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Generator of Highly Concentrated Pure ^{99m}Tc from Low Specific Activity ^{99}Mo Produced by Reactor and/or Electron Linear Accelerator

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ABSTRACT

Technetium-99m (^{99m}Tc) extraction from ^{99}Mo using the newly developed Technetium Master Milker (TcMM) process was examined. This process combined activated carbon (AC) and/or alumina (AL), with or without an ion exchange resin (IER). It was found that the chemical yield and purity of the ^{99m}Tc produced using the TcMM process were 90-95% and 6N (99.9999 %), respectively, even in a short time (<30min.) at room temperature. Therefore, this process is capable of generating high quality $^{99m}TcO_4^-$ (pertechnetate), which means that the process satisfies the requirements of the pharmaceutical affairs act as a practical ^{99m}Tc generator, even with an activity level in the range from a few tens of kBq to TBq. Conclusively, it was shown that ^{99m}Tc can be supplied domestically and further locally on demand by the TcMM process after production of ^{99}Mo by the ^{98}Mo(n,γ) and/or ^{100}Mo(γ,n) reactions, using a neighboring reactor and/or an electron linear accelerator without enriched uranium (HEU and LEU), and furthermore, the advanced use for diagnosis can be available everywhere in the world.

Keywords: Molybdenum-99, Technetium-99m, Technetium Master Milker (TcMM), reactor, bremsstrahlung photon, electron linear accelerator, (n,γ) reaction, (γ,n) reaction, activated carbon, activated alumina, ion exchange resin

1. Introduction

Shortage in the supply of ^{99}Mo owing to the shutdown of reactors used for its production is a global problem now. Since ^{99}Mo is an indispensable source of ^{99m}Tc, which is used in nuclear medicine to make treatments and diagnoses using techniques such as scintigraphy and single photon emission computed tomography (SPECT), a stable supply of ^{99}Mo is most essential and important. Therefore, production of ^{99}Mo using nuclear reactors and/or accelerators has been investigated [1–3]. For the practical use of ^{99}Mo/^{99m}Tc, both a stable supply of ^{99}Mo and separation and purification of the ^{99m}Tc are required. To separate ^{99m}Tc from ^{99}Mo produced by nuclear reactors and/or accelerators, methods based on sublimation, solvent extraction, and ion-exchange column chromatography have been examined and developed [2, 4–6]. However, according to the pharmaceutical affairs act, the extraction method using organic materials, the gel method using heavy metal elements, and the sublimation method can not be suitable and not be approved as ^{99m}Tc separation methods.

In this study, we developed a new method, the "technetium master milker (TcMM)" process, for separating ^{99m}Tc from ^{99}Mo and purifying the extracted ^{99m}Tc. The TcMM process was applied to low specific activity (LSA) ^{99}Mo, and the subsequent yield of ^{99m}Tc was evaluated. Consequently, we proposed a practical ^{99m}Tc generating process and system (^{99m}Tc generator) from ^{99}Mo produced in a reactor and/or accelerator.

2. Experiment

2.1 Preparation of ^{99}Mo

2.1.1 Using a reactor

The ^{99}Mo was generated by the ^{98}Mo(n,γ) reaction of natural isotopic Mo oxide ($^{nat}MoO_3$; 99.9% purity, made by Taiyo-Koukou Co., Tokyo, Japan) pellets, which were sintered from $^{nat}MoO_3$ powder (20 g per pellet) using the spark plasma sintering (SPS) method [7] at 550 °C for 10 min under a compressive force of 10-15 kN. Each $^{nat}MoO_3$ pellet, with a theoretical density (TD) of 80-85%, had a diameter of about 20 mm and a thickness of 16-17 mm. The pellets were irradiated by neutrons in a nuclear reactor (JRR-3 at the Japan Atomic Energy Agency, maximum neutron flux: 8.7-9.6× 10^{13} n/cm^2/s). The neutron irradiation of 15 MoO_3 pellets, sintered by the SPS method, with a total weight of 293.4 g (195.6 g Mo), lasted for 7 days. The generated ^{99}Mo had an activity of 2.99× 10^{12} Bq with a specific activity of 1.48× 10^{10} Bq/g for the ^{nat}Mo immediately after irradiation. The irradiated MoO_3 pellets were dissolved in 679 mL of 6 M NaOH solution, which was adjusted to 1 L by adding water. Subsequently, the Mo solution was prepared with a concentration of 200 g of Mo/L with neutral pH.

