

DESCRIPTION

Title of the Invention: METHOD FOR PRODUCING ^{225}Ac SOLUTION

Technical Field

[0001]

5 An aspect of the present invention relates to a method
for producing ^{225}Ac solution.

Background Art

[0002]

10 In the field of nuclear medicine, radionuclide therapy
has been performed in which a drug containing a radioisotope
(RI) is selectively taken into a lesion such as a tumor for
treatment. Among radiations, alpha-ray has a characteristic
that the effect of unnecessary exposure on the surrounding
normal cells is small because the range is short. ^{225}Ac being
15 one of the alpha-ray-emitting nuclides is a radionuclide with
a half-life of 10 days, and has expected as a therapeutic
nuclide in a cancer treatment and the like in recent years.

[0003]

20 ^{225}Ac is, produced by a nuclear reaction of (p, 2n), for
example, by irradiating a ^{226}Ra target with a proton using an
accelerator. Patent Literature 1 discloses a method for
separation and that purification of an ^{225}Ac component from a
solution containing ^{226}Ra ions and ^{225}Ac ions, which is
obtained by dissolving the ^{226}Ra target after irradiation.

Citation List

Patent Literature

[0004]

Patent Literature 1: JPA 2009-527731

5 Summary of Invention

[0005]

However, it has been found that conventional methods such as that described in Patent Literature 1 have at least one of the following problems.

10 It has been found that, according to conventional methods, a substantial amount of ^{226}Ra remains in the ^{225}Ac solution obtained, and thus the ^{225}Ac purity of the ^{225}Ac solution obtained remains to be improved.

The amount of ^{225}Ac generated from a ^{226}Ra target is
15 minute, and most ^{226}Ra remains unreacted; however, since ^{226}Ra is a precious nuclide and is not easy to discard, the ^{226}Ra solution after separation of ^{225}Ac is frequently recovered (hereinafter, this recovered solution may be referred to as the "Ra recovered solution") and reused. It has been found
20 that, according to the conventional methods, a large amount of solvent must be used to separate ^{226}Ra and ^{225}Ac , and thus the amount of the solvent used and the dilution of the Ra recovered solution remain to be improved.

[0006]

One aspect of the present invention provides a method for producing ^{225}Ac solution that can produce an ^{225}Ac solution having a high ^{225}Ac purity even when the amount of the solvent used in separating ^{225}Ac ions from a solution containing ^{226}Ra ions and ^{225}Ac ions (while obtaining a Ra recovered solution having a high ^{226}Ra concentration) is small.

[0007]

The present inventors have conducted extensive studies to solve the problems described above, and found that the problems can be solved by employing a particular production method, and thus the present invention has been made.

[0008]

An aspect of the present invention provides a method for producing ^{225}Ac solution that includes steps (I) to (III)

below:

step (I): a step of passing a Ra-Ac solution (1) containing ^{226}Ra ions and ^{225}Ac ions through a solid-phase extraction agent (a) that contains a compound represented by formula (A) below so as to cause the solid-phase extraction agent (a) to retain the ^{225}Ac ions;

step (II): a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (a) from the solid-phase extraction agent (a) by using an acid-containing eluent (a), and passing a liquid containing an obtained eluate (2)

through a solid-phase extraction agent (b) that contains a compound represented by formula (B) below so as to cause the solid-phase extraction agent (b) to retain the ^{225}Ac ions; and

step (III): a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (b) from the solid-phase extraction agent (b) by using an acid-containing eluent (b) so as to obtain an ^{225}Ac solution having a higher ^{225}Ac purity than the Ra-Ac solution (1).

[0009]

Another aspect of the present invention provides a method for producing ^{225}Ac solution that includes steps (Ia) and (IIa) below:

step (Ia): a step of passing a Ra-Ac solution (1) containing ^{226}Ra ions and ^{225}Ac ions through a solid-phase extraction agent (a) that contains a compound represented by formula (A1) below so as to cause the solid-phase extraction agent (a) to retain the ^{225}Ac ions; and

step (IIa): a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (a) from the solid-phase extraction agent (a) by using an acid-containing eluent (a).

[0010]

A yet another aspect of the present invention provides a production method for producing ^{225}Ac that includes

an irradiating step of irradiating a ^{226}Ra target with

at least one kind selected from charged particles, photons, and neutrons to generate ^{225}Ac by nuclear reaction;

a step of dissolving, in an acidic solution, the ^{226}Ra target irradiated in the irradiating step to obtain a Ra-Ac
5 solution (1) that contains ^{226}Ra ions and ^{225}Ac ions; and

a step of obtaining an ^{225}Ac solution by using the method for producing ^{225}Ac solution described above.

[0011]

According to an aspect of the present invention, an
10 ^{225}Ac solution having a high ^{225}Ac purity can be produced from a solution that contains ^{226}Ra ions and ^{225}Ac ions.

According to another aspect of the present invention, an ^{225}Ac solution having a high ^{225}Ac purity can be produced from a solution containing ^{226}Ra ions and ^{225}Ac ions by using a
15 small amount of a solvent in separating the ^{225}Ac ions (while obtaining a Ra recovered solution having a high ^{226}Ra concentration).

By using an ^{225}Ac solution having a high ^{225}Ac purity, ^{225}Ac can be efficiently used for the desired usage, and, for
20 example, radioactive medicines having a higher ^{225}Ac purity and containing less contaminants such as ^{226}Ra and daughter nuclides thereof can be produced.

Description of Embodiments

[0012]

[Method for producing ^{225}Ac solution]

An embodiment of the method for producing ^{225}Ac solution according to one aspect of the present invention includes steps (I) to (III) below:

5 step (I): passing a Ra-Ac solution (1) containing ^{226}Ra ions and ^{225}Ac ions through a solid-phase extraction agent (a) that contains a compound represented by formula (A) below so as to cause the solid-phase extraction agent (a) to retain the ^{225}Ac ions;

10 step (II): eluting the ^{225}Ac ions retained on the solid-phase extraction agent (a) from the solid-phase extraction agent (a) by using an acid-containing eluent (a) and passing the obtained eluate (2) through a solid-phase extraction agent (b) that contains a compound represented by formula (B)
15 below so as to cause the solid-phase extraction agent (b) to retain the ^{225}Ac ions; and

 step (III): eluting the ^{225}Ac ions retained on the solid-phase extraction agent (b) from the solid-phase extraction agent (b) by using an acid-containing eluent (b)
20 so as to obtain an ^{225}Ac solution having a higher ^{225}Ac purity than the aforementioned Ra-Ac solution (1).

[0013]

< Step (I) >

In the step (I), a Ra-Ac solution (1) containing ^{226}Ra

ions and ^{225}Ac ions is passed through a solid-phase extraction agent (a) that contains a compound represented by formula (A) below so as to cause the solid-phase extraction agent (a) to retain the ^{225}Ac ions.

