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Comparison of standard and modified $^{99}Mo/^{99m}Tc$ radionuclide generators

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Abstract
^{99m}Tc is the most widely used radionuclide in medical diagnostics and typically obtained from high-specific-activity (HSA) ^{99}Mo produced in nuclear reactors. However, recent reactor shutdowns have led to supply shortages and prompted efforts to implement alternative production methods. One promising approach is neutron activation of ^{98}Mo, which yields low-specific-activity (LSA) ^{99}Mo. Since conventional Al_2O_3-based $^{99}Mo/^{99m}Tc$ generators are designed for HSA ^{99}Mo, adaptations are required for LSA ^{99}Mo usage. In this study, we evaluated the feasibility of modifying existing Al_2O_3-based $^{99}Mo/^{99m}Tc$ generators for use with LSA ^{99}Mo, anticipating production at the planned high brilliance neutron source (HBS) at Forschungszentrum Jülich. Key modifications included adjustments to the amount of Al_2O_3 on the column and the elution volume of ^{99m}Tc to enhance ^{99}Mo adsorption and ^{99m}Tc elution efficiency. The performance of the modified "mock-up" system was compared with a standard clinical generator. The results demonstrated that only minor modifications are required for LSA ^{99}Mo to be effectively utilized in a future generator, with elution efficiencies remaining comparable to conventional generators, while maintaining parameters like size, form, number, activity of the individual generator comparable. However, ^{99}Mo breakthrough levels exceeded regulatory limits, highlighting the need for further optimization. Nevertheless, these findings support the feasibility of using LSA ^{99}Mo in clinical applications with minimal changes to existing infrastructure.

Keywords Technetium-99 m · Molybdenum-99 · Radionuclide generators · Adsorbent · Alumina column · Neutron activation · Medical radionuclide production

Introduction

Aim of this work

The aim of this work is to demonstrate it is feasible to develop a separation procedure that uses not more than 100 mg of Mo. We consider that 100 mg of low-specific-activity (LSA) ^{99}Mo is sufficient for commercial generators (see below). This will allow that the established generators can be modified without drastically changing key parameters like column size, generator size or elution volume. This shall ensure that the current system of generator handling and distribution can remain mainly unchanged. To achieve this, we developed a modified Al_2O_3-based "mock-up" generator system in a laboratory scale. The modifications of the existing generator system for proper clinical use are planned for the future. We compare our mock-up system with a conventional design, focusing on Mo adsorption characteristics, elution efficiency, and regulatory compliance.

1.2. $^{99m}Tc/^{99}Mo$ nuclide generators in general.

Technetium-99 m (^{99m}Tc) is the most widely used radionuclide in nuclear medicine due to its short half-life (6 h) and ideal gamma emission energy (140.5 keV) for single photon emission computed tomography (SPECT) imaging [2,

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3]. It is obtained from the decay of molybdenum-99 (^{99}Mo, $T_{1/2}=66$ h), which is typically produced in nuclear reactors and supplied via radionuclide generators. Conventional ^{99}Mo/^{99m}Tc generators rely on high-specific-activity (HSA) ^{99}Mo, which is separated from the fission products of highly-enriched uranium-235 (^{235}U), and adsorbed onto aluminum oxide (Al_2O_3) separation columns [4]. Roughly 5–10 g of Al_2O_3 is used in this solvent extraction technique, depending on the total activity of ^{99}Mo [5]. The ^{99m}Tc formed during decay of ^{99}Mo can then be eluted with physiological saline solution (0.9% NaCl). A generator with 20 GBq ^{99}Mo and an elution scheme with 2 "milkings" each day provides roughly a total of 160 GBq over a lifespan of 7 days [6].

An established process for the separation of fission-based ^{99}Mo from ^{235}U is the ROMOL-99 process that has been developed at the Radio-Isotope department in Dresden-Rossendorf [1]. The basic principles of this process are seen in Fig. 1.