2.1.2 Using an accelerator

The ^{99}Mo was generated by the ^{100}Mo(γ,n) reaction of natural isotopic Mo oxide (^{nat}MoO, 99.99% purity, made by Kojundo Chemical Laboratory Co. Ltd., Japan) pellets, which were sintered from $^{nat}MoO_3$ powder (1.6–1.7 g per pellet) using the SPS method at 520-550 °C for 5 min under a compressive force of 5–6 kN. Each $^{nat}MoO_3$ pellet, with TD of 83-89%, had a

diameter of about 10 mm and a thickness of 5 mm. The pellets were stacked between gold foils (10 mm diameter × 0.02 mm thickness), which were used as a fluence monitor for bremsstrahlung photons. Each pellet stacked between the gold foils was enclosed in a quartz tube. The stacked samples in the quartz tube were irradiated by bremsstrahlung photons generated by a 2-mm-thick platinum converter and cooled with running tap water. The generated ^{99}Mo immediately after irradiation had a total activity of 1.59×10^{7} Bq with a specific activity of $1.37\text{-}3.48\times 10^{6}$ Bq/g for the ^{nat}Mo and $1.43\text{-}3.62\times 10^{7}$ Bq/g for the ^{100}Mo. Each irradiated $^{nat}MoO_3$ pellet was dissolved in 6 M NaOH of 3.8 mL with weak heating and the resulting Na_2MoO_4 solution with neutral pH was adjusted to 10 mL by adding water.

2.2 TcMM (Technetium master milker)

The TcMM process based on a newly discovered phenomenon, a general activated carbon (AC) has a peculiar characteristics to be able to adsorb ^{99m}Tc preferentially and completely, was developed to separate ^{99m}Tc from ^{99}Mo, and consisted of six steps. The TcMM process was applied to the irradiated $^{nat}MoO_3$ pellets, and the six steps for ^{99m}Tc separation from the irradiated $^{nat}MoO_3$ pellets were as follows, in which high purity common reagents were used:

(1) Dissolution of irradiated $^{nat}MoO_3$ pellets

The irradiated $^{nat}MoO_3$ pellets including ^{99}Mo were dissolved in a molar equivalent NaOH solution with weak heating. The resulting $Na_2Mo(^{99}Mo)O_4$ solution had neutral pH and a fixed volume of 1.0 L was obtained by adding water.

(2) Adsorption of ^{99m}Tc in the AC

The $Na_2Mo(^{99}Mo)O_4$ solution with a maximum volume of 1.0 L was poured into an AC column packed with activated carbon (4.5 g) at a flow velocity of 100 mL/min for 10 min to adsorb ^{99m}Tc onto the AC column. In a flow velocity ranging from 10 mL/min to 200 mL/min, the AC column worked sufficiently because a trace amount of ^{99m}Tc was preferentially and completely adsorbed to the activated carbon in comparison to an enormous amount of Mo.

(3) Removal of Mo(^{99}Mo) contaminants from the AC

The Mo(^{99}Mo) contaminant, which usually remains in the holes of the activated carbon particles during the second step, was removed by sequential water treatments. Firstly, 100 mL of water was flushed through the column at a rate of 50 mL/min to wash Mo out from the AC column. Secondly, 30 mL of 6.0 M NaOH was flushed through at a rate of 10 mL/min to remove Mo; and thirdly, 25 mL of water was flushed through at a rate of 10 mL/min to remove remaining Mo and any NaOH.

(4) Elution of ^{99m}Tc from the AC

In order to elute ^{99m}Tc collected in the AC column, 85 mL of water was flushed through the AC column at a rate of 10 mL/min and all the ^{99m}Tc adsorbed on the AC column was eluted as a weak alkaline solution.