5 [0014]

By performing the step (I), the ^{225}Ac ions can be retained on the solid-phase extraction agent (a), and the ^{226}Ra ions not retained on the solid-phase extraction agent (a) can pass through. The flow-through solution obtained in the step (I) contains most of ^{226}Ra ions contained in the Ra-Ac solution (1), and thus is preferably recovered and reused. Thus, typically, the flow-through solution of this step (I) constitutes a Ra recovered solution. Here, the Ra recovered solution refers to the flow-through solution in the step (I) in the following first purification step, and does not refer to the flow-through solution of a step that corresponds to the step (I) in a second purification step described below or in an optional third or onward purification step described below.

20 The Ra recovered solution is, for example, subjected to steps such as a purification step as necessary, and then used as, for example, an electrodeposition solution for producing a ^{226}Ra target.

The amounts of the ^{226}Ra ions contained in the flow-

through solution passing through the solid-phase extraction agent (b) in the step (II) below and in a wash solution obtained in the washing step described below are usually extremely small compared to the amount of the ^{226}Ra ions in the aforementioned Ra recovered solution; thus, such a flow-through solution and a wash solution are usually not reused and are usually discarded since the disadvantage of reducing the ^{226}Ra ion concentration outweighs the advantage of the reuse. Thus, in the present description, such a flow-through solution and such a wash solution are not referred to as the Ra recovered solutions.

[0015]

The solid-phase extraction agent (a) can selectively retain the ^{225}Ac ions by passing a high concentrated acid (for example, 0.3 M or higher for nitric acid), and can thus cause ^{226}Ra ions to pass through. As described above, the concentration of the acid used to separate ^{226}Ra ions and ^{225}Ac ions (causing ^{225}Ac ions to be retained on the solid-phase extraction agent (a) and allowing ^{226}Ra ions to pass through) by using the solid-phase extraction agent (a) is high; thus, the amount of the solvent necessary for separating the ^{226}Ra ions and ^{225}Ac ions is decreased. Accordingly, when the solid-phase extraction agent (a) is used in this step (I), the ^{226}Ra ions and the ^{225}Ac ions can be satisfactorily

separated even when the amount of the solvent used to separate ^{225}Ac ions from the solution containing ^{226}Ra ions and ^{225}Ac ions is small.

[0016]

5 << Ra-Ac solution (1) >>

The Ra-Ac solution (1) is not particularly limited as long as ^{226}Ra ions and ^{225}Ac ions are contained, but is preferably a solution that contains ^{226}Ra ions, ^{225}Ac ions, and an acid.

10 A preferable example of an embodiment of the Ra-Ac solution (1) is a solution obtained by irradiating a ^{226}Ra target with at least one kind selected from charged particles, photons, and neutrons and preferably with protons, and then dissolving the ^{226}Ra target after the irradiation.

15 Irradiating the ^{226}Ra target with particles generates ^{225}Ac through, for example, decay in some cases, and thus the solution obtained by dissolving the ^{226}Ra target contains ^{226}Ra ions and ^{225}Ac ions. Here, in dissolving the ^{226}Ra target, an acid may be used.

20 [0017]

Examples of the acid include inorganic acids such as nitric acid, hydrochloric acid, phosphoric acid, sulfuric acid, boric acid, and hydrofluoric acid. Among these, from the viewpoint such as the capability to sufficiently dissolve

^{226}Ra ions and ^{225}Ac ions and efficiently carry out separation purification using a solid-phase extraction agents (a) and (b), nitric acid and hydrochloric acid are preferable, and nitric acid is particularly preferable.

5 One acid or two or more acids may be used in the Ra-Ac solution (1).

[0018]

When nitric acid is used as the aforementioned acid, from the viewpoint such as the capability to more efficiently
10 separate ^{226}Ra and ^{225}Ac by passing the solution through the solid-phase extraction agent (a) (perform separation with a less amount of ^{225}Ac passing through and a less amount of ^{226}Ra retained), the acid concentration of the Ra-Ac solution (1) is preferably 0.3 M or higher and more preferably 0.5 M or
15 higher, and is preferably 4.0 M or lower.

When hydrochloric acid is used as the aforementioned acid, the acid concentration of the Ra-Ac solution (1) is preferably 1 M or higher and preferably 8 M or lower.

[0019]

20 In order to dissolve the ^{226}Ra target, the amount of the solvent is preferably at least 10 times and more preferably at least 20 times the molar amount of ^{226}Ra , and is preferably at most 50 times and more preferably at most 40 times the molar amount of ^{226}Ra ; for example, when 25 mg of ^{226}Ra is to

be dissolved, the amount of the acid used having the
aforementioned concentration range is preferably 1 mL or
more, more preferably 2 mL or more, and yet more preferably 3
mL or more, and is preferably 20 mL or less, more preferably
5 15 mL or less, and yet more preferably 10 mL or less.

[0020]

The flow rate of the Ra-Ac solution (1) passing through
the solid-phase extraction agent (a) is preferably 0.01
mL/min or more, more preferably 0.1 mL/min or more, and yet
10 more preferably 0.5 mL/min or more, and is preferably 5
mL/min or less, more preferably 3 mL/min or less, and yet
more preferably 2 mL/min or less from the viewpoint such as
the capability to more efficiently separate ^{226}Ra and ^{225}Ac .

[0021]

15 << Solid-phase extraction agent (a) >>

The solid-phase extraction agent (a) is not
particularly limited as long as the solid-phase extraction
agent (a) contains a compound represented by formula (A)
below, and may further contain known components contained in
20 solid-phase extraction agents.

The solid-phase extraction agent (a) may be solely
composed of a compound represented by formula (A), or may
contain a compound represented by formula (A) below and other
components (for example, known additives and inactive

substrates) (including a solid-phase extraction agent that contains an inactive substrate and a compound represented by formula (A) introduced into the inactive substrate).

The solid-phase extraction agent (a) may contain one or
5 more compounds represented by formula (A) below.

[0022]

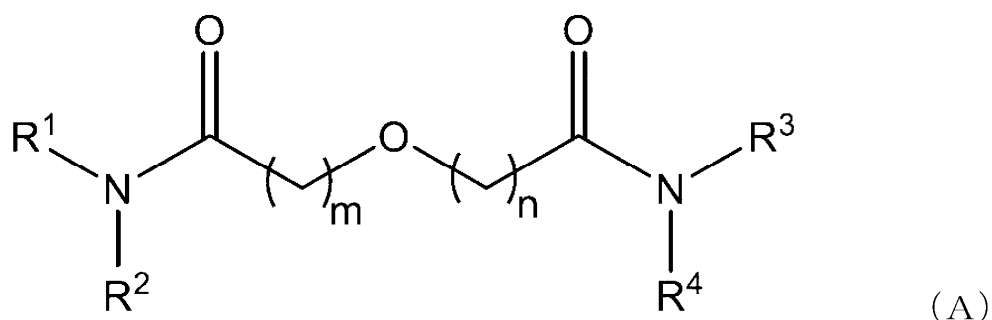
The solid-phase extraction agent (a) is preferably an inactive substrate that contains a compound represented by formula (A) below, and more preferably a porous silica or an
10 organic polymer that contains a compound represented by formula (A) below. The pore size of the porous silica is not particularly limited but is preferably about 50 to 150 μm in diameter.

