A semi-automated module for the separation and purification of $^{99m}$Tc from simulated molybdenum target

Przemysław Koźmiński¹ · Magdalena Gumiela¹ · Rafał Walczak¹ · Kamil Wawrowicz¹ · Aleksander Bilewicz¹

Received: 6 February 2021 / Accepted: 1 April 2021 / Published online: 27 April 2021
© The Author(s) 2021

Abstract

A semi-automated purification module for the cyclic separation of $^{99m}$Tc was designed for production of $[^{99m}\text{Tc}]\text{TcO}_4^-$ from $\gamma$ irradiated $^{100}$Mo target. The separation process was carried out by using a 3-column purification system and the final product, $[^{99m}\text{Tc}]\text{TcO}_4^-$, was obtained in a total volume of 7 mL. To confirm proper separation achieved for $^{99m}$Tc, a radiolabeling procedure using DTPA chelator was performed. The radiochemical purity was higher than 95%, which meets the strict radiopharmaceutical requirements. The yielded $^{99m}$Tc can be separated with high efficiency from Mo in a quick and repeated way. Loss of $^{99m}$Tc radioactivity during such a three-column separation process was not larger than 10%.

Keywords AnaLig® Tc-02 · $^{99m}$Tc · Separation · Radiopharmaceutical

Introduction

The radionuclide technetium-99 m ($^{99m}$Tc) is a gamma emitter ideal for diagnostic applications due to its relativitively short half-life ($t_{1/2} = 6.0$ h) and the emitted photon energy ($\gamma = 140.5$ keV) which are well suited for Single-Photon Emission Computed Tomography (SPECT) imaging. In addition, it allows for exploiting its multi-oxidation states thus resulting in the ability to produce a variety of complexes. Due to these peculiar properties, $^{99m}$Tc is the most widely used radionuclide in nuclear medicine and currently more than 80% of imaging diagnostic procedures are based upon this radioisotope [1, 2]. $^{99m}$Tc is easily available in hospitals via $^{99m}$Mo/$^{99m}$Tc generator systems. The parent isotope, molybdenum-99 ($^{99}$Mo) is routinely produced in nuclear reactors by fission of highly- or low-enriched uranium-235 targets.

In recent years, $^{99m}$Mo supplies have been limited by extended or unplanned shutdown of designated reactors around the world. Whereas there used to be about 400 research nuclear reactors in operation, this number has halved to-date and is continuing to decline rapidly [3]. Conversely, due to the aging of society, the demand for diagnostic tests using $^{99m}$Tc is markedly increasing. In order to mitigate the $^{99m}$Mo/$^{99m}$Tc shortage occurred in the last decade, a variety of alternatives production routes, including both reactor and accelerator, are being investigated with the aim of achieving sustainable direct production of $^{99m}$Mo or $^{99m}$Tc for clinical use [4, 5]. Alternative technologies classified as short-term approaches include uranium fission in homogeneous solution reactors, neutron activation and cyclotron production. Molybdenum-99 production via neutron-induced activation of $^{98}$Mo is simple, however the $^{98}$Mo($n,\gamma$)$^{99}$Mo nuclear reaction produces only low specific $^{99m}$Mo activity [6]. Accelerator-based production of $^{99m}$Mo through the $^{238}$U($\gamma$,f)$^{99m}$Mo reaction is feasible [7], but the production efficiency is poor due to the low cross section of the nuclear reaction. Direct cyclotron production of $^{99m}$Tc via the $^{100}$Mo(p,2n)$^{99m}$Tc identified almost 40 years ago, is now considered as the best route [8]. Since then, its production parameters have been investigated using a wide range of cyclotrons [9–13]. Using this method, it is possible to produce large quantities of $^{99m}$Tc, by using proton beams with energies of 16 meV, featured by hundreds of medical cyclotrons all over the world. This may suggest that small cyclotrons, which are typically used in PET isotope manufacturing, could also be used to produce $^{99m}$Tc. This technology requires >99% $^{100}$Mo-enriched targets, and the recycling of target material is very important from the economic point of view of this process. Furthermore, direct $^{99m}$Tc production by using proton cyclotrons can only meet local needs.
The $^{100}$Mo($\gamma$,n)$^{99}$Mo photonuclear reaction, where high-energy photons obtained from an electron accelerator are used, is considered as a “mid-term” technology (available up to 2025) [14]. The photo-neutron absorption cross section presents its maximum at 14 meV. The bremsstrahlung process exploited by such linear accelerators with beam powers as high as 50 kW are used to generate high flux of such energetic photons [15]. Unfortunately, the specific activity of $^{99m}$Tc thus obtained following such a production pathways however too poor to be considered for a commercial supply of $^{99m}$Tc generator systems that use alumina columns and which require other separation methods.

