

Review Article

^{99m}Tc Generator Development: Up-to-Date ^{99m}Tc Recovery Technologies for Increasing the Effectiveness of ⁹⁹Mo Utilisation

Van So Le

MEDISOTEC and CYCLOPHARM Ltd., 14(1) Dwyer Street, Gymea, NSW 2227, Australia

Correspondence should be addressed to Van So Le; vansole01@gmail.com

Received 30 June 2013; Accepted 5 August 2013; Published 16 January 2014

Academic Editor: Pablo Cristini

Copyright © 2014 Van So Le. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

A review on the ⁹⁹Mo sources available today and on the ^{99m}Tc generators developed up to date for increasing the effectiveness of ⁹⁹Mo utilisation is performed in the format of detailed description of the features and technical performance of the technological groups of the ⁹⁹Mo production and ^{99m}Tc recovery. The latest results of the endeavour in this field are also surveyed in regard of the technical solution for overcoming the shortage of ⁹⁹Mo supply. The technological topics are grouped and discussed in a way to reflect the similarity in the technological process of each group. The following groups are included in this review which are high specific activity ⁹⁹Mo: the current issues of production, the efforts of more effective utilisation, and the high specific activity ⁹⁹Mo-based ^{99m}Tc generator and ^{99m}Tc concentration units; low specific activity ⁹⁹Mo: the ⁹⁹Mo production based on neutron capture and accelerators and the direct production of ^{99m}Tc and the methods of increasing the specific activity of ⁹⁹Mo using Szilard-Chalmers reaction and high electric power isotopic separator; up-to-date technologies of ^{99m}Tc recovery from low specific activity ⁹⁹Mo: the solvent extraction-based ^{99m}Tc generator, the sublimation methods for ⁹⁹Mo/^{99m}Tc separation, the electrochemical method for ^{99m}Tc recovery, and the column chromatographic methods for ^{99m}Tc recovery. Besides the traditional ^{99m}Tc-generator systems, the integrated ^{99m}Tc generator systems (^{99m}Tc generator column combined with postelution purification/concentration unit) are discussed with the format of process diagram and picture of real generator systems. These systems are the technetium selective sorbent column-based generators, the high Mo-loading capacity column-based integrated ^{99m}Tc generator systems which include the saline-eluted generator systems, and the nonsaline aqueous and organic solvent eluent-eluted generator systems using high Mo-loading capacity molybdategel and recently developed sorbent columns. ^{99m}Tc concentration methods used in the ^{99m}Tc recovery from low specific activity ⁹⁹Mo are also discussed with detailed process diagrams which are surveyed in two groups for ^{99m}Tc concentration from the saline and nonsaline ^{99m}Tc-eluates. The evaluation methods for the performance of ^{99m}Tc-recovery/concentration process and for the ^{99m}Tc-elution capability versus Mo-loading capacity of generator column produced using low specific activity ⁹⁹Mo source are briefly reported. Together with the theoretical aspects of ^{99m}Tc/⁹⁹Mo and sorbent chemistry, these evaluation/assessment processes will be useful for any further development in the field of the ^{99m}Tc recovery and ⁹⁹Mo/^{99m}Tc generator production.

1. Introduction

The development of the original ^{99m}Tc generator was carried out by Walter Tucker and Margaret Greens as part of the isotope development program at Brookhaven National Laboratory in 1958 [1]. ^{99m}Tc is currently used in 80–85% of diagnostic imaging procedures in nuclear medicine worldwide every year. This radioisotope is produced mainly from the ^{99m}Tc generators via β -particle decay of its parent nuclide ⁹⁹Mo. ⁹⁹Mo nuclide decays to ^{99m}Tc with an efficiency of

about 88.6% and the remaining 11.4% decays directly to ⁹⁹Tc. A ^{99m}Tc generator, or colloquially a “technetium cow,” is a device used to extract the ^{99m}Tc-pertechnetate generated from the radioactive decay of ⁹⁹Mo ($T_{1/2} = 66.7$ h). As such, it can be easily transported over long distances to radiopharmacies where its decay product ^{99m}Tc ($T_{1/2} = 6$ h) is extracted for daily use. ⁹⁹Mo sources used in different ^{99m}Tc generators are of variable specific activity (SA) depending on the production methods applied. Based on the nuclear reaction data

TABLE 1: Current application of ^{99m}Tc for clinical SPECT imaging and activity dose requirement; (*) The injection activity dose (mCi ^{99m}Tc) normally delivered in 1 mL solution of the ^{99m}Tc -based radiopharmaceutical [167].

Organ	^{99m}Tc radiopharmaceutical	Injection activity dose (*)	Organ	^{99m}Tc radiopharmaceutical	Injection activity dose (*)
Brain	^{99m}Tc -ECD	10–20 mCi	Kidney	^{99m}Tc -MAG3	5–15 mCi
	^{99m}Tc -ceretec (HmPAO)	10–2 mCi		^{99m}Tc -DTPA	5–15 mCi
	^{99m}Tc -MAA	2–4 mCi		^{99m}Tc -Glucaptate	5–15 mCi
Lung	^{99m}Tc -DTPA aerosol	30 mCi/3 mL (10 mCi/mL)	Skeleton	^{99m}Tc -DMSA	2–5 mCi
	^{99m}Tc -Technegas	100–250 mCi/mL		^{99m}Tc -MDP	10–20 mCi
Thyroid	^{99m}Tc -pertechnetate	5–10 mCi	Heart	^{99m}Tc -HDP	10–20 mCi
Liver	^{99m}Tc -IDA	5–10 mCi		^{99m}Tc -Sestamibi	10–30 mCi
	Spleen	^{99m}Tc -sulfur/albumine colloid	5–15 mCi	Tumour	^{99m}Tc -PYP
^{99m}Tc -sulfur/albumine colloid		2–3 mCi	^{99m}Tc -Tetrofosmin		5–25 mCi
^{99m}Tc -red blood cells		2–3 mCi	^{99m}Tc -Sestamibi		15–20 mCi

available today, two types of ^{99}Mo sources of significantly different SA values (low and high SA) can be achieved using different ^{99}Mo production ways. Accordingly, ^{99m}Tc generators using low or high SA ^{99}Mo should be produced by suitable technologies to make them acceptable for nuclear medicine uses. The safe utilisation of the ^{99m}Tc generators is definitely controlled by the quality factors required by the health authorities. However, the acceptability of the ^{99m}Tc generator to be used in nuclear diagnostic procedures, the effective utilisation of ^{99m}Tc generator, and the quality of ^{99m}Tc -based SPECT imaging diagnosis are controlled by the generator operation/elution management, which is determined by the ^{99m}Tc concentration of the ^{99m}Tc eluate/solution. This also means that the efficacy of the ^{99m}Tc generator used in nuclear medicine depends on the ^{99m}Tc concentration of the solution eluted from the generator, because the volume of a given injection dose of ^{99m}Tc -based radiopharmaceutical is limited. The current clinical applications of ^{99m}Tc are shown in Table 1. As shown, the injection dose activity of ^{99m}Tc -based radiopharmaceutical delivered in 1 mL solution is an important factor in determining the efficacy of the ^{99m}Tc solution produced from the generators. So it is clear that the ^{99m}Tc concentration of the solution eluted from the generator is the utmost important concern in the process of the generator development, irrespectively using either fission-based high specific activity ^{99}Mo or any ^{99}Mo source of low specific activity. It is realised that a complete review on the ^{99}Mo and ^{99m}Tc production/development may contribute and stimulate the continuing efforts to understand the technological issues and find out the ways to produce a medically acceptable $^{99}\text{Mo}/^{99m}\text{Tc}$ generator and to overcome the shortage/crisis of $^{99}\text{Mo}/^{99m}\text{Tc}$ supply. So this review is to give a complete survey on the technological issues related to the production and development of high and low specific activity ^{99}Mo and to the up-to-day ^{99m}Tc recovery technologies, which are carried out in many laboratories, for increasing the effectiveness of ^{99}Mo

utilisation. The evaluation methods for the performance of the ^{99m}Tc -recovery/concentration process and for the ^{99m}Tc -elution capability versus Mo-loading capacity of the generator column produced using (n, γ) ^{99}Mo (or any low specific activity ^{99}Mo source) are briefly reported. Together with the theoretical aspects of $^{99m}\text{Tc}/^{99}\text{Mo}$ and sorbent chemistry, these evaluation/assessment processes could be useful for any further development in the field of the ^{99m}Tc recovery and $^{99}\text{Mo}/^{99m}\text{Tc}$ generator production. The achievements gathered worldwide are extracted as the demonstrative examples of today progress in the field of common interest as well.