[0023]

15 The solid-phase extraction agent (a) can selectively retain the ^{225}Ac ions by passing a high concentrated acid, and the retained ^{225}Ac ions can be eluted by passing a low concentration acid through the solid-phase extraction agent (a).

20 Such a solid-phase extraction agent (a) is not particularly limited, and a commercially available product, such as "DGA Resin" and "DGA Branched Resin" produced by Eichrom Technologies Inc., may be used.

[0024]



[0025]

In formula (A), m and n each independently represent 0 or 1, and preferably 1.

5 In formula (A), R¹ to R⁴ each independently represent a linear or branched alkyl group having 8 or more and 12 or less carbon atoms. R¹ to R⁴ preferably each independently represent an octyl group or a 2-ethylhexyl group.

[0026]

10 < Other steps >

After the step (I) and before the step (II) described below, a step of washing the solid-phase extraction agent (a), which is retaining the ²²⁵Ac ions, with an acid-containing wash solution (solid-phase extraction agent (a) washing step) may be performed for purposes such as washing away the ²²⁶Ra ions that may remain in the solid-phase extraction agent (a).

[0027]

Examples of the acid used in the solid-phase extraction agent (a) washing step are the same as those for the acid

20

used in the Ra-Ac solution (1) described above, and preferable acids are also the same. One acid or two or more acids may be used.

The concentration of this acid is not particularly limited as long as the retained ^{225}Ac ions do not elute, but is preferably the same or about the same as the concentration of the Ra-Ac solution (1) described above.

[0028]

< Step (II) >

In step (II), the ^{225}Ac ions retained on the solid-phase extraction agent (a) are eluted from the solid-phase extraction agent (a) by using an acid-containing eluent (a), and a liquid containing the obtained eluate (2) is passed through a solid-phase extraction agent (b) that contains a compound represented by formula (B) below so as to cause the solid-phase extraction agent (b) to retain ^{225}Ac ions.

By performing the step (II), the ^{225}Ac ions contained in the eluate (2) can be retained on the solid-phase extraction agent (b), and the ^{226}Ra ions that can be contained in the eluate (2) can be allowed to pass through.

[0029]

In eluting ^{225}Ac ions from the solid-phase extraction agent (a), an acid-containing eluent (a) is used. Examples of the acid are the same as those for the acid used in the

Ra-Ac solution (1) described above, and preferable acids are also the same. One acid or two or more acids may be used.

[0030]

The acid concentration of the eluent (a) is not particularly limited as long as the retained ^{225}Ac ions can be sufficiently eluted from the solid-phase extraction agent (a); however, when the same acid as that used with the Ra-Ac solution (1) described above is used as the acid used in the eluent (a), the difference in concentration is preferably large. When nitric acid is used as the acid, the acid concentration of the eluent (a) is preferably 0.2 M or lower, more preferably 0.1 M or lower, and yet more preferably 0.01 M or lower, and the lower limit of the concentration may be any as long as nitric acid is contained, in other words, as long as the nitric acid concentration is greater than 0 M.

When hydrochloric acid is used as the aforementioned acid, the acid concentration of the eluent (a) is preferably greater than 0 M and 0.2 M or lower.

[0031]

In addition, since there is a possibility that the acid used in the Ra-Ac solution (1) would remain in the solid-phase extraction agent (a), in order to ensure, for example, elution of ^{225}Ac ions from the solid-phase extraction agent (a) in such a case also, the concentration of the acid used

in the Ra-Ac solution (1) is preferably different from the acid concentration of the eluent (a), and is preferably 15 or more provided that the acid concentration of the eluent (a) is 1.

5 [0032]

The flow rate of the eluent (a) is preferably 0.1 mL/min or more and more preferably 0.5 mL/min or more, and preferably 20 mL/min or less and more preferably 10 mL/min or less from the viewpoint such as the capability to
10 sufficiently elute the retained ^{225}Ac ions from the solid-phase extraction agent (a).

[0033]

The obtained eluate (2) may be directly passed through the solid-phase extraction agent (b) or adjusted for the acid
15 concentration, the flow rate and the like, and then passed through the solid-phase extraction agent (b).

By passing the eluate (2) having an acid concentration in the aforementioned range through the solid-phase extraction agent (b), ^{225}Ac ions can be retained on the solid-
20 phase extraction agent (b), and thus the acid concentration of the obtained eluate (2) need not be adjusted.

The flow rate in which the liquid containing the eluate (2) passes through the solid-phase extraction agent (b) is preferably 1 mL/min or more and more preferably 1.5 mL/min or

more, and preferably 30 mL/min or less and more preferably 20 mL/min or less from the viewpoint such as the capability to sufficiently retain ^{225}Ac ions on the solid-phase extraction agent (b).

5 [0034]

<< Solid-phase extraction agent (b) >>

The solid-phase extraction agent (b) is not particularly limited as long as the solid-phase extraction agent (b) contains a compound represented by formula (B)

10 below, and may further contain known components contained in solid-phase extraction agents.

The solid-phase extraction agent (b) may be solely composed of a compound represented by formula (B), or may contain a compound represented by formula (B) below and other
15 components (for example, known additives and inactive substrates) (including a solid-phase extraction agent that contains an inactive substrate and a compound represented by formula (B) introduced into the inactive substrate).

The solid-phase extraction agent (b) may contain one or
20 more compounds represented by formula (B) below.

[0035]

The solid-phase extraction agent (b) is preferably an inactive substrate that contains a compound represented by formula (B) below, and more preferably a porous silica or an

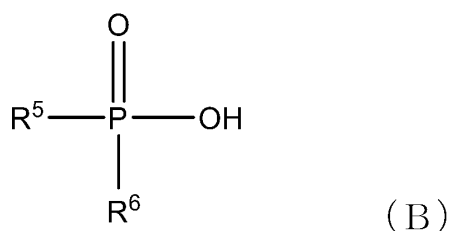
organic polymer that contains a compound represented by formula (B) below. The pore size of the porous silica is not particularly limited but is preferably about 50 to 150 μm in diameter.

5 [0036]

The solid-phase extraction agent (b) can selectively retain the ^{225}Ac ions by passing a low concentration acid, and the retained ^{225}Ac ions can be eluted by passing a high concentrated acid through the solid-phase extraction agent
10 (b).

Such a solid-phase extraction agent (b) is not particularly limited, and a commercially available product, such as "Ln Resin", "Ln2 Resin", and "Ln3 Resin" produced by Eichrom Technologies Inc., may be used.