The separation of $^{99m}$Tc from Mo target mass has been investigated with the aim of extracting higher quantities of $^{99m}$Tc from low specific activity $^{99}$Mo. Several processes, such as sublimation [16, 17], solvent–solvent extraction with Methyl Ethyl Ketone (MEK) [18] have been developed. In this process, Mo target is dissolved and mixed with MEK, forming two phases which are then separated. The MEK phase containing $^{99m}$Tc is passed through the alumina column to trap any trace amounts of Mo. In the next step, the MEK phase is evaporated off and the $^{99m}$Tc residue is dissolved in saline. This method is effective and the separation system has been fully automated as described by Martini et al. [19]. It has been later replaced by extraction chromatography techniques [20–23], automation of which is easily achievable. Extraction chromatography combines the advantages of selectivity in solvent extraction and high separation efficiency. During this approach, the extractant is immobilized on the surface of inert resin beads. The most commonly used resin in extraction chromatography for technetium separation is TEVA®, produced and commercialized by Eichrom Technologies Inc (USA). The functional group of which is an aliphatic quaternary amine. Column chromatography is the most commonly used technique and the uptake of technetium on TEVA resin from a variety of matrices is high in mildly acidic conditions [24]. Various resins selective to $[^{99m}\text{Tc}]\text{TcO}_4^-$, such as zirconium molybdate gel [25], ion-exchange resin [26], PEG modified C18 [27] and AnaLig®Tc-02 resin [28–30], have been tested.

The $^{99m}$Tc separation technology needs to be automated for purposes of routine production. Morley et al. [31] and Dash et al. [32] described automated module systems based upon column chromatography. In those systems the target dissolution occurs outside the separation and purification system and $\text{TcO}_4^-/\text{MoO}_4^-$ solution is passed through the module. Conversely, a dissolution reactor is included in the solvent-extraction module setup described by Martini et al. [19, 33] and Capogni et al.[34], composing a fully-automated, remotely controlled module for the extraction and purification of $^{99m}$Tc.

Molecular recognition technology (MRT) is the most advanced approach among separation techniques, by using specially designed organic chelating agents or ligands where the metal-selective ligand can bind metal in a particular form. The selectivity of MRT is affected by ion radius, coordination chemistry, geometry, charge. For example, $\text{ReO}_4^-$ will compete with $\text{TcO}_4^-$ for binding sites due to these compounds sharing almost the same ion radius. The composition of the matrix has no influence on the efficiency of the separation process even in the presence of high concentrations of competing species. The effectiveness of AnaLig® Tc-02 resin in separation procedures has been already reported [28, 29, 35].

Here the design and development of a separation system is described, based upon column chromatography with an AnaLig®Tc-02 resin for the isolation of $^{99m}$Tc from $^{100}$Mo target irradiated with high energy $\gamma$ photons. The aim of this study was to set up a semi-automated purification module for cyclic $[^{99m}\text{Tc}]\text{TcO}_4^-$ separation $^{100}$Mo-enriched target irradiated by a gamma beam. This is the first study, where AnaLig®Tc-02 resin has been used to construct a $^{99m}$Tc generator from the low specific activity $^{99}$Mo.