(5) Removal of Na^+ ion in the eluted alkaline ^{99m}Tc solution

The solution was flushed through 5 cc of strong acid in an ion exchange resin (IER) and 6 g of activated alumina (AL). The Na^+ ion in the eluted ^{99m}Tc solution was captured by the IER

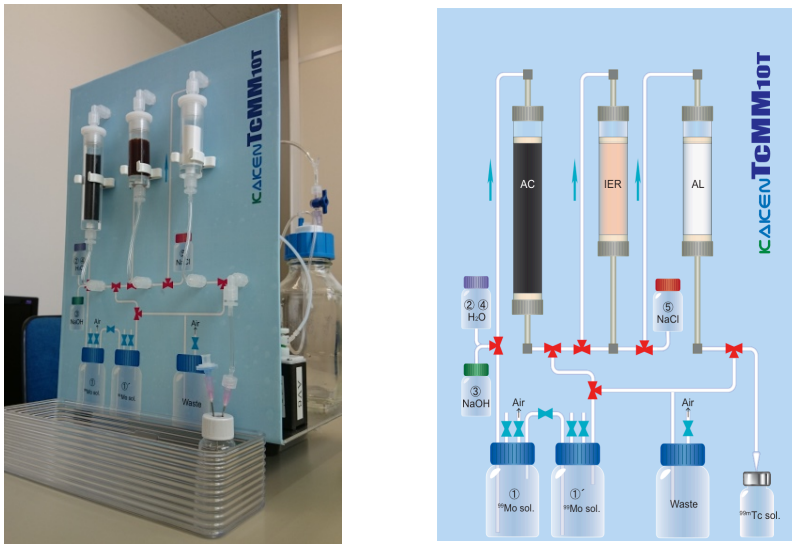
column and the ^{99m}Tc was caught in the AL column.

If the IER column was not used, the TcMM process was performed with a combined AC-AL column system with AL 12 g .

(6) Elution of ^{99m}Tc

Highly pure ^{99m}Tc was recovered from the AL column by flowing 10-20 mL of saline (0.9% NaCl solution) at a rate of 10 mL/min through the column. The resulting ^{99m}Tc had a concentration of 50-100 times that of the initial Mo (^{99}Mo) solution.

The TcMM ^{99m}Tc generator system is shown in Fig. 1 and the TcMM process is outlined in Fig. 2. The columns made by polypropylene (PP) or polyethylene (PE) resin were packed with AC and AL for the AC-AL process (Fig. 2 (a)) with an additional IER column for the AC-IER-AL process (Fig. 2(b)). The AC, AL, and IER can be described as follows.



10TBq type, AC-IER-AL columns **TcMM Flow line**

Fig. 1 TcMM System

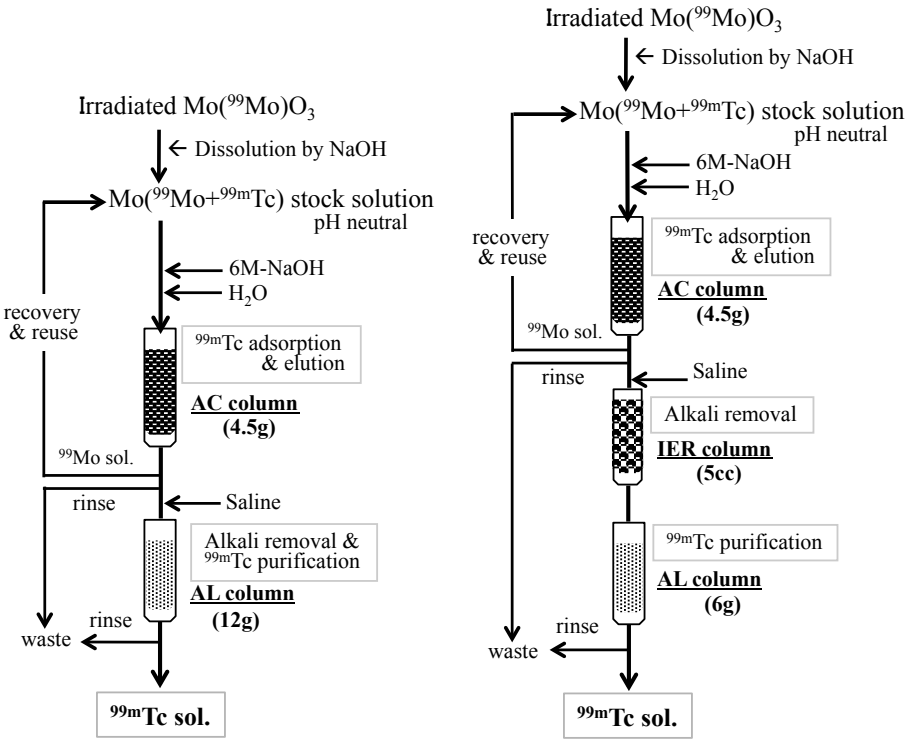


Fig. 2 TcMM Process

Activated carbon (AC)

