



Molybdenum-99 production pathways and the sorbents for $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator systems using (n, γ) ^{99}Mo : a review

Shameem Hasan¹ · Mark A. Prelas² Received: 16 July 2020 / Accepted: 16 September 2020 / Published online: 7 October 2020
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Abstract

Technetium-99 m ($^{99\text{m}}\text{Tc}$) is a widely used and versatile radioisotope obtained from the beta decay of molybdenum (^{99}Mo). ^{99}Mo can be produced by thermal fission or neutron activation process. Production of ^{99}Mo via the neutron capture method draws attention as an alternative to fission derived ^{99}Mo due to non-proliferation issues. The main concern with neutron capture-produced ^{99}Mo (n, γ) over the common fission-produced involves both lower Curie yield and lower specific activity. In this work, different adsorbents using low specific activity ^{99}Mo for $^{99\text{m}}\text{Tc}$ generator have been discussed.

Keywords Technetium-99 m · Molybdenum-99 · Adsorbent · Medical isotope production

1 Introduction

Commercially prepared radioisotope generators are vital for the supply of short-lived radioisotopes. The radioisotope generators contain relatively long-lived parent radioisotopes that continually replenish the supply of a shorter-lived daughter nuclide through radioactive decay. This daughter nuclide can then be chemically extracted for conversion into a useful radiopharmaceutical to be used as either treatment or diagnostic tool. The radionuclides that are used in radiopharmaceuticals should [1, 2]:

- Possess sufficient half-life, decay mode.
- Be pure gamma emitter with sufficient energy for physiological study of interest.
- Have high radiochemical and chemical purities.
- Possess suitable chemical properties for labeling.
- Be carrier-free or no-carrier added in order to limit the toxicity.
- Follow or be trapped by the metabolic process of interest.

- Have a short effective biological half-life so that it is eliminated from the body as quickly as possible.
- Have a high target to non-target ratio so that the resulting image has a high contrast.

Among all radioisotopes, $^{99\text{m}}\text{Tc}$ is the most widely used medical isotope in the world. It is the “daughter” isotope of molybdenum (Mo-99), which used in 80–85% of approximately 30 million diagnostic nuclear medical procedures performed each year [3]. The first $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator was developed in 1958 at Brookhaven National Laboratory. A process called column chromatography is utilized in most $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators for chemical separation of the parent and daughter isotopes [4]. Molybdenum-99 in the form of molybdate, MoO_4^{2-} , is absorbed onto aluminum oxide, Al_2O_3 (alumina) as an adsorbent, so that when it decays the resulting pertechnetate, TcO_4^- , is less tightly bound to the alumina and can be removed via saline flush [5].

The $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator that is used in nuclear medicine today follows the decay scheme in which ^{99}Mo decays

✉ Mark A. Prelas, PrelasM@missouri.edu | ¹Advanced Isotope Technologies, LLC., 182 St, Francis Street, Suite 101, Mobile, AL 36602, USA. ²EECS & NSEI, University of Missouri, Columbia, MO 65211, USA.



into a meta-stable isomer of ^{99}Tc through emission of a beta particle with a 66 h half-life (Fig. 1).

Technetium-99 m then (6 h half-life) decays into ^{99}Tc , which is also unstable but has a long half-life (2.13 E5 years). The daughter product of this generator type, $^{99\text{m}}\text{Tc}$, is a pure gamma-emitter (~ 0.14 MeV) ideal for use in medical applications. The ideal characteristics of $^{99\text{m}}\text{Tc}$ such as proper decay mode, half-life, adequate penetrating power, and minimal biological damage from absorbed doses, make it a useful radiopharmaceutical that is used in several diagnostic procedures [6]. The nuclear properties of $^{99\text{m}}\text{Tc}$ are ideal for medical imaging as it emits readily available photon energy (~ 140 keV) that is sufficient to determine the exact molecular structure of the coordination compounds by scintillation instruments such as gamma cameras [7]. The data collected by the camera are analyzed to produce detailed structural and functional images of certain human organs that are otherwise difficult or impossible to image.

The problem now shifts toward obtaining significant quantities of ^{99}Mo at low cost and reliable availability. Since ^{99}Mo does not occur naturally, it can be produced by thermal fission or neutron activation of stable ^{98}Mo (24.1 percent abundance). A particle accelerator is also considered an important technique to produce medical radioisotope such as $^{99\text{m}}\text{Tc}$ [8]. Currently, the majority of the world's ^{99}Mo supply comes from the thermal fission of highly enriched uranium (HEU, approximately 97 percent ^{235}U) as a target material. This process, however, generates large quantities of radioactive waste and does not permit reprocessing of the unused uranium targets due to proliferation concerns [9]. Low enriched uranium (LEU, 20 percent ^{235}U or less) could be used as a substitute but would yield large volumes of waste due to the large quantities of un-useable ^{238}U present [10]. The cyclotron-based ^{100}Mo ($p, 2n$) $^{99\text{m}}\text{Tc}$ transformation has been proposed as a viable alternative to the reactor based ^{235}U (n, f) $^{99}\text{Mo} \rightarrow ^{99\text{m}}\text{Tc}$ strategy for production of $^{99\text{m}}\text{Tc}$ [11]. However, the abundance of other molybdenum isotopes other than ^{100}Mo in the target and

beam energy is the main factor that determines the impurities in the final $^{99\text{m}}\text{Tc}$ product [12]. Many of these problems could be reconciled by a net production change to the neutron activation method, but the presence of large quantities of ^{98}Mo in the samples would serve to act as a contaminant and yield product of low specific activity [12].

Production of ^{99}Mo via the neutron capture method draws attention as an alternative of fission-derived ^{99}Mo due to non-proliferation issues. The main concern with neutron capture-produced ^{99}Mo (n, γ) over the common fission-produced involves both lower Curie yield and lower specific activity [13] which has impacts on the efficiency, functionality and size of the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator. These limitations, however, can be overcome by the use of adsorbent with higher capacity for molybdenum. Generators that utilize neutron capture-produced ^{99}Mo will need to be larger or equipped with a more efficient absorbent to accommodate the large quantity of ^{98}Mo . The purpose of this paper is to review the major technologies associated with this unique radioisotope and its production as well as possible ion-exchange resin based $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator systems.

2 Methods of ^{99}Mo production

2.1 Some basic aspects of radionuclide production

Nuclear data plays an important role for the production of medical isotopes [14]. The basic concern in the production of radioisotopes is to minimize radioactive impurities while maximizing product yield. Therefore, it is necessary to investigate all the possible factors such as physical form of target material, energy range, and time of irradiation etc., to achieve the best results. In general, charge particle induced reactions, nuclear fission, neutron activation processes, and radionuclidic generator (chemical method) are the four principle methods of radionuclide production [15]. Each method of radionuclide production process provides useful isotopes with differing characteristics for nuclear imaging and therapy. In this attempt, ^{99}Mo production by charge particle induced reactions, nuclear fission, and neutron activation processes are discussed.

2.1.1 Fission

Radioisotope production via the fission route is accomplished through irradiation of special uranium targets rather than by direct irradiation of the reactor fuel. The majority of ^{99}Mo produced for medical use comes from the fission of highly enriched uranium (HEU) based target such as uranium-aluminum alloy. Production of ^{99}Mo is also possible from low-enriched uranium (LEU) based

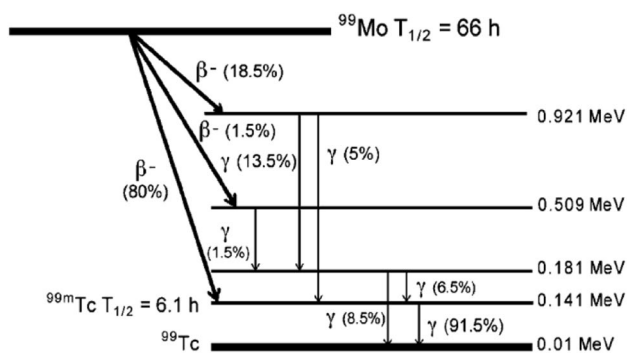


Fig. 1 Decay scheme of ^{99}Mo and $^{99\text{m}}\text{Tc}$ [3]

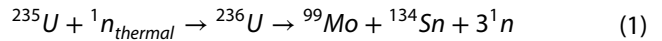
target. However, it would reduce the ⁹⁹Mo yield to approximately 20% of that generated from HEU with respect to target mass. The ²³⁵U content in the enriched uranium is given in the Table 1.

In a nuclear reactor, the thermal energies and fission neutron spectrum are important to produce ⁹⁹Mo, as the ²³⁵U nuclei absorb thermal neutrons to induce fission. The fission of the ²³⁵U nucleus produces two to three lower mass nuclei referred to as fission fragments. The target is monitored to determine optimum time to remove from the reactor, which is based on the build-up of ⁹⁹Mo from the fission of ²³⁵U. In practice, the uranium targets are inserted into a research reactor and exposed to a high neutron flux for five to seven days in which ⁹⁹Mo is created from approximately six percent of the fission. The amount of ⁹⁹Mo produced in a target is a function of irradiation time, the thermal neutron fission cross section for ²³⁵U, the thermal neutron flux on the target, the mass of ²³⁵U in the target, and the half-life of ⁹⁹Mo. Figure 2 shows the example of fission fragments and the fission yield as a function of mass number of the fission product.

Table 1 Uranium enriched grade

Uranium	²³⁵ U content (%)
Natural uranium (NU)	~0.7
Low enriched uranium (LEU)	≤ 20
High enriched uranium (HEU)	> 20
Weapon grade (HEU)	≥ 90

The most common radioisotopes produced by fission are ⁹⁹Mo (which decays to ^{99m}Tc), ¹³¹I, and ¹³³Xe where the pertinent fission reaction for this work is



Per Eq. (1) ⁹⁹Mo will accumulate at a rate proportional to both the amount of target material present (in this case, ²³⁵U) and thermal neutron flux. During the irradiation process, some of the ⁹⁹Mo is also lost due to radioactive decay so that a simplified expression for the amount present with respect to time can be developed (assuming a thin target)

$$N_{\text{Mo-99}} = \frac{\varphi \sigma_{\text{U-235},f} \gamma_{\text{Mo-99}} N_{\text{U-235},0}}{\lambda_{\text{Mo-99}}} [1 - e^{-\lambda_{\text{Mo-99}}t}] \quad (2)$$

where φ is the neutron flux, $\lambda_{\text{Mo-99}}$ is the decay constant, $N_{\text{U-235},0}$ is the amount of target initially present in the system, $\gamma_{\text{Mo-99}}$ is the fission production probability, and $\sigma_{\text{U-235},f}$ is the fission cross-section. A detailed derivation of Eq. (2) is provided in ‘‘Appendix A’’. Note that reaction cross-sections are generally given in ‘barn’ (abbreviated by the letter b) and describe the effective cross-sectional area of a target nucleus as seen by an incoming projectile where 1 barn is 10⁻²⁴ cm². These values are energy-dependent and reaction-specific so that ratio of any particular cross-section (i.e., scattering or absorption) to the sum of all cross-sections denotes the probability of occurrence per collision.

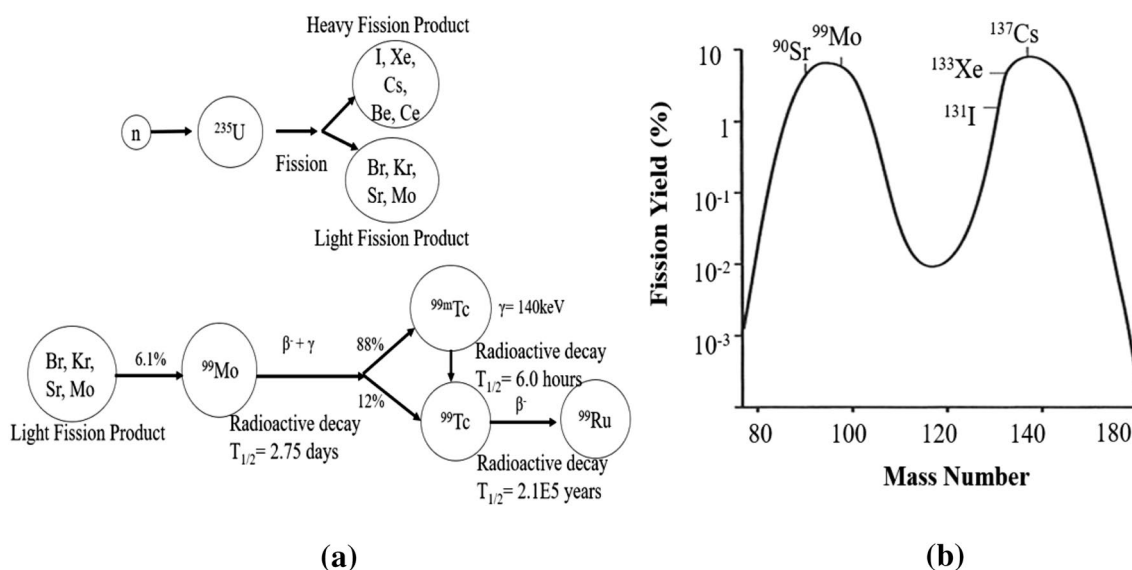


Fig. 2 **a** example of fission fragments, and **b** the fission yield as a function of mass number of the fission product

Table 2 Isotopic composition of natural and enriched molybdenum [8, 16]

Isotope	Natural Abundance (%)	Enriched Abundance (%)	Half-life
Mo-92	14.85	0.06	Stable
Mo-94	9.25	0.03	Stable
Mo-95	15.92	0.06	Stable
Mo-96	16.68	0.08	Stable
Mo-97	9.55	0.67	Stable
Mo-98	24.13	98.63	Stable
Mo-100	9.63	0.47	1.2×10^{19} years

2.1.2 Neutron activation

The neutron activation of molybdenum is another route for ^{99}Mo production. Seven out of 35 known isotopes of molybdenum occur naturally. Of these naturally occurring isotopes, five are stable, with atomic masses from 94 to 98. Molybdenum-98 (natural molybdenum) is the most common isotope, comprising approximately 24% of all molybdenum on earth. Table 2 shows isotopic composition of natural and enriched molybdenum.

In this process, ^{99}Mo is produced by the irradiation of molybdenum (^{98}Mo) in a thermal neutron flux, $\{^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}\}$. The thermal (~ 0.025 eV) or epithermal (0.025–1.0 eV) neutrons produced by the fission of uranium in a nuclear reactor can be used to generate ^{99}Mo radionuclide by bombarding stable ^{98}Mo target material

placed in the reactor [17, 18]. In this process, the ^{98}Mo nuclei capture neutron and transform into ^{99}Mo isotope as shown in Fig. 3. The excitation function of a typical neutron capture reaction is shown in Fig. 4. Reaction cross-sections such as the plot (Fig. 4) depict how the probability of a particular reaction occurrence changes with respect to projectile energy (in this case neutron energy). It can be divided into a number of regions, with the most important being: thermal (~ 0.025 eV), resonance, and fast [18].