**Experimental**

**Materials**

AnaLig® Tc-02 was purchased from IBC Advanced Technologies Inc. (USA). Dowex-50 WX2100–200 mesh and Alumina A were obtained from SERVA Electrophoresis GmbH (Germany) and MP Biomedicals GmbH (Germany), respectively. Other reagents and solvents (reagent grade) were purchased from Sigma-Aldrich, Merck and Avantor Performance Materials (USA) and were used without further purification. Deionized water (18.2 MΩ·cm) was prepared in a Hydrolab water purification system (Hydrolab, Poland).

The radioactivity measurement was performed by $\gamma$-spectrometry on Coaxial High Purity Germanium (HPGe) detector (GX 1080) connected to a DSA-1000 multichannel analyzer (Canberra, Meriden, CT, USA). The radiochemical purity of the preparation on the ITLC sheets was determined by Perkin Elmer Cyclone Plus Radiometric TLC Reader and analyzed using Optiquant software.

$^{99m}$Tc separation and purification process on a semi-automated purification module to cyclic isolation of $[^{99m}\text{Tc}]\text{TcO}_4^-$ from the gamma irradiated $^{100}$Mo target

The process of separation of $^{99m}$Tc from Mo target was tested on a solution simulating a dissolved $^{100}$Mo target irradiated with a gamma beam. For this purpose, we used $^{99}$Mo ($\geq 99.99\%$, Merck) and $[^{99m}\text{Tc}]\text{TcO}_4^-$ eluate obtained from Polgentec $^{99}$Mo/$^{99m}$Tc isotope generator (POLATOM,
The \textsuperscript{nat}Mo solution was prepared by dissolving 250 mg in 3 mL 30\% H\textsubscript{2}O\textsubscript{2}. Next, 3 mL of 2 M NaOH or 2 M (NH\textsubscript{4})\textsubscript{2}CO\textsubscript{3} was added to the Mo solution and finally the solution was spiked with \[^{99m}\text{Tc}\text{O}_4^-\] obtained from \(^{99}\text{Mo}/^{99m}\text{Tc}\) generator. These mixtures were separated on plastic columns (d = 9 mm, h = 20 mm) packed with 70 or 100 mg resin.

The semi-automated system developed during this study for the separation \[^{99m}\text{Tc}\text{O}_4^-\] from the Mo mass concerned comprises two four-channel peristaltic pumps and three plastic columns. The first column (d = 9 mm, h = 20 mm) was packed with 100 mg AnaLig\textsuperscript{®} Tc-02 suspended in 1 M (NH\textsubscript{4})\textsubscript{2}CO\textsubscript{3}, the second (d = 13 mm, h = 65 mm) packed with 1.5 g Dowex-50 WX2 suspended in 2 M HCl and third (d = 9 mm, h = 65 mm) packed with 1 g Alumina A suspended in 0.01 M HNO\textsubscript{3}. The pumps and columns in the system were connected by polymer tubing (Tygon\textsuperscript{®} S3\textsuperscript{™} E-LFL, 1.52 mm ID, Tygon\textsuperscript{®} Chemical 2001, 1.52 mm ID) and 3 channel valves. All components for the module were purchased from Ismatec REGLO ICC, Cole Parmer GmbH (Germany).

The primary parameters for \(^{99m}\text{Tc}\) radionuclide separation from Mo target material on the AnaLig\textsuperscript{®}Tc-02 resin have already been tested by Pawlak et al. [29] in developing the technology for the accelerator-produced \(^{99m}\text{Tc}\) by proton irradiation of the \(^{100}\text{Mo}\) target.

In our case, we have a completely different problem. The separation system we propose concerns a \(^{100}\text{Mo}\) target irradiated with gamma quanta, where as a result of the nuclear reaction \(^{99}\text{Mo}\) the parent radionuclide for \(^{99m}\text{Tc}\) is produced. Therefore, the proposed system must provide multiple \(^{99m}\text{Tc}\) elution and works as a \(^{99}\text{Mo}/^{99m}\text{Tc}\) generator.

The experiments were performed on the columns packed with AnaLig\textsuperscript{®} Tc-02 resin. In order to develop a semi-automated method, it was also necessary to characterize several parameters, including resin mass in the column, flow rates during the adsorption on the bed as well as the specific conditions required for efficient \(^{99m}\text{Tc}\) elution. After sorption, \(^{99m}\text{Tc}\) was eluted with several milliliters of deionized water and the activities in the 1 mL fractions were measured. Experiments were carried out with different resin quantities (70 and 100 mg), various flow rates (0.2–0.4 mL/min) and various water elution flow rates (0.2–1 mL/min).