15 [0037]



[0038]

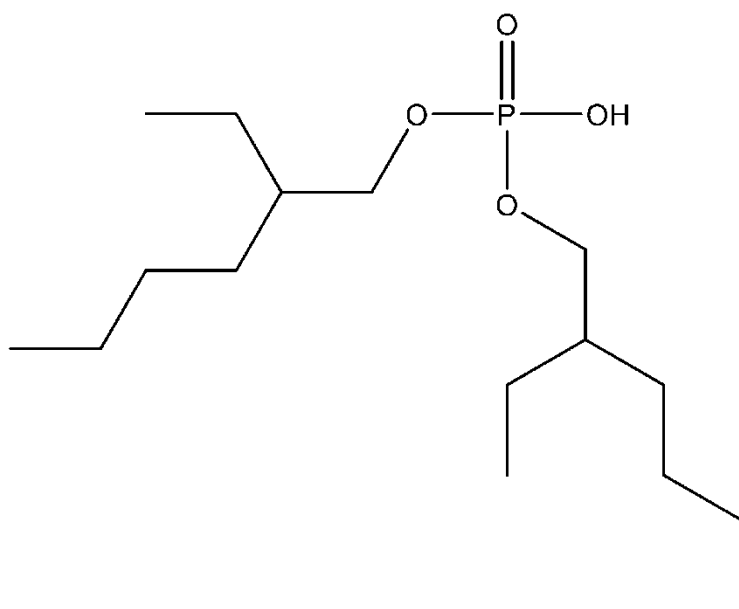
In formula (B), R^5 and R^6 each independently represent -
20 R' or $-\text{OR}'$ (R' represents an alkyl group having 8 carbon atoms). The alkyl group having 8 carbon atoms represented by R' may be linear or branched, and preferable examples thereof

include an octyl group, a 2-ethylhexyl group, and 2-methyl-4,4-dimethylpentyl group.

[0039]

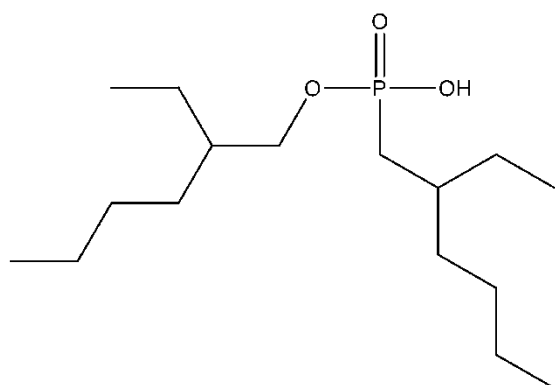
Preferable examples of the compound represented by
5 formula (B) are compounds represented by formulae (B-1) to (B-3) below.

[0040]



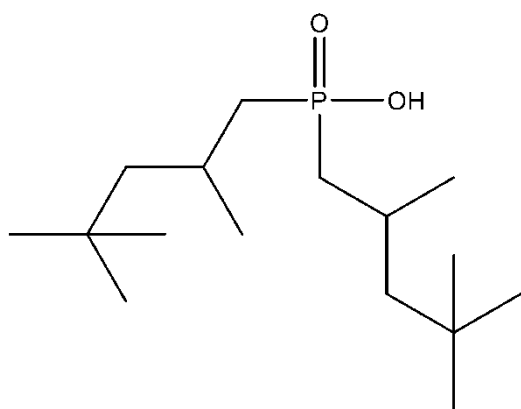
(B - 1)

[0041]



(B - 2)

[0042]



(B-3)

[0043]

< Other steps >

After the step (II) and before the step (III) described
 5 below, for example, a step of washing the solid-phase
 extraction agent (b), which is retaining the ^{225}Ac ions, with
 an acid that has an acid concentration higher than the liquid
 containing the eluate (2) but lower than the acid
 concentration of the eluent (b) below (solid-phase extraction
 10 agent (b) washing step) may be performed for the purposes
 such as washing away ^{226}Ra ions that may remain in the solid-
 phase extraction agent (b).

[0044]

This solid-phase extraction agent (b) washing step is
 15 preferably performed separately from the step (II) described
 above; however, if ^{226}Ra ions had been sufficiently removed in
 the aforementioned solid-phase extraction agent (a) washing
 step, the concentration of the eluent (a) and the
 concentration of the acid in the eluate (2) may be adjusted

so that the step of passing the liquid containing the eluate (2) through the solid-phase extraction agent (b) would simultaneously serve as the solid-phase extraction agent (b) washing step.

5 From the viewpoint such as the capability to obtain an ^{225}Ac solution having a high ^{225}Ac purity, the solid-phase extraction agent (b) washing step is preferably performed after the step (II).

[0045]

10 Examples of the acid used in the solid-phase extraction agent (b) washing step are the same as those for the acid used in the Ra-Ac solution (1) described above, and preferable acids are also the same. One acid or two or more acids may be used.

15 The acid concentration is preferably such that the ^{226}Ra ions are eluted but the retained ^{225}Ac ions are not, and is preferably higher than the acid concentration of the liquid containing the eluate (2) but lower than the acid concentration of the eluent (b) below. When nitric acid is
20 used as the acid, the concentration is preferably 0.01 M or higher and preferably 0.2 M or lower.

[0046]

 The flow rate of the liquid passing through in the solid-phase extraction agent (b) washing step is preferably

0.5 mL/min or more and more preferably 1 mL/min or more and preferably 30 mL/min or less and more preferably 20 mL/min or less from the viewpoint such as the capability to sufficiently elute ^{226}Ra ions that may remain on the solid-phase extraction agent (b).

[0047]

< Step (III) >

In the step (III), the ^{225}Ac ions retained on the solid-phase extraction agent (b) are eluted from the solid-phase extraction agent (b) by using an acid-containing eluent (b) so as to obtain an ^{225}Ac solution having a higher ^{225}Ac purity than the aforementioned Ra-Ac solution (1).

[0048]

In eluting ^{225}Ac ions from the solid-phase extraction agent (b), an acid-containing eluent (b) is used. Examples of the acid are the same as those for the acid used in the Ra-Ac solution (1) described above, and preferable acids are also the same. One acid or two or more acids may be used.

[0049]

When nitric acid is used as the acid, the acid concentration of the eluent (b) is preferably 0.2 M or higher, more preferably 0.3 M or higher, and yet more preferably 0.5 M or higher, and is preferably 4 M or lower, more preferably 2 M or lower, and yet more preferably 1 M or

lower from the viewpoint such as the capability to sufficiently elute the retained ^{225}Ac ions from the solid-phase extraction agent (b).

When hydrochloric acid is used as the aforementioned
5 acid, the acid concentration of the eluent (b) is preferably 0.3 M or higher and preferably 8 M or lower.

[0050]

The flow rate of the eluent (b) is preferably 0.5 mL/min or more, more preferably 1 mL/min or more, and yet
10 more preferably 2 mL/min or more, and preferably 30 mL/min or less, more preferably 25 mL/min or less, and yet more preferably 20 mL/min or less from the viewpoint such as the capability to sufficiently elute the retained ^{225}Ac ions from the solid-phase extraction agent (b).

15 [0051]

An ^{225}Ac solution having a high ^{225}Ac purity can be produced through the steps described above. The obtained ^{225}Ac solution may be re-purified if necessary. An ^{225}Ac solution having a yet higher ^{225}Ac purity can be produced
20 through the re-purification.