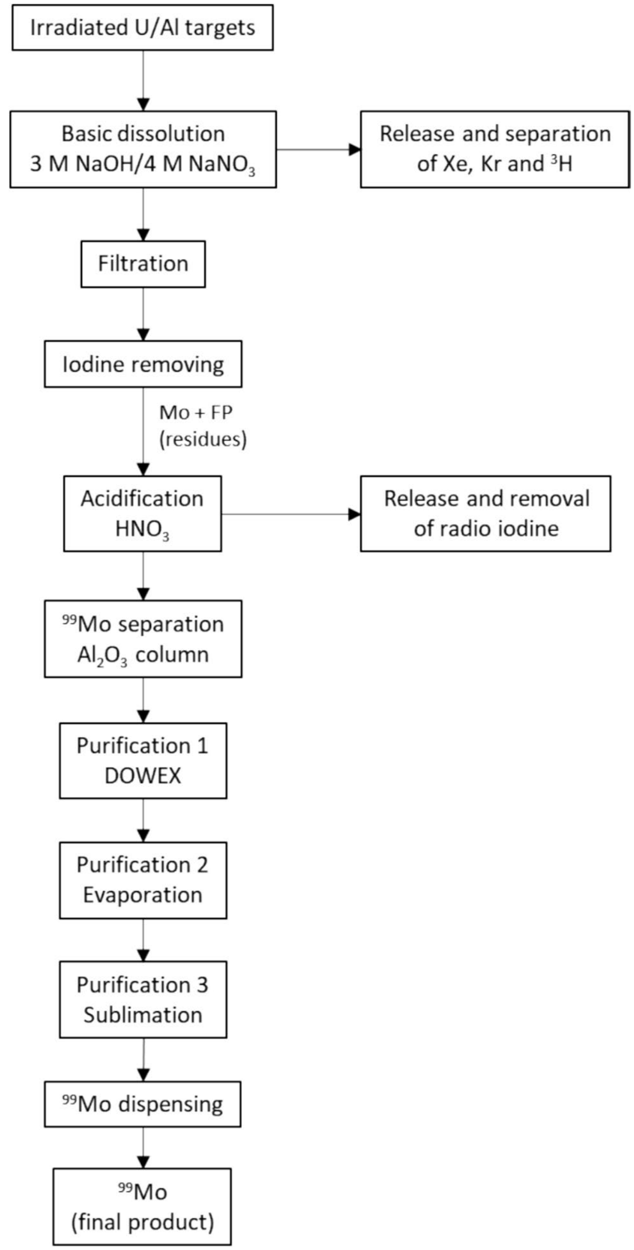

Fig. 1 Process flow scheme of the ROMOL-99 process to separate fission-based ^{99}Mo for production. Adapted from [1]

Over the past 2 decades, increasing efforts have been directed towards alternative production methods for ^{99}Mo as shown in Fig. 2. [1, 7–11] This shift gained momentum following the 2008 global ^{99}Mo supply crisis, when 4 of the 6 major production reactors temporarily ceased operation. Compared to nuclear reactor produced ^{99}Mo with HSA (high specific activity) – schemes 1, 2 & 3 in Fig. 2 in Sect. "Generation of 99Mo via neutron activation and separation methods of 99Mo/99mTc", the other schemes will yield LSA (low specific activity) ^{99}Mo. The general advantage of neutron activation of Mo is that it eliminates the need for uranium targets and their associated nuclear waste. However, unlike reactor-based HSA ^{99}Mo production, activation produces low-specific-activity (LSA) ^{99}Mo, requiring significantly larger Mo quantities for equivalent ^{99m}Tc yields. One possibility to optimization is to use Mo targets enriched in stable isotopes ^{98}Mo or ^{100}Mo (schemes 2, 4 and 5). Scheme 5 (on site production) cannot be applied within the established generator concept. Schemes 2 and 4 will generally increase the yield, but we consider this not very practicable because it would be necessary to reprocess the irradiated material.

Generation of ^{99}Mo via neutron activation and separation methods of ^{99}Mo/^{99m}Tc

In this work we consider a scheme like 1 but with relying on natural Mo and the irradiation epithermal neutrons. The decrease in yield to 20% (changing from ^{98}Mo to ^{nat}Mo) can be compensated by the enhanced cross section of epithermal neutrons.

The "high-brilliance neutron source (HBS)" system, currently under development at Forschungszentrum Jülich aims to generate ^{99}Mo through a compact accelerator-driven neutron source [12].

A distinctive feature of ^{99}Mo production at HBS will be the use of neutron fluxes in the epithermal region. We expect a thermal neutron flux of around 9.5 10^{12} N/s·cm^2 and an epithermal neutron flux of 3.6 10^{11} N/s·cm^2 with a lead reflector on the HBS system. Since the epithermal neutron cross-section for the ^{98}Mo neutron capture reaction (6.7 barn) is about 50 times higher than the thermal neutron cross-Sect. (0.13 barn) (Fig. 3) [8], epithermal neutron activation of natural or enriched ^{98}Mo can significantly enhance the yields and specific activities of ^{99}Mo produced via ^{98}Mo(n,γ)^{99}Mo reaction [13, 14].