The \[^{99m}\text{Tc}\text{O}_4^-\] obtained from the semi-automated system developed during this study was used for the radio-labeling of DTPA ligand. The radio-labeling process was as follow: 1 mL of \[^{99m}\text{Tc}\text{O}_4^-\] was added to a kit formulation (homemade) containing 10 mg of DTPA, 3 mg of NaCl and 0.1 mg of SnCl\textsubscript{2} in lyophilized form. The mixture was allowed to stand at room temperature for 5–10 min. The radiochemical purity was determined by ITLC method.

### Results and discussion

#### \(^{99m}\text{Tc}\) separation process on AnaLig\textsuperscript{®}Tc-02 resin

The obtained results from independent experiments with different resin quantities (70 and 100 mg), various flow rates (0.2–0.4 mL/min) and various water elution flow rates (0.2–1 mL/min) are shown in Figs. 1 and 2.

In Fig. 1, elution profiles for the two resin masses, 70 and 100 mg, are plotted and in Fig. 2 the effect of different flow rates on the elution curves are shown.
Optimal results were obtained by using 100 mg of resin, loading the solution at a flow rate of 0.2 mL/min and eluting $^{99m}\text{Tc} \text{TcO}_4^-$ at a flow rate of 0.5 mL/min. When using 70 mg of resin, no loss of $^{99m}\text{Tc} \text{TcO}_4^-$ activity was recorded and recovery efficiency of up to 92% was achieved, but the $^{99m}\text{Tc}$ elution curve is wide and has a non-Gaussian shape. Passing sample through the column at flow rates higher than 0.2 mL/min results in insufficient retention of $^{99m}\text{Tc} \text{TcO}_4^-$. Moreover, if water elution flow rate is kept above 0.5 mL/min, $^{99m}\text{Tc} \text{TcO}_4^-$ is eluted with low efficiency.

**Semi-automated module of three-column purification system based on AnaLig® Tc-02 resin**

Due to high cost of the target material, recovery of $^{100}\text{Mo}$ target material is anyway highly recommended. Contamination of recovered $^{100}\text{Mo}$ should be avoided and therefore Na$^+$ and K$^+$ salts cannot be used due to risk of activation of these ions by repeated irradiation. The use of ammonium carbonate (NH$_4$)$_2$CO$_3$ salt is instead recommended to increase the ionic strength, as this salt decomposes at high temperatures to volatile gaseous products, which are easily removed. This is unquestionable advantage of the (NH$_4$)$_2$CO$_3$ salt in terms of recycling Mo-100.

After optimization of ideal resin mass and flow parameters, a three-column separation system was constructed aimed at $^{99m}\text{Tc}$ isolation. As show in Fig. 3 a, b, three columns, containing respectively AnaLig® Tc-02 resin, Dowex-50WX2 ion exchange resin and alumina were set up.

The first column, which was packed with AnaLig® Tc-02 resin, $^{99m}\text{Tc}$ is separated from the Mo target mass. The first fraction eluted from the column, containing $^{100}\text{Mo}$ target material and $^{99m}\text{Mo}$, is collected in the tank and after growing of $^{99m}\text{Tc}$ is returned to the AnaLig® Tc-02 column. The fraction containing pertechnetate ions, eluted with water, must then be passed through a cation exchange resin, in order to improve binding of pertechnetate to the alumina column, which is sensitive to pH increase above neutral. Therefore, on the second column, NH$_4^+$ ions are removed by Dowex-50WX2 ion exchange resin and replaced by H$^+$. Finally, $^{99m}\text{Tc} \text{TcO}_4^-$ is trapped on the alumina column and eluted with 0.9% saline solution, delivering $^{99m}\text{Tc}$ ready for medical applications. This system includes two four-channel peristaltic pumps in a configuration allowing users to run two or more processes simultaneously. Primary advantages of the proposed semi-automatic system include a guarantee of repeatability, convenient operation and shorter duration of $^{99m}\text{Tc} \text{TcO}_4^-$ separation process in comparison with a system based on a single-channel peristaltic pump.