2. High Specific Activity ^{99}Mo : Current Issues of Production and Efforts of More Effective Utilisation

2.1. Production of High Specific Activity ^{99}Mo . High SA ^{99}Mo is currently produced from the uranium fission. The fission cross-section for thermal fission of ^{235}U is of approximately 600 barns. 37 barns of this amount result in the probability of a ^{99}Mo atom being created per each fission event. In essence, each one hundred fission events yields about six atoms of ^{99}Mo (6.1% fission yield). Presently, global demand for ^{99m}Tc is met primarily by producing high specific activity (SA) ^{99}Mo from nuclear fission of ^{235}U and using mainly five government-owned and funded research reactors (NRU, Canada; HFR, the Netherland; BR2, Belgium; Osiris, France; Safari, South Africa). After neutron bombardment of solid uranium targets in a *heterogeneous research reactor*, the target is dissolved in a suitable solution and the high SA ^{99}Mo is extracted, purified and packed in four industrial facilities (MDS Nordion, Canada; Covidien, the Netherland; IRE, Belgium; NTP, South Africa), and supplied to manufacturers of ^{99m}Tc generators around the world [2–12]. CNEA/INVAP (Argentina), ANSTO (Australia), Russia, and

BATAN (Indonesia) also produce fission ^{99}Mo and total supply capacity of these facilities is about 5% of the global demand of ^{99}Mo [3]. The weekly demand of ^{99}Mo is reported to be approximately 12000 Ci at the time of reference (6-day Ci). This is equivalent to 69300 Ci at the end of bombardment (EOB). All five of the major production reactors use highly enriched uranium (HEU) targets with the isotope ^{235}U enriched to as much as 93% to produce ^{99}Mo (except Safari 1 in South Africa which uses 45% HEU). As mandated by the US Congress, non-HEU technologies for ^{99}Mo and $^{99\text{m}}\text{Tc}$ production should be used as a Global Initiative to Combat Nuclear Terrorism (GICNT) [13, 14]. The ^{99}Mo production plans for conversion of HEU to low enriched uranium (LEU) based technology, using heterogeneous research reactors, achieved a major milestone in years 2002–2010 and currently the production of high SA ^{99}Mo from LEU targets is routinely performed in Argentina (from 2002), in Australia (from 2009), and in South Africa (from 2010). CNEA/NVAP (Argentina) is a pioneer in the conversion of HEU to LEU by starting LEU-based ^{99}Mo production in 2002 after decommissioning of HEU technology which has been operated 17 years ago [15, 16]. INVAP also demonstrated the maturity of LEU technology via technology transfer to ANSTO for a modest industrial scale manufacture of a capacity of 300–500 6-day curies per batch. With an announcement last year on a great expansion of production capacity of LEU-based facility being started in 2016 in Australia [17], ANSTO and CNEA/INVAP will become the first organisations confirming the sustained commercial large-scale production of ^{99}Mo based on LEU technology. High SA ^{99}Mo is of approximately 50,000 Ci $^{99}\text{Mo/g}$ of total Mo at EOB (The OPAL reactor, Australia, thermal neutron flux: $9.10^{13} \text{ n/cm}^{-2} \text{ sec}^{-1}$), irrespectively using either HEU or LEU-based fission technologies. With the effort in maintaining the supply of high SA ^{99}Mo , several alternative non-HEU technologies are being developed. Fission of ^{235}U to produce ^{99}Mo is also performed using *homogeneous (solution) nuclear reactor* and ^{99}Mo recovery system, so-called Medical Isotope Production System (MIPS) [18]. The reactor fuel solution in the form of an LEU-based nitrate or sulphate salt dissolved in water and acid is also the target material for ^{99}Mo production. In essence, the reactor would be operated for the time required for the buildup of ^{99}Mo in the fuel solution. At the end of reactor operation, the fuel solution pumped through the ^{99}Mo -recovery columns, such as Termoxid 52, Termoxid 5M, titana, PZC sorbent, and alumina, which preferentially sorbs molybdenum [19, 20]. The ^{99}Mo is then recovered by eluting the recovery column and subsequently purified by one or more purification steps. It is estimated that a 200 kW MIPS is capable of producing about 10,000 Ci of ^{99}Mo at the end of bombardment (five-day irradiation) [2, 18, 21]. The possibility of using the *high power linear accelerator-driven proton* (150–500 MeV proton with up to 2 mA of beam current, $\sim 10^{16}$ particles/s) to generate high intensities of thermal-energy neutrons for the fission of ^{235}U in metallic LEU foil targets has been proposed [2, 22]. This accelerator can produce an order of magnitude more secondary neutrons inside the target from

fission. The *low energy accelerator* (300 keV deuteron with 50 mA of beam current)-based neutron production via the D,T reaction for the fission of ^{235}U in LEU solution targets has been reported [2]. The fission of ^{235}U for the ^{99}Mo production can be performed with neutrons generated from the $>2.224 \text{ MeV}$ *photon-induced breakup of D_2O* in a sub-critical LEU solution target. *Accelerator-driven photon-fission $^{238}\text{U}(\gamma, f)^{99}\text{Mo}$* is also proposed as an approach to produce high SA ^{99}Mo using natural uranium target [2, 23–25].

Under the consultation for the fission ^{99}Mo plant in ANSTO, the author of this review paper has proposed a project of “*Automated modular process for LEU-based production of fission ^{99}Mo* ” [26]. The consent of the Chief Executive Officer of ANSTO is a positive signal that might get scientists ahead of the game with next generation (cheaper, better, and faster) Mo-99 plant design. The aim of this project is to provide the integrated facility, composed of automated compact high technology modules, to establish medium-scale production capability in different nuclear centres running small reactors around the world. In essence, this project is to decentralize the ^{99}Mo production/supply and the radioactive waste treatment burden in the large facilities and to bring ^{99}Mo production closer to users ($^{99\text{m}}\text{Tc}$ generator manufacturers) to minimize the decay ^{99}Mo loss. The modular technology-based production is standardized for the secure operation sustainable with the supply of replaceable standardized modules/components for both ^{99}Mo processing and radioactive waste treatment. The above-mentioned objectives are in combination to solve basically the ^{99}Mo undersupply problem or crisis by increasing the numbers of smaller ^{99}Mo processing facilities in hundreds of nuclear centres owning ^{99}Mo production-capable reactors in the world and to reduce the cost of ^{99}Mo for patient use. The brief of the modular ^{99}Mo technology is the following. Currently, three main medical radioisotopes ^{99}Mo , ^{131}I , and ^{133}Xe are routinely produced from uranium fission. So, it is conceivable to say that the fission uranium based medical isotope production facility is composed of 6 main technological modules: target digestion module, ^{99}Mo separation module, ^{131}I separation module, ^{133}Xe separation module, uranium recovery module, and waste treatment modules (gas, solid, and liquid waste modules). For ^{99}Mo production alone, the numbers of main modules can be reduced to 4, comprising main module for uranium target digestion; main module for ^{99}Mo separation; main module for uranium recovery; main module for waste treatment (gas, solid, and liquid waste modules).