When re-purification is to be performed, the concentration of the acid used to elute ^{225}Ac ions from the solid-phase extraction agent (b) may be the same as the concentration of the acid used to retain ^{225}Ac ions on the

solid-phase extraction agent (a); thus, the eluate from the solid-phase extraction agent (b) can be directly passed through the solid-phase extraction agent (a) to allow the solid-phase extraction agent (a) to retain the ^{225}Ac ions.

5 Thus, re-purification can be performed easily without adjusting the concentration of the acid, and an ^{225}Ac solution having a yet higher ^{225}Ac purity can be produced.

[0052]

The re-purification preferably includes a first
10 purification step of obtaining an ^{225}Ac solution by performing the aforementioned steps (I) to (III) and other steps described above, and a second purification step of re-purifying the ^{225}Ac solution obtained in the first purification step.

15 The second purification step may be part of the first purification step, may be the same as the first purification step, or may be a step that repeats these steps.

[0053]

The second purification step preferably includes: a
20 step of passing the ^{225}Ac solution, which is obtained in the first purification step, through the same solid-phase extraction agent (a) used in the first purification step or a different solid-phase extraction agent (a) (a solid-phase extraction agent (a) that contains a compound represented by

formula (A) above) so as to cause the solid-phase extraction agent (a) to retain ^{225}Ac ions; and

a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (a) from the solid-phase extraction agent (a) by using an acid-containing eluent so as to obtain an ^{225}Ac solution having a higher ^{225}Ac purity than the ^{225}Ac solution obtained in the first purification step.

The method for producing ^{225}Ac solution that includes such a second purification step is preferable since the acid concentration in the obtained ^{225}Ac solution is low and thus the ^{225}Ac solution can be directly used in labeling reaction, for example.

[0054]

In addition, the second purification step may further include: a step of passing the ^{225}Ac solution, which is obtained by elution from the solid-phase extraction agent (a) as described above, through the same solid-phase extraction agent (b) used in the first purification step or a different solid-phase extraction agent (b) (a solid-phase extraction agent (b) that contains a compound represented by formula (B) above) so as to cause the solid-phase extraction agent (b) to retain ^{225}Ac ions; and

a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (b) from the solid-phase extraction

agent (b) by using an acid-containing eluent so as to obtain an ^{225}Ac solution having a yet higher ^{225}Ac purity than the ^{225}Ac solution obtained in the first purification step.

The method for producing ^{225}Ac solution that includes such a second purification step increases the ^{225}Ac purity of the obtained ^{225}Ac solution, and thus when the ^{225}Ac solution is appropriately adjusted for the acid concentration and used in the labeling reaction, for example, a high labeling ratio and a high synthetic yield can be achieved.

[0055]

The acid-containing eluent used in the second purification step preferably has a composition similar to that of the eluent used in the corresponding first purification step, and more preferably has the same composition as the eluent used in the corresponding first purification step. Furthermore, the second purification step preferably further includes a solid-phase extraction agent (a) washing step and a solid-phase extraction agent (b) washing step, and more preferably, the same steps as the washing steps performed in the first purification step are performed.

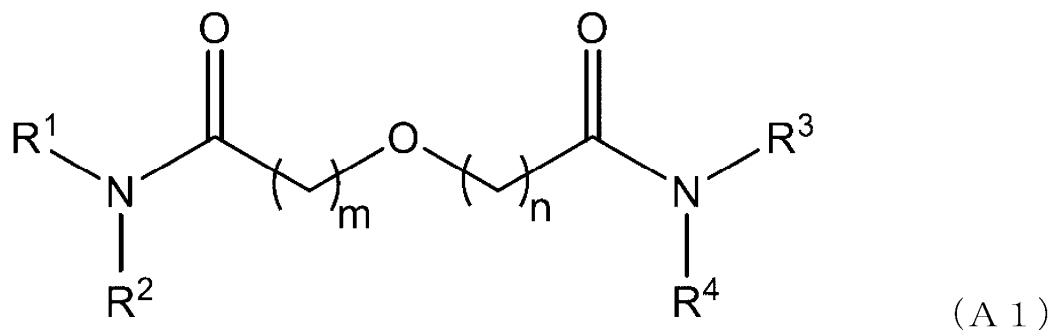
[0056]

< Step (Ia) >

According to another embodiment of the present

invention, a step (Ia) may be performed instead of the
 aforementioned step (I). In the step (Ia), a Ra-Ac solution
 (1) containing ^{226}Ra ions and ^{225}Ac ions is passed through a
 solid-phase extraction agent (a) that contains a compound
 5 represented by formula (A1) below so as to cause the solid-
 phase extraction agent (a) to retain the ^{225}Ac ions.

[0057]



[0058]

10 In formula (A1), m and n each independently represent
 1.

In formula (A1), R^1 to R^4 each independently represent a
 linear or branched alkyl group having 8 or more and 12 or
 less carbon atoms. R^1 to R^4 preferably each independently
 15 represent an octyl group or a 2-ethylhexyl group.

[0059]

The Ra-Ac solution (1) used in the step (Ia) may have a
 similar composition to the Ra-Ac solution (1) used in the
 step (I) described above, and the flow rate of the solution
 20 passing through the solid-phase extraction agent (a) is also

similar to that of the Ra-Ac solution (1) used in the step (I) described above.

The solid-phase extraction agent (a) used in the step (Ia) is also the same as the solid-phase extraction agent (a) used in the step (I) described above except that the compound represented by formula (A1) above is used instead of the compound represented by formula (A) above.

[0060]

< Step (IIa) >

According to another embodiment of the present invention, after the step (Ia) above, a step (IIa) may be performed instead of the aforementioned steps (II) and (III). In the step (IIa), the ^{225}Ac ions retained on the solid-phase extraction agent (a) are eluted from the solid-phase extraction agent (a) by using an acid-containing eluent (a) so as to obtain an ^{225}Ac solution having a higher ^{225}Ac purity than the aforementioned Ra-Ac solution (1).

[0061]

The acid-containing eluent (a) used in eluting the ^{225}Ac ions from the solid-phase extraction agent (a) in the step (IIa) can be a solution having a composition similar to that of the eluent (a) used in the step (II), and the flow rate of the solution passing through the solid-phase extraction agent (a) is also similar to that of the eluent (a) used in the

step (II) described above.

[0062]

[Method for producing ^{225}Ac]

A method for producing ^{225}Ac according to one embodiment
5 of the present invention includes:

a step of irradiating a ^{226}Ra target with at least one
kind selected from charged particles, photons, and neutrons
to generate ^{225}Ac by nuclear reaction;

a step of dissolving, in an acidic solution, the ^{226}Ra
10 target irradiated in the aforementioned irradiating step to
obtain a Ra-Ac solution (1) that contains ^{226}Ra ions and ^{225}Ac
ions; and

a step of obtaining an ^{225}Ac solution by using the
method for producing ^{225}Ac described above.

15 The details of the irradiating step and the step of
obtaining the Ra-Ac solution (1) are as described in the
section explaining the Ra-Ac solution (1) above.