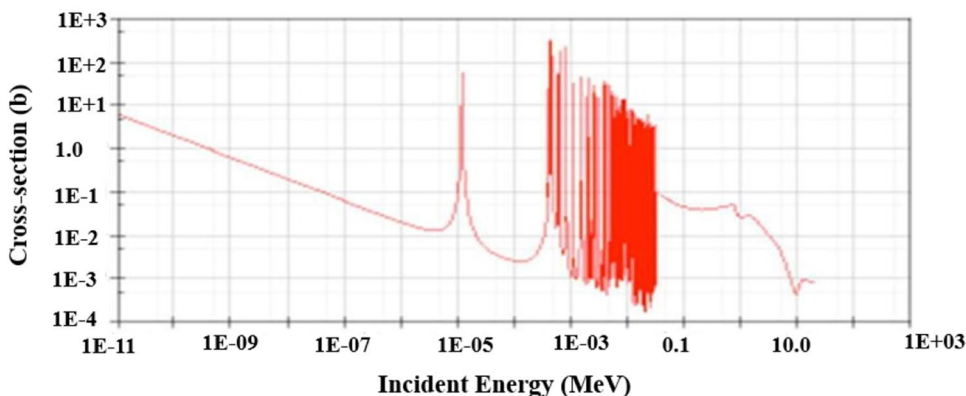
Neutrons are produced by nuclear fission in the fast region (1–2 meV) and pass through the resonance region toward the thermal region as they lose energy from collisions. As the neutrons enter the resonance region, they may experience resonance absorption. The resonance absorption occurs when a neutron is captured by the nucleus and the energy of the resulting compound nucleus is equal to the excited state of the nucleus. Note that this region appears exaggerated in Fig. 4 due to the use of a log scale.

The major interest is in the thermal energy region where both the cross-section and the neutron flux are high. In the thermal region, microscopic cross-section of ^{98}Mo is approximately 0.13b and the target containing ^{98}Mo are irradiated with neutron flux of 10^{13} to 10^{14} $\text{n cm}^{-2} \text{s}^{-1}$. Irradiation of molybdenum (natural or enriched) with thermal neutron fluxes greater than 10^{13} $\text{n cm}^{-2} \text{s}^{-1}$ in a nuclear reactor are necessary to produce ^{99}Mo with certain specific activities of practical importance [12]. Note that enrichment refers to artificially increasing the amount of ^{98}Mo present in the target relative to the approximate

Fig. 3 The neutron activation of ^{98}Mo to generate ^{99}Mo [19]



Fig. 4 Excitation function of the $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$ reaction



24 percent found in natural molybdenum. The enriched ^{98}Mo usually has 4 times higher ^{98}Mo atoms (up to fourfold for > 98% enrichment) compared to the natural Mo. It is reported that the specific activity of ^{99}Mo production with 8-day irradiation in a reactor with thermal flux $1.0 \times 10^{14} \text{ n cm}^{-2} \text{ s}^{-1}$ can reach the value of about 1.6 Ci $^{99}\text{Mo}/\text{g}$ of natural and 6 Ci $^{99}\text{Mo}/\text{g}$ of enriched molybdenum target at the end of bombardment (EOB) [20].

In the epithermal region, the cross-section has a resonance character and the integrated cross-section (resonance integral) has a high value for ^{98}Mo . For instance, the resonance integral ^{98}Mo is of 0.7b. Therefore, the effective cross-section by resonance neutrons is 50 times higher than the thermal neutron cross-section. Several studies investigated the thermal and resonance neutrons input into the ^{99}Mo activation process. [16, 17, 21]. Ryabchikov et al. [21] reported that the resonance part of the neutron spectra enhance the yield of ^{99}Mo significantly by increasing the effective cross-section of $^{98}\text{Mo}(n, \gamma)^{99}\text{Mo}$ reaction from 0.14b to 0.7b. These experiments were carried out in a reactor with neutron flux of $1.7 \times 10^{14} \text{ n}^{-2} \text{ s}^{-1}$. Due to the contribution of resonance integral, after irradiation of MoO_3 sample for 120 h, the specific activity of ^{99}Mo was reported to be 3.4 Ci/g for natural molybdenum and 15 Ci/g for enriched ^{98}Mo . Matyskin et al. [16] investigated the effect of thermal and resonance neutrons input into ^{98}Mo activation process. It was reported that the effective cross-section of $^{98}\text{Mo}(n, \gamma)^{99}\text{Mo}$ reaction, for the activation of ^{98}Mo in a reactor with total fluxes of $7.5 \times 10^{11} \text{ n cm}^{-2} \text{ s}^{-1}$, found to be 0.4–0.5b, compared to 0.136b for thermal neutrons. After 120 h of irradiation, the specific activity of ^{99}Mo was reported to be 16 GBq/g ($\sim 0.432 \text{ Ci/g}$) for enriched sample and 5 GBq/g (0.135 Ci/g) for natural sample. Yields of ^{99}Mo can be significantly enhanced by the epithermal neutron activation, hence the selection of the irradiation position is critical particularly in lower flux reactors [12, 20]. Toth et al. [22] reported that there are several factors such as self-shielding, parasitic absorption, and depletion of the product that must be accounted to identify the effective cross-section as these factors may change the results by 10 to 50%. Blaauw et al. [17] reported that the careful estimation of the epithermal neutron contribution and neutron self-shielding correction can provide specific saturation activity of ^{99}Mo with good accuracy for the $^{98}\text{Mo}(n, \gamma)^{99}\text{Mo}$ reaction. It is reported that the use of enriched Mo has a minor effect of the activation rate through the self-shielding of epithermal neutron by the other Mo isotopes [17, 21]. In (n, γ) process, the targets are not irradiated indefinitely as Mo decays while in the reactor. Therefore, a balance must be struck between specific activity, processing cost, and reactor operation cost [12]. The high energy components of the neutron

spectrum contributions to the formation of the (n, γ) product are often neglected since both the reaction cross-section and the neutron flux have low values compared to the fission (n, f)-based product.

The ^{99}Mo produced by the neutron capture method is not “carrier free” as it contains some unreacted ^{98}Mo which is chemically identical with ^{99}Mo . Thus, the specific radioactivity (defined as radioactivity per unit mass) achieved in an (n, γ) (neutron capture) reaction is about 4 to 5 orders of magnitude lower than fission ^{99}Mo . Note that the use of highly enriched ^{98}Mo enhance the yield of ^{99}Mo and its specific activity by a factor of about 4. In comparison to the fission process, the radionuclide ^{99}Mo produced by neutron capture process would require a larger generator system in order to produce the same activity required for medical procedure. For the production of considerable quantities of ^{99}Mo , a very large target is required. Note that the specific activity cannot be artificially increased by ^{99}Mo isotopic enrichment (i.e., removal of the ^{98}Mo) as current methods require long time periods in which large quantities of ^{99}Mo would be lost to decay.

As with fission production, the amount of ^{99}Mo produced in a target is a function of irradiation time, the thermal neutron capture cross section for ^{98}Mo , the thermal neutron flux on the target, the mass of ^{98}Mo in the target, and the half-life of ^{99}Mo . Molybdenum-99 will accumulate at a rate proportional to both the amount of target material present (in this case, ^{98}Mo) and thermal neutron flux. During the irradiation process, some of the ^{99}Mo is also lost due to radioactive decay so that a simplified expression for the amount present with respect to time can be developed (assuming a thin target)

$$N_{\text{Mo-99}} = \frac{\varphi \sigma_{\text{Mo-98}} N_{\text{Mo-98,0}}}{\lambda_{\text{Mo-99}}} [1 - e^{-\lambda_{\text{Mo-99}} t}] \quad (3)$$

where φ is the neutron flux, $\lambda_{\text{Mo-99}}$ is the decay constant, $N_{\text{Mo-98,0}}$ is the amount of target initially present in the system, and $\sigma_{\text{Mo-98}}$ is the neutron absorption cross-section. A detailed derivation is provided in “Appendix B”. Equation (3) can be changed to express the sample activity by multiplying both sides by the decay constant

$$\text{Act}_{\text{Mo-99}} = \varphi \sigma_{\text{Mo-98}} N_{\text{Mo-98,0}} [1 - e^{-\lambda_{\text{Mo-99}} t}] \quad (4)$$

In where, the reaction cross section for $^{98}\text{Mo}(n, \gamma)^{99}\text{Mo}$ is approximately 0.13 barns so that

$$\sigma = (0.13 \text{ b}) \left(\frac{10^{-24} \text{ cm}^2}{1 \text{ b}} \right) = 1.3 \times 10^{-25} \text{ cm}^2 \quad (5)$$

And the decay constant for ^{99}Mo (66 h half-life) is determined by

$$\lambda = \frac{\ln(2)}{t_{1/2}} = \frac{0.693}{66 \text{ hours}} = 0.0105 \text{ h}^{-1} \quad (6)$$

It is important to note that ^{99}Mo will accumulate during target exposure to a neutron flux while simultaneously decaying via beta emission. After removal from the flux, no more ^{99}Mo is created so that the only change in its population is due to radioactive decay.

2.1.3 Accelerator

Particle accelerators are generally used to study the nature of matter and energy. It is also considered as an important technique to produce medical radioisotopes such as $^{99\text{m}}\text{Tc}$. The most widely discussed accelerator-based routes of ^{99}Mo or $^{99\text{m}}\text{Tc}$ production are summarized in Fig. 5 [23].

In a linear accelerator (linac), an alternating voltage of high magnitude is applied to push particles along in a straight line. A cyclotron is somewhat like a linac wrapped into a tight spiral. In accelerator-based technologies, the isotope $^{99\text{m}}\text{Tc}$ or its parent ^{99}Mo can be produced directly by the interaction of bombarding particles with the target material. The primary accelerated charged particles (electrons, protons, deuterons, etc.) can also be used to produce energetic secondary particles (photons, neutrons) which are then interacted with the target material to produce ^{99}Mo . The binding energy of a nucleon is roughly 8 MeV and the Coulomb barrier for the incoming proton is approximately 1.75 MeV. Based on the binding energy of nucleon and Coulomb barrier for incoming proton, it is reported that the bombardment energy of 22–24 MeV

is sufficient to irradiate a 500-micron thick target foil [24]. Ruth [25] reported that a photon of around 14 MeV is needed to knock out a neutron efficiently. Thus, electron energy of 35–50 MeV can provide photons that cover the energy region of 10–20 MeV with sufficient intensity. In Proton accelerator [Reaction of $^{100}\text{Mo} (p, 2n)^{99\text{m}}\text{Tc}$] route, $^{99\text{m}}\text{Tc}$ is directly produced for immediate use via the reaction of an accelerated proton with a ^{100}Mo nucleus yielding $^{99\text{m}}\text{Tc}$ and two neutrons [26]. This technology is useful for small-scale local production because $^{99\text{m}}\text{Tc}$ is a short-lived radioisotope. In electron accelerator [Reaction of $^{100}\text{Mo} (\gamma, n)^{99}\text{Mo}$], ^{99}Mo can be produced through the photon-to-neutron reaction (γ, n) on a molybdenum target with enriched ^{100}Mo [27]. The isotope ^{100}Mo , which is mostly used in accelerator or cyclotron to produce ^{99}Mo or $^{99\text{m}}\text{Tc}$, comprises about 9.6% of the isotopic composition of naturally-occurring molybdenum (Table 2). An electron accelerator is used to irradiate a special target made of purified ^{100}Mo to produce ^{99}Mo using the photo-neutron reaction. Photons for this reaction are provided from the electron deceleration radiation. This technology uses high-energy X-rays produced by a 30–35 MeV, 100 kW electron beam to irradiate a ^{100}Mo target. The induced X-rays, from incident electrons on a specific target, transmute the ^{100}Mo into ^{99}Mo .

Ruth, T. reported that high-energy photons produced at accelerators has the potential to be used for the production of high specific activity ^{99}Mo via photo-fission of ^{235}U [28]. The photo-fission cross-section of ^{235}U is 0.16b. The yield of ^{99}Mo would be several orders of magnitude lower than that in the neutron induced fission of ^{235}U . A high intensity beam is needed to overcome the smaller

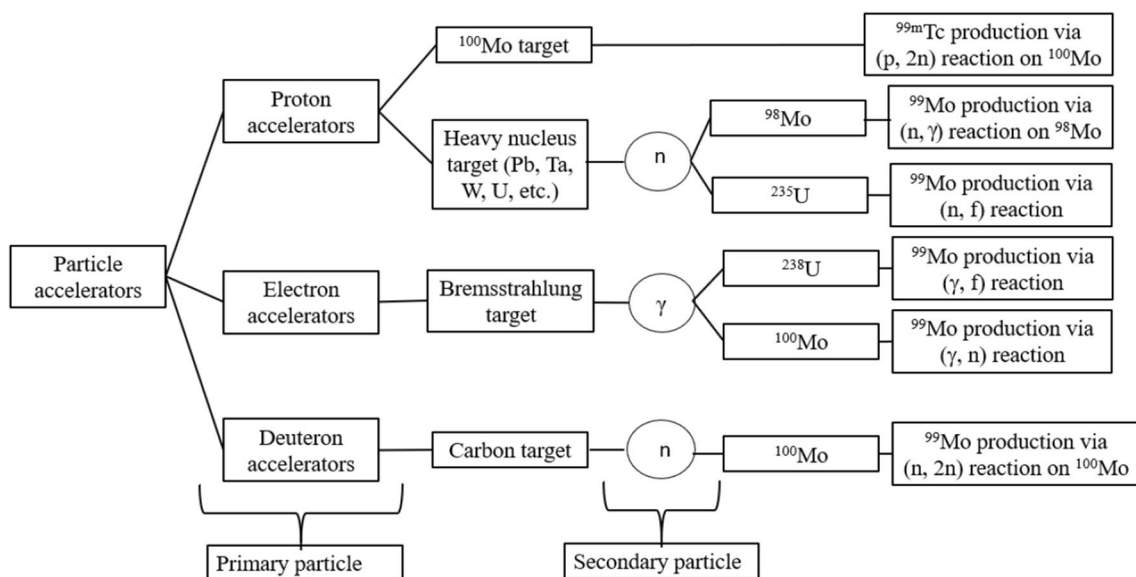


Fig. 5 Summary of potential accelerator-based $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ production technologies

cross-section factor for this reaction versus neutron fission of ^{235}U but this has yet to be demonstrated [9, 29]. In deuteron accelerators [Reaction of $^{100}\text{Mo}(n, 2n)^{99}\text{Mo}$] ^{99}Mo is produced through the $^{100}\text{Mo}(n, 2n)^{99}\text{Mo}$ reaction using an enriched ^{100}Mo target [24, 30]. High energy neutrons for this reaction are provided by energetic deuterons bombarding a natural carbon target.

2.2 Comparison of ^{99}Mo production process

The current demand of medical isotopes in the diagnostic area has increased the interest for an economically feasible production technology for medical isotopes. The production of ^{99}Mo from the fission of highly enriched uranium (HEU) enables the supply of high specific activity ^{99}Mo . This has been threatened by reactor closings, concern over the safety of processing and waste disposal, and the use of HEU targets as approximately 97 percent of the uranium is unused during the process and handled as waste. Significant work has been done to lower the uranium enrichment present in the targets to lower the proliferation concerns, but this simply results in the need for more targets to obtain the same Curie content and therefore larger quantities of hazardous waste for the same amount of end-product.

Neutron capture of stable ^{98}Mo can be accomplished using either a natural molybdenum target, or in one which the ^{98}Mo content has been enriched to provide higher probabilities of interaction. The specific activity of enriched ^{99}Mo is factor of about 4 times more than the natural molybdenum source. Therefore, it is possible to conceive of an approach using enriched ^{98}Mo targets to produce $(n, \gamma)^{99}\text{Mo}$ in reactors with a neutron flux of 8×10^{13} to $2 \times 10^{14} \text{ n cm}^{-2} \text{ s}^{-1}$ for alumina column generators and recovery of enriched ^{98}Mo from spent generators for recycling [31].