The following parameters were optimized for $^{99m}\text{Tc} \text{TcO}_4^-$ separation: 250 mg of Mo was dissolved into 3 mL of 30% H$_2$O$_2$. To this solution, 3 mL of 2 M (NH$_4$)$_2$CO$_3$ was added and the solution was spiked with $^{99m}\text{Tc}$ TcO$_4^-$ obtained from the $^{99m}\text{Mo}/^{99m}\text{Tc}$ generator. The solution was passed through the first column packed with AnaLig® Tc-02 resin (arrow no. 4 in Fig. 3). After loading, the column was washed with 3 mL of 1 M (NH$_4$)$_2$CO$_3$ (arrow no. 5 in Fig. 3) and $^{99m}\text{Tc} \text{TcO}_4^-$ was eluted in 1 mL fractions using 17 mL of water (arrow no. 6 in Fig. 3) at a flow rate of 0.5 mL/min. The aqueous $^{99m}\text{Tc}$ eluate was passed through the Dowex-50WX2 ion exchange resin, removing NH$_4^+$ ions and replacing them with H$^+$ ions. For this purpose, 1.5 g of Dowex-50WX2 resin was washed and equilibrated with water, conditioned with 15 mL of 2 M HCl (arrow no. 1 in Fig. 3) and rinsed again with water to reach pH level equal to 3 (arrow no. 2 in Fig. 3). The flow-through from the Dowex-50WX2 column was applied to the Al$_2$O$_3$ column and $^{99m}\text{Tc} \text{TcO}_4^-$ was eluted from this column by using 7 mL of 0.9% NaCl (arrow no. 7 in Fig. 3) as is shown in Fig. 4. The solution from the first column containing $^{99m}\text{Mo}$, obtained in the process of loading and rinsing with (NH$_4$)$_2$CO$_3$, is transferred to the tank, where, after the decay time required for the generation of new $^{99m}\text{Tc}$ daughter nuclei, it can be loaded onto AnaLig® Tc-02 resin once again. When the activity of $^{99m}\text{Mo}$ decreases, the solution is transferred to another reservoir and, after complete $^{99m}\text{Mo}$ decay, recovery of $^{100}\text{Mo}$ can be carried out.

The proposed semi-automatic process of separating $^{99m}\text{Tc}$ from the Mo target mass appears to be very efficient: the whole process, including $^{99m}\text{Tc}$ separation from Mo and purification can be carried out in 90 min and $^{99m}\text{Tc}$ loss during three-column separation was below 10% (Table 1).

The $^{99m}\text{Tc}$ recovery yield turned out to be above 90% (Table 1.) and losses of $^{99m}\text{Tc}$ were less than 10%. When eluting $^{99m}\text{Tc}$ from alumina columns by means of 0.9% NaCl, 8% of $^{99m}\text{Tc}$ activity is still retained on the resin. The concentration of molybdenum in the final solution is about 0.04 ppm.

Also it should be taken into account that, the enriched $^{100}\text{Mo}$ material (NorthStar) consists of $^{100}\text{Mo}$ (97.39%) and $^{98}\text{Mo}$ (2.59%) but also other elements are present at ppm level (among others Fe, Cr, W). Apart from $^{99m}\text{Tc}$ some side-products are formed due to presence of these impurities.

The major side products identified after irradiation of enriched targets are $^{95,96,97,98}\text{Nb}$ isotopes and $^{95}\text{Zr}$ [36]. These radionuclides are not retained by AnaLig® Tc-02 and at first step of separation procedure these side-reaction products are separated from final $^{99m}\text{Tc}$ TcO$_4^-$ solution. AnaLig® Tc-02 resin retained only Tc in form of pertechnetate ion; only the ReO$_4^-$ could compete with $^{99m}\text{Tc} \text{TcO}_4^-$ for binding sites but this ion is not present. If there are other than $^{99m}\text{Tc}$ technetium isotopes they will necessarily follow the same extraction route as $^{99m}\text{Tc}$. Isotopes of the same element cannot be chemically separated.
but fortunately $^{99m}\text{Tc}$ isotopes are not identified in the irradiated targets.