The method for producing ^{225}Ac according to an
embodiment of the present invention may further include other
20 steps such as a step of removing the solvent from the ^{225}Ac
solution.

In one embodiment of the present invention, the ^{225}Ac
solution may be used in producing an ^{225}Ac -containing
therapeutic drug. In one embodiment of the present

invention, a pharmaceutically acceptable ^{225}Ac -containing radionuclide composition obtained by this method for producing ^{225}Ac may be provided.

EXAMPLES

5 [0063]

Hereinafter, an embodiment of the present invention is further described through Examples which do not limit the present invention in any way.

Since a test that uses ^{226}Ra cannot be easily carried
10 out due to issues such as radiation issues, barium, which is considered to give similar results to ^{226}Ra , was used in the test described below. Radium is an alkaline earth metal and has similar properties to barium, which is also an alkaline earth metal and has a mass number close to radium.

15 Furthermore, radium and barium are known to have similar properties as indicated by the fact that coprecipitation action with barium sulfate has been utilized in extracting radium from a pitch blend after uranium extraction in the past.

20 [0064]

[Test Example 1]

· Step (I)

^{225}Ac ions (produced by Oak Ridge National Laboratory (ORNL)) were dissolved in a solution prepared by diluting

53.3 mL of nitric acid having a concentration of 60% with water to 1 L so as to prepare a 0.7 M aqueous nitric acid solution (radioactivity concentration of ^{225}Ac : 0.04 to 1 MBq/run). Furthermore, 16 mL of a solution (1-1) prepared by dissolving barium chloride in the obtained aqueous solution such that the mass of Ba was 30 mg was passed through a solid-phase extraction agent (a) ("DGA Resin" produced by Eichrom Technologies Inc., DGA normal resin, 1 mL cartridge, containing a compound represented by formula (A) above) at a flow rate of 0.8 mL/min (actual measured value). By passing this solution, ^{225}Ac ions were retained on the DGA Resin, and a flow-through solution containing Ba (this flow-through solution corresponds to the Ra recovered solution) was obtained.

Next, DGA Resin after the passage of the solution (1-1) was washed by passing 20 mL of a 0.7 M aqueous nitric acid solution therethrough at a flow rate of 0.8 mL/min (actual measured value) (the wash solution that has passed through the DGA resin is also referred to as the wash solution (x)).

[0065]

The radioactivity was measured with a germanium semiconductor detector produced by EURISYS MESURES to determine the amounts of ^{225}Ac in the obtained Ra recovered solution and the wash solution (x); however, the amounts of

^{225}Ac were below the detection limit of the detector and ^{225}Ac could not be detected. The measured masses of radioactive substances described below are the values measured by using a similar detector.

5 In addition, the result of the amount of ^{225}Ac in Test Example 1 is an average value obtained by performing the same process three times.

[0066]

· Step (II)

10 An eluate (2-1) containing ^{225}Ac ions was obtained by passing 20 mL of a 0.005 M aqueous nitric acid solution through the DGA Resin, which had been washed with the 0.7 M aqueous nitric acid solution, at a flow rate of 0.8 mL/min (actual measured value), and the obtained eluate (2-1) was
15 passed through a solid-phase extraction agent (b) ("Ln Resin" produced by Eichrom Technologies Inc., 1 mL cartridge, containing a compound represented by formula (B) above) at a flow rate of 2.5 mL/min (actual measured value). By passing this solution, ^{225}Ac ions were retained on the Ln Resin. The
20 flow-through solution that has passed through Ln Resin during this process is also referred to as a flow-through solution (y).

[0067]

The amount of ^{225}Ac in the obtained flow-through

solution (y) was measured and was found to be below the detection limit of the detector, and thus ^{225}Ac could not be detected.

In addition, the amount of ^{225}Ac in the DGA Resin after the passage of the 0.005 M aqueous nitric acid solution was measured, and the average value ($n = 3$) of the amount of ^{225}Ac was 1.6% relative to 100% of the amount of ^{225}Ac used.

[0068]

· Solid-phase extraction agent (b) washing step

Next, the Ln Resin after the passage of the eluate (2-1) was washed by passing 10 mL of a 0.05 M aqueous nitric acid solution therethrough at a flow rate of 1 mL/min (actual measured value) (the wash solution that has passed through the Ln Resin is also referred to as the wash solution (z)).

The amount of ^{225}Ac in the obtained wash solution (z) was measured and was found to be below the detection limit of the detector, and thus ^{225}Ac could not be detected.

[0069]

· Step (III)

10 mL of a 0.7 M aqueous nitric acid solution was passed through the Ln Resin, which had been washed with the 0.05 M aqueous nitric acid solution, at a flow rate of 2.5 mL/min (actual measure value) to obtain an ^{225}Ac solution that contains ^{225}Ac .

The amount of ^{225}Ac in the obtained ^{225}Ac solution was measured, and the average value ($n = 3$) of the amount of ^{225}Ac was 98.4% relative to 100% of the amount of ^{225}Ac used.

The amounts of ^{225}Ac in the Ln Resin after the passage
5 of the 0.7 M aqueous nitric acid solution and in the members
such as a syringe and a tube used in the aforementioned
operation were measured and were found to be below the
detection limit of the detector, and thus ^{225}Ac could not be
detected.

10 [0070]

[Test Example 2]

A Ra recovered solution was obtained as in the step (I)
described above in Test Example 1 except that, instead of 16
mL of the 0.7 M aqueous nitric acid solution containing
15 dissolved ^{225}Ac , 20 mL of a 4 M aqueous nitric acid solution
containing dissolved ^{225}Ac , 15 mL of a 1 M aqueous nitric acid
solution containing dissolved ^{225}Ac , or 15 mL of a 0.5 M
aqueous nitric acid solution containing dissolved ^{225}Ac (in
every one of these solutions, the ^{225}Ac concentration was 0.04
20 to 0.1 MBq/run) was used, and the amount of ^{225}Ac in this Ra
recovered solution was measured. The amount of ^{225}Ac was
below the detection limit of the detector when the 4 M or 1 M
aqueous nitric acid solution was used, and was 0.6% relative
to 100% of the amount of ^{225}Ac used when the 0.5 M aqueous

nitric acid solution was used.

[0071]

[Test Example 3]

The steps (I) and (II) were performed as described
5 above except that, in the step (I) of Test Example 1, a 4 M
aqueous nitric acid solution containing dissolved ^{225}Ac
(radioactivity concentration of ^{225}Ac : 0.04 to 0.1 MBq/run)
was used instead of the 0.7 M aqueous nitric acid solution
containing dissolved ^{225}Ac and a 4 M aqueous nitric acid
10 solution was used as the solution for washing the DGA Resin
and that, in the step (II) of Test Example 1, a liquid
containing 30 mL of water and 5 mL of a 0.01 M aqueous nitric
acid solution was used instead of 20 mL of the 0.005 M
aqueous nitric acid solution. The amount of ^{225}Ac in the
15 flow-through solution (y) obtained was 0.3% relative to 100%
of the amount of ^{225}Ac used, and the amount of ^{225}Ac in the DGA
Resin after the passage of the 0.01 M aqueous nitric acid
solution was 1.3% relative to 100% of the amount of ^{225}Ac
used.