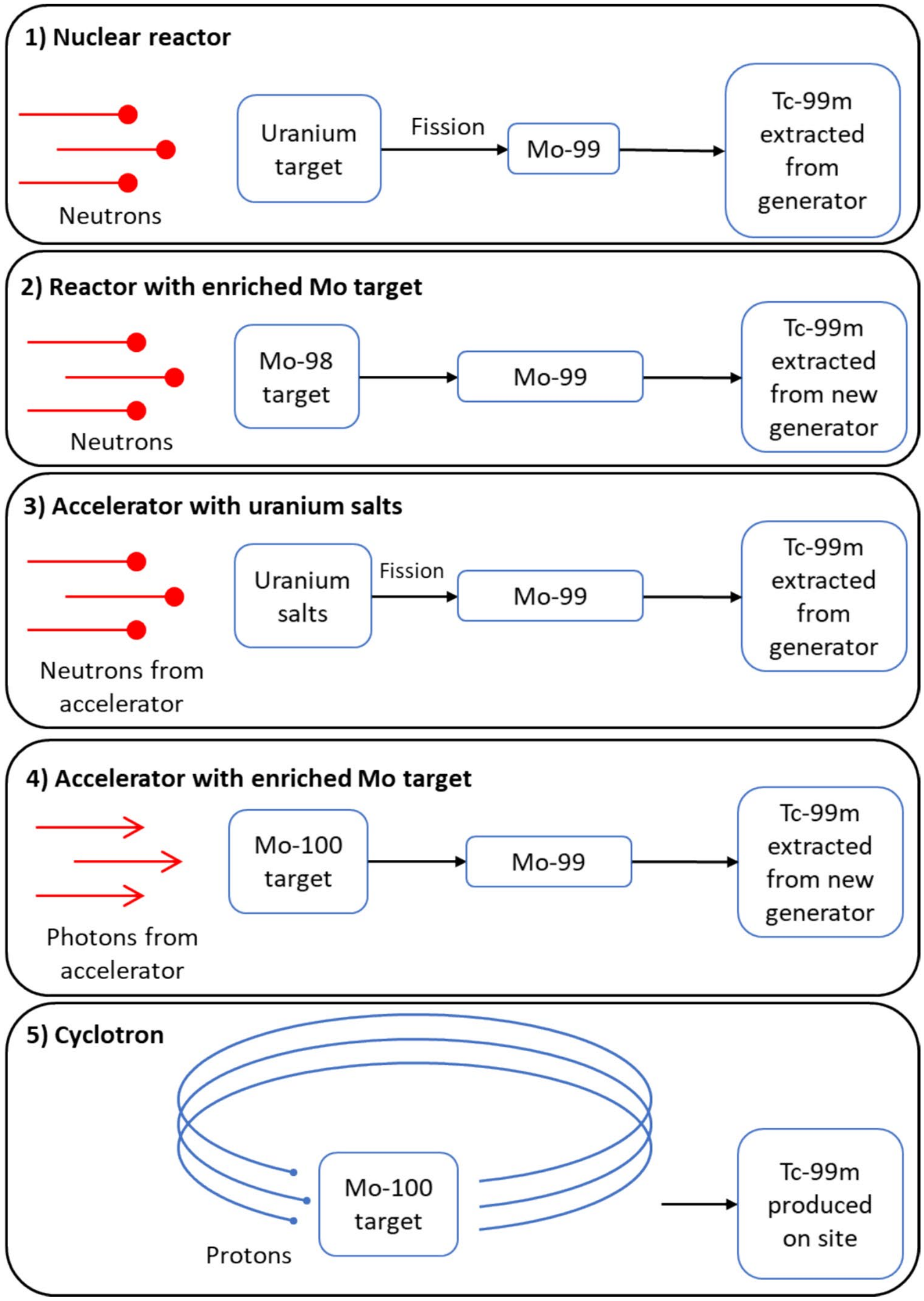

Fig. 2 Scheme of the several production processes of ^{99}Mo. Adapted from [7]

Furthermore, in relation to activation, an effective cross section of up to 0.5 barn has already been achieved in the work of Matyskin and co-workers with epithermal neutrons, allowing specific activities of 5 GBq/g for natural Mo. It is aimed at the HBS based accelerator system to reach a specific activity of 5 GBq/100 mg of Mo. 5 GBq is currently the minimum activity of a commercial generator. Therefore, we chose 100 mg of irradiated Mo as the reference value of our modified "mock-up" generator system [12, 15].

However, the specific activity of LSA ^{99}Mo (~ 1–10 Ci/g) [16], thus obtained is still several orders of magnitude below that of reactor-produced HSA ^{99}Mo (> 1,000 Ci/g) [16], which necessitates modification of existing Al_2O_3-based ^{99}Mo/^{99m}Tc generators to maintain efficiency while ensuring compliance with regulatory and practical limits. In this regard, key challenges include i) maintaining generator size within practical limits for hospital use while ensuring compliance with radiation protection regulations, ii) achieving elution volumes that align with the clinical workflow, iii)