In order to collect ^{99m}Tc present in a highly concentrated $Na_2Mo(^{99}Mo)O_4$ solution, the AC column was utilized by packing 4.5 g of AC in the column. The inside diameter and length of the column was 15.2 mm and 66 mm, respectively. Shirasagi-charcoal was used as the palm shell raw material, (particle size of 0.30-0.85 mm, made by Japan-Environment Chemicals Co., Osaka, Japan).

Activated alumina (AL)

The AL column was utilized to adsorb and purify the ^{99m}Tc collected from the $Mo(^{99}Mo)$ solution by removing trace amounts of $^{nat}Mo(^{99}Mo)$ and radioactive niobium as well as other impurities generated from the molybdenum stable isotopes. The column was made by packing 6 g of AL with an IER column or 12 g of AL without an IER column. The column had an inside diameter of 15.2 mm and lengths of 33 mm and 66 mm. The AL was made by MP Biochemicals (Santa Ana, CA, USA) with a particle size of 0.063-0.20 mm and a pH of 4.3 (acid alumina).

Ion exchange resin (IER)

A strong acid type IER was used to remove Na^+ from the ^{99m}Tc solution in the AC column with 5 mL of water containing a small amount of NaOH. The column had an inside diameter of 15.2 mm and a length of 28 mm. The IER was the DIAION SK H 1B made by Mitsubishi Chemical Co. with a particle size of 0.15 mm with pre-conditioning by HCl.

2.3 ^{99m}Tc purity and quality

The TcMM process was applied to ^{99}Mo produced by a reactor and an accelerator. The radiopharmaceuticals of ^{99m}Tc are explained below.

A NaCl concentration meter with measurement accuracy of 0.02% (TOA DKK MM-60R/CT-57101B, Tokyo, Japan), pH meter (TOA DKK RM-31P/ELP035) and Ge semiconductor detector (ORTEC GMX-20190-P-PLUS, Oak Ridge, TN, USA) were used, respectively, to measure the NaCl concentration, pH, and radioactivity and radiochemical purity of the collected ^{99m}Tc solution.

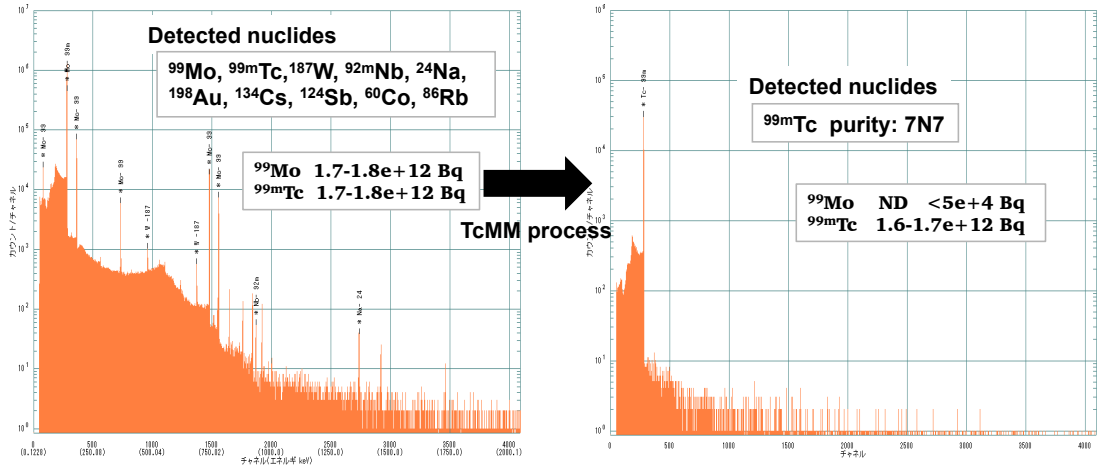
Several analytical methods were performed to confirm the chemical form and quality of the ^{99m}Tc recovered from the TcMM process. The analytical methods used were thin layer chromatography with γ-ray detector (γ-TLC, γ-mini GITA Star, Raytest, Strubenhardt, Germany), Cellulose Acetate film Electrophoresis (CAE), Reversed Phase-High Performance Liquid Chromatography, (RP-HPLC, Hitachi-L2130/Ratest-GABI Star, Tokyo, Japan and Strubenhardt, Germany with a Unison US-C18 column), and SPECT (Triumph SPECT4/CT, TriFoil Imaging Inc., Chatsworth, CA, USA) by labeling experiments using the conventional ^{99m}Tc generators. Radiopharmaceutical kits of MAG_3 (mercaptoacetylglycylglycylglycine), HM-PAO (hexamethylpropyleneamine oxine), MIBI (methoxyisobutylisonitrile), MDP (methylene diphosphonate), and Tetrofosmin, which were purchased from Nihon Medi-Physics and Fujifilm RI Pharma (Tokyo, Japan) were also used. Detail on the TcMM process conditions can be found in ref [8].