20 [0072]

[Test Example 4]

The steps (I) and (II) were performed as described
above except that, in the step (I) of Test Example 1, a 0.5 M
aqueous nitric acid solution containing dissolved ^{225}Ac (0.04

to 0.1 MBq/run) was used instead of the 0.7 M aqueous nitric acid solution containing dissolved ^{225}Ac and that a 0.5 M aqueous nitric acid solution was used as the solution for washing the DGA Resin. The amount of ^{225}Ac in the flow-
5 through solution (y) obtained was below the detection limit of the detector, and the amount of ^{225}Ac in the DGA Resin after the passage of the 0.005 M aqueous nitric acid solution was 3.4% relative to 100% of the amount of ^{225}Ac used.

[0073]

10 [Test Example 5]

The same test was performed as described above except that, in the solid-phase extraction agent (b) washing step of Test Example 1 above, 10 mL of a 0.01 M aqueous nitric acid was used instead of 10 mL of the 0.05 M aqueous nitric acid
15 solution. The amount of ^{225}Ac in the obtained wash solution (z) was below the detection limit of the detector, and ^{225}Ac could not be detected.

[0074]

[Test Example 6]

20 The same test was performed as described above except that, in the step (III) of Test Example 1 above, a 1 M or 0.5 M aqueous nitric acid solution was used instead of the 0.7 M aqueous nitric acid solution. The amount of ^{225}Ac in the Ln Resin after the passage of the 1 M or 0.5 M aqueous nitric

acid solution was below the detection limit of the detector,
and ^{225}Ac could not be detected.

[0075]

[Reference Example 1]

5 In order to study the behavior of ^{226}Ra ions removed
from the Ra-Ac solution (1) by the method for producing ^{225}Ac
solution according to an embodiment of the present invention,
the following experiment was carried out. Here, instead of
 ^{226}Ra ions, ^{133}Ba , which is considered to have a similar
10 behavior, was used.

[0076]

· Step (I)

16 mL of a solution (1-2) obtained by dissolving ^{133}Ba
in a 0.7 M aqueous nitric acid solution containing dissolved
15 ^{133}Ba (the ^{133}Ba concentration: 0.8 MBq/run) by using barium
chloride such that the mass of Ba was 15 mg was passed
through a solid-phase extraction agent (a) (DGA Resin). As a
result, a flow-through solution containing ^{133}Ba (this flow-
through solution corresponds to the Ra recovered solution)
20 was obtained.

Next, the DGA Resin after the passage of the solution
(1-2) was washed by passing 20 mL of a 0.7 M aqueous nitric
acid solution therethrough (the wash solution that has passed
through the DGA resin is also referred to as the wash

solution (x')).

[0077]

The radioactivity was measured with a germanium semiconductor detector to determine the amounts of ^{133}Ba in the obtained ^{133}Ba -containing flow-through solution (corresponds to the Ra recovered solution) and in the wash solution (x'). The amount of ^{133}Ba was 99.8% relative to 100% of the amount of ^{133}Ba used.

[0078]

10 · Step (II) and solid-phase extraction agent (b) washing step

An eluate (2-2) was obtained by passing 20 mL of a 0.005 M aqueous nitric acid solution through the DGA Resin, which had been washed with a 0.7 M aqueous nitric acid solution, and the obtained eluate (2-2) was passed through a solid-phase extraction agent (b) ("Ln Resin"). The flow-through solution that has passed through the Ln Resin during this process is also referred to as a flow-through solution (y').

20 Next, the Ln Resin after the passage of the eluate (2-2) was washed with 10 mL of a 0.05 M aqueous nitric acid solution (the wash solution that has passed through the Ln resin is also referred to as the wash solution (z')).

[0079]

The amounts of ^{133}Ba in the obtained flow-through

solution (y') and in the wash solution (z') were measured, and the amount of ^{133}Ba was 0.2% relative to 100% of the amount of ^{133}Ba used.

The amount of ^{133}Ba in the DGA Resin after the passage
5 of the 0.005 M aqueous nitric acid solution was measured, and was below the detection limit of the detector, and thus ^{133}Ba could not be detected.

[0080]

· Step (III)

10 10 mL of a 0.7 M aqueous nitric acid solution was passed through the Ln Resin, which had been washed with a 0.05 M aqueous nitric acid solution, to obtain a flow-through solution.

The amount of ^{133}Ba in the obtained flow-through
15 solution was measured and was found to be below the detection limit of the detector, and thus ^{133}Ba could not be detected.

The amounts of ^{133}Ba in the Ln Resin after the passage of the 0.7 M aqueous nitric acid solution and in the members such as a syringe and a tube used in the aforementioned
20 operation were measured and were found to be below the detection limit of the detector, and thus ^{133}Ba could not be detected.

[0081]

[Comparative Test Example 1]

5 mL of a 0.7 M aqueous nitric acid solution obtained by dissolving proton-irradiated ^{226}Ra target and containing 80 μCi of ^{226}Ra and 0.08 μCi of ^{225}Ac was passed through a solid-phase extraction agent (a) (DGA resin). Then the DGA resin
5 was washed with 20 mL of a 0.7 M aqueous nitric acid solution.

Subsequently, 20 mL of a 0.005 M aqueous nitric acid solution was passed through the DGA Resin, which had been washed with the 0.7 M aqueous nitric acid solution, to obtain
10 an eluate that contained ^{225}Ac .

The amount of ^{226}Ra in the obtained eluate was measured and was 0.5 μCi , and 0.6% of ^{226}Ra remained relative to 100% of the amount of ^{226}Ra used.

CLAIMS

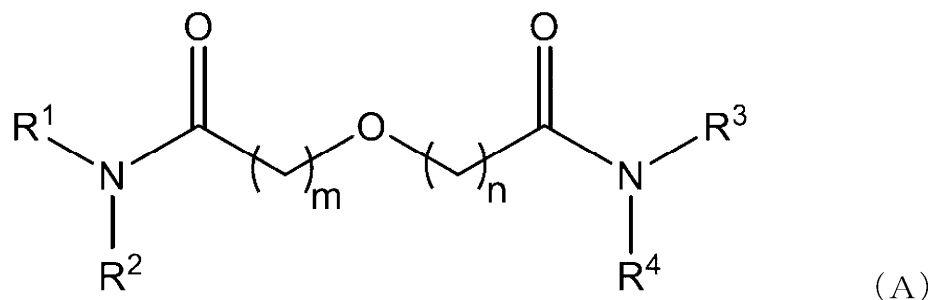
1. A method for producing ^{225}Ac solution comprising steps (I) to (III) below:

step (I): a step of passing a Ra-Ac solution (1)