**Radiolabelling of DTPA ligand**

In order to confirm that the $^{99m}\text{Tc}$ separated in the procedure described above will meet radiopharmaceutical standards, thus allowing to considering its use in diagnostic procedures, synthesis of a diethylenetriaminepentaacetic acid (DTPA) complex of $^{99m}\text{Tc}$ was carried out. In nuclear medicine, [$^{99m}\text{Tc}$]Tc-DTPA is routinely used to assess kidney function in a variety of conditions and to measure the glomerular filtration rate. Synthesized [$^{99m}\text{Tc}$]Tc-DTPA complex was analyzed by Instant Thin-Layer Chromatography (ITLC). As showed in Fig. 5, the [$^{99m}\text{Tc}$]Tc-DTPA complex migrated with the 0.9% NaCl eluent front ($R_f = 1$) and stayed at the origin in acetone ($R_f = 0$). Lack of $^{99m}\text{Tc}$ colloidal forms at the origin in both solvents and absence of signal from free, unbound pertechnetate in [$^{99m}\text{Tc}$] TcO$_4^{-}$ which migrated with the 0.9% NaCl solvent front, indicates high radio-labeling yield. Based on these results, the radio-labeling was estimated as higher than 95%.
Conclusions

A semi-automated module prototype set up for the separation and use of $^{99m}$Tc radionuclide yielded by decay of parent $^{99}$Mo, obtained from $^{100}$Mo targets irradiated by high-energy gamma beams is here described, along with subsequent extraction of $[^{99mTc}]TcO_4^-$ from Mo using new AnaLig® Tc-02 extraction resin. The three-column module allows for the purification and preparation of $^{99m}$Tc in a 7 mL final volume. The procedure is fast and can be repeated every 24 h (the time needed to achieve the maximum activity for $^{99m}$Tc). The suitability of the separation process based on AnaLig® Tc-02 resin has been confirmed by > 95% yield of $[^{99mTc}]Tc$-DTPA synthesis. The other quality control parameters, reported in the European Pharmacopoeia, have to be fulfilled prior to finally claim that the $^{99m}$Tc product could be used for medical application. In the future we plan to do experiments on gamma-irradiated target to confirm purity of the final product to assess radionuclide, radiochemical and chemical purity values. It should be noted that the module can also be applied to separate $^{99m}$Tc from neutron-irradiated $^{98}$Mo target.

Acknowledgements

This research was funded by International Atomic Energy Agency (IAEA), Research Contract No 22521-GamaTech “Cyclic $^{99m}$Tc Isolation from the Gamma Irradiated $^{100}$Mo Target”, and the Ministry of Science and Higher Education, grant number 3882/IAEA/2018/0. The contribution of Kamil Wawrowicz was realized within Project No. POWR.03.02.00-00-I009/17-00 (Operational Project Knowledge Education Development 2014–2020 co-financed by European Social Fund).