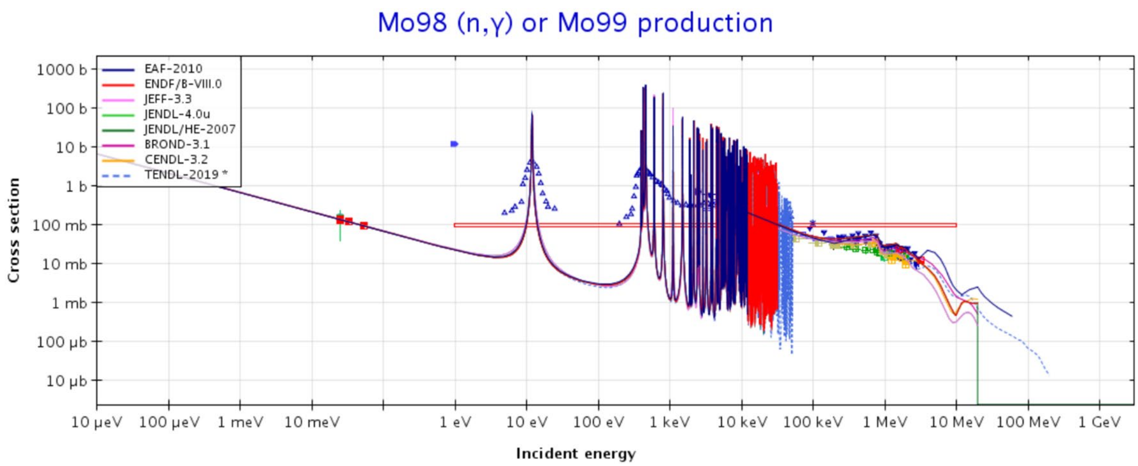

Fig. 3 Neutron activation calculations for the ^{98}Mo(n,γ)^{99}Mo reaction [18]

ensuring that Mo breakthrough (MBT) meets regulatory standards, which specify maximum allowable ^{99}Mo activity levels in the eluate of < 0.015% (United States Pharmacopeia) or < 0.1% (European Pharmacopeia) with respect to the activity of eluted ^{99m}Tc [17] and (iv) the regulatory of the respective pharmaceutical laws.

To address these issues, several alternative ^{99}Mo/^{99m}Tc separation methods have already been investigated. Ramadan et al. [19] evaluated nano $Zr(OH)_4$ gels as sorbent materials, achieving ^{99}Mo adsorption capacities tenfold higher than with Al_2O_3 while maintaining ^{99m}Tc elution efficiencies of ~ 83% and ^{99}Mo breakthrough of only 0.005%.

Another approach by Chattopadhyay et al. [20] utilized solvent extraction with methyl ethyl ketone followed by column chromatography with Al_2O_3 yielding 78–90% of the ^{99m}Tc activity with minimal ^{99}Mo contamination of 10^{-4}%.

Ion-exchange chromatography using Dowex-1-×8 resin and tetrabutylammonium bromide (TBAB) elution followed by column chromatography with Al_2O_3 enabled 90% ^{99m}Tc recovery with similarly low ^{99}Mo contamination (< 10^{-4}%) [21].

Thermochromatographic separation has also been explored, particularly using enriched [^{100}Mo]MoO_3 samples which can be almost completely recycled after the process. Studies by Kawabata et al. and Nagai et al. [22, 23] demonstrated that ^{99m}Tc yields of around 90% could be achieved with multiple elutions.

These separation procedures that have been described in literature exhibit stronger adsorption of Mo and/or a higher specific capacity compared to the common generators using Al_2O_3 with an adsorption capacity of Mo of < 20 mg Mo/g column material. The work of Ramadan et al. shows that alternative other column materials can achieve significantly higher adsorption capacities. However, within the aim of this work, taking into account individual factors such as optimizing the irradiation conditions, we can have a greater influence on the total amount of ^{99}Mo generated. To accomplish this, a more efficient and faster separation method involving Mo sample dissolution, adsorption and elution can lead to a relocation of the end of bombardment, which can achieve higher total activities of ^{99}Mo. An important factor is the Al_2O_3 column with an optimized amount of column material (~ 5 g).

Despite these promising results, a key disadvantage of all alternative separation methods is that they would necessitate the design of new generator systems and, consequently, large investments into infrastructure. As such this study evaluated the feasibility of modifying existing Al_2O_3-based ^{99}Mo/^{99m}Tc generators for use with LSA ^{99}Mo produced by epithermal neutron activation at the HBS system. We hypothesize that optimized irradiation conditions could yield LSA ^{99}Mo with specific activities sufficient to adapt existing ^{99}Mo/^{99m}Tc generator systems with only minor modifications, ensuring a stable and sustainable supply of ^{99m}Tc for medical applications while maintaining compatibility with current clinical infrastructure.

Considering the utilization of epithermal neutrons form the HBS, an optimization of the current generator system with Al_2O_3 can be might be sufficient to obtain LSA generators, even with natural Mo as a target material. Taking into account the practical challenges to establish new distribution infrastructure, we consider this to be the most promising strategy to reach an equal specific activity of at least 5 GBq/100 mg for ^{99}Mo.

