [0050], [0066]; claims 1,30,38; figures 1,2 -----	1-6
X	WO 2012/039037 A1 (NAT INST RADIOLOG [JP]; TAGAMI KEIKO [JP]; UCHIDA SHIGEO [JP]; NAGATSU) 29 March 2012 (2012-03-29) abstract; figure 11 -----	1-5



Further documents are listed in the continuation of Box C.



See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

5 May 2014

Date of mailing of the international search report

13/05/2014

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/016661

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012139220 A1	18-10-2012	AU 2012243407 A1	09-05-2013
		CA 2832750 A1	18-10-2012
		CN 103733270 A	16-04-2014
		EP 2697798 A1	19-02-2014
		US 2014029710 A1	30-01-2014
		WO 2012139220 A1	18-10-2012

WO 2012039037 A1	29-03-2012	EP 2620950 A1	31-07-2013
		JP 5294180 B2	18-09-2013
		WO 2012039037 A1	29-03-2012