Direct $^{99\text{m}}\text{Tc}$ production using cyclotrons has potential advantages in terms of cost, waste management, proliferation resistance, and ease of approval, but can only provide local needs. The technology also needs significant amounts of highly enriched molybdenum (^{100}Mo). As a result, a large number of cyclotrons would be required to meet the US demand. The technology based on the photonuclear reaction $^{100}\text{Mo}(\gamma, n)^{99}\text{Mo}$ has high production yield, but has the same difficulties as the reactor-based neutron activation technology. This technology requires highly enriched molybdenum targets and would require recycling to improve economics. The predicted specific activity of molybdenum from this route is not sufficiently high to use in existing technetium generators. Rather, a gel generator or other types of generators would be needed as in the neutron activation route.

Although, all the accelerator-based strategies are under development as major alternatives but the issues related to the practical limits of irradiation volumes and low cross-sections of the reaction routes need careful assessment [3]. For example, the direct $^{99\text{m}}\text{Tc}$ production from proton-bombarded ^{100}Mo -enriched targets using cyclotron is considered as reliable and cost-effective alternative production routes [32]. Qaim et al. [33] reported that the ratio of atoms of long-lived $^{99\text{g}}\text{Tc}$ and ^{98}Tc to those of $^{99\text{m}}\text{Tc}$ is appreciably higher in cyclotron production than in generator production of $^{99\text{m}}\text{Tc}$. This may adversely affect the preparation of $^{99\text{m}}\text{Tc}$ -chelates, affect the image resolution and contrast, and moreover additional radiation dose to patient [34].

It is reported that the number of isotopes produces during proton-bombarded ^{100}Mo -enriched target depends on isotopic composition of the target, cross-section of each isotope, beam energy, and irradiation time [35, 36]. Therefore, controlling isotopic composition of the starting material together with irradiation parameters may improve the radioisotopic purity of the final product [34]. Several studies investigated the effect of isotopic composition of the target and irradiation parameters for the radionuclidic purity of cyclotron-produced $^{99\text{m}}\text{Tc}$ [34–37]. Selivanova et al. [35] reported cyclotron-produced $^{99\text{m}}\text{Tc}$ -pertechnetate by the irradiation of enriched ^{100}Mo (99.815%; 0.17% ^{98}Mo ; 0.003% each ^{92}Mo - ^{97}Mo) at 24 meV for 2 h. They demonstrated that the cyclotron-produced $^{99\text{m}}\text{Tc}$ -pertechnetate obtained at 17 meV was safe in humans. Uzunov et al. [38] investigated cyclotron-produced $^{99\text{m}}\text{Tc}$ using $^{100}\text{Mo}(p, 2n)^{99\text{m}}\text{Tc}$ reaction at a proton beam energy in the range 15.7–19.4 meV. The isotopic composition of the enriched molybdenum material that was used in these experiments was ^{100}Mo (99.05%), ^{98}Mo (0.54%), ^{97}Mo (0.07%), ^{96}Mo (0.11%), ^{95}Mo (0.10%), ^{94}Mo (0.05%), and ^{92}Mo (0.08%). It was reported that the energy region of 15–20 MeV is the best operative solution for the accelerator production of $^{99\text{m}}\text{Tc}$. It was further noted that the image properties obtained using cyclotron-produced $^{99\text{m}}\text{Tc}$ are comparable with those from the generator eluted $^{99\text{m}}\text{Tc}$. In order to make $^{99\text{m}}\text{Tc}$ production effective by cyclotron, following basic requirements are suggested [29]:

- Use of highly enriched ^{100}Mo target, including efficient recycling of enriched ^{100}Mo ,
- Radiochemical separation immediately after irradiation,
- Daily production schedule,
- Good logistics.

A summary of the methods discussed in this section is shown in Table 3.

Table 3 Summary of ⁹⁹Mo production methods [2, 3, 39]

Items	Thermal fission	Accelerator	Neutron capture
Principle of production	Target material inserted in the neutron flux field undergoes fission into radionuclide of interest	Target material irradiation by charged particle beams inducing nuclear reactions that transmute the material into radionuclide of interest	Target material inserted in the neutron flux field undergoes neutron activation transmuted into radionuclide of interest
Target	²³⁵ U (HEU or LEU); enriched ²³⁵ U in the form of uranium aluminum alloy, foil or pellet	Highly enriched molybdenum target. The isotope ¹⁰⁰ Mo, which is mostly used in accelerator or cyclotron to produce ⁹⁹ Mo	⁹⁸ Mo (natural or enriched) in the form of MoO ₃ , molybdenum metal, or pellet
Nuclear Reaction	$n + {}^{235}\text{U} \rightarrow {}^{99}\text{Mo} + \text{F.P.} + 2.5n$; $\sigma_{\text{fission}} \rightarrow 586 \text{ b}$; Fission yield of ⁹⁹ Mo = 6%	$p + {}^{100}\text{Mo} \rightarrow {}^{99}\text{Mo} + p + n$; $\sigma_{\text{transmutation}} \rightarrow 0.15 \text{ b}$; $p + {}^{100}\text{Mo} \rightarrow {}^{99}\text{mTc} + 2n$; $\sigma_{\text{transmutation}} \rightarrow 0.20 \text{ b}$;	$n + {}^{98}\text{Mo} \rightarrow {}^{99}\text{Mo}$; $\sigma_{\text{th}} \rightarrow 0.14 \text{ b}$
Advantages	High specific activity ⁹⁹ Mo suitable for the preparation of chromatographic ^{99m} Tc Well proven process (HEU) or at least proven in some cases (LEU) High reaction cross-section	Production of proton rich elements used as β ⁺ emitters for PET scans High specific activity in most cases Small investment compared to nuclear reactor Little long-lived radioactive waste	Low quantity of contaminant nuclides Less sophisticated target design Simple purification technology required Suitable for small scale production
Disadvantages	High investment required Sophisticated purification technology required High quantities of radioactive waste Proliferation concerns that warrant safeguards (HEU)	The cost of ¹⁰⁰ Mo target is relatively high (\$2000/gram) Electron accelerator uses high-energy X-rays produced by a 30–35 meV Require 100 kW electron beam energy to irradiate a ¹⁰⁰ Mo target	Low specific activity ⁹⁹ Mo with carrier No ideal preparation of chromatographic ^{99m} Tc

3 Separation of ^{99m}Tc radionuclide in a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator

High elution yield and low breakthrough of ^{99}Mo [40] are the two basic requirements for a good generator system. Several studies reviewed the separation technologies that have been traditionally used for the fabrication of $^{99}\text{Mo}/^{99m}\text{Tc}$ generator systems. A detail discussion on comparative advantage, disadvantage, and technical challenges toward adapting the emerging requirements are discussed in these studies [20, 41]. A number of methods including column chromatography, solvent extraction, sublimation and elution of metallic molybdenum gel [42] have been reported for the separation of daughter ^{99m}Tc nuclide from the parents with a varying degree of success. Among these techniques, the alumina based chromatographic column are used most widely in $^{99}\text{Mo}/^{99m}\text{Tc}$ generator systems.

3.1 Column chromatography

In a typical column chromatography, ^{99}Mo in the form of molybdate, MoO_4^{2-} is adsorbed onto acid alumina (Al_2O_3) as an adsorbent in a column. In ^{99}Mo loaded alumina column, when the ^{99}Mo decays it forms pertechnetate (TcO_4^-) which, because of its single charge, is less tightly

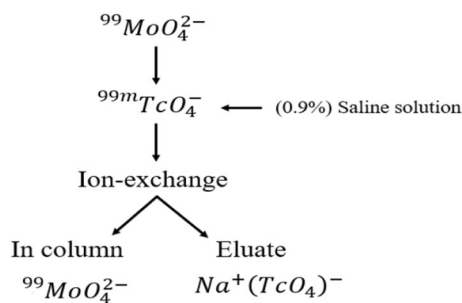
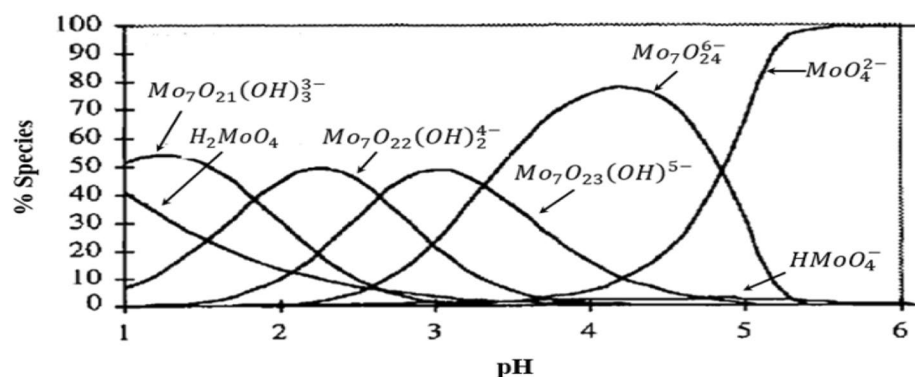


Fig. 6 Typicssor

Fig. 7 Typical example of species distribution of the hydrolysis products formed in the H^+ -Mo(VI) system in the pH range 1.0–6.0 [44]



bound and has very limited interaction to the alumina. When saline (0.9% NaCl) is passed through the column, an ion exchange process takes place between the chloride and pertechnetate ions so that the ^{99m}Tc is washed off or eluted, from the column containing ^{99}Mo loaded alumina as sodium pertechnetate, which should be crystal clear in appearance. With a pH of 4.5–7.5, hydrochloric acid and/or sodium hydroxide may have been used for pH adjustment. Over the life of the generator, an elution will contain a yield of > 80% of the theoretical amount of ^{99m}Tc available from the molybdenum ^{99}Mo on the generator column. A typical elution profile is given in Fig. 6.

3.1.1 The chemistry of molybdenum in aqueous solution

Molybdenum-99 in the form of molybdate, MoO_4^{2-} , is highly soluble in alkaline than acidic solution. The degree of molybdenum ionization in an aqueous solution depends on the equilibrium concentration as well as the pH value of the solution [43]. Figure 7 shows that at pH of approximately 3, $\text{Mo}_7\text{O}_{23}(\text{OH})_5^{5-}$ is the predominant species primarily at higher concentrations [approximately 50% of the molybdate species with approximately 22% of both $\text{Mo}_7\text{O}_{24}^{6-}$ and $\text{Mo}_7\text{O}_{22}(\text{OH})_2^{4-}$] [44]. It is reported that at relatively high and low pH values both the MoO_4^{2-} and various isopolyanions (mainly $\text{Mo}_7\text{O}_{24}^{6-}$) predominate [45].

The MoO_4^{2-} anion undergoes formation of many different polyanions in acidic solutions where the presence of both *para* $\text{Mo}_7\text{O}_{24}^{6-}$ molybdate and *octa* $\text{Mo}_8\text{O}_{26}^{4-}$ molybdate anions in the solution at acidic pH values (pH ~ 4) [46–48]. The formation of polyanions may be represented by the following equations:

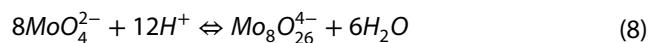
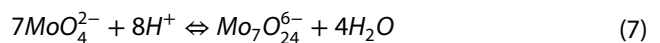


Figure 7 shows that $\text{Mo}_7\text{O}_{24}^{6-}$ is present in the solution in the pH range of 2–6. Saptima et al. [49] reported that the Mo anions, both MoO_4^{2-} and $\text{Mo}_7\text{O}_{24}^{6-}$ are commonly found

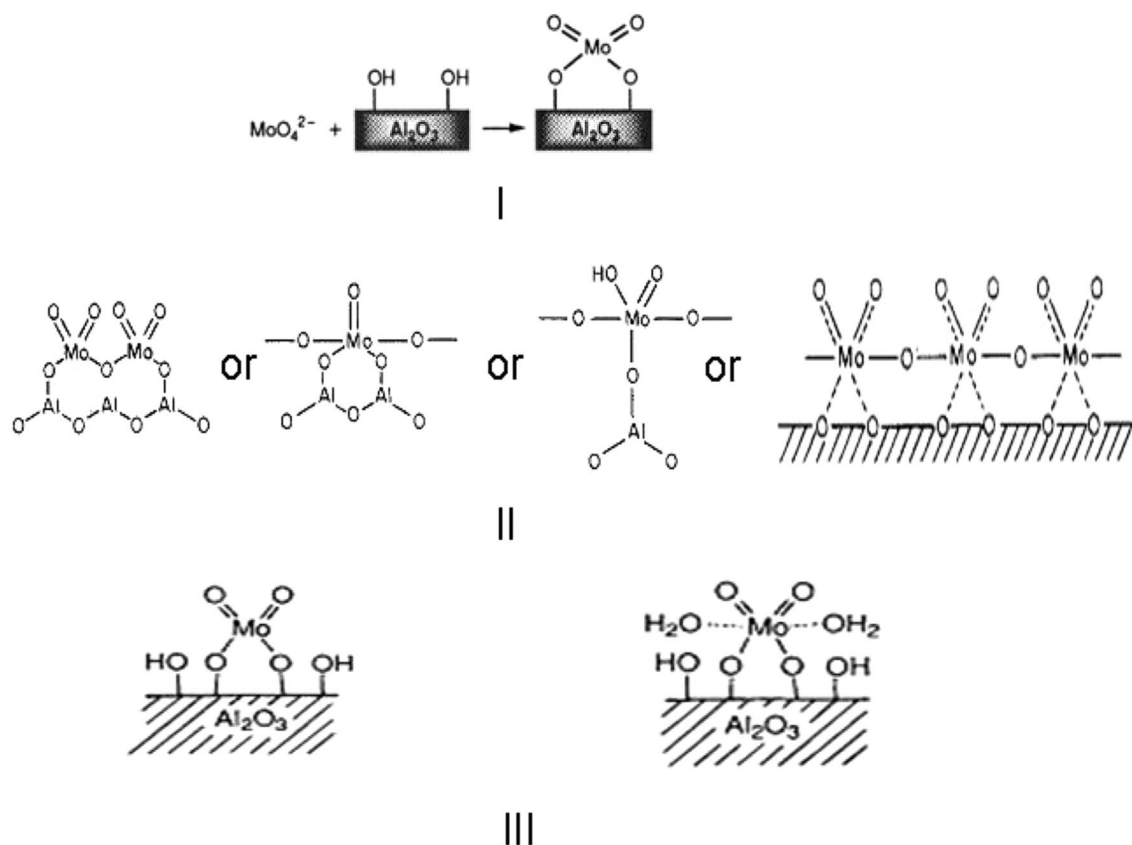


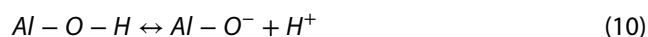
Fig. 8 Chemical reaction structure of MoO_3 with alumina surface [50]

in the pH range of 6–8, whereas MoO_4^{2-} predominates at a higher pH than 8. It is reported that even if the polyanion is present in the solution the adsorption still occurs via MoO_4^{2-} formation [45, 50]. The degradation of polyanions in the solution occurs due to an increased local pH close to the adsorbent surface [50].