Each main module in this description is composed of several different functional modules. As an example, the main module for ^{99}Mo separation incorporates 7 functional modules, such as five ion exchange resin/sorption functional modules and two solution delivery functional modules (radioactive and nonradioactive).

A pictorial description of the structure of one main module which is capable of incorporating five functional modules (below illustrated with two functional modules as examples) is shown in Figure 1.

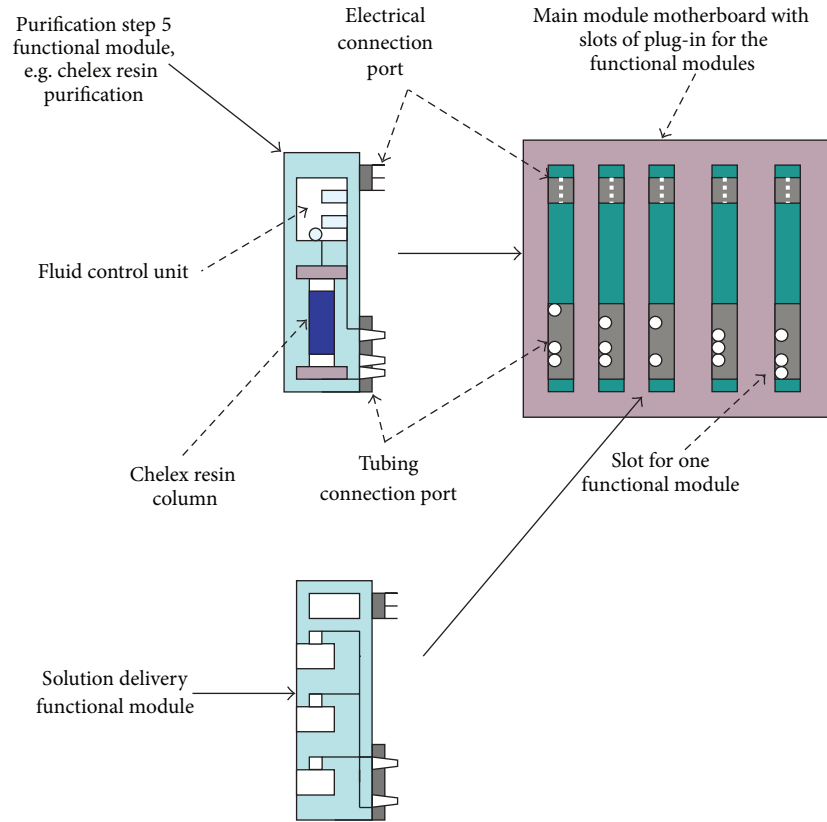


FIGURE 1: Conceptual diagram of the modular technology of fission- ^{99}Mo recovery [26].

The operation of this main module is automated and computerized. The integrated fluid flow and radioactivity monitoring system using photo and/or radiation diode sensors provides the feedback information for safe and reliable process control. The in-cell maintenance based on the replacement of failed functional module is completed quickly ensuring continuous production run. Advantages of this facility setup are the following: compact system with controllable and reliable process; less space required that minimizes the cost of the facility (one double-compartment hot cell for whole process); minimal maintenance work required that due to highly standardized modular integration; high automation capability; low cost production of ^{99}Mo making this modular technology feasible for small nuclear research centres in many countries of the world; centralizing the module supply and maintenance giving high security and sustainability of production to small producers with few resources; high capability of the network-based ^{99}Mo production/supply to overcome any global ^{99}Mo crisis.

The W impurity in massive LEU targets is still challenging the quality of ^{99}Mo obtained from different ^{99}Mo recovery processes, because the WO_4^{2-} ions and radioactive impurity (^{188}Re) generated from neutron-activated W cause serious problems in the $^{99\text{m}}\text{Tc}$ generator manufacture and in the use of $^{99\text{m}}\text{Tc}$ -pertechnetate solution, respectively. The effort to

remove W impurity from the ^{99}Mo solution produced from LEU target is being performed as shown in Figure 2 [27].

2.2. High Specific Activity Fission ^{99}Mo -Based $^{99\text{m}}\text{Tc}$ Generators and Concentrators. The isolation of ^{99}Mo from uranium fission typically generates ^{99}Mo with a specific activity greater than $>10,000$ Ci/g at the six-day-Ci reference time (specific activity of carrier-free ^{99}Mo is 474,464.0 Ci/g [28]). This SA value permits extraction of the $^{99\text{m}}\text{Tc}$ daughter nuclide using chromatographic alumina column [1, 29–35]. Today, most commercial $^{99\text{m}}\text{Tc}$ generators are designed by taking advantage of much stronger retaining of the MoO_4^{2-} anions compared with the TcO_4^- anions on acidic alumina sorbent. Although the adsorption capacity of the alumina for MoO_4^{2-} anions is low (<10 mg Mo/g), the very low content of Mo in the high SA ^{99}Mo solution (0.1 mg Mo per Ci ^{99}Mo), which is loaded on a typical column containing 2-3 g of alumina for a 4 Ci activity generator, ensures a minimal ^{99}Mo breakthrough in the medically useful $^{99\text{m}}\text{Tc}$ -pertechnetate solution extracted from the generator system. When the ^{99}Mo decays it forms pertechnetate ($^{99\text{m}}\text{TcO}_4^-$) which is easily eluted with saline solution from the alumina column resulting an injectable saline solution containing the $^{99\text{m}}\text{Tc}$ in the form of sodium-pertechnetate. The most stable form of the radionuclide $^{99\text{m}}\text{Tc}$ in aqueous solution is the tetraoxopertechnetate