3. Results and discussion

Initial radioactivity of ^{99}Mo was at the TBq level. The ^{99m}Tc milking was performed once a day and this milking was repeated 10 times. As a result, the collection rate of ^{99m}Tc was 93.5% on average.

The recovery rate of ^{99m}Tc was not influenced by the radioactivity of ^{99}Mo or ^{99m}Tc in the 1×10^4-2×10^{12} Bq range, and a recovery rate of 90-98% was stably obtained. The production time of ^{99m}Tc was approximately net 30 min per batch influenced by the liquid volume of the Mo(^{99}Mo) solution.

The radiochemical purity of the collected ^{99m}Tc was 99.9999-99.99999% on average. The Mo (^{99}Mo) solution had many radioactive impurities such as radioactive niobium (^{92m}Nb, ^{95}Nb, and ^{96}Nb generated from Mo stable isotopes) and other radionuclides (^{60}Co, ^{187}W, ^{198}Au, etc.) generated from trace elements impurities in the $^{nat}MoO_3$ pellets. However, the ^{99m}Tc solution collected and purified by the TcMM process was free from such impurities including ^{99}Mo as shown in Fig. 3. However, these radioactive impurities were not found in the ^{99m}Tc solution collected by the TcMM process developed in this study. The 83-85% of radioactive Nb was distributed in the AC column and residual radioactive Nb was distributed in the IER and AL columns.



a) Mo(^{99}Mo) solution
50h elapsed after irradiation stop

b) Collected ^{99m}Tc solution: 4th milking

Fig. 3 γ-spectra of (n,γ)^{99}Mo and ^{99m}Tc collected by TcMM process.
Radiochemical purity of ^{99m}Tc was confirmed by measuring for a long time after ^{99m}Tc decay.

The γ-TLC and CAE analyses showed that the collected ^{99m}Tc exhibited a single peak at retention values (R_f) similar to those of $^{99m}TcO_4^-$ (pertechnetate), Furthermore, a single form of $^{99m}TcO_4^-$ was confirmed, as well as the form of ^{99m}Tc made from fission-^{99}Mo by enriched uranium.

The labeling experiments using radiopharmaceutical kits of ^{99m}Tc-tetrofosmin, ^{99m}Tc-MIBI, ^{99m}Tc-HMPAO, and ^{99m}Tc-MAG_3 of the ^{99m}Tc collected from the TcMM process showed TLC, RP-HPLC, and CAE profiles similar to those of ^{99m}Tc-labeled radiopharmaceuticals prepared with ^{99m}Tc solutions eluted from the conventional ^{99}Mo/^{99m}Tc generator system. The results mentioned above are explained in detail in a previous study [8-9].