Materials and methods

Materials

The Al_2O_3 powder used as column material was obtained from ‘J.T. Baker’ (Batch number ‘0000288122’). Ammonium heptamolybdate tetrahydrate used as molybdenum source was obtained from ‘Merck’ (CAS-No. 12054–85–2). Chromatography columns, with a length of 10.5 cm and a diameter of 1 cm were obtained from ‘ThermoScientific’.

Irradiation and ^{99}Mo preparation

To simulate LSA ^{99}Mo production as expected from the HBS system, ammonium heptamolybdate tetrahydrate as a model compound was irradiated at the TRIGA research reactor at the Johannes Gutenberg University Mainz. The irradiation was performed for 40 min at a neutron flux of $1.7 \cdot 10^{12}\ cm^{-2}\ s^{-1}$. An amount of 1.5 g of ammonium heptamolybdate, which results in the amount of 815 mg of Mo, was irradiated. Under these conditions, a very low specific activity (~ 0.04 mCi/g) is obtained.

Four our mock-up experiments, we each used 100 mg of this to resemble the samples which are expected to be finally obtained at the HBS, in which 100 mg Mo are expected to show a specific activity of 5 GBq/100 mg of Mo, see above [15, 24].

Measurement and analysis

^{99}Mo and ^{99m}Tc activities were measured using a Ge(Li) semiconductor gamma detector and analyzed with Gamma-Vision software. Samples from the conventional generator system were measured using dose calibrators for high activity readings or (after partial decay of ^{99m}Tc) a high purity germanium (HPGe) detector and analyzed with Gamma-W software.

The general procedure for dissolution of the irradiated Mo samples, column loading and elution of ^{99m}Tc from the modified “mock-up” generator system is summarized and Fig. 4.

For each experiment a total of 100 mg of irradiated Mo was dissolved in a solution of $NaOH/HNO_3$ (pH 1). The NaOH was added to dissolve Mo in the form of sodium molybdate (Na_2MoO_4) while addition of HNO_3 was used to lower the pH to 1, ensuring optimal adsorption onto the Al_2O_3 columns. The dissolved Mo was then loaded onto columns containing 5.0 g of Al_2O_3 and ^{99m}Tc was eluted with 0.9% saline solution in 5 ml fractions. The eluate was collected in 10 mL vials and used for subsequent activity measurements, where the ^{99m}Tc activity and the ^{99}Mo breakthrough were investigated and determined. The general setup of the experiments with the adapted Al_2O_3 columns is exemplified in Fig. 5, where experiments were performed to determine the ideal amount of Al_2O_3 for the maximum Mo adsorption capacity.

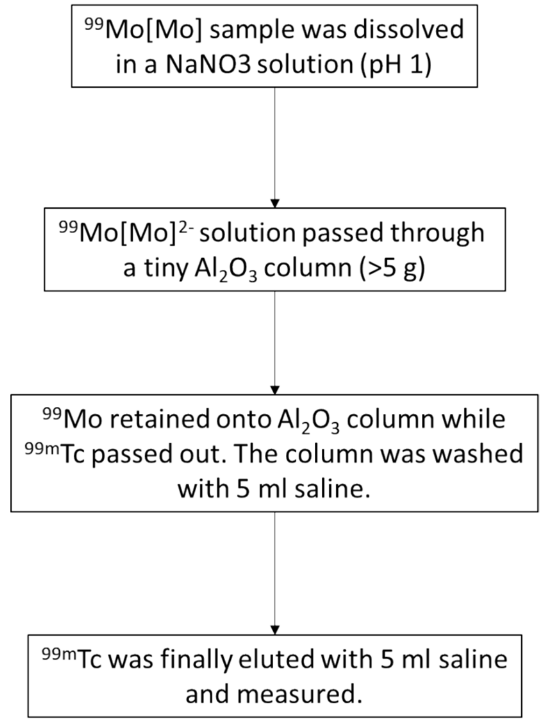

Fig. 4 General procedure for column loading and elution of ^{99m}Tc from the modified “mock-up” generator system

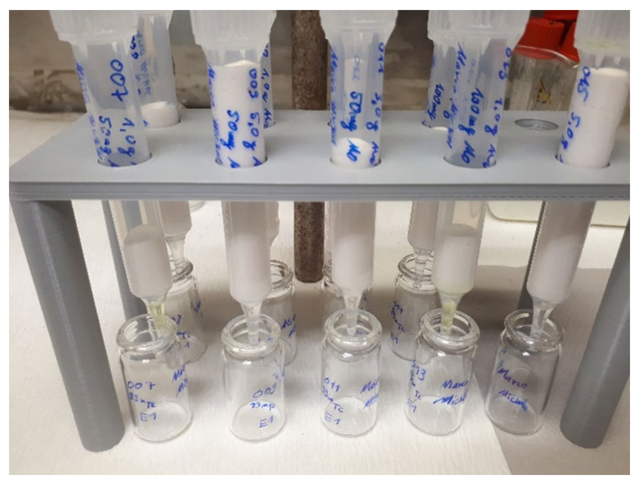

Fig. 5 General setup of the experiments with the modified Al_2O_3 columns. 3 times (at 24-h intervals) using 5 ml of saline solution and the elution efficiency was determined by comparing the measured ^{99m}Tc activity in the eluate with the expected decay-corrected activity on the column