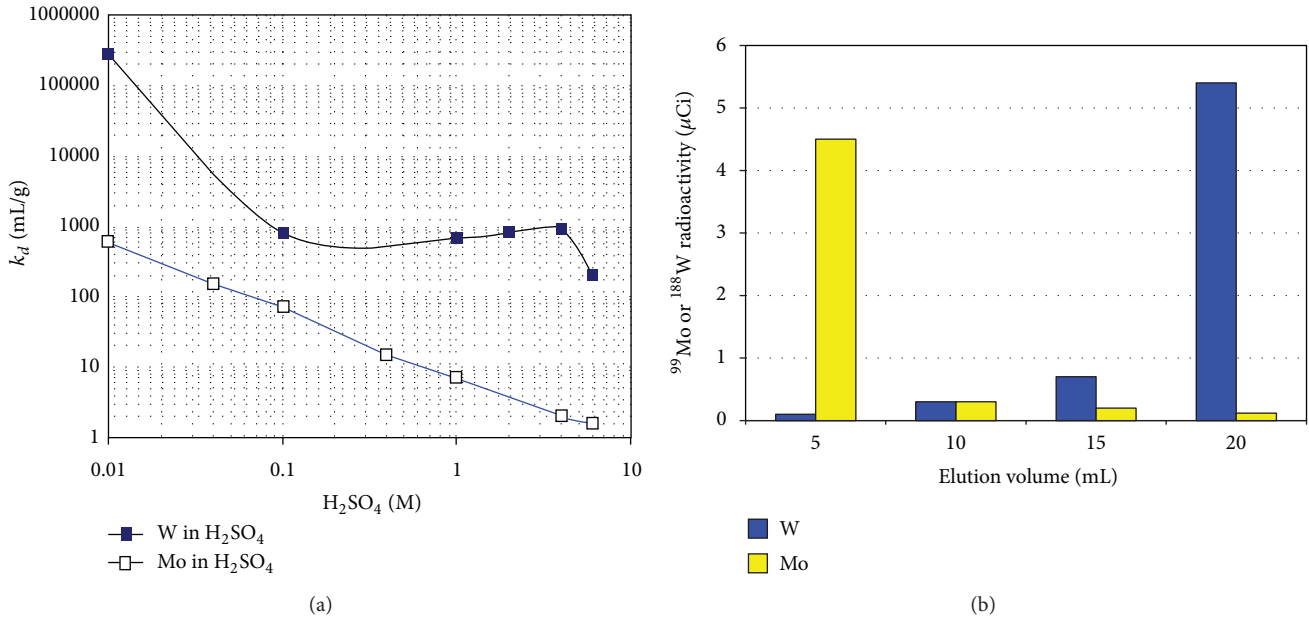


FIGURE 2: W/Mo adsorption and separation using alumina column: (a) weight distribution coefficients of WO_4^{2-} and MoO_4^{2-} ions on alumina versus acidity of H_2SO_4 solution; (b) elution profile of WO_4^{2-} and MoO_4^{2-} ions (column: 1 g alumina; eluent: 6 M H_2SO_4 for MoO_4^{2-} elution and 1 M NH_4OH for WO_4^{2-} stripping; loading solution: 8 mg Mo + 10 mg W) [27].

anion. The most important requirement for the design of an alumina column-based ^{99m}Tc recovery system is that it must exhibit both a high elution efficiency (typically >85%) and minimal ^{99}Mo breakthrough (<0.015%) [36, 37]. The generators are sold on the world market with different sizes from 200 mCi to 4000 mCi and the elution of ^{99m}Tc is performed with 5–10 mL normal saline. Fission ^{99}Mo -based $^{99}Mo/^{99m}Tc$ generators commercially available in the US are of the activity range between 0.2 Ci and 4.0 Ci at the six-day curies reference time and in ANSTO (Australia) between 0.45 Ci to 3.2 Ci. The cost-effective utilisation of a $^{99}Mo/^{99m}Tc$ generator and the quality of ^{99m}Tc based single photon emission computed tomography (SPECT) imaging diagnoses is controlled by the generator operation/elution management. The primary factor pertaining to the nuclear medicine diagnostic scans' quality is the concentration of ^{99m}Tc obtained from the $^{99}Mo/^{99m}Tc$ generator elution, which is expressed as activity per mL. The injection dose activity of ^{99m}Tc -based radiopharmaceuticals delivered in 1 mL solution (^{99m}Tc -concentration, mCi/mL) is an important factor in determining the useful life time of the ^{99m}Tc generators and the quality of ^{99m}Tc based SPECT imaging diagnosis as well. Generally, a ^{99m}Tc eluate is produced from the $^{99}Mo/^{99m}Tc$ generator in fixed volume and the concentration of the ^{99m}Tc in the eluted solution decreases with the life time of the $^{99}Mo/^{99m}Tc$ generator due to the radioactive decay of the parent nuclide ^{99}Mo . Consequently, the useful life time of the generator is also a function of available ^{99m}Tc concentration of the eluate. If we consider that the value 10–20 mCi of ^{99m}Tc per mL is used as a limit of the medically useful ^{99m}Tc solution, the assessment of the ^{99m}Tc generator utilisation effectiveness shows the following:

wasted residual activity of a used generator of 2 Ci activity eluted with 10 mL saline is 5–10% of its total activity, while smaller generators of 500 mCi activity waste up to 20–40%. In case of the concentrator used to increase the ^{99m}Tc concentration of the eluate eluted from these generators, all the activity of the generator will efficiently be exploited. So, the radioisotope concentrator device should be developed to increase the concentration and quality of injectable ^{99m}Tc eluates and consequently the generator life time or the effectiveness of the generator utilisation. Some concentration methods have been developed for increasing ^{99m}Tc concentration of the saline eluate for extension of the life time of the fission- ^{99}Mo -based ^{99m}Tc generators [38–44]. All these methods used a chloride-removing column containing Ag^+ ions, which couple with a pertechnetate-concentrating sorbent column such as alumina, Bonelut-SAX, QMA, and multifunctional sorbent. Alternative concentration methods have also been developed. The alternatives are based on the elution of the alumina column of the generator with a nonchloride aqueous eluent (such as ammonium-acetate solution and less-chloride acetic acid solution) or with a nonchloride organic eluent (such as tributylammonium-bromide and acetone solvent). ^{99m}Tc -pertechnetate of this eluate is concentrated using a sorbent column (concentration column) or an organic solvent evaporator, respectively. Then ^{99m}Tc -pertechnetate is recovered in a small volume of normal saline for medical use [45–60]. These methods have significantly increased the life time of the generators. The use of nonchloride eluent in replacement of saline normally used in a commercial generator may not be preferable due to legal issues of the amended registration requirement. Unfortunately, no concentrator device prototypes developed based

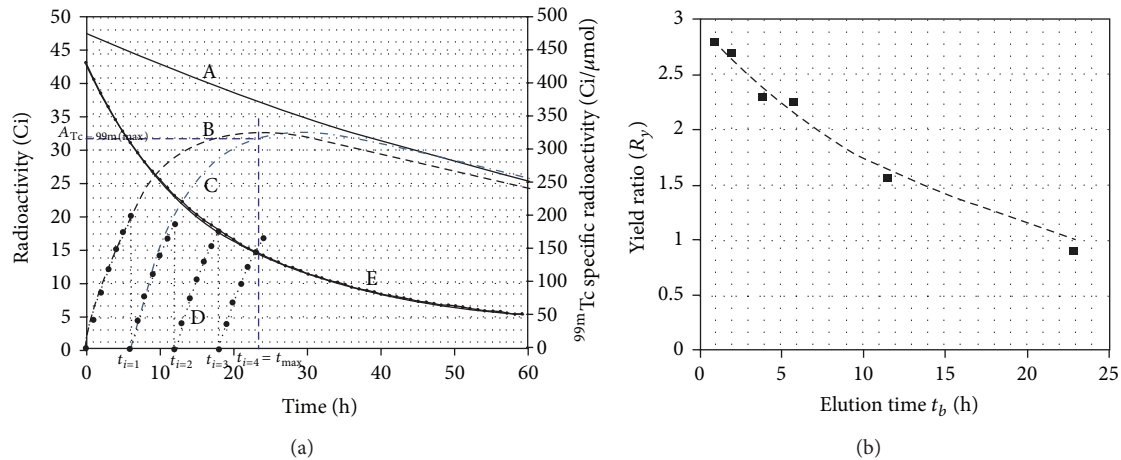


FIGURE 3: Radioisotope concentrator ULTRALUTE (patent-pending) and Effectiveness of $^{99m}\text{Tc}/^{99}\text{Mo}$ utilisation: (a) kinetics of radioactive decay/ ^{99m}Tc -activity buildup in the generator eluted with an early elution regime (A: ^{99}Mo -activity; B: ^{99m}Tc -activity buildup from beginning; C: ^{99m}Tc -activity growth/eluted at 6-hour elutions; D: ^{99m}Tc -activity growth/eluted at 6-hour elutions; E: ^{99m}Tc -SA in the system of ^{99m}Tc -radioactivity buildup from beginning) [58]; (b) effectiveness of "early" elution regime for increasing ^{99m}Tc -elution yield of the generator compared with that normally eluted at the time point of maximal ^{99m}Tc -buildup (square is experimental and dashed line is theoretical calculation result) [58]; (c) ULTRALUTE concentrator device [41, 61]; (d) ULTRALUTE concentrator device inline-coupled with a ^{99m}Tc generator.