Declarations

Conflict of interest The authors declare no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. International Atomic Energy Agency (IAEA) (2008) Technical report series 466: technetium-$99m$ radiopharmaceuticals: manufacture of kits. IAEA
4. Pillai MR, Dash A, Knapp FF Jr (2013) Sustained availability of
19. Martini P, Boschi A, Cicoria G, Uccelli L, Pasquali M, Duatti A,
12. Manenti S, Holzwarth U, Loriggiola M, Gini L, Esposito J, Groppi
1 3
9. Takács S, Szűcs Z, Tárkányi F, Hermanne A, Sonck M (2003)
3. Fujiwara M, Nakaia K, Takahashi N, Hayakawa T, Shizuma T,
2. https:// www. world- nuclear. org/ infor mation- library/ non- power-
11. Esposito J, Vecchi G, Pupillo G, Taibi A, Uccelli L, Boschi A, Gam-
7. Stichelbaut F, Jongen Y (2010) Design of accelerator-based solu-
6. Hasan S, Prelas MA (2020) Molybdenum-99 production path-
15. Ross C, Galea R, Saull P, Davidson W, Brown P, Brown D, Harvey J,
14. Non-HEU Production Technologies for Molybdenum-99 and Tech-
17. Tachimor S, Nakamura H, Amano H (1971) Diffusion of Tc-99m
25. Messina G, Wassenaar R, de Jong M (2010) Using the 100Mo photo-
26. Chattopadhyay S, Das SS, Das MK, Goomer NC (2008) Recovery of
10. 1023/A: 10247 90520 036
6. Hasan S, Prelas MA (2020) Molybdenum-99 production path-
18. Rao BB, Verma SN (2013) Preparation of 99mTc using 100Mo(p, n)99mTc.
23. Viglašová E, Daňo M, Galamboš M, Rosskopfová O, Rajec P, Novák
1 3
20. Rogers R, Horwitz EP, Bond AH (1997) Process for recovering pertechnetate ions from an aqueous solution also containing other ions. US Patent Specification 5603834
21. Bartosova A, Rajec P, Reich M (2004) Preparation and characterization of an extraction chromatography column for technetium separation based on Aliquat-336 and silica gel support. J Radioanal Nucl Chem 261:119–124. https://doi.org/10.1023/B:JRNC.0000030944. 93883.58
22. Dilip M, Griffin ST, Spear SK, Rijksen C, Rodriguez H, Rogers RD (2006) Dual nature of polyethylene glycol-based aqueous biphasic extraction chromatographic (ABEC) resins: uptakes of perchlorate versus mercury(II). Ind Eng Chem Res 47:7390–7396. https://doi.org/10.1021/ie060884j
24. Capogni M, Pietropaolo A, Quintieri L, Angelone M, Boschi A,
25. Andersson JD, Wilson JS, Romaniuk JA, McEwan AJB, Abrams
29. Pawlak DW, Wojdowska W, Parus LJ, Mikołajczak R (2016) Appli-
27. Andersson JD, Wilson JS, Romaniuk JA, McEwan AJB, Abrams
28. Wojdowska W, Pawlak D, Parus JL, Mikolajczak R (2015) Studies on the separation of 99mTc from large excess of molybdenum. Nucl Med Rev 18:65–69. https://doi.org/10.5603/NMR.2015.0017
20. Rogers R, Horwitz EP, Bond AH (1997) Process for recovering pertechnetate ions from an aqueous solution also containing other ions. US Patent Specification 5603834
21. Bartosova A, Rajec P, Reich M (2004) Preparation and characterization of an extraction chromatography column for technetium separation based on Aliquat-336 and silica gel support. J Radioanal Nucl Chem 261:119–124. https://doi.org/10.1023/B:JRNC.0000030944. 93883.58
22. Dilip M, Griffin ST, Spear SK, Rijksen C, Rodriguez H, Rogers RD (2006) Dual nature of polyethylene glycol-based aqueous biphasic extraction chromatographic (ABEC) resins: uptakes of perchlorate versus mercury(II). Ind Eng Chem Res 47:7390–7396. https://doi.org/10.1021/ie060884j
24. Capogni M, Pietropaolo A, Quintieri L, Angelone M, Boschi A,
experiments simulations and perspectives. Molecules 23:1872. 
https://doi.org/10.3390/molecules23081872

35. Bénard F, Buckley KR, Ruth TJ, Zeisler SK, Klug J, Hanemaayer V, Vuckovic M, Hou X, Celler A, Appiah JP, Valliant J, Kovacs MS, Schaffer P (2014) Implementation of multi-curie production of 99mTc by conventional medical cyclotrons. J Nucl Med 55:1017–1022. https://doi.org/10.2967/jnumed.113.133413

36. Tkac P, Chemerisov S, Gromov R, Song J, Nolen J, Makarashvili V, Vandegrift G (2020) Side-reaction products identified for photo-nuclear production of 99Mo. J Radioanal Nucl Chem 326:543–553. https://doi.org/10.1007/s10967-020-07307-1

**Publisher’s Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.