3.1.2 Properties of alumina

In general alumina is used for radiochemical separation of isotopes due to its high radiation resistance and affinity for certain inorganic ions [51]. Alumina can exhibit both anion and cation exchange characteristics based on the surface treatment and chemical environment.[52]. Depending on the solution pH, the surface sites of alumina can undergo protonation, and the extent of protonation will be dependent on the solution pH. Therefore, the surface charge on the alumina will determine the type of bond formed between the metal ion and the surface sites of alumina. It is suggested [47, 53] that surface charge of alumina appears due to dissociation at surface of AlOH groups and detachment of either H^+ or OH^- . In simplest

term this can be represented by dissociation equilibria equations [53, 54]:



3.1.3 Reaction mechanism of Mo with alumina

Acid treatment of alumina in a technetium generator is common practice so it is assumed that at acidic $\text{pH} < 4$, the surface sites of alumina become protonated. The anions can then be adsorbed onto the surface of aluminum oxides either by ion-pair formation with positively charged surface sites or ligand exchange with surface hydroxyl groups [55]. Steigman [48] concluded that acid treated aluminum ions on the surface will complex with some octahedral polymeric variety of MoO_3 , most likely via hydroxyl group displacement. Based on the hydroxyl group surface protonation of alumina, the molybdenum species can undergo different chemical reactions with the alumina surface. It is suggested that the adsorption of MoO_4^{2-} on the surface of alumina is either monofunctional

or bifunctional type [45, 56, 57]. The chemical structures that may form are shown in Fig. 8.

3.1.4 Chromatographic column preparation

It is important to note that the preparation of column using alumina is very important. The adsorbent should be packed very carefully into the column in order to avoid any channeling or disruption in the bed. Failure to do so will result in excessive amounts of breakthrough. The preparation procedures of a typical chromatographic generator (100 mCi generator) from ^{99}Mo produced by irradiating ^{98}Mo and adsorbing it on alumina are as follows [58]: In this process, approximately 10 g of acid alumina (80–100 mesh) was transferred to a glass column containing a glass frit at the end and a Teflon disc was placed on top of the alumina bed. The column was then washed with sterile pyrogen free 0.1 N HCl or 0.1 N HNO_3 until the effluent is strongly acidic (pH ~ 1–2). In another attempt, a solution containing predetermined concentration of ^{99}Mo with solution pH ~ 3.0 was prepared. The solution was then passed through the alumina column slowly and allowed to drain. The column was then washed with pyrogen free 0.1 N HCl. The column was further washed with isotonic (0.9% NaCl) solution. In order to check the ^{99}Mo breakthrough, a few drops of isotonic wash solution (effluent) was collected in a vial containing a few mg of potassium ethyl xanthate. To this, about two drops of 2 N HCl was added. No red color should be observed. If a red color is observed, ^{99}Mo is breaking through the column and the column should be rejected. A final check for ^{99}Mo should be made on this spot test sample by γ -ray spectrometry.

The column is then sealed at both ends with septa and placed in a shield and autoclaved. It is reported [59] that the procedure for preparing a fission product $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator is significantly less complex than the (n, γ) ^{99}Mo generator described above as the fission product ^{99}Mo is carrier-free and therefore a much smaller alumina column can be used for the same activity. A schematic and cross-section of a commercial $^{99\text{m}}\text{Tc}$ - ^{99}Mo generator is shown in Fig. 9.

3.1.5 $^{99\text{m}}\text{Tc}$ accumulation and ^{99}Mo decay kinetics

Since $^{99\text{m}}\text{Tc}$ is produced from the decay of ^{99}Mo and lost through its own decay to ^{99}Tc , its kinetics can be described with the following rate equation.

$$N_{\text{Tc-99m}} = \frac{\lambda_{\text{Mo-99}}}{\lambda_{\text{Tc-99m}} - \lambda_{\text{Mo-99}}} N_{\text{Mo-99},0} [e^{-\lambda_{\text{Mo-99}}t} - e^{-\lambda_{\text{Tc-99m}}t}] \quad (11)$$

Derivation of Eq. 11 is presented in the "Appendix C". To determine the time at which the maximum amount of $^{99\text{m}}\text{Tc}$ is present in the system, it is necessary to take the derivative of Eq. (11) with respect to time and setting it equal to zero so that

$$t_{\text{max}} = \frac{\ln\left(\frac{\lambda_{\text{Mo-99}}}{\lambda_{\text{Tc-99m}}}\right)}{(\lambda_{\text{Mo-99}} - \lambda_{\text{Tc-99m}})} \quad (12)$$

It is important to realize that while this maximum time value is constant, the maximum amount of available activity will decrease with time due to the constant decay of

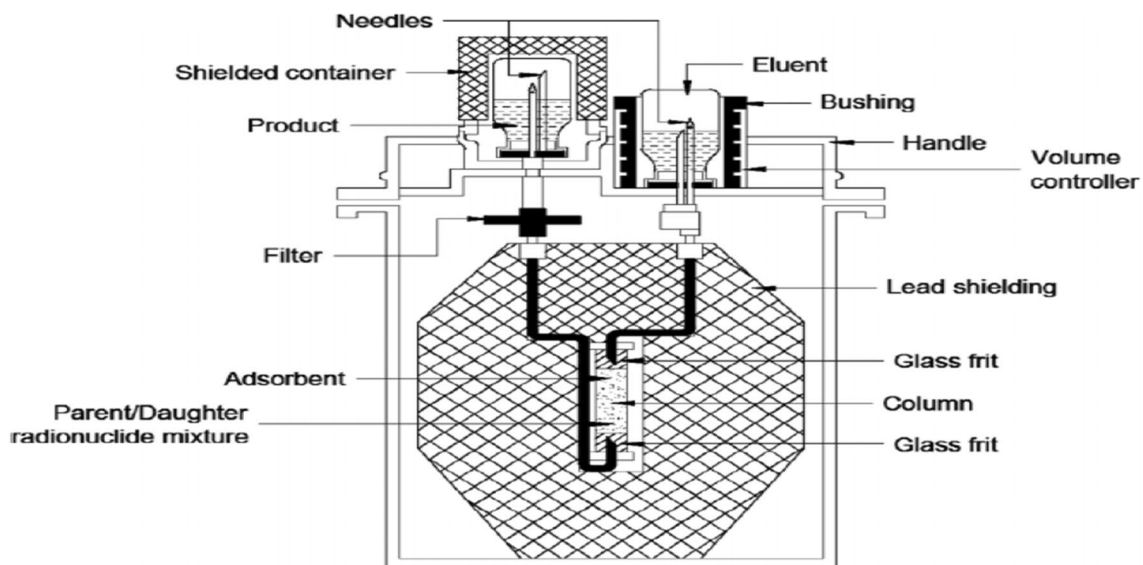
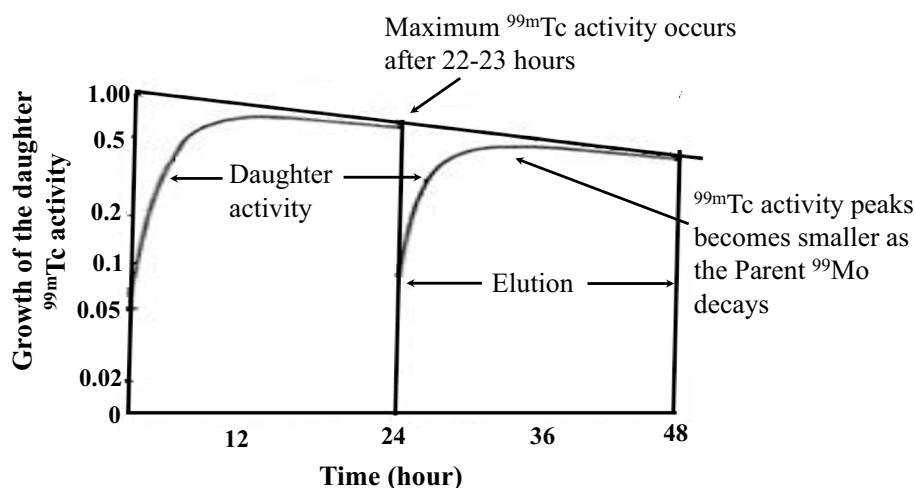


Fig. 9 Schematic diagram of a typical $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ Generator [59]

Fig. 10 Profile of transient equilibrium in ^{99m}Tc - ^{99}Mo generator



the parent isotope. A good rule of thumb to follow is that Eq. (12) can be approximated by four daughter half-lives. As with previous Eq. 11, a detailed derivation of Eq. (12) is shown in Appendix C.

The activity of ^{99m}Tc is maximum after approximately 23 h as shown in Appendix C. As shown in Fig. 10, the production rate of daughter (^{99m}Tc) and the decay rate of Parent (^{99}Mo) are equal after approximately 23 h and the parent and daughter are said to be in transient equilibrium. The daughter (^{99m}Tc) can be repeatedly eluted (extracted) from the parent/daughter pair in a column (Fig. 9) as pertechnetate ($^{99m}\text{TcO}_4^-$) using saline (0.9% NaCl) solution.

3.1.6 Different adsorbents for molybdenum in the generator

The chemical structure mentioned in the Fig. 8 depends on several factors:

- pH of the solution that defines the dominant species present in the solution
- Concentration of Mo in the solution
- The surface charge of the adsorbent
- The pore structure of the adsorbent materials

Molybdate in acid forms quite stable heteropoly complexes with a large number of cations, including Al^{3+} [48]. The adsorption capacity of alumina for molybdenum is reported to be in the range of 2–26 mg/gram of alumina [60, 61]. Several studies described processes to enhance adsorption capacity of alumina for molybdenum [51, 62, 63]. Takahashi et al. [51] studied molybdenum adsorption capacity for commercially available alumina. They found that molybdenum uptake capacity of alumina increases when it was heated at 400 °C for 10 h and subsequent

treatment with boiling hydrochloric acid (2 N) for 1 h. The adsorption capacity of treated alumina for molybdenum is reported to be pH dependent. They also observed that the dissolution of treated alumina is least in sodium chloride solution compared to sodium hydroxide, hydrochloric acid, nitric acid, and ammonium hydroxide. Suzuki et al. [62] studied the effect of sintering temperature on molybdenum uptake by Gibbsite- Al_2O_3 , P-Boehmite- Al_2O_3 , and Bayerite- Al_2O_3 . They reported that the molybdenum adsorption properties are influenced by the crystal structure and specific surface area of the alumina. The average adsorption of molybdenum on Gibbsite- Al_2O_3 , P-Boehmite- Al_2O_3 , and Bayerite- Al_2O_3 samples sintered at 300 °C was reported to be 67.5, 82.4, and 91.1 mg/g of, respectively. Guides-Silva et al. [63] investigated effect of sintering temperature on alumina phases and their subsequent molybdenum uptake capacity. They reported that the alumina powder calcined at 900 °C for 5 h had high chemical stability. The molybdenum adsorption capacity of the alumina heated at 900 °C was reported to be 92.45 mg Mo/g alumina.

Chakravarty et al. [60] studied molybdenum uptake on to nanocrystalline Al_2O_3 that was prepared by solid state mechanochemical reaction of aluminum nitrate with ammonium bicarbonate. It was reported that the sorbent possessed selectivity properties for ^{99}Mo and demonstrated a maximum sorption capacity of 200 ± 5 mg Mo/g, which is ~ 10 times higher than that of ordinary acidic alumina. In this work, a tandem columns generator concept has been proposed using two columns containing ^{99}Mo loaded mesoporous alumina that were connected in series. A 26 GBq (700 mCi) $^{99}\text{Mo}/^{99m}\text{Tc}$ generator was developed using $(n,\gamma)^{99}\text{Mo}$ having specific activity of ~ 18.5 GBq (500 mCi)/g of Mo. In this method ^{99m}Tc eluted from the first column was fed to the second column to achieve higher radioactive concentration (RAC) as well as

the purity of ^{99m}Tc . It was reported that the double tandem column generator provided consistently high yields (> 82% of the theoretical yields) of ^{99m}Tc over a period of 1 week while the single column generator gave low yields (~50% of the theoretical yields). The ^{99m}Tc eluted from the generator possessed high radionuclidic, radiochemical, and chemical purity and was amenable for the preparation of ^{99m}Tc -labeled radiopharmaceuticals.

Several studies investigated the adsorption characteristics of enriched molybdenum-98 on to alumina [64–66]. Skurudin et al. [64] investigated the effect of acid treatment on the adsorption capacity of aluminum oxides for enriched molybdenum-98. It was reported that the adsorption of molybdenum occurs through chemisorption on to the active surface sites of acid treated alumina instead of weak physical adsorption. The maximum adsorption capacity of enriched molybdenum was 23.5 mg/g of activated alumina. The adsorption of ^{99m}Tc under static and dynamic conditions was also carried out on acid treated aluminum oxides [65]. Upon reduction of ^{99m}Tc with bivalent tin, approximately 93% ^{99m}Tc was reported to be adsorbed on to aluminum oxide. It was envisaged that ^{99m}Tc with high specific activity can be obtained by concentrating ^{99m}Tc onto nanosized colloidal particles of aluminum oxide. In another work Skurudin et al. [66] investigated the factors that influence the elution characteristics of ^{99m}Tc in a generator column. The chromatographic generator column was prepared from ^{99}Mo produced by irradiating enriched ^{98}Mo and adsorbing it on alumina. The ^{99m}Tc elution profile of the generator is reported to be dependent on the adsorbed mass of molybdenum. It was suggested that a higher yield of ^{99m}Tc can be obtained from a pretreated alumina column filled with molybdenum approximately 85% of its uptake capacity. It was noted that a generator column loaded with 50–60% of its capacity requires additional volume of normal saline to complete ^{99m}Tc elution. At lower uptake, ^{99m}Tc can occupy the vacant active sites of aluminum oxide thus reduce the yield.

A review article by Le, V.S [20]. provided a detail description of available ^{99}Mo sources and also the technical aspect of ^{99m}Tc generators. This review discussed technical solution for overcoming the shortage of ^{99}Mo supply and various technologies to recover ^{99m}Tc from high and low specific activity $^{99}\text{Mo}/^{99m}\text{Tc}$ generators systems. Various processes using selective sorbents used to purify and concentrate ^{99m}Tc from low specific activity ^{99}Mo are also discussed. Chattapadhyaya et al. [67] reported a ^{99m}Tc delivery system using (n, γ) ^{99}Mo adsorbed onto a large alumina column tandem with Dowex-1, a strong base anion-exchange resin, column and column with AgCl. In their work, a ^{99m}Tc generators containing as much as 80–100 g alumina for holding 14.8–18.5 GBq (400–500 mCi) ^{99}Mo

(at the reference time) has been discussed. A large volume of saline solution (50–70 mL) was used to elute pertechnetate from the ^{99}Mo loaded alumina column. The eluate with low specific activity ^{99m}Tc was then passed through the Dowex-1 column to concentrate the ^{99m}Tc in it. About 5–6 mL of 0.2 M NaI solution was used to elute pertechnetate from the Dowex-1 column followed by washing with 1.5–1.8 mL water. Iodide was removed from the pertechnetate eluate by passing it through a 1 g AgCl column. The average yield of ^{99m}Tc was 70–80% compared to the yield of 80–90% from the conventional chromatographic generator systems. In another attempt, Chattopadhyay et al. [68] discussed the possibility of using Dowex-1 column to separate ^{99m}Tc from ^{99}Mo . In their work, low to medium specific activity ^{99}Mo -molybdate solution of 7.4–18.5 GBq (200–500 mCi) in sodium hydroxide was passed through a tiny Dowex-1 column (25 mg) to separate the ^{99m}Tc from the ^{99}Mo . ^{99m}Tc was then eluted using tetrabutylammonium bromide (TBAB) solution (1 mg/5 ml methylene chloride). The TBAB solution containing ^{99m}Tc was then passed through a small alumina column where ^{99m}Tc retained in the column. ^{99m}Tc was finally eluted with 5 mL saline solution. The average separating yield was reported to be 90% ($n = 10$).