Radionuclide generator experiments

Determination of elution efficiency

Elution efficiency was determined using 3 identical Al_2O_3 columns, loaded with 100 mg of irradiated Mo. Each column was eluted with 5 mL of 0.9% saline solution, and the collected eluates were analyzed for ^{99m}Tc activity. The elution efficiency was then determined by comparing the measured ^{99m}Tc activity in the eluate with the expected activity on the column based on calculated decay-corrected values. The elution process was repeated three times at 24-h intervals. After this period the ^{99m}Tc activity on the column reaches ~ 93% of the ^{99}Mo activity due to 4 half-lives of ^{99m}Tc had passed.

Determination of elution profile

To evaluate the elution profile, 3 identical Al_2O_3 columns loaded with 100 mg of irradiated Mo were subjected to sequential elutions using 2 mL fractions of saline solution, repeated 10 times per elution cycle at 24-h intervals. The collected eluates were analyzed for their ^{99m}Tc activity, and the percentage elution efficiency was calculated relative to the expected activity remaining on the column.

^{99}Mo breakthrough measurements

^{99}Mo breakthrough was assessed by eluting an Al_2O_3 column loaded with 100 mg of irradiated Mo every 24 h over 5 days using 5 mL of 0.9% saline solution. The activity of ^{99}Mo in each eluate was measured and compared to the total amount of ^{99}Mo adsorbed onto the column. The breakthrough percentage was calculated by determining the ratio of ^{99}Mo activity in the eluate to the initial activity loaded onto the column.

Decay curve of ^{99m}Tc eluate

To confirm the expected radioactive decay behavior of the eluted ^{99m}Tc, a complete decay curve was recorded over three weeks, covering approximately 10 half-lives of the parent ^{99}Mo isotope. A sample containing approximately 100 MBq of ^{99m}Tc was measured at multiple time points. Early measurements (first 48 h) were performed using a dose calibrator, while subsequent measurements were conducted using a HPGe detector for enhanced precision.

Results and discussion

Optimization of the Al_2O_3 column system for ^{99}Mo adsorption

Modifications to the generator system focused on optimizing Mo adsorption on the Al_2O_3 column while ensuring efficient elution of ^{99m}Tc. The primary objective was to achieve these improvements with minimal deviation from conventional radionuclide generator designs to maintain practical applicability. Through a series of initial experiments, an Al_2O_3 amount of 5.0 g Al_2O_3 per column was found to be optimal for maximizing Mo adsorption in the system as shown in Table 1. In these experiments, the activity of ^{99}Mo that was contained in a first extraction with NaCl solution (5 mL) was compared to the total activity of ^{99}Mo on the column (see Table 1). The data indicate that with 2 g of Al_2O_3, the column capacity is clearly surpassed while when 5 g of Al_2O_3 are used, less than 1% of the total ^{99}Mo activity is found in the first elution (following elutions show less activity, see below).

To evaluate the performance of the "mock-up" Al_2O_3-based ^{99}Mo/^{99m}Tc generator, additional experiments were conducted to determine elution efficiency, elution profiles, and minimize ^{99}Mo breakthrough levels.

Elution efficiency and elution profile of ^{99m}Tc in the modified "mock-up" generator system

An elution curve of ^{99m}Tc was investigated to determine the optimal elution volume to capture the highest possible activity and to determine the elution efficiency of the adapted system. Therefore, experiments were performed with 3 columns of the same set-up, where elution was carried out a total of 3 times at an interval of 24 h. This was done because it can be assumed that after 24 h ^{99}Mo and ^{99m}Tc are in equilibrium. The activity of ^{99}Mo was measured after adsorption on the column and the expected activities after 24, 48 and 72 h respectively were calculated. The ^{99}Mo activity obtained in

Table 1 Different Al_2O_3 amounts and the respective ^{99}Mo activity ratios of the first elution step before further optimizations of the provided column generators in this work