on the developed methods are commercially available up to date. Recently, Cyclopharm Ltd. (Australia) in cooperation with Medisotec (Australia) has developed a $^{99m}\text{Tc}/^{188}\text{Re}$ concentrator device ULTRALUTE [40–42] using a new sorbent as a concentrator column coupled with the saline-eluted commercial generator. This device (Figures 3(c) and 3(d)) is a sterile multielution cartridge which is operated/eluted by evacuated-vial through disposable sterile filters to increase the ^{99m}Tc concentration of the saline eluate of aged commercial ^{99m}Tc generators. The increase in ^{99m}Tc concentration in the eluate enhances the utilisation of ^{99m}Tc in Technegas generator-based lung perfusion (100–250 mCi/mL) and other SPECT (20–30 mCi/mL) imaging studies. The ^{99m}Tc -pertechnetate of the generator eluate was concentrated more than 10-fold with a ^{99m}Tc recovery yield of >85% using this radioisotope concentrator device. Five repeated elutions were successfully performed with each cartridge. So, each

cartridge can be effectively used for one week in daily hospital environment for radiopharmaceutical formulation. The useful lifetime of the ^{99m}Tc generator was significantly extended depending on the activity of the generator as shown in Table 2. The ^{99}Mo impurity detectable in the ^{99m}Tc solution directly eluted from Gentech generator was totally eliminated by this radioisotope concentrator device and ultrapure, concentrated ^{99m}Tc -pertechnetate solution was achieved. The concentrated ^{99m}Tc solution is well suited to labeling in vivo kits and to loading the crucibles of Technegas aerosol generator for V/Q SPECT imaging. The useful life time of the ^{99m}Tc generator (Table 2) was significantly extended from 10 to 20 days for the generators of 300–3000 mCi activity, respectively. This means that about 20% of the generator activity is saved by extending the life time of the generator. Besides that about 20% of the generator ^{99m}Tc -activity can be saved as a result of the extension of ^{99m}Tc -generator life time,

the use of radioisotope concentrator for the optimization of generator elution to increasing the ^{99m}Tc -activity yield and the effectiveness of ^{99}Mo utilization was reported by Le (2013) [58, 61]. This fact is shown as follows. ^{99m}Tc continuously decays to ^{99}Tc during his buildup from the decay of ^{99}Mo . This process not only reduces the ^{99m}Tc -activity production yield of the generator (i.e. a large quantity of ^{99m}Tc activity wasted during ^{99m}Tc activity buildup results in a lower ^{99m}Tc -activity production yield of the generator, so it is noneconomically exploited), but also makes the specific activity (SA) of ^{99m}Tc continuously decreased. The low SA may cause the labelling quality of ^{99m}Tc eluate degraded. This means that the elutions of the generator at a shorter build-up time of daughter nuclide will result in a higher accumulative daughter-activity production yield (more effectiveness of $^{99m}\text{Tc}/^{99}\text{Mo}$ activity utilisation) and a better labelling quality of the generator eluate. Accumulative production yield is the sum of all the yields achieved in each early elution performed before the maximal build-up time. However, each early ^{99m}Tc -elution at shorter build-up time ("early" elution) will result in a lower ^{99m}Tc -elution yield and thus yields an eluate of lower ^{99m}Tc -concentration because ^{99m}Tc is eluted from the generator in fixed eluent volume. These facts show that a high labelling quality solution of clinically sufficient ^{99m}Tc concentration could be achieved if the generator eluate obtained at an "early" elution is further concentrated by a certified radioisotope concentrator device.

A general method described in previous work of V. S. Le and M. K. Le [58] was applied for evaluation of the effectiveness of "early" elution regime in comparison with a single elution performed at maximal build-up time point of the radionuclide generators. For this evaluation, the daughter nuclide-yield ratio (R_y) is set up and calculated based on quotient of the total of daughter nuclide-elution yields ($\sum_{i=1}^{i=n} A_{d(E_i)}$) eluted in all i elutions (E_i is the index for the i th elution) divided by the maximal daughter nuclide-yield or daughter nuclide-activity ($A_{d(\text{Max})}$) which could be eluted from the generator at maximal build-up time t_{Max} : $R_y = \sum_{i=1}^{i=n} A_{d(E_i)} / A_{d(\text{Max})}$.

Starting from the basic equation of radioactivity buildup/yield (A_d) of a daughter nuclide and the maximal build-up time (t_{Max}) for attaining the maximal activity buildup of daughter nuclide radioactivity growth-in in a given radionuclide generator system, the equation for calculation of daughter nuclide-yield ratio (R_y) was derived as follows [58]:

$$R_y = \frac{\sum_{i=1}^{i=n} A_{d(E_i)}}{A_{d(\text{Max})}} = \frac{\sum_{x=0}^{x=i-1} \left[e^{-\lambda_p \cdot x \cdot t_b} \times (e^{-\lambda_p \cdot t_b} - e^{-\lambda_d \cdot t_b}) \right]}{(e^{-\lambda_p \cdot t_{\text{Max}}} - e^{-\lambda_d \cdot t_{\text{Max}}})}. \quad (1)$$

(The subscripts p and d in the above equations denote the parent and daughter radionuclides, resp.).

As an example, the details of the case of $^{99m}\text{Tc}/^{99}\text{Mo}$ generator system are briefly described as follows:

numbers of radioactive ^{99}Mo nuclides:

$$N_{\text{Mo}} = N_{0,\text{Mo}} \times e^{-\lambda_{\text{Mo}} \cdot t}. \quad (2)$$

Radioactivity of ^{99m}Tc nuclides in the generator:

$$A_{\text{Tc-99m}} = \lambda_{\text{Tc-99m}} \times N_{0,\text{Mo}} \times b \times \left(\frac{\lambda_{\text{Mo}}}{\lambda_{\text{Tc-99m}} - \lambda_{\text{Mo}}} \right) \times (e^{-\lambda_{\text{Mo}} \cdot t} - e^{-\lambda_{\text{Tc-99m}} \cdot t}), \quad (3)$$

the maximal build-up time (at which the maximal ^{99m}Tc -activity buildup/yield in $^{99}\text{Mo}/^{99m}\text{Tc}$ generator system is available):

$$t_{\text{Max}} = \frac{[\ln(\lambda_{\text{Tc-99m}}/\lambda_{\text{Mo-99}})]}{(\lambda_{\text{Tc-99m}} - \lambda_{\text{Mo-99}})}. \quad (4)$$

Numbers of Tc atoms at build-up time:

$$\begin{aligned} N_{\text{Tc}} &= N_{\text{Tc-99}} + N_{\text{Tc-99m}} \\ &= N_{0,\text{Mo}} - N_{\text{Mo}} = N_{0,\text{Mo}} \times (1 - e^{-\lambda_{\text{Mo}} \cdot t}). \end{aligned} \quad (5)$$

Specific activity of carrier-included ^{99m}Tc in the ^{99m}Tc generator system or ^{99m}Tc -eluate is calculated using (3) and (5) as follows:

$$\begin{aligned} SA_{\text{Tc-99m}} &= \frac{A_{\text{Tc-99m}}}{N_{\text{Tc}}} \\ &= \frac{\lambda_{\text{Tc-99m}} \cdot b \cdot (e^{-\lambda_{\text{Mo}} \cdot t} - e^{-\lambda_{\text{Tc-99m}} \cdot t})}{0.6144 \times 10^{-7} \times ((\lambda_{\text{Tc-99m}}/\lambda_{\text{Mo}}) - 1) \times (1 - e^{-\lambda_{\text{Mo}} \cdot t})} \\ &\quad (\text{Ci/mol}). \end{aligned} \quad (6)$$

^{99m}Tc -Yield Ratio (R_y) Calculation for Multiple "Early" Elution Regime. The R_y value is calculated based on quotient of the total ^{99m}Tc -elution yields eluted (or ^{99m}Tc -activity produced/used for scans) in all i elution numbers (E_i is the index for the i th elution) divided by the maximal ^{99m}Tc -activity ($A_{\text{Tc-99m}(\text{Max})}$) which would be eluted from the generator at maximal build-up time t_{Max} .