Xu et al. [69] reported mesoporous alumina materials prepared from the precursors of aluminum isopropoxide/ HNO_3 in the presence of glucose in aqueous system. In another study Chakravarty et al. [70] prepared mesoporous alumina using the process given by Xu et al. [69] and developed clinical scale $^{99}\text{Mo}/^{99m}\text{Tc}$ generator. The molybdenum adsorption capacity of the prepared mesoporous alumina was reported to be 225 ± 20 and 168 ± 12 mg Mo/g of sorbent under static and dynamic process. It was reported that the ^{99}Mo strongly and selectively retained by mesoporous alumina at acidic pH condition. ^{99m}Tc was obtained from the generator in > 80% yields with high radionuclidic (> 99.99%) and radiochemical purity (> 99%). The compatibility of the product in the preparation of ^{99m}Tc -radiopharmaceuticals was evaluated by radiolabeling standard kits with > 95% yield. Saptiama et al. [71] investigated the calcination temperature, surface area, and crystallinity of mesoporous alumina preparation and their effect on molybdenum uptake capacity. They found that the molybdenum uptake capacity was 12.5 mg/g, 31 mg/g, and 17.5 mg/g of alumina sample that was prepared at 600 °C, 700 °C and 900 °C, respectively. Denkova et al. [72] have investigated the potential of mesoporous aluminum oxides as adsorbent materials for $^{99}\text{Mo}/^{99m}\text{Tc}$ generators utilized in nuclear medicine. It was reported that the maximum adsorption capacity of the mesoporous alumina sample was 112 mg/g. Furthermore, they added that approximately 40–50% of ^{99m}Tc could be removed from the molybdenum loaded sorbents

in a single elution with negligible loss of ^{99}Mo but the aluminum breakthrough was reported to be higher than the NRC accepted limit (10 mg/L).

In another study, Saptiama et al. [58, 73] reports the fabrication of alumina-embedded mesoporous silica (MPS) particles by solution-phase method. In this work different ratio of Al/Si and calcination temperature was chosen to prepare the adsorbent material. The Mo adsorption experiments conducted using the batch method show the following trend in Mo adsorption capacity in relation to the calcination temperature: $750\text{ }^\circ\text{C} > 600\text{ }^\circ\text{C} > 900\text{ }^\circ\text{C} > 1050\text{ }^\circ\text{C}$ and Al/Si molar ratio: $\text{Al}0.1\text{-MPS} < \text{Al}0.3\text{-MPS} < \text{Al}0.5\text{-MPS} < \text{Al}0.6\text{-MPS}$. Among all the studied samples, the Al0.6-MPS sample calcined at $750\text{ }^\circ\text{C}$ shows the highest Mo adsorption capacity (16.8 mg Mo/g of adsorbent).

Lee et al. [74] reported that Sulfated alumina or alumina-sulfated Zirconia exhibits adsorption capacity that is superior to that of conventional alumina adsorbents, and is stable and is thus loaded in a dry state in an adsorption column. The molybdenum adsorption capacity of sulfated alumina was reported to be 392 mg/g from a solution of 10,500 mg/L molybdenum solution under dynamic condition and subsequent $^{99\text{m}}\text{Tc}$ elution efficiency was reported to be 60–80%. Qazi and Mushtaq [75] studied hydrous titanium oxide as an adsorbent for $^{99\text{m}}\text{Tc}$ generator. Adsorption behavior of molybdate on hydrous titanium oxide was evaluated at boiling water bath temperature ($\sim 100\text{ }^\circ\text{C}$) using radiotracer technique. The effect of pH, molybdenum concentration in solution, incubation time etc., on molybdenum uptake by the titanium oxide were evaluated. The performance of a generator loaded with 230 mg of ^{99}Mo ($\sim 14\text{ mCi}$) on 1 g of hydrous titanium oxide column showed that the elution efficiency of $^{99\text{m}}\text{Tc}$ was 85–90% and more than 90% of the activity was obtained in the first 2 mL of saline. In order to comply with US Pharmacopoeia, an additional mini column of alumina for the removal of excess ^{99}Mo was suggested. In another work, Chakaravarty et al. [76] reported polymer embedded nano crystalline titania based adsorbent for $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator. The surface area of this polymer was $30\text{ m}^2/\text{g}$ with an average pore size of 40 nm. The adsorption capacity of molybdenum for this adsorbent was found to be 100 mg/g. A $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator with 30 mCi ^{99}Mo activity level demonstrated 80% $^{99\text{m}}\text{Tc}$ recovery and the data was reported to be consistent over a period of one week using this adsorbent. Toth et al. [22] has proposed the use of self-absorbed monolayers on mesoporous support (SAMMS) materials for its proven ability to selectively remove ionic species from aqueous solutions and complex liquids as a potential separation mechanism for $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$. It was reported that SAMMS material can adsorb almost 70 mg molybdenum/gram of resin.

Le [77] described a process for the synthesis of polymer compound of Zirconium (PZC) based adsorbent and its use in chromatographic $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ (n,γ) generators with low specific activity. It was reported that a PZC based generator with specific activity ranging from 200 to 1000 mCi Mo-99 can be satisfactorily used in the clinical nuclear medicine application. Tanase et al. [78] reported an inorganic polymer adsorbent (PZC) for use in low specific activity ^{99}Mo generators synthesized from heating a solution of zirconium chloride and isopropyl alcohol. It was reported that about 200 mg ^{99}Mo (Mo) was adsorbed on to per gram of PZC resin from a molybdenum solution containing ^{99}Mo (1.8 mCi/mL). Meta-stable technetium-99 was eluted with a small volume of saline solution for 80% yields. In addition, the ^{99}Mo breakthrough was reported to be less than 0.5% in good test conditions.

A US patent is reported by Hasan [79] described an alternative adsorbent of alumina in neutron activation (n,γ) ^{99}Mo based $^{99\text{m}}\text{Tc}/^{99}\text{Mo}$ generator. This work describes a method of preparing biopolymer based microporous composite material (MPCM) resin. It is reported that the MPCM resin, porous in nature, is found to be resistant to radiation exposure (50 MRad), extreme pH conditions, strong oxidizing agents, and temperatures exceeding 100 degrees Celsius without substantial physical degradation of the resin [79]. Molybdenum-99 in the form of molybdate, MoO_4^{2-} , is absorbed onto resin, so that when it decays the resulting pertechnetate, TcO_4^- , is less tightly bound to the resin surface and can be removed via saline flush [80]. Figure 11 shows possible reaction mechanism of molybdenum uptake on to MPCM resin. Figure 12 shows the surface charge pattern for Mo (VI) loaded MPCM sample with or without oxidization. It was reported that the chitosan-based composite (MPCM) resin requires further surface charge conditioning by oxidation to facilitate $^{99\text{m}}\text{Tc}$ release from the column [79]. A detailed description of the adsorption mechanism of ^{99}Mo on to resin and simultaneous release of $^{99\text{m}}\text{Tc}$ from the column has been described based on surface charge analysis of the MPCM resin [79].

Chattopadhyay et al. [81] reproduced Hasan's work and reported that the molybdenum adsorption efficiency of the resin is approximately 50–60% (500–600 mg Mo/g of resin) of the loaded activity. A column prepared with the resin was evaluated for routine elution of $^{99\text{m}}\text{Tc}$ with 30 mL saline. The $\text{Na}[^{99\text{m}}\text{Tc}]\text{TcO}_4^-$ eluates obtained were clear solutions with pH 5–6 and the radiochemical (RC) purities of 99%. The ^{99}Mo breakthrough in the $^{99\text{m}}\text{Tc}$ fraction with alumina guard column (0.5 g) was 0.002 ± 0.003 ($n=9$). The Al and Mo content in the eluted $^{99\text{m}}\text{Tc}$ was less than 10 $\mu\text{g}/\text{mL}$. The RC purity of the labeled compounds was greater than 95%. The radionuclidic purity of $^{99\text{m}}\text{TcO}_4^-$ was more than 99.99%. It was concluded that chitosan resin based

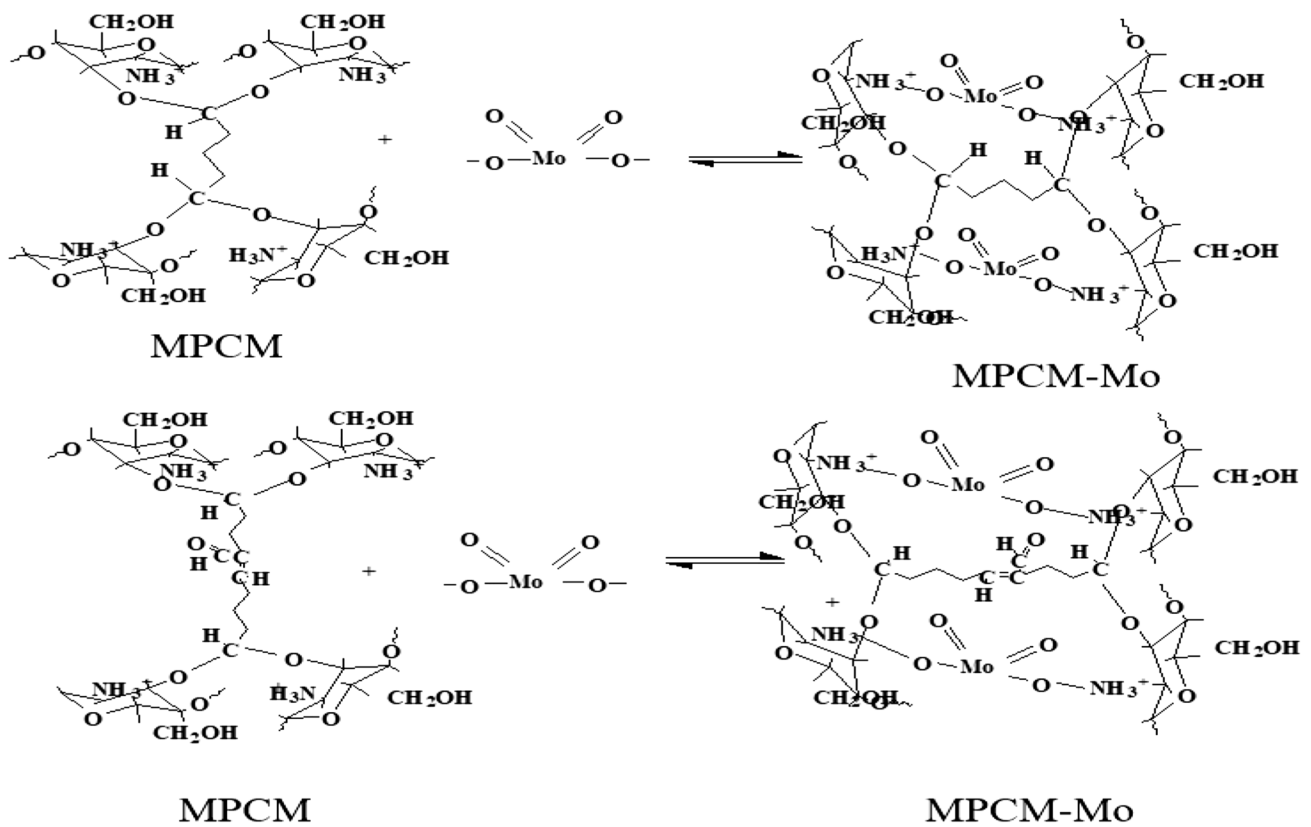


Fig. 11 Reactions mechanism for the adsorption of Mo (VI) on to composite resin from aqueous solution [79]

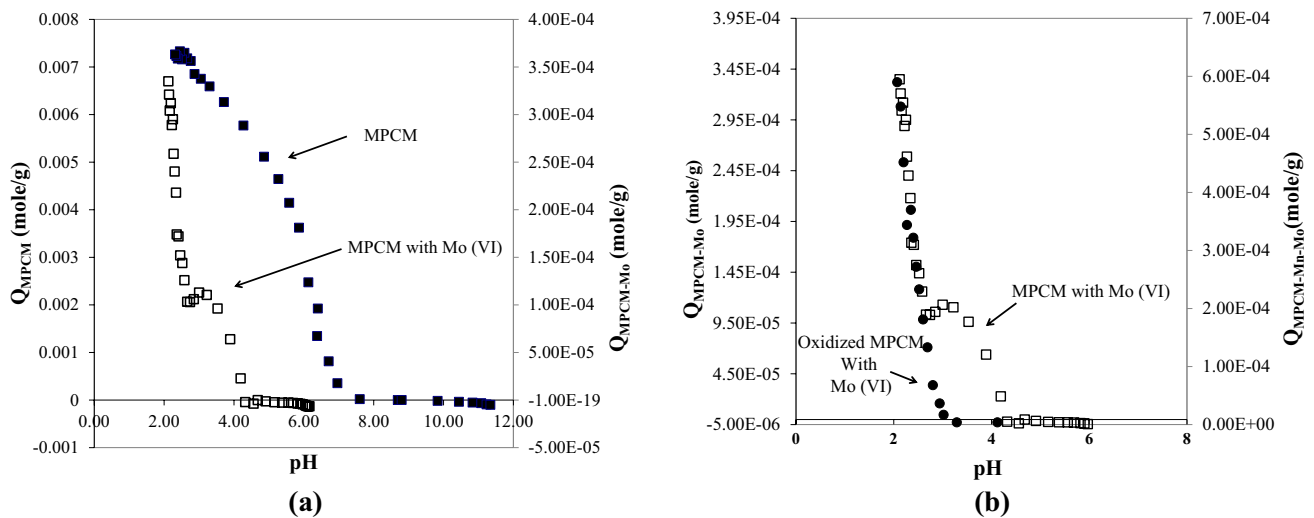


Fig. 12 Surface charge of **a** MPCM and MPCM exposed to 1% of Mo (VI) in solution in the presence of 1 M NaNO₃, respectively and **b** oxidized and non-oxidized MPCM exposed 1% of Mo(VI) in solution in presence of 1 N NaNO₃, respectively [79]

⁹⁹Mo/^{99m}Tc generator using low-specific activity (n, γ)⁹⁹Mo may find an application in nuclear medicine.

In case of molybdenum (Mo) uptake onto MPCM resin, Hasan [79] reported that the adsorption follows Type-1

isotherm and the Mo adsorption mostly occurs at the monolayer of active surface sites of the resin. Based on the above findings [79], Hasan [82] pointed out that the critical structures of the resin that absorb irradiated molybdenum

needs to be protected from the negative impact of higher radiation dose. In order to address this issue, following points are considered [82]:

- Since the active region of the resin structure is assumed to be thin, due to range consideration; a new type of shielding concept can be used to protect the critical structure of the resin from the negative impact of absorbed dose.
- The possibility of micro-shielding on the critical surface of the resin needs to be investigated which may reduce the impact of high radiation flux and minimize the radiolytic effect on to the resin surface.
- High Z elements, for instance Hf, can be used as micro-shielding candidate which, may cut down the dose on the active surface sites of the resin.
- Other high Z elements with higher stopping power are also good candidates as micro-shielding materials.
- Since the main constituents of MPCM resin are low Z elements (with less stopping power), the negative impact of high energy particles can also be minimized by maintaining a proper aspect ratio of the column.