Amount of Al_2O_3 [g]	^{99}Mo activity in first NaCl elution [%]
2.0	5.0
2.5	4.7
3.0	2.5
3.5	1.0
5.0	0.5

this way also corresponded to the expected ^{99m}Tc activity on the column in the efficiency calculations. After elution with 5 ml of the saline solution, the ^{99m}Tc activities of the eluate were compared with that expected on the Al_2O_3 column and the efficiency was thus determined. The received data for the elution efficiency are shown in Fig. 6. As shown in Fig. 6, on average, 80–90% of the ^{99m}Tc activity, which was expected to be on the column after $^{99}Mo/^{99m}Tc$ activity equilibrium, was successfully eluted from the column. A slight decrease in elution efficiency was observed after repeated elutions, but the efficiency remained above 80% throughout the experiments. For the experiments to determine the elution curve of ^{99m}Tc, 3 Al_2O_3 columns were prepared with an adapted system and these were washed 10 times each with 2 ml of saline solution three times at 24 h intervals. The eluates were measured for their ^{99m}Tc activity and the percentage ratio to the expected activity on the column was calculated. The data from the elution curve of ^{99m}Tc from the modified "mock-up" Al_2O_3 radionuclide generator is shown in Fig. 7. These elution curves determined by sequential elution with 2 ml fractions indicated that the majority of ^{99m}Tc activity (~80%) was eluted within an elution volume of 6 ml. However, it seems that the elution efficiency shown in Fig. 6 with a continuous flow is somewhat higher (~80–85% in 5 ml). Both elution schemes provided relevant ^{99m}Tc activities, while maintaining a manageable elution volume.

^{99}Mo breakthrough in the "mock-up" generator system

Breakthrough of ^{99}Mo into the eluate was assessed over a period of 5 days. As shown in Fig. 8, the average ^{99}Mo breakthrough into the eluate was 0.35%, with variations depending on the time of elution. Due to the dead volume of the column, very low ^{99}Mo breakthrough was observed during the first elution 24 h after column loading. The highest breakthrough value (~0.8%) was observed after 48 h. However, breakthrough levels gradually decreased over subsequent elutions, reaching approximately 0.25% after multiple elution cycles as shown in Fig. 8. Despite this reduction, breakthrough values remained above the European Pharmacopoeia (EuPharm) limit of < 0.1% for medical use, which require more experiments for further optimization [17].

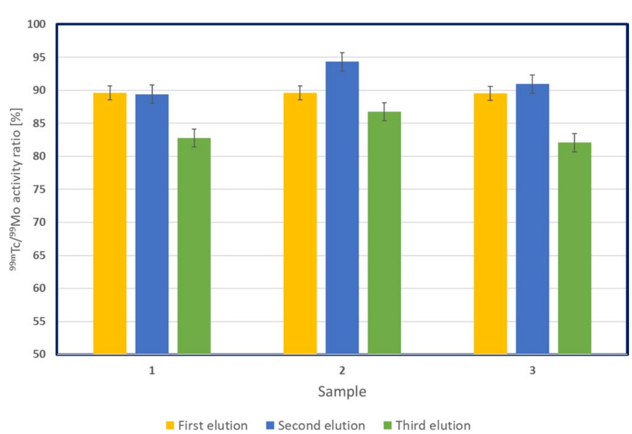

Fig. 6 Determination of the elution efficiency of ^{99m}Tc from the "mock-up" generator system. Each column was eluted

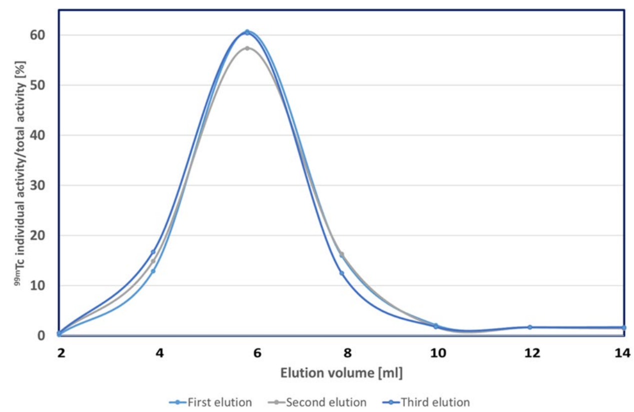

Fig. 7 Representative elution curves of ^{99m}Tc from the "mock-up" generator system. 3 elution cycles with 10 successive 2 ml fractions of saline solution per cycle were performed at 24-h intervals and the elution efficiencies for each fraction were plotted as a function of the total elution volume

Comparison with conventional $^{99}Mo/^{99m}Tc$ generators

To assess the practical viability of the modified system, its performance was compared with that of a conventional Al_2O_3-based $^{99}Mo/^{99m}Tc$ generator at the University Hospital Cologne. Key parameters, including ^{99}Mo breakthrough, elution volume, and elution duration, are summarized in Table 1.