The total ^{99m}Tc -elution yields eluted in all i elutions are the sum of ^{99m}Tc -radioactivities at a different elution number i ($A_{\text{Tc-99m}(E_i)}$). This amount is described as follows:

$$\begin{aligned} \sum_{i=1}^{i=n} A_{\text{Tc-99m}(E_i)} &= \lambda_{\text{Tc-99m}} \times \sum_{i=1}^{i=n} N_{\text{Tc-99m}(E_i)} \\ &= \lambda_{\text{Tc-99m}} \sum_{x=0}^{x=i-1} \left[N_{0,\text{Mo}} \times e^{-\lambda_{\text{Mo}} \cdot x \cdot t_b} \times b \right. \\ &\quad \times \left(\frac{\lambda_{\text{Mo}}}{\lambda_{\text{Tc-99m}} - \lambda_{\text{Mo}}} \right) \\ &\quad \left. \times (e^{-\lambda_{\text{Mo}} \cdot t_b} - e^{-\lambda_{\text{Tc-99m}} \cdot t_b}) \right]. \end{aligned} \quad (7)$$

TABLE 2: Performance of ^{99m}Tc radioisotope concentrator device ULTRALUTE (effect of concentrator on generator useful life) [41, 61].

Generator activity, mCi (GBq)	Generator useful life for SPECT imaging, days		Generator useful life for lung imaging with Technegas, days	
	Without concentrator	Postelution concentrator	Without concentrator	Postelution concentrator
100 (3.7)	1	6	0	1
300 (11.1)	4	10	0	4
500 (18.5)	6	12	0	6
1000 (37.0)	9	15	1	9
3000 (111.0)	14	20	4	14

The maximal ^{99m}Tc -activity buildup/yield in $^{99}\text{Mo}/^{99m}\text{Tc}$ generator system is described using (3) and (4) as follows:

$$A_{\text{Tc-99m(Max)}} = \lambda_{\text{Tc-99m}} \times N_{0,\text{Mo}} \times b \times \left(\frac{\lambda_{\text{Mo}}}{\lambda_{\text{Tc-99m}} - \lambda_{\text{Mo}}} \right) \times \left(e^{-\lambda_{\text{Mo}} \cdot t_{\text{Max}}} - e^{-\lambda_{\text{Tc-99m}} \cdot t_{\text{Max}}} \right). \quad (8)$$

^{99m}Tc -yield ratio (R_y) is derived from (7) and (8) as follows:

$$R_y = \frac{\sum_{i=1}^{i=n} A_{\text{Tc-99m}(E_i)}}{A_{\text{Tc-99m(Max)}}} = \frac{\sum_{x=0}^{x=i-1} \left[e^{-\lambda_{\text{Mo}} \cdot x \cdot t_b} \times \left(e^{-\lambda_{\text{Mo}} \cdot t_b} - e^{-\lambda_{\text{Tc-99m}} \cdot t_b} \right) \right]}{\left(e^{-\lambda_{\text{Mo}} \cdot t_{\text{Max}}} - e^{-\lambda_{\text{Tc-99m}} \cdot t_{\text{Max}}} \right)}, \quad (9)$$

where b is the ^{99m}Tc -branch decay factor of ^{99}Mo ($b = 0.875$); i is the number of the early elutions needed for a practical schedule of SPECT scans. The build-up time (t_b) for each elution is determined as $t_b = (t_{\text{Max}}/i)$; x is the number of the elutions which have been performed before starting a ^{99m}Tc -build-up process for each consecutive elution. At this starting time point no residual Tc atoms left in the generator from a preceding elution are assumed (i.e., ^{99m}Tc -elution yield of the preceding elution is assumed 100%).

The results of the evaluation (Figures 3(a) and 3(b)) based on (3), (6), and (9) show that the ^{99m}Tc -activity production yield of the generator eluted with an early elution regime of build-up/elution time <6 hours increases by a factor >2 and the ^{99m}Tc specific activity values of the eluates are remained higher than 160 Ci/ μmol .

Obviously, the radioisotope concentrator not only may have positive impact on the extension of useful life time of the generators, but also is capable to increase both the ^{99m}Tc -activity production yield of the generator/effectiveness of $^{99m}\text{Tc}/^{99}\text{Mo}$ utilisation and the specific activity by performing the early elutions of the generator at any time before maximal buildup of ^{99m}Tc .

With the utilization of ^{99m}Tc concentrator device which gives a final ^{99m}Tc -solution of 1.0 mL volume, the experimental results obtained from a 525 mCi generator, as an example, confirmed that the concentration and the yield of ^{99m}Tc solution eluted with a 6-hour elution regime is much better than that obtained from the elution regime performed at the maximal build-up time (22.86 hours). Within first 6 days of elution, ^{99m}Tc -concentration of the generator eluates

is in the range 200–44 mCi/mL and total ^{99m}Tc -activity eluted is 1715.7 mCi for a 6-hour elution regime (including the zero day elution) while the concentration of 83–18.2 mCi/mL and the total activity of 1015.1 mCi are for the elution regime performed at the maximal build-up time, respectively [58, 61]. The effectiveness of this early elution mode was also confirmed experimentally in the prior-of-art of $^{68}\text{Ga}/^{68}\text{Ge}$ generator [62–64].

3. Low Specific Activity ^{99}Mo : Current Issues of Production and Prospects

$^{99}\text{Mo}/^{99m}\text{Tc}$ generators can be produced using low specific activity ^{99}Mo . Some technologies for producing low SA ^{99}Mo have been established. Unfortunately, several alternatives are not yet commercially proven or still require further development. Presently, no nuclear reaction-based nonfission method creates a ^{99}Mo source of reasonably high or moderate specific activity. The reason is that the cross-section of all these types of nuclear reactions, which are performed by both the nuclear reactor and accelerator facility, is low ranging from several hundreds of millibarns to <11.6 barns, compared with ^{99}Mo -effective fission cross-section (37 barns) of ^{235}U -fission used in the production of high SA ^{99}Mo as mentioned above. As shown below, SA of nonfission ^{99}Mo produced from nuclear reactor and accelerator facilities is in a range of 1–10 Ci/g Mo. To produce the ^{99m}Tc generators of the same activity size (1–4 Ci) as in case of high SA ^{99}Mo mentioned above, the ^{99m}Tc recovery system capable for processing Mo-target of several grams weight should be available, even though the enriched ^{98}Mo and/or ^{100}Mo targets are used instead of natural Mo target [2].