It was reported that the radiation tolerance limit and selectivity of the MPCM resin for certain isotopes, was further enhanced by the high Z element crosslinked MPCM resin as it was not being limited by the radiolytic driven reaction [82]. The micro-shielded resin was termed as MPCM-Z resin. The performance of the MPCM-Z resin for molybdenum was evaluated using batch process. It was found that the resin is capable of adsorbing > 95% of available molybdenum (500–600 mg Mo/gram resin) within an hour from 1% solution at solution pH ~ 3.0, when the solid to liquid ratio was 2:100. A generator consisting of MPCM-Z resin loaded with low specific activity (n, γ)⁹⁹Mo was prepared. The ^{99m}Tc recovery was ± 70% when sodium nitrate (1 g/L) as an additive was used with saline solution. The breakthrough of ⁹⁹Mo and the pH of the eluent that pass through an alumina guard column were within the US Pharmacopeia limit.

Several studies reported technetium selective resin such as Dowex, TEVA (TetraValent Actinides), ABEC (aqueous biphasic extraction chromatographic) resin for the selective adsorption of pertechnetate from aqueous solution [83–85]. The possible uses of these technetium selective resins in the integrated production of ^{99m}Tc-generator are promising provided that ^{99m}Tc can be collected and concentrated in a small column and then eluted easily with saline, water or any suitable solvents. Keiko et al. [84] described a method for separating and purifying technetium from technetium-containing molybdenum using TEVA resin. However, the strong acidic solution (8 M

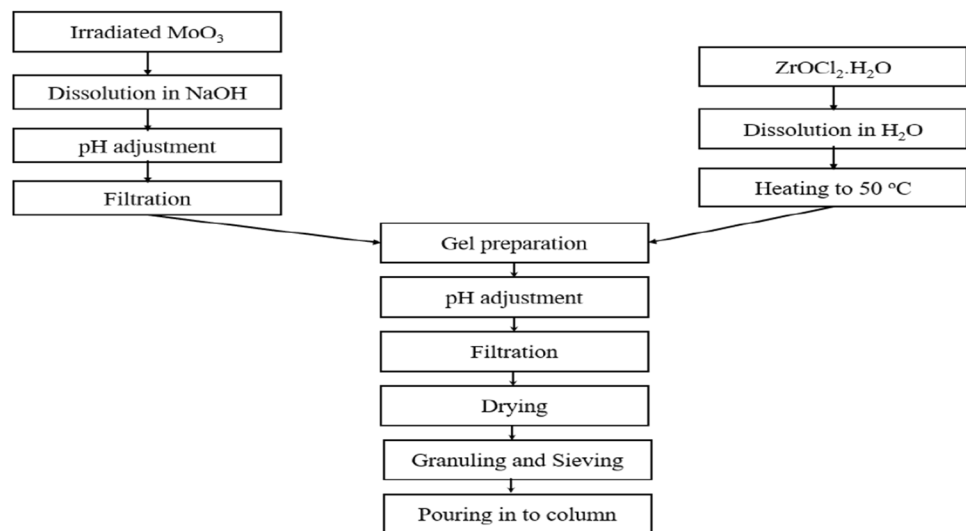
HNO₃) required for recovery of TcO₄⁻ ions from the TEVA resin. In practice, pertechnetate in strong acid solution is not preferred on the basis of daily use in nuclear medicine [20]. Wojdowska et al. [86] studied the separation of ^{99m}Tc from large excess of molybdenum using column containing Dowex-1 and AnaLig Tc-02 resin, respectively. It was reported that ^{99m}Tc is quantitatively bound to both Dowex-1 × 8 and AnaLig Tc-02 resin whereas molybdenum was found to be retained slightly and that can be rinsed out with 2 M NaOH. ^{99m}Tc was eluted with TBAB solution from the Dowex-1 column and the elution yield amounted to 78%. In case of AnaLig Tc-02 resin, ^{99m}Tc was eluted using small volume of water. The recovery was equal to about 85%. A US patent by Le VS et al. [87] described the preparation process for silica-based multifunctional resin. The molybdenum adsorption capacity of this multifunctional resin was reported to be 456–692 mg Mo/g and 313–445 mg Mo/g of sorbent under static and dynamic process. Due to its high capacity for molybdenum uptake, this multifunctional resin can be considered as a potential candidate for ⁹⁹Mo/^{99m}Tc (n, γ) generator. It was reported that one derivative of this multifunctional resin can be used to purify and concentrate ^{99m}Tc in a small column. It was further noted that the recovery yield of the daughter nuclide ^{99m}Tc was greater than 95%. An integrated generator system using this multifunctional resin and its derivative can be used to concentrate ^{99m}Tc, therefore, ^{99m}Tc with high specific activity (1 Ci/mL) is possible from a ⁹⁹Mo/^{99m}Tc (n, γ) generator. Table 4 shows typical example of adsorption capacity of different sorbents for molybdenum from aqueous solution.

3.2 Molybdate gel-generator

Several researchers proposed a zirconium molybdate based gel generator which is applicable to ⁹⁹Mo obtained easily by the (n, γ) reaction of natural molybdenum [90–92]. El-Amir et al. [93] prepared cerium (IV) tellurium molybdate based gel bed for chromatographic ⁹⁹Mo/^{99m}Tc generator. The ^{99m}Tc elution yield from this generator was 77.8 ± 3.0% with a radionuclidic purity of ≥ 99.99%, radiochemical purity of 96.5 ± 1.3% (as ^{99m}TcO₄⁻) and pH-value in the range of 5–7. Sarkar et al. [94] reported zirconium [⁹⁹Mo]molybdate (Zr⁹⁹Mo) gel column generator. Generator was prepared using 6–7 g Zr⁹⁹Mo gel column containing up to 22.2 GBq (600 mCi) ⁹⁹Mo. The radioactive concentration of ^{99m}Tc up to 4 GBq/mL (110 mCi/mL) was obtained on the first day of use. An acidic alumina guard column was used to remove the co-eluted traces of ⁹⁹Mo and to retain the pertechnetate. The overall recovery of ^{99m}Tc was > 90%, ⁹⁹Mo breakthrough was 10⁻³ to 10⁻⁴% and the duration

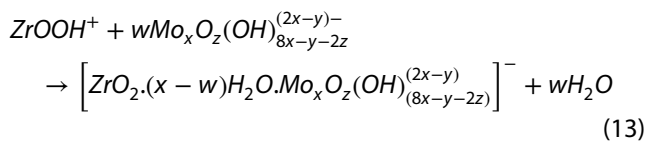
Table 4 Adsorption capacity of various adsorbents for molybdenum

Adsorbent	Adsorbent conditioning	Initial conc. (mg/L)	Exposure time (Hour)	pH	Uptake (mg/g)	Reference
Nanocrystalline Al ₂ O ₃	–	10,000	0.17	3	200	[60]
Gibbsite-Al ₂ O ₃	300 °C	10,000	3	4	67.5	[62]
P-Boehmite-Al ₂ O ₃	300 °C				82.4	
Bayerite-Al ₂ O ₃	300 °C				91.1	
Al ₂ O ₃	900 °C	1000	0.5	1.5	92.45	[63]
Alumina				2–3	20–25	[67]
Mesoporous Al ₂ O ₃			24	Acidic	225	[70]
Mesoporous Al ₂ O ₃	600 °C	886	2	3	12.5	[49]
Mesoporous Al ₂ O ₃	700 °C	732			31.0	
Mesoporous Al ₂ O ₃	900 °C	877			17.5	
Commercial-Al ₂ O ₃	–	842			42.6	
Al ₂ O ₃ embedded mesoporous Silica	–	1000	2	3	3.5	[73]
	600 °C				11.7	
	750 °C				16.8	
	900 °C				10.0	
	1050 °C				3.6	
Sulfated Al ₂ O ₃	–	10,500	Dynamic	10.5	392	[74]
Polymer embedded nanocrystalline titanium		10,000	1	Acidic	~ 100	[76]
Activated alumina				Acidic	23.5	[64]
Al ₂ O ₃ nanofiber	–			5.1	197	[88]
Zr-based material				Neutral	177	[89]
PZC		13,350	24	Neutral	285	[88]
PZC				Neutral	200–295	[78]
Chitosan based microporous composite	Partially oxidized	10,000	1	3	500	[79]
Mesoporous silica- based resin	Static dynamic	–	–	–	436–692 313–445	[87]

Fig. 13 Typical flow-chart of gel processing plant [92]

of concentration was 3–5 min. Monroy-Guzman et al. [91] suggested to prepare gels from molybdate solutions at pH 4.5, where a mixture of $Mo_7O_{24}^{6-}$ and $Mo_xO_y^{x-y-}$

ions is present, and 0.1 mol/L $ZrOCl_2 \cdot 8H_2O$ solutions aged for 1 day, where the formation of $ZrOOH^+$ ions is favored. The overall reaction is given in Eq. 13 [91]:



A typical zirconium molybdenum gel preparation flow sheet is given in Fig. 13. Marageh et al. [92] reported that the produced sodium pertechnetate solution from the zirconium molybdate gel-type $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators fulfills all requirements of U.S. pharmacopoeia as all of these generators provide high-yield and pure elution as well as sterile and pyrogen-free pertechnetate solutions. In addition, it shows favorable-quality features to prepare various $^{99\text{m}}\text{Tc}$ complexes.

Several difficulties of the gel preparations have been reported due to its dependence on many complex factors such as molybdenum and zirconium concentrations (ratio of Mo and Zr in the gel) and gel reaction temperatures which can greatly influence the $^{99\text{m}}\text{Tc}$ elution.

Chakravarty et al. [95] uses electrochemical method to concentrate $^{99\text{m}}\text{Tc}$ obtained from a zirconium molybdate (Zr^{99}Mo) gel generator. The overall recovery of $^{99\text{m}}\text{Tc}$ was 90% with 99.99% radionuclidic purity and 99% radiochemical purity. Saraswathy et al. [96] reported the effect of subtle variations on zirconium molybdate- ^{99}Mo gel preparatory conditions to achieve high $^{99\text{m}}\text{Tc}$ release and minimal ^{99}Mo breakthrough upon elution with normal saline. They prepared Zirconium molybdate- ^{99}Mo gels at a pH of 4–5 by reacting [Zr]: [Mo] in the mole ratio of 1.25:1. Monoroy-Guzman et al. [91] reported that a rigid and regular lattice (structure) of the zirconium molybdate gels acts as a “molecular sieve” preventing the mobility of the $^{99\text{m}}\text{Tc}$ in the gel and causing the decrease of the generator efficiency. The best performances of the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ zirconium molybdate gel generators are attained using gels with random network which allow a more diffusion of the $^{99\text{m}}\text{TcO}_4^-$ increasing the generator efficiency.

3.3 Solvent extraction

The $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ separation processes in solvent extraction systems are carried out in well shielded hot cells usually installed within the premises of a nuclear research establishment under the supervision of well trained and qualified staff. It essentially consists of a glass-quartz or stainless steel apparatus in which activated $^{99}\text{MoO}_3$ is dissolved in an acid or base (HCl , NaOH) and mixed with an organic solvent such as methyl-ethyl-ketone (MEK) to preferentially concentrate $^{99\text{m}}\text{Tc}$ over ^{99}Mo . Once equilibrium is reached, the organic solvent containing decay-produced $^{99\text{m}}\text{Tc}$ is separated from the aqueous layer into a different vessel and evaporated out leaving behind a white powder of technetium salt. This water soluble salt is then dissolved in a sterilized physiological saline solution (0.9% NaCl) for distribution to the users in hospitals after proper quality control procedures have been satisfactorily performed. The parent ^{99}Mo contained in the aqueous layer continues to produce further $^{99\text{m}}\text{Tc}$ which, after a proper equilibration period of approximately one day, is ready for subsequent extractions with an organic solvent.

3.4 Sublimation generator

The separation of $^{99\text{m}}\text{Tc}$ from ^{99}Mo in the sublimation generator is achieved by subjecting the activated MoC_3 to high temperatures of over 900°C to sublimate an oxide of $^{99\text{m}}\text{Tc}$ for collection and dissolution in a physiological saline solution. While sublimation systems produce $^{99\text{m}}\text{Tc}$ of the highest purity and high radioactivity concentration, they must be installed in a shielded hot cell.

3.5 Comparison of separation techniques

Alternative technologies for $^{99\text{m}}\text{Tc}$ generator using relatively low specific activity ^{99}Mo produced by the neutron

Table 5 Various methods used to separate $^{99\text{m}}\text{Tc}$ from ^{99}Mo [4, 41, 97]

Separation of ^{99}Mo and $^{99\text{m}}\text{Tc}$	^{99}Mo	Physical/chemical property	Separation efficiency of $^{99\text{m}}\text{Tc}$ (%)	Advantage	Disadvantage
Chromatography (Fission process)	(n, f)	Charge	80–95	Simple, portable	High cost
Chromatography (Neutron capture process)	(n, γ)	Charge	80–95	Simple, portable	Low specific activity; Small scale
Solvent extraction	(n, γ)	Hydrophobicity	50–75	Low cost, high separation efficiency	Complex, fire hazard; Limited prospect
Sublimation	(n, γ)	Vapor pressure	30–50	No chemical processing	Complex, fixed Further development required
Gel	(n, γ)	Solubility	80–95	Simple, portable	Low specific activity; Small scale

activation of natural molybdenum would provide a less complex, less expensive, and more practical route for indigenous production and use of ^{99m}Tc . Many attempts have been made to develop different alternative technologies based on (n, γ) ^{99}Mo by exploiting the differences in the volatility of technetium and molybdenum oxides (sublimation generators) [4]. The separation can be achieved by extraction, usually by using methyl ethyl ketone (extraction generator). The chromatographic-type generators are very simple to use and safe for handling. It has several advantages over other separation methods that include compact size, easy transportability, single step rapid operation, radiological and pharmaceutical safety, and ^{99m}Tc separation with high yield and purity [97]. Note that solvent extraction and sublimation separation techniques are also widely utilized in India, Peru, and Thailand with low specific activity ^{99}Mo while Kazakhstan and Romania employ gel-generators. Typical example of different separation methods used in $^{99m}\text{Tc}/^{99}\text{Mo}$ generator systems to separate ^{99m}Tc is given in Table 5.

4 Generator performance

The performance of a chromatographic generator involves several factors including elution profile, elution efficiency, radionuclidic purity, chemical purity, and the radiochemical purity of the eluted ^{99m}Tc [97].

4.1 Elution efficiency

The elution efficiency of a generator can be defined as the fraction of the theoretically available ^{99m}Tc activity in the system which is separated during the elution process. In practice, the ^{99m}Tc elution efficiency is determined by the following relation:

$$\text{Elution Yield}(\%) = \frac{A_{\text{Tc}(\text{measured})}}{A_{\text{Tc}(\text{theoretical})}} \times 100 \quad (14)$$

where $A_{\text{Tc}(\text{measured})}$ is the activity of ^{99m}Tc measured in the eluate, and $A_{\text{Tc}(\text{theoretical})}$ is the activity of ^{99m}Tc calculated according to the activity of ^{99}Mo adsorbed on the column and time elapsed after adsorption or previous elution. The elution efficiency of a generator mainly depends on physical size and shape of a generator. It may vary randomly time to time, possibly due to complex chemical, physico-chemical and radiochemical processes in the generator [4].