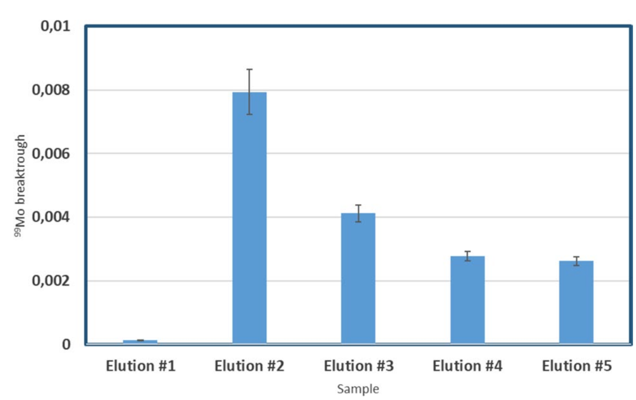

Fig. 8 Determination of ^{99}Mo breakthrough in the "mock-up" generator system. Elutions were performed every 24 h over 5 days using 5 ml of saline solution per elution

Table 2 Comparison of the data from a conventional ^{99}Mo/^{99m}Tc radionuclide generator with the data obtained using the modified system and goal that should be reached for an actual commercial modified generator system

	Conventional generator system	"Mock-up" generator	Modified generator system (goal)
^{99}Mo breakthrough	< 1 ppm	~ 0.2–0.3%	(< 0.1%)
Elution volume	5 ml	5–7 ml	(5 ml)
Elution duration	1–2 min (under vacuum)	5–7 min	(2 min)

The conventional generator exhibited very low ^{99}Mo breakthrough (< 1 ppm, ~ 40 Bq), well below the 0.1% regulatory limit, whereas this modified system showed higher breakthrough (0.2–0.3%), requiring further refinement. The elution volume remained almost consistent (5–7 ml) between both systems, confirming that the modifications did not impact this parameter. In addition, the "mock-up" system required slightly longer elution times (5–7 min vs. 1–2 min under vacuum), but this difference should be negligible for practical applications (Table 2).

A complete decay curve of ^{99m}Tc activity of the conventional generator system was recorded over a period of 3 weeks, covering approximately ten half-lives of ^{99}Mo. The obtained data Fig. 1 in Supplementary information, confirmed that the measured decay behavior follows the known half-lives of ^{99m}Tc (6 h) and ^{99}Mo (66 h). Early high-activity measurements (first 48 h) from a dose calibrator were consistent with later HPGe detector measurements, confirming the accuracy of the readings.

Conclusion and outlook

The findings of this study demonstrate that the "mock-up" Al_2O_3-based radionuclide generator system is highly promising for accommodating LSA ^{99}Mo produced via epithermal neutron activation. When comparing the performance of the modified system with a conventional ^{99}Mo/^{99m}Tc radionuclide generator, key parameters such as elution efficiency, elution volume, and elution duration were found to be at comparable levels, even with a likely increase in the amount of column material. This suggests that only minor modifications to the established Al_2O_3 generator system are necessary for its adaptation to the planned HBS production route for ^{99}Mo. However, ^{99}Mo breakthrough remains higher than the regulatory limit of 0.1%, currently ranging between 0.2 and 0.3%. This indicates that further optimization of column material quantity and chemical conditions – such as solvent selection and Mo adsorption behavior – will be necessary to reduce breakthrough to acceptable levels. This will be done in upcoming experiments with minimal change to the elution column, maintaining the overall mass and volume of the columns.

In addition, further activity calculations and optimization of the irradiation conditions are required to achieve the target activity of 5 GBq ^{99}Mo per generator necessary for clinical applications. These investigations are ongoing as part of the collaborative 99MoBest project, which aims to improve the specific activity of ^{99}Mo and enhance the adsorption capacity of Al_2O_3 columns. In this study, currently a calculated specific activity of 0.7 GBq per 100 mg ^{99}Mo was achieved. By incorporating the discussed optimization factors-specifically, increasing the specific activity of ^{99}Mo and enhancing the adsorption properties of the Al_2O_3 column-it is expected that the target of 5 GBq per generator can be realized while maintaining compatibility with existing generator infrastructure.

Moving forward, our efforts will focus on i) reducing ^{99}Mo breakthrough by refining the column's chemical environment and exploring alternative solvent conditions, ii) optimizing irradiation conditions to maximize the specific activity of neutron-activated ^{99}Mo, and iii) enhancing Mo adsorption on Al_2O_3 through targeted modifications in column composition and material properties. Also in the next steps, a vacuum assisted setup will be used to obtain comparable conditions as are used in commercial generators (see Sect. "Comparison with conventional 99Mo/99mTc generators").

These refinements will help to ensure that LSA ^{99}Mo produced via epithermal neutron activation can be efficiently utilized in clinical settings using only minor modifications to the current generator system. The successful implementation of this approach would provide a sustainable and reliable production pathway for ^{99}Mo, helping to mitigate global supply challenges and strengthen the long-term availability of ^{99m}Tc for diagnostic nuclear medicine.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10967-025-10423-5.

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Declarations

Competing interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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