3.1. ^{99}Mo Production Based on Reactor Neutron Capture. Neutron capture-based ^{99}Mo production is a viable and proven technology established in the years 1960s. There are thirty-five isotopes of molybdenum known today. Of seven naturally occurring isotopes with atomic masses of 92, 94, 95, 96, 97, 98, and 100, six isotopes are stable with atomic masses from 92 to 98. ^{100}Mo is the only naturally occurring radioactive isotope with a half-life of approximately 8.0E18 years, which decays double beta into ^{100}Ru . All radioactive isotopes of molybdenum decay into isotopes of Nb, Tc, and Ru. ^{98}Mo , ^{94}Mo , and ^{100}Mo (with natural abundance 24.1%, 9.25%, and 9.6%, resp.) are the most common isotopes used in

the targetry for production of two important medical isotopes ^{99m}Tc and ^{94}Tc .

High SA ^{99}Mo cannot be produced via (n, γ) reaction using Mo targets because the thermal neutron cross-section for the (n, γ) reaction of ^{98}Mo is relatively small at about 0.13 barn, a factor of almost 300 times less than that of the ^{235}U fission cross-section. In this respect, irradiation of Mo targets in an epithermal neutron flux could be economically advantageous with respect to producing higher SA ^{99}Mo . The epithermal neutron capture cross-section of ^{98}Mo is about 11.6 barn. The assessment of reaction yield and SA of the Mo targets irradiated with reactor neutrons [28, 65] shows that the irradiation time needed to reach a maximum yield and maximum SA in Mo targets is too long, while the improvement in reaction yield/SA is insignificant due to the low cross-section of $^{98}\text{Mo}(n, \gamma)^{99}\text{Mo}$ reactions. Neutron capture-based ^{99}Mo production with an 8-day irradiation in a reactor of $1.0\text{E}14 \text{ n} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$ thermal neutron flux gives a ^{99}Mo product of low SA as evaluated at EOB as follows: $\sim 1.6 \text{ Ci } ^{99}\text{Mo/g}$ of natural isotopic abundance molybdenum and/or $6 \text{ Ci } ^{99}\text{Mo/g}$ of 98%-enriched ^{98}Mo target. These values show a factor of 10^4 times less than that of fission-produced high SA ^{99}Mo as mentioned above. The loose-packed MoO_3 powder (density of $> 2.5 \text{ g/cm}^3$), pressed/sintered Mo metal powder (density of $< 9.75 \text{ g/cm}^3$), and granulated Mo metal can be used as a target material. High-density pressed/sintered ^{98}Mo metal targets are also commercially available for the targetry. MoO_3 powder can be easily dissolved in sodium hydroxide. Molybdenum metallic targets can be dissolved in alkaline hydrogen peroxide or electrochemically. The metal form takes more time to dissolve than the MoO_3 powder form. However, the advantage of using Mo metal target is that larger weight of Mo can be irradiated in its designated irradiation position in both the research and power nuclear reactors [66, 67]. The neutron flux depression in the MoO_3 target may cause decreasing in ^{99}Mo production yield when a large target is used [68–70]. The production capacities of 230 6-day Ci/week and 1000 6-day Ci/week are estimated for the irradiation with JMTR research reactor in Oarai and with a power reactor BWR of Hitachi-GE Nuclear Energy, Ltd., in Japan, respectively [66, 71]. The use of enriched ^{98}Mo target material of 95% isotopic enrichment offers the ^{99}Mo product of higher SA. The W impurity in the natural Mo target material should be $< 10 \text{ ppm}$ and that is not detectable in the enriched ^{98}Mo targets. Due to high cost of highly enriched ^{98}Mo , the economical use of this target material requires a well-established recycling of irradiated target material [2, 24, 25, 66, 67, 72–74].

3.2. Accelerator Based $^{99}\text{Mo}/^{99m}\text{Tc}$ Production. All of the accelerator-based nonfission approaches rely on highly enriched ^{100}Mo target. While the 99% enrichment ^{100}Mo is sufficient for all accelerator-based ^{99}Mo productions, the direct production of ^{99m}Tc may require enrichments exceeding $> 99.5\%$ due to the possible side reactions which generate long-lived technetium and molybdenum isotopes because these impure radionuclides would cause an unnecessary

radiation dose burden to the patient and the waste disposal issues as well. The SA of ^{99}Mo produced from the accelerators is too low for use in existing commercial ^{99m}Tc generator systems that use alumina columns. New ^{99m}Tc recovery technology that is suitable for processing the accelerator targets of low specific activity ^{99}Mo and allowing effective recycling of ^{100}Mo should be developed [2].

While the specific activity of ^{99}Mo produced using accelerators (ranging up to 10 Ci/g at EOB) is not significantly higher than that of ^{99}Mo produced by neutron capture using nuclear reactor, the ^{99}Mo production using accelerator is presently focused in many research centres with regards to its safer and less costing operation compared with nuclear reactor operation. It is important to be addressed that all of the accelerator-based nonfission- ^{99}Mo production routes need a well-established technology for recycling of the ^{100}Mo target material. This will be somewhat complicated since the ^{100}Mo target material is contaminated with the ^{99}Mo left from the used ^{99m}Tc generator systems. Handling this material presents some complicated logistics in that the target material will have to be stored until the level of ^{99}Mo is sufficiently low so as to not present radiation handling problems. Moreover, the purification of the used ^{100}Mo target must be addressed to ensure completely removing all impurities which are brought from the chemicals and equipment used in the production processes.

3.2.1. Photon-Neutron Process $^{100}\text{Mo}(\gamma, n)^{99}\text{Mo}$. High energy photons known as Bremsstrahlung radiation are produced by the electron beam (50 MeV electron energy with 20–100 mA current) as it interacts and loses energy in a high-Z converter target such as liquid mercury or water-cooled tungsten. The photon-neutron process is performed by directing the produced Bremsstrahlung radiation to another target material placed just behind the converter, in this case ^{100}Mo , to produce ^{99}Mo via the $^{100}\text{Mo}(\gamma, n)^{99}\text{Mo}$ reaction (maximal cross-section around 170 millibarns at 14.5 MeV photon energy [25]). Although the higher SA ^{99}Mo (360 Ci/g) can be achieved with a smaller weight target ($\sim 300 \text{ mg } ^{100}\text{Mo}$), the ^{99}Mo produced based on a routine production base has a much lower SA, approximately 10 Ci/g [75].

3.2.2. Proton-Neutron Process $^{100}\text{Mo}(p, pn)^{99}\text{Mo}$. 30 MeV cyclotron can be used for ^{99}Mo production based on ^{100}Mo (p, pn) ^{99}Mo reaction (maximal cross-section around 170 millibarns at 24 MeV proton energy). ^{99}Mo production yield of $< 50 \text{ Ci}$ can be achieved with a bombardment current 500 mA for 24 hours [76–79].

3.2.3. Neutron-Neutron Process $^{100}\text{Mo}(n, nn)^{99}\text{Mo}$. ^{99}Mo production based on $^{100}\text{Mo}(n, 2n)^{99}\text{Mo}$ reaction (maximal cross-section around 1000 millibarns at 14 MeV neutron energy) using fast neutron yielded from the $D(T, n)$ reaction. The established targetry, sufficient flux of neutrons, and improvement in ^{99m}Tc separation are issues to be addressed for further development [80].