The valence state of technetium may also play a role on elution yield [98]. Boyd [97] concluded that extensively washed and frequently eluted generators have the sharpest elution profiles and highest elution efficiencies. Improper eluent, reduction of pertechnetate by radiolysis, organic impurities, mechanical problems etc., are few noted factors that may cause low elution yield [48, 58]. The

dissolved oxygen aids in keeping the technetium in the pertechnetate form i.e., oxygen is essential in maintaining a high elution yield.

4.2 Breakthrough

One major concern with ^{99m}Tc generators is ^{99}Mo 'breakthrough' i.e., partial elution of the ^{99}Mo parent along with ^{99m}Tc from the generator. From the stand point of patient radiation safety, the amount of ^{99}Mo in the elution should be as low as possible because the presence of ^{99}Mo in the elution may interfere with labeling process and lead to clumping of red blood cells and possible microemboli. In case of alumina as adsorbent in the column, some possible causes of ^{99}Mo breakthrough are [58]:

- Exceeding the ion exchange capacity of the alumina
- pH of the alumina is greater than 7
- channeling or disrupted alumina bed
- excessive elution

According to NRC regulation, the acceptable limit of ^{99}Mo breakthrough is $1.0 \mu\text{Ci } ^{99}\text{Mo}/\text{mCi } ^{99m}\text{Tc}$ ($10^{-3}\text{Bq } ^{99}\text{Mo}/\text{Bq } ^{99m}\text{Tc}$), not to exceed $5 \mu\text{Ci}$ (185 kBq) per human dose at the time of injection. The breakthrough of a generator can be calculated as follows:

$$\text{Breakthrough} = \frac{A_{^{99}\text{Mo}}}{A_{^{99m}\text{Tc}}} \quad (15)$$

where $A_{^{99}\text{Mo}}$ is the measured activity of the ^{99}Mo and $A_{^{99m}\text{Tc}}$ that of ^{99m}Tc . A NaI (TI) counting systems is capable of detecting the activity of ^{99}Mo in the presence of much larger amounts of ^{99m}Tc and some dose calibrators with a lead-lined container are available specifically for this purpose.

4.3 Radionuclide purity

Radionuclidic purity for ^{99m}Tc refers to the percentage of radioactivity of ^{99m}Tc present in the total radioactivity of product. For effective utilization of the radioisotope ^{99m}Tc , it must be free of isotopic contamination when it is used for labeling or intravenous administration to humans. Current U.S. Pharmacopeia requires ^{99m}Tc from a generator (fission) to be at least 99.96% pure as a radionuclide, whereas European Pharmacopeia expects 99.88% radioactivity due to ^{99m}Tc . Boyd [97] reported that an ideal generator would produce ^{99m}Tc with a purity that satisfies Pharmacopeia specification for a period of three ^{99m}Tc half-lives (~ 18 h). Table 6 shows that the sodium pertechnetate (^{99m}Tc) injection should contain not less than 90%

Table 6 Sodium pertechnetate (^{99m}Tc) injection (fission) US and European Pharmacopeia [99, 100]

Parameters	Units	Limits	
		US pharmacopeia	European pharmacopeia
Sources of ^{99}Mo		Fission-based	Fission-based
Characteristic		A clear colorless solution. Half-life of ^{99m}Tc 6.02 h, emits gamma radiation 140 keV	A clear colorless solution. Half-life of ^{99m}Tc 6.02 h, emits gamma radiation 140 keV
pH	S.U	4.0–8.0	4.0–8.0
Radionuclidic purity	% of Total activity	$^{99}\text{Mo} \leq 0.15 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ (0.015%)	$^{99}\text{Mo} \leq 0.15 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ (0.015%)
	% of Total activity	$^{131}\text{I} \leq 0.05 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ (0.005%)	$^{131}\text{I} \leq 0.05 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ (0.005%)
	% of Total activity	$^{103}\text{Ru} \leq 0.05 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ (0.005%)	$^{103}\text{Ru} \leq 0.05 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ (0.005%)
	% of Total activity	$^{89}\text{Sr} \leq 0.0006 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ ($6 \times 10^{-5}\%$)	$^{89}\text{Sr} \leq 0.0006 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ ($6 \times 10^{-5}\%$)
	% of Total activity	$^{90}\text{Sr} \leq 0.00006 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ ($6 \times 10^{-6}\%$)	$^{90}\text{Sr} \leq 0.00006 \mu\text{Ci}/\text{mCi}^{99m}\text{Tc}$ ($6 \times 10^{-6}\%$)
	% of Total activity	α -emitting impurities $\leq 0.001 \text{nCi}/\text{mCi}^{99m}\text{Tc}$ ($1 \times 10^{-7}\%$)	α -emitting impurities $\leq 0.001 \text{nCi}/\text{mCi}^{99m}\text{Tc}$ ($1 \times 10^{-7}\%$)
	% of Total activity	other γ emitting impurities $\leq 0.01\%$ of ^{99m}Tc activity	other γ emitting impurities $\leq 0.01\%$ of ^{99m}Tc activity
Radiochemical purity	% of ^{99m}Tc activity	$\geq 95\%$ as pertechnetate	$\geq 95\%$ as pertechnetate
Chemical purity	$\mu\text{g}/\text{mL}$	$\text{Al} \leq 10$	$\text{Al} \leq 10$
Sterility and pyrogenicity	Injections- USP Chap 1	Pass sterility test-71 Pass pyrogens test-151	Release before completion of test
Endotoxins	Injections- USP Chap 1	Pass endotoxin test γ [85]	Release before completion of test
Radioactivity (yield of ^{99m}Tc)	% of declared activity	90–110%	90–110%

and not more than 110% of the declared ^{99m}Tc radioactivity stated on the label at the reference date and time.

The European and the US Pharmacopeia specifies the limits of radionuclidic impurities that should not exceed at the time of administration (Table 6). The most probable radionuclide contaminant in the final product of ^{99m}Tc is the parent ^{99}Mo (most likely due to excessive breakthrough). The choice of target material and its purity are also important factors as some radionuclidic impurities may occur from the activation of impurities present in the target. The radioactivity due to ^{99}Mo does not exceed 0.1% of the total radioactivity of the test solution. Other γ -ray emitting radionuclidic impurities including ^{99}Mo , ^{131}I , ^{132}I , ^{103}Ru , and ^{89}Sr shall not exceed 0.5 μCi per mCi of ^{99m}Tc at the time of administration. Some of the possible causes of fission-product contamination are [58, 101]:

- production route of the parent ^{99}Mo
- Improper separation procedures used in the manufacture of the ^{99}Mo
- Insufficient washing of the generator during preparation

4.4 Chemical purity

The presence of chemical impurity in the final ^{99m}Tc product may cause detrimental effect on the clinical application

and is to be controlled strictly. The chemical impurity of ^{99m}Tc , that reflects the composition of non-radioactive components, may originate from the generator bed or from the eluent. The most probable chemical impurity that may be detected in the eluent is aluminum. In general, the generator column is prepared using aluminum oxide (alumina) as a support for the parent ^{99}Mo . Aluminum cations can be formed during adsorption of ^{99}Mo as the bed is exposed to acidic pH condition. Cationic aluminum can be washed away from the generator column during the subsequent elution of the daughter radionuclide ^{99m}Tc (pertechnetate). The aluminum ion concentration in the eluent should not be more than 10 $\mu\text{g}/\text{mL}$ of the generator eluate.

4.5 Radiochemical purity

Radiochemical purity of radiopharmaceuticals is defined as the proportion of the total radioactivity in the sample associated with desired radiolabeled species [102]. For instance, the presence of ^{99m}Tc in pertechnetate form (+7 state) is most desirable as this species can easily be converted to other oxidation states prior to complexation with suitable ligands [70]. Radiochemical purity is also used as the index of biological performance of radiopharmaceuticals that are administered to human. The possible radiochemical contamination in the ^{99m}Tc labeled product may occur from decomposition due to action of solvent,

change in temperature or pH, light and radiolysis in the generator systems [103]. The presence of any undesirable radiochemical impurity will reduce efficacy of the final radiopharmaceutical product.

5 Conclusion

The growing demand of ^{99m}Tc and the inherent problem associated with ^{99}Mo production from fission products has increased the interest for economically feasible alternative sources of ^{99}Mo . Production of ^{99}Mo via the neutron capture method can be a feasible alternative to fission derived ^{99}Mo but the significant lower Curie yield and lower specific activity is of great concern. Therefore, use of lower specific activity molybdate is only feasible with a more efficient adsorbent to reduce the generator size. Several highly efficient adsorbents for molybdenum have been reported in the literature with some success. In addition, several technetium selective resins are also reported for their use in purification and concentration of ^{99m}Tc . Therefore, it was envisaged that ^{99m}Tc with high specific activity can be obtained by adding a concentrator column unit in a chromatographic $^{99}\text{Mo}/^{99m}\text{Tc}$ (n,γ) generator system.

Appendix A: Fission Production Derivation

Molybdenum-99 (^{99}Mo) is generally produced through the thermal fission of highly enriched uranium (HEU). The amount of ^{99}Mo produced from this reaction is dependent on the thermal neutron flux, the amount of ^{235}U present in the system, and the time exposed. Since the amount of ^{98}Mo present in the system is continuously changing, it is first necessary to establish the ^{235}U population with respect to time. Since ^{235}U is long lived (half-life of seven billion years) and is not being produced by other reactions, loss due to decay is neglected so the change in its population is due entirely to thermal neutron interactions. Therefore, the amount of ^{235}U present in the system at time, t , is determined through integration of

$$\frac{dN_{U-235}}{dt} = -\varphi(\sigma_{U-235,a} + \sigma_{U-235,f})N_{U-235} \quad (16)$$

where φ is the neutron flux, $\sigma_{U-235,a}$ and $\sigma_{U-235,f}$ are the thermal neutron absorption and fission cross sections, respectively, and N_{U-235} is the number of ^{235}U nuclei present in the system at time t . Note that it is assumed that the neutron cross sections and flux are constant with

respect to time. Both sides of Eq. (1) are divided by N_{U-235} to separate the variables and yield

$$\int \frac{dN_{U-235}}{N_{U-235}} = - \int \varphi(\sigma_{U-235,a} + \sigma_{U-235,f}) dt \quad (17)$$

Both sides of Eq. (2) may now be integrated so that

$$\ln(N_{U-235}) = -\varphi(\sigma_{U-235,a} + \sigma_{U-235,f})t + C \quad (18)$$

where C is a constant of integration. The imposed initial condition is

$$N_{U-235}(t = 0) = N_{U-235,0} \quad (19)$$

where $N_{U-235,0}$ is the number of ^{235}U atoms present prior to exposure to the neutron field. The initial condition is used to determine the constant of integration

$$C = \ln(N_{U-235,0}) \quad (20)$$

which is then substituted back into Eq. (3) to yield

$$\ln(N_{U-235}) - \ln(N_{U-235,0}) = -\varphi(\sigma_{U-235,a} + \sigma_{U-235,f})t \quad (21)$$

Finally, Eq. (21) is rearranged and the natural log terms removed with exponentials to express the number of ^{235}U atoms present at time, t

$$N_{U-235} = N_{U-235,0} e^{-\varphi(\sigma_{U-235,a} + \sigma_{U-235,f})t} \quad (22)$$

Now that the amount of target material is known, it is necessary to develop an expression for the amount of ^{99}Mo present in the system at time, t . Molybdenum-99 is produced by approximately six percent of all thermal fissions of Uranium and can be lost through radioactive decay or further neutron capture. The amount of ^{99}Mo present in the system at time, t , is determined through integration of

$$\frac{dN_{Mo-99}}{dt} = \varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235} - \lambda_{Mo-99}N_{Mo-99} - \varphi\sigma_{Mo-99}N_{Mo-99} \quad (23)$$

where N_{Mo-99} is the number of ^{99}Mo atoms present with respect to time, σ_{Mo-99} is the thermal neutron absorption cross section, γ_{Mo-99} is the probability of ^{99}Mo production through fission, and λ_{Mo-99} is the decay constant which is calculated using ^{99}Mo 's half-life as

$$\lambda_{Mo-99} = \frac{\ln(2)}{t_{\frac{1}{2}}} = \frac{0.693}{66 \text{ hours}} = 0.0105 \text{ hours}^{-1} \quad (24)$$

The terms corresponding to the ^{99}Mo population are moved to the left side of Eq. (23) while Eq. (22) is substituted into the right side so that

$$\frac{dN_{Mo-99}}{dt} + (\lambda_{Mo-99} + \varphi\sigma_{Mo-99})N_{Mo-99} = \varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0}e^{-\varphi(\sigma_{U-235,a} + \sigma_{U-235,f})t} \tag{25}$$

$$N_{Mo-99} = \frac{\varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0}}{k - \varphi(\sigma_{U-235,a} + \sigma_{U-235,f})} \left[e^{-\varphi(\sigma_{U-235,a} + \sigma_{U-235,f})t} - e^{-kt} \right] \tag{34}$$

and the final answer can be obtained by combining Eqs. (34) and (26)

$$N_{Mo-99} = \frac{\varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0}}{\lambda_{Mo-99} + \varphi(\sigma_{Mo-99} - \sigma_{U-235,a} - \sigma_{U-235,f})} \left[e^{-\varphi(\sigma_{U-235,a} + \sigma_{U-235,f})t} - e^{-(\lambda_{Mo-99} + \varphi\sigma_{Mo-99})t} \right] \tag{35}$$

The integral can be further simplified by defining a dummy variable

$$k = \lambda_{Mo-99} + \varphi\sigma_{Mo-99} \tag{26}$$

and multiplying both sides of Eq. (25) by the integrating factor

$$IF = e^{kt} \tag{27}$$

so that Eq. (25) reduces to

$$\frac{dN_{Mo-99}}{dt} e^{kt} + kN_{Mo-99} e^{kt} = \varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0} e^{(k-\varphi(\sigma_{U-235,a} + \sigma_{U-235,f}))t} \tag{28}$$

and then further reduces to

$$\int d(N_{Mo-99} e^{kt}) = \int \varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0} e^{(k-\varphi(\sigma_{U-235,a} + \sigma_{U-235,f}))t} dt \tag{29}$$

Both sides of Eq. (29) may now be integrated so that

$$N_{Mo-99} e^{kt} = \frac{\varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0}}{k - \varphi(\sigma_{U-235,a} + \sigma_{U-235,f})} e^{(k-\varphi(\sigma_{U-235,a} + \sigma_{U-235,f}))t} + C \tag{30}$$

Since the ⁹⁹Mo is created entirely from the six percent of ²³⁵U fissions, it can be assumed that there is none present at the beginning of irradiation so that

$$N_{Mo-99}(t = 0) = 0 \tag{31}$$

which can be used in conjunction with Eq. (30) to determine the constant of integration

$$C = -\frac{\varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0}}{k - \varphi(\sigma_{U-235,a} + \sigma_{U-235,f})} \tag{32}$$

and can be substituted back into Eq. (30) to yield

$$N_{Mo-99} e^{kt} = \frac{\varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0}}{k - \varphi(\sigma_{U-235,a} + \sigma_{U-235,f})} \left[e^{(k-\varphi(\sigma_{U-235,a} + \sigma_{U-235,f}))t} - 1 \right] \tag{33}$$

Equation (33) can now be expanded by dividing both sides by the integrating factor

Note that Eq. (35) can be simplified to

$$N_{Mo-99} = \frac{\varphi\sigma_{U-235,f}\gamma_{Mo-99}N_{U-235,0}}{\lambda_{Mo-99}} \left[1 - e^{-\lambda_{Mo-99}t} \right] \tag{36}$$

by neglecting secondary absorptions.