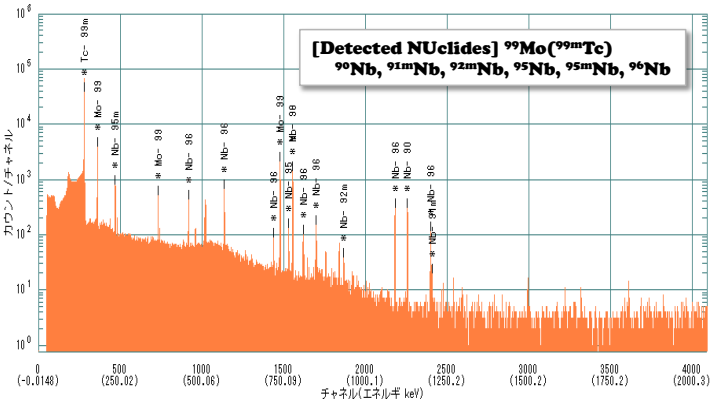
Based on the results of the above experiment, 293.4 g of $^{nat}MoO_3$ pellets (195.6 g as ^{nat}Mo, 47.1 g as ^{98}Mo) were irradiated with neutrons for 7 days, and the activity of ^{99}Mo produced was 2.99×10^{12} Bq in total just after irradiation, which corresponds to a specific activity of 1.48×10^{10} Bq/g for ^{nat}Mo. In Japan, this value is equivalent to the amount of ^{99m}Tc required in a few days.

The results of the TcMM process applied to ^{99}Mo produced using an electron linear accelerator was shown in our recent work [10] in detail, and will be briefly discussed here.

The chemical yield of ^{99m}Tc ranged from 83 to 99% over the four runs of the TcMM using $^{nat}MoO_3$ pellets irradiated with bremsstrahlung photons. In particular, the activity of ^{99}Mo in the solution collected by the TcMM process was below the detection limit of g-ray spectrometry. This was confirmed by the g-ray spectra of the $^{nat}MoO_3$ solution before the TcMM process and the solution collected by the TcMM process. ^{99m}Tc of >99.9999% purity was obtained in 0.9% saline solution at neutral pH by using the TcMM process. The radioactive impurities in (γ,n) reaction were also found (Fig. 4). The assembly of a TcMM process with an electron linear accelerator system was proposed based on the results [10].

Linac-(γ,n)^{99}Mo

$^{nat}MoO_3$ pellet Irradiated by Linac



Nuclides generated in Linac-irradiation $^{nat}MoO_3$

[main nuclear reactions]
^{97}Mo(γ,p)^{96}Nb
^{96}Mo(γ,p)^{95m}Nb&^{95}Nb
^{94}Mo(γ,pn)^{92m}Nb
^{92}Mo(γ,p)^{91m}Nb
^{92}Mo(γ,pn)^{90m}Nb

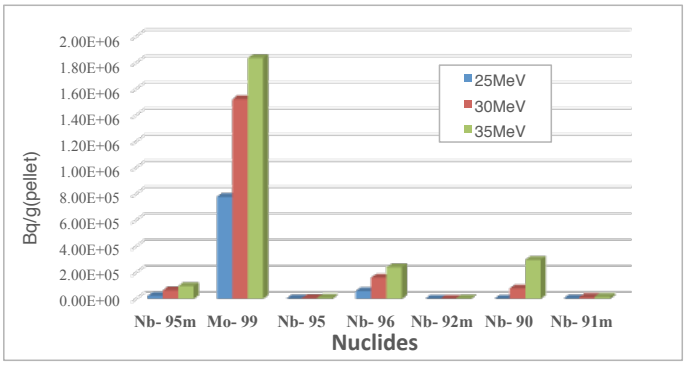


Fig. 4 Linac-(γ,n)^{99}Mo and impurity nuclides generated

Finally, the TcMM conditions of the AC-AL column process and/or the AC-IER-AL column process are summarized in Table-1. AC-AL process and AC-IER-AL process are nearly similar, but the ^{99m}Tc concentration rate using IER can be obtained higher than that of AC-AL process. By using the TcMM system, a highly concentrated pure ^{99m}Tc of kBq-TBq from a low specific activity ^{99}Mo can automatically be collected in a short time (<30min.), furthermore that can also be utilized as a ^{99m}Tc concentrator.

The role of the TcMM process developed in this work is shown as Kaken ^{99}Mo-^{99m}Tc Process in Fig. 5.