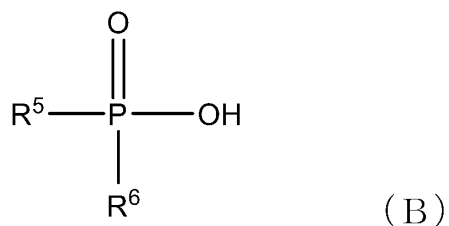
5 containing ^{226}Ra ions and ^{225}Ac ions through a solid-phase extraction agent (a) that contains a compound represented by formula (A) below so as to cause the solid-phase extraction agent (a) to retain the ^{225}Ac ions;

step (II): a step of eluting the ^{225}Ac ions retained on
10 the solid-phase extraction agent (a) from the solid-phase extraction agent (a) by using an acid-containing eluent (a), and passing a liquid containing an obtained eluate (2) through a solid-phase extraction agent (b) that contains a compound represented by formula (B) below so as to cause the
15 solid-phase extraction agent (b) to retain the ^{225}Ac ions; and

step (III): a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (b) from the solid-phase extraction agent (b) by using an acid-containing eluent (b) so as to obtain an ^{225}Ac solution having a higher ^{225}Ac purity
20 than the Ra-Ac solution (1),



wherein, in formula (A), m and n each independently represent 0 or 1, and R¹ to R⁴ each independently represent a linear or branched alkyl group having 8 or more and 12 or less carbon atoms,



wherein, in formula (B), R⁵ and R⁶ each independently represent an alkyl group having 8 carbon atoms or an alkoxy group having 8 carbon atoms.

2. The method for producing ²²⁵Ac solution according to Claim 1, wherein the Ra-Ac solution (1) is a solution obtained by dissolving a ²²⁶Ra target that has been irradiated with at least one kind selected from charged particles, photons, and neutrons.

3. The method for producing ²²⁵Ac solution according to

Claim 1 or 2, wherein the Ra-Ac solution (1) contains an acid having a concentration of 0.3 M or higher.

4. The method for producing ^{225}Ac solution according to any one of Claims 1 to 3, wherein, after the step (I), the solid-phase extraction agent (a) retaining the ^{225}Ac ions is washed with an acid-containing wash solution, and then the step (II) is performed.

5. The method for producing ^{225}Ac solution according to any one of Claims 1 to 4, wherein, after the step (II), the solid-phase extraction agent (b) retaining the ^{225}Ac ions is washed with an acid that has an acid concentration higher than that of the liquid that contains the eluate (2) but lower than that of the eluent (b), and then the step (III) is performed.

6. The method for producing ^{225}Ac solution according to any one of Claims 1 to 5, wherein the eluent (b) has a higher acid concentration than the eluent (a).

7. The method for producing ^{225}Ac solution according to any one of Claims 1 to 6, wherein the eluent (a) has an acid concentration of 0.2 M or lower.

8. The method for producing ^{225}Ac solution according to any one of Claims 1 to 7, wherein the eluent (b) has an acid concentration of 0.2 M or higher.

5

9. The method for producing ^{225}Ac solution according to any one of Claims 1 to 8, wherein acids contained in the eluent (a) and the eluent (b) each contain at least one inorganic acid selected from the group consisting of hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, boric acid, and hydrofluoric acid.

10. The method for producing ^{225}Ac solution according to any one of Claims 1 to 9, wherein acids contained in the eluent (a) and the eluent (b) each contain hydrochloric acid or nitric acid.

11. The method for producing ^{225}Ac solution according to any one of Claims 1 to 10, wherein, after the step (III), at least part of the steps (I) to (III) is further performed by using the obtained ^{225}Ac solution so as to obtain an ^{225}Ac solution having a yet higher ^{225}Ac purity.

12. A method for producing ^{225}Ac solution comprising:

a first purification step of obtaining an ^{225}Ac solution by carrying out the method for producing ^{225}Ac solution according to any one of Claims 1 to 10; and

a second purification step of re-purifying the ^{225}Ac solution obtained in the first purification step,

wherein the second purification step includes:

a step of passing the ^{225}Ac solution, which is obtained in the first purification step, through the same solid-phase extraction agent (a) used in the first purification step or a different solid-phase extraction agent (a) so as to cause the solid-phase extraction agent (a) to retain ^{225}Ac ions, and

a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (a) from the solid-phase extraction agent (a) by using an acid-containing eluent so as to obtain an ^{225}Ac solution having a yet higher ^{225}Ac purity than the ^{225}Ac solution obtained in the first purification step.

13. The method for producing ^{225}Ac solution according to Claim 12, comprising:

a step of passing the ^{225}Ac solution, which is obtained by elution from the solid-phase extraction agent (a) in the second purification step, through the same solid-phase

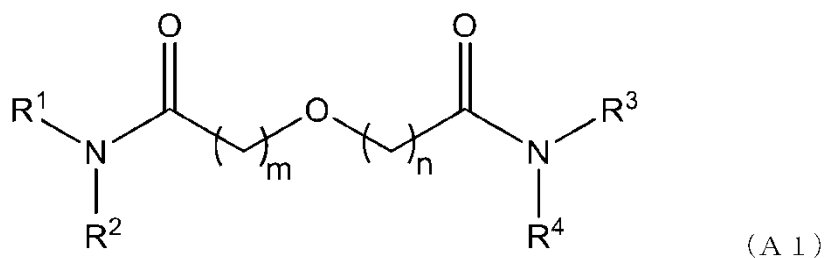
extraction agent (b) used in the first purification step or a different solid-phase extraction agent (b) so as to cause the solid-phase extraction agent (b) to retain ^{225}Ac ions; and

a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (b) from the solid-phase extraction agent (b) by using an acid-containing eluent so as to obtain an ^{225}Ac solution having a yet higher ^{225}Ac purity than the ^{225}Ac solution obtained in the first purification step.

14. A method for producing ^{225}Ac solution comprising steps (Ia) and (IIa) below:

step (Ia): a step of passing a Ra-Ac solution (1) containing ^{226}Ra ions and ^{225}Ac ions through a solid-phase extraction agent (a) that contains a compound represented by formula (A1) below so as to cause the solid-phase extraction agent (a) to retain the ^{225}Ac ions; and

step (IIa): a step of eluting the ^{225}Ac ions retained on the solid-phase extraction agent (a) from the solid-phase extraction agent (a) by using an acid-containing eluent (a),



wherein, in formula (A1), m and n each independently

represent 1, and R¹ to R⁴ each independently represent a linear or branched alkyl group having 8 or more and 12 or less carbon atoms.

5 15. An ²²⁵Ac production method comprising:

an irradiating step of irradiating a ²²⁶Ra target with at least one kind selected from charged particles, photons, and neutrons to generate ²²⁵Ac by nuclear reaction;

10 a step of dissolving, in an acidic solution, the ²²⁶Ra target irradiated in the irradiating step to obtain a Ra-Ac solution (1) that contains ²²⁶Ra ions and ²²⁵Ac ions; and

a step of obtaining an ²²⁵Ac solution by using the method for producing ²²⁵Ac solution according to any one of Claims 1 to 14.