Appendix B: Neutron Capture Production Derivation

Molybdenum-99 (⁹⁹Mo) can also be produced via neutron capture in which a ⁹⁸Mo target is bombarded with a neutron flux for a given time. As with the thermal fission case, the amount of ⁹⁹Mo produced from this reaction is dependent on the thermal neutron flux, the amount of ⁹⁸Mo present in the system, and the irradiation time. Since some amount of ⁹⁸Mo will be consumed by the reaction, it is first necessary to establish the variable ⁹⁸Mo population. Since ⁹⁸Mo is stable and is not being produced by other reactions, the change in its population is due entirely to thermal neutron capture. Therefore, the amount of ⁹⁸Mo present in the system at time, *t*, is determined through integration of

$$\frac{dN_{Mo-98}}{dt} = -\varphi\sigma_{Mo-98}N_{Mo-98} \tag{37}$$

where φ is the neutron flux, σ_{Mo-98} is the thermal neutron absorption cross section for ⁹⁸Mo, and N_{Mo-98} is the number of ⁹⁸Mo nuclei present in the system at time *t*. Both sides of Eq. (37) are divided by N_{Mo-98} to separate the variables and yield

$$\int \frac{dN_{Mo-98}}{N_{Mo-98}} = - \int \varphi\sigma_{Mo-98} dt \tag{38}$$

Both sides of Eq. (38) may now be integrated so that

$$\ln(N_{Mo-98}) = -\varphi\sigma_{Mo-98}t + C \tag{39}$$

where C is a constant of integration. The imposed initial condition is

$$N_{Mo-98}(t = 0) = N_{Mo-98,0} \tag{40}$$

where $N_{Mo-98,0}$ is the number of ^{98}Mo atoms present prior to exposure to the neutron field. The initial condition is used to determine the constant of integration

$$C = \ln(N_{Mo-98,0}) \tag{41}$$

which is then substituted back into Eq. (39) to yield

$$\ln(N_{Mo-98}) - \ln(N_{Mo-98,0}) = -\varphi\sigma_{Mo-98}t \tag{42}$$

Finally, Eq. (42) is rearranged and the natural log terms removed with exponentials to express the number of ^{98}Mo atoms present at time, t

$$N_{Mo-98} = N_{Mo-98,0}e^{-\varphi\sigma_{Mo-98}t} \tag{43}$$

Now that the amount of target material is known, it is necessary to develop an expression for the amount of ^{99}Mo present in the system at time, t . Molybdenum-99 is produced only through the neutron capture of ^{98}Mo and can be lost through radioactive decay or further neutron capture. The amount of ^{99}Mo present in the system at time, t , is determined through integration of

$$\frac{dN_{Mo-99}}{dt} = \varphi\sigma_{Mo-98}N_{Mo-98} - \lambda_{Mo-99}N_{Mo-99} - \varphi\sigma_{Mo-99}N_{Mo-99} \tag{44}$$

$$N_{Mo-99} = \frac{\varphi\sigma_{Mo-98}N_{Mo-98,0}}{\lambda_{Mo-99} + \varphi(\sigma_{Mo-99} - \sigma_{Mo-98})} \left[e^{-\varphi\sigma_{Mo-98}t} - e^{-(\lambda_{Mo-99} + \varphi\sigma_{Mo-99})t} \right] \tag{45}$$

where N_{Mo-99} is the number of ^{99}Mo atoms present with respect to time and σ_{Mo-99} is the thermal neutron absorption cross section. The terms corresponding to the ^{99}Mo population are moved to the left side of Eq. (44) while Eq. (43) is substituted into the right side so that

$$\frac{dN_{Mo-99}}{dt} + (\lambda_{Mo-99} + \varphi\sigma_{Mo-99})N_{Mo-99} = \varphi\sigma_{Mo-98}N_{Mo-98,0}e^{-\varphi\sigma_{Mo-98}t} \tag{45}$$

The integral can be further simplified by using the dummy variable defined in Eq. (26) and integrating factor in Eq. (27) so that Eq. (45) reduces to

$$\frac{dN_{Mo-99}}{dt}e^{kt} + kN_{Mo-99}e^{kt} = \varphi\sigma_{Mo-98}N_{Mo-98,0}e^{(k-\varphi\sigma_{Mo-98})t} \tag{46}$$

and then further reduces to

$$\int d(N_{Mo-99}e^{kt}) = \int \varphi\sigma_{Mo-98}N_{Mo-98,0}e^{(k-\varphi\sigma_{Mo-98})t}dt \tag{47}$$

Both sides of Eq. (47) may now be integrated so that

$$N_{Mo-99}e^{kt} = \frac{\varphi\sigma_{Mo-98}N_{Mo-98,0}}{k - \varphi\sigma_{Mo-98}}e^{(k-\varphi\sigma_{Mo-98})t} + C \tag{48}$$

Since the ^{99}Mo is created entirely from the ^{98}Mo being consumed in the neutron field, it can be assumed that there is none present at the beginning of irradiation so that

$$N_{Mo-99}(t = 0) = 0 \tag{49}$$

which can be used in conjunction with Eq. (48) to determine the constant of integration

$$C = -\frac{\varphi\sigma_{Mo-98}N_{Mo-98,0}}{k - \varphi\sigma_{Mo-98}} \tag{50}$$

and can be substituted back into Eq. (48) to yield

$$N_{Mo-99}e^{kt} = \frac{\varphi\sigma_{Mo-98}N_{Mo-98,0}}{k - \varphi\sigma_{Mo-98}} \left[e^{(k-\varphi\sigma_{Mo-98})t} - 1 \right] \tag{51}$$

Equation (51) can now be expanded by dividing both sides by the integrating factor

$$N_{Mo-99} = \frac{\varphi\sigma_{Mo-98}N_{Mo-98,0}}{k - \varphi\sigma_{Mo-98}} \left[e^{-\varphi\sigma_{Mo-98}t} - e^{-kt} \right] \tag{52}$$

and the final answer can be obtained by combining Eqs. (52) and (26)

As with Eq. (35), Eq. (53) can be simplified to

$$N_{Mo-99} = \frac{\varphi\sigma_{Mo-98}N_{Mo-98,0}}{\lambda_{Mo-99}} \left[1 - e^{-\lambda_{Mo-99}t} \right] \tag{54}$$

if secondary absorptions are neglected.

Appendix C: Radioactive decay derivation

Once the ^{99}Mo has been removed from the reactor, it can only be lost through radioactive decay so that

$$\frac{dN_{Mo-99}}{dt} = -\lambda_{Mo-99}N_{Mo-99} \tag{55}$$

where N_{Mo-99} is the number of ^{99}Mo atoms present with respect to time and λ_{Mo-99} is the decay constant which is calculated using ^{99}Mo 's half-life as

$$\lambda_{Mo-99} = \frac{\ln(2)}{t_{\frac{1}{2}}} = \frac{0.693}{66 \text{ hours}} = 0.0105 \text{ hours}^{-1} \tag{56}$$

Both sides of Eq. (55) are divided by N_{Mo-99} to separate the variables and yield

$$\int \frac{dN_{Mo-99}}{N_{Mo-99}} = - \int \lambda_{Mo-99} dt \tag{57}$$

Both sides of Eq. (57) may now be integrated so that

$$\ln(N_{Mo-99}) = -\lambda_{Mo-99}t + C \tag{58}$$

where C is a constant of integration. The imposed initial condition is

$$\frac{dN_{Tc-99m}}{dt} e^{\lambda_{Tc-99m}t} + \lambda_{Tc-99m}N_{Tc-99m}e^{\lambda_{Tc-99m}t} = \lambda_{Mo-99}N_{Mo-99,0}e^{(\lambda_{Tc-99m}-\lambda_{Mo-99})t} \tag{67}$$

$$N_{Mo-99}(t = 0) = N_{Mo-99,0} \tag{59}$$

where $N_{Mo-99,0}$ is the number of ^{99}Mo atoms present after the sample is removed from the neutron source. The initial condition is used to determine the constant of integration

$$C = \ln(N_{Mo-99,0}) \tag{60}$$

which is then substituted back into Eq. (58) to yield

$$\ln(N_{Mo-99}) - \ln(N_{Mo-99,0}) = -\lambda_{Mo-99}t \tag{61}$$

Finally, Eq. (61) is rearranged and the natural log terms removed with exponentials to express the number of ^{99}Mo atoms present at time, t

$$N_{Mo-99} = N_{Mo-99,0}e^{-\lambda_{Mo-99}t} \tag{62}$$

Since the purpose of creating the ^{99}Mo is to obtain a continually replenished supply of ^{99m}Tc , it is necessary to determine the amount of ^{99m}Tc present in the system with respect to time. Technetium-99 m is produced solely from the decay of ^{99}Mo and is lost through gamma decay to ^{99}Tc with a six hour half-life. Therefore, the amount of ^{99m}Tc present in the system at time, t , is determined through integration of

$$\frac{dN_{Tc-99m}}{dt} = \lambda_{Mo-99}N_{Mo-99} - \lambda_{Tc-99m}N_{Tc-99m} \tag{63}$$

where N_{Tc-99m} is the number of ^{99m}Tc atoms present with respect to time and λ_{Tc-99m} is the decay constant which is calculated using ^{99m}Tc 's half-life as

$$\lambda_{Mo-99} = \frac{\ln(2)}{t_{\frac{1}{2}}} = \frac{0.693}{6 \text{ hours}} = 0.1155 \text{ hours}^{-1} \tag{64}$$

The terms corresponding to the ^{99m}Tc population are moved to the left side of Eq. (62) while Eq. (61) is substituted into the right side so that

$$\frac{dN_{Tc-99m}}{dt} + \lambda_{Tc-99m}N_{Tc-99m} = \lambda_{Mo-99}N_{Mo-99} = \lambda_{Mo-99}N_{Mo-99,0}e^{-\lambda_{Mo-99}t} \tag{65}$$

an integrating factor may be used to simplify the differential equation

$$IF = e^{\lambda_{Tc-99m}t} \tag{66}$$

so that Eq. (64) reduces to

and then further reduces to

$$\int d(N_{Tc-99m}e^{\lambda_{Tc-99m}t}) = \int \lambda_{Mo-99}N_{Mo-99,0}e^{(\lambda_{Tc-99m}-\lambda_{Mo-99})t} dt \tag{68}$$

Both sides of Eq. (68) may now be integrated so that

$$N_{Tc-99m}e^{\lambda_{Tc-99m}t} = \frac{\lambda_{Mo-99}}{\lambda_{Tc-99m} - \lambda_{Mo-99}} N_{Mo-99,0} e^{(\lambda_{Tc-99m}-\lambda_{Mo-99})t} + C \tag{69}$$

Although ^{99m}Tc accumulates during the irradiation period, it is assumed that all traces are removed from the ^{99}Mo source prior to creation of the generator. Therefore, it is assumed that there is no ^{99m}Tc present initially so that

$$N_{Tc-99m}(t = 0) = 0 \tag{70}$$

which can be used in conjunction with Eq. (69) to determine the constant of integration

$$C = -\frac{\lambda_{Mo-99}}{\lambda_{Tc-99m} - \lambda_{Mo-99}} N_{Mo-99,0} e^{(\lambda_{Tc-99m}-\lambda_{Mo-99})t} \tag{71}$$

and can be substituted back into Eq. (69) to yield

$$N_{Tc-99m}e^{\lambda_{Tc-99m}t} = \frac{\lambda_{Mo-99}}{\lambda_{Tc-99m} - \lambda_{Mo-99}} N_{Mo-99,0} \left[e^{(\lambda_{Tc-99m}-\lambda_{Mo-99})t} - 1 \right] \tag{72}$$

The final answer can be obtained by removing the integrating factor from the both sides

$$N_{Tc-99m} = \frac{\lambda_{Mo-99}}{\lambda_{Tc-99m} - \lambda_{Mo-99}} N_{Mo-99,0} \left[e^{\lambda_{Mo-99}t} - e^{\lambda_{Tc-99m}t} \right] \tag{73}$$

The $^{99}Mo / ^{99m}Tc$ generator is eluted with saline to remove the ^{99m}Tc for use in diagnostic and treatment facilities. Due to the nature of this type of decay, there

is a optimum time required between elution so that the maximum amount of ^{99m}Tc is acquired. To determine the time at which the maximum amount of ^{99m}Tc is present in the system, it is necessary to take the derivative of Eq. (73) with respect to time so that

$$\frac{dN_{\text{Tc-99m}}}{dt} = \left(\frac{\lambda_{\text{Mo-99}}}{\lambda_{\text{Tc-99m}} - \lambda_{\text{Mo-99}}} \right) N_{\text{Mo-99},0} \left[\lambda_{\text{Tc-99m}} e^{-\lambda_{\text{Tc-99m}} t} - \lambda_{\text{Mo-99}} e^{-\lambda_{\text{Mo-99}} t} \right] \quad (74)$$

Setting the right side of Eq. (74) equal to zero and solving for time

$$0 = \left(\frac{\lambda_{\text{Mo-99}}}{\lambda_{\text{Tc-99m}} - \lambda_{\text{Mo-99}}} \right) N_{\text{Mo-99},0} \left[\lambda_{\text{Tc-99m}} e^{-\lambda_{\text{Tc-99m}} t_{\text{max}}} - \lambda_{\text{Mo-99}} e^{-\lambda_{\text{Mo-99}} t_{\text{max}}} \right] \quad (75)$$

$$\lambda_{\text{Mo-99}} e^{-\lambda_{\text{Mo-99}} t_{\text{max}}} = \lambda_{\text{Tc-99m}} e^{-\lambda_{\text{Tc-99m}} t_{\text{max}}} \quad (76)$$

$$\ln \left(\frac{\lambda_{\text{Mo-99}}}{\lambda_{\text{Tc-99m}}} \right) = \ln \left(\frac{e^{-\lambda_{\text{Tc-99m}} t_{\text{max}}}}{e^{-\lambda_{\text{Mo-99}} t_{\text{max}}}} \right) = (\lambda_{\text{Mo-99}} - \lambda_{\text{Tc-99m}}) t_{\text{max}} \quad (77)$$

$$t_{\text{max}} = \left| \frac{\ln \left(\frac{\lambda_{\text{Mo-99}}}{\lambda_{\text{Tc-99m}}} \right)}{(\lambda_{\text{Mo-99}} - \lambda_{\text{Tc-99m}})} \right| \quad (78)$$

So, the maximum amount of ^{99m}Tc will accumulate every

$$t_{\text{max}} = \frac{\ln \left(\frac{0.0105 \text{ hour}^{-1}}{0.1155 \text{ hour}^{-1}} \right)}{(0.0105 \text{ hour}^{-1} - 0.1155 \text{ hour}^{-1})} = 22.8371 \text{ hours} \quad (79)$$

So that elution should occur every 22.8371 h to obtain the maximum amount of ^{99m}Tc from the generator.

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