Table-1 TcMM conditions

TcMM type (TcMM process)	TcMM 10T (AC-AL)	TcMM<IER> 10T (AC-IER-AL)
amounts of ^{99}Mo	kBq-10TBq	kBq-10TBq
Mo solution	200g(Mo)/L	200g(Mo)/L
AC column	LH2c-AC 4.5g, Flow rate of Mo sol. 100mL/min 6M-NaOH 30mL ^{99m}Tc elute H_20 85mL	LH2c-AC 4.5g, Flow rate of Mo sol. 100mL/min 6M-NaOH 30mL ^{99m}Tc elute H_2O 85mL
IER column	-----	DIAION(SK1B H) 5cc
AL column	MP-acid AL 12g Saline 20mL	MP-acid AL 6.0g Saline <10mL
^{99m}Tc milking time	≤30min	≤30min
^{99m}Tc collected volume concentration rate radiochemical purity	20mL 50 folds >99.99%	≤10mL 100 folds or more >99.99%
wastes per batch	Liquid: 250 mL Solid: 17g	Liquid: 250 mL Solid: 16g

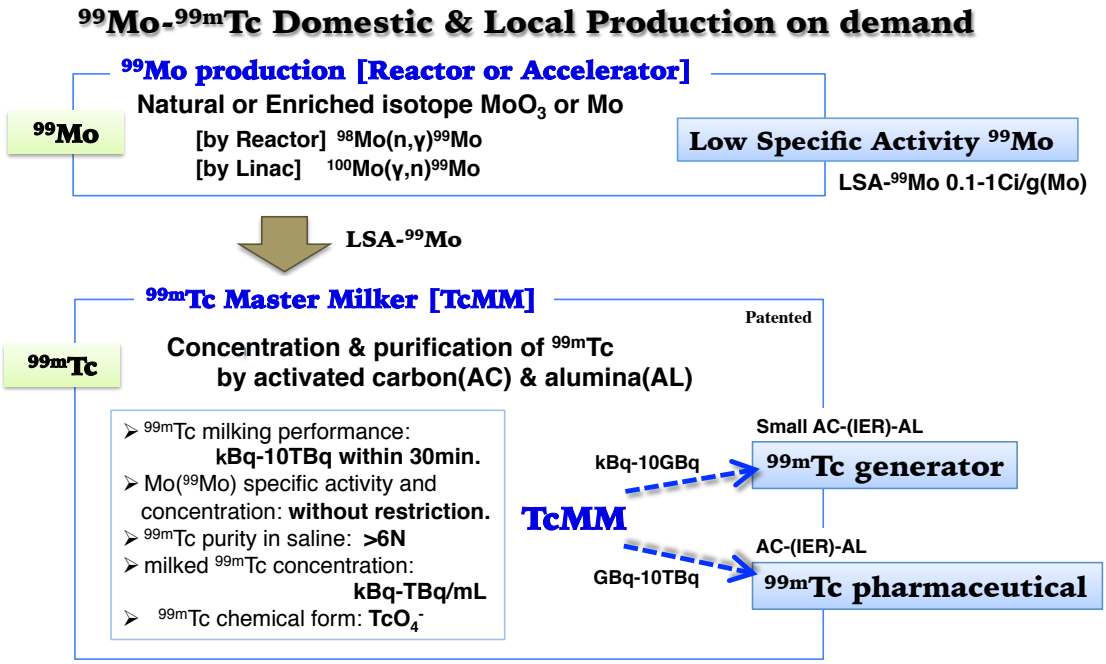


Fig. 5 Kaken ^{99}Mo-^{99m}Tc Process

4. Conclusions

To separate ^{99m}Tc from ^{99}Mo and to purify the ^{99m}Tc, the TcMM process was developed and presented in detail. Using the TcMM process, ^{99m}Tc was separated and purified from $1\times 10^{4} \sim 2\times 10^{12}$ Bq of ^{99}Mo, which was produced by a reactor and/or accelerator. The TcMM process produced highly pure ^{99m}Tc (radiochemical purity of >99.99%) with a chemical yield of 90% on average. The activity of ^{99}Mo in the solution collected by the TcMM process was extremely low. The TcMM process also produced high quality $^{99m}TcO_4^-$ (pertechnetate) to satisfy the pharmaceutical affairs act. It was found that ^{99m}Tc can be supplied domestically and locally on demand by the TcMM process after production of ^{99}Mo by the ^{98}Mo(n, γ) in reactor and/or ^{100}Mo(γ,n) reactions in electron linear accelerator.

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