3.2.4. *Direct Production of ^{99m}Tc .* The first report on the feasibility of producing ^{99m}Tc by proton irradiation of ^{100}Mo stated that a theoretical yield of 15 Ci ^{99m}Tc per hour can be achieved with 22 MeV proton bombardment at 455 μA [81]. More recently, Takács et al. found a peak cross-section of 211 ± 33 mb at 15.7 MeV [79]. Scholten and colleagues suggested that the use of a >17 MeV cyclotron could be considered for regional production of ^{99m}Tc with a production yield of 102.8 mCi/ μA at saturation [78]. Estimated yield of ^{99m}Tc production based on a routine production basis is 13 Ci ^{99m}Tc (at EOB), using 18 MeV proton beam of 0.2 mA current for a 6-hour irradiation. A irradiation of highly enriched ^{100}Mo target (pressed/sintered metallic ^{100}Mo powder) using GE PET Trace cyclotron (16.5 MeV proton beam, 0.04 mA current, and 6-hour bombardment) at Cyclopet (Cyclopharm Ltd., Australia) can achieve >2.0 Ci ^{99m}Tc at EOB as reported by Medisotec (Australia). Using >99.5% enriched ^{100}Mo target produces very pure ^{99m}Tc . The ^{99m}Tc product of >99.6% radionuclide purity can be achieved. The major contaminants include ^{99g}Tc , ^{95}Tc , and ^{96}Tc . Trace amounts of ^{95}Nb are produced from the $^{98}\text{Mo}(p, \alpha)^{95}\text{Nb}$ reaction [75–83].

3.3. Methods of Increasing the Specific Activity of ^{99}Mo

3.3.1. *Szilard-Chalmers Recoiled ^{99}Mo .* A method to increase the specific activity of neutron activated ^{99}Mo in the natural and/or enriched Mo targets using Szilard-Chalmers recoiled atom chemistry was recently reported by the scientists at the Delft University of Technology in the Netherland. The targets used in this process are ^{98}Mo containing compounds such as molybdenum(0)hexacarbonyl [$\text{Mo}(\text{CO})_6$] and molybdenum (VI)dioxodioxinate [$\text{C}_4\text{H}_3(\text{O})-\text{NC}_5\text{H}_3$] $_2$ - MoO_2 , molybdenum nanoparticles (~100 nm), and other molybdenum tricarbonyl compounds. The neutron irradiated targets are first dissolved in an organic solvent such as dichloromethane ($\text{C}_2\text{H}_2\text{Cl}_2$), chloroform (CH_3Cl), benzene (C_6H_6), and toluene ($\text{CH}_3-\text{C}_6\text{H}_5$). Then the ^{99}Mo is extracted from this target solution using an aqueous buffer solution of pH 2–12. The target material is to be recycled. This process is currently in the stage of being scaled up towards demonstration of commercial production feasibility. The specific activity of ^{99}Mo increased by a factor of more than 1000 was achieved, making the specific activity of neutron capture-based ^{99}Mo comparable to that of the high SA ^{99}Mo produced from the ^{235}U fission. So the ^{99}Mo produced by this way can be used in existing commercial ^{99m}Tc generator systems that use alumina columns [84, 85].

3.3.2. *High Electric Power Off-Line Isotopic Separator for Increasing the Specific Activity of ^{99}Mo .* A high power ion source coupled to a high resolution dipole magnet would be used to generate beams of Mo ions and separate the respective isotopes with the aim of producing ^{99}Mo with specific activity of greater than 1000 Ci/gram. The construction of a high power off-line isotope separator to extract high specific activity ^{99}Mo that had been produced via $^{98}\text{Mo}(n, \gamma)$ and/or $^{100}\text{Mo}(p, n)$ routes would allow for rapid introduction of

the ^{99}Mo into existing supply chain. The feedstock for the separator system will be low specific activity ^{99}Mo generated from the thermal neutron capture of ^{98}Mo or the photon induced neutron emission on ^{100}Mo . The proposed system would have the advantage that the ^{99}Mo produced will fit directly into the existing commercial generator system, eliminating the use of HEU and LEU targets, and can be used to generate the required target material ($^{98}\text{Mo}/^{100}\text{Mo}$) during the separation process. In addition, it can be used in conjunction with a neutron or photon sources to create a distributed low cost delivery system [2, 86].

4. Up-to-Date Technologies of ^{99m}Tc Recovery from Low Specific Activity ^{99}Mo : $^{99}\text{Mo}/^{99m}\text{Tc}$ Separation Methods, ^{99m}Tc Purification/Concentration, and ^{99m}Tc Generator Systems

Unfortunately, the low SA ^{99}Mo produced using the methods mentioned above contains the overwhelming excess of nonradioactive molybdenum so as the alumina columns used in existing commercial ^{99m}Tc generator systems would be sufficiently loaded to produce the medically useful ^{99m}Tc doses because the ^{99m}Tc recovery from this ^{99}Mo source of low SA requires significantly more alumina resulting in a large elution volumes. Consequently, a solution of low ^{99m}Tc -concentration is obtained from these generator systems. To make a low SA ^{99}Mo source useful for nuclear medicine application, some ^{99m}Tc recovery technologies for producing medically applicable ^{99m}Tc solution have been established. Unfortunately, several alternatives are not yet commercially proven or still require further development. The primary factor pertaining to the nuclear medicine scans' quality is the concentration of ^{99m}Tc in the solution produced from the $^{99}\text{Mo}/^{99m}\text{Tc}$ generator, which is expressed as ^{99m}Tc activity per mL. The injection dose activity of ^{99m}Tc -based radiopharmaceuticals delivered in 1 mL solution is an important factor in determining the efficacy of the ^{99m}Tc generators and the quality of ^{99m}Tc -based SPECT imaging diagnosis as well. So, the ^{99m}Tc recovery technologies should be developed so as a sterile injectable ^{99m}Tc solution of high activity concentration and low radionuclidic and radiochemical/chemical impurity is obtained.

Up-to-date ^{99m}Tc recovery technologies fall into four general categories: solvent extraction, sublimation, electrolysis, and column chromatography.

4.1. *Solvent Extraction for $^{99}\text{Mo}/^{99m}\text{Tc}$ Separation and Solvent Extraction-Based ^{99m}Tc Generator Systems.* Solvent extraction is the most common method for separating ^{99m}Tc from low specific activity ^{99}Mo dated back to the years 1980s. The solvent extraction method can produce ^{99m}Tc of high purity comparable to that obtained from alumina column-based ^{99m}Tc generator loaded with fission- ^{99}Mo of high specific activity. Several extraction systems (extractant-solvent/back-extraction solution) using different extractant agents (such as

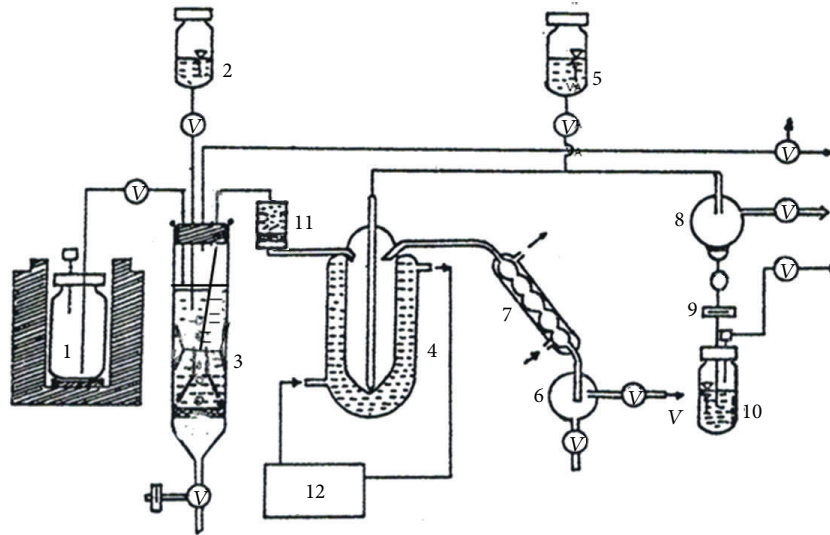


FIGURE 4: Diagram of MEK extraction-based $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator [60]. 1: alkaline ^{99}Mo -molybdate solution; 2: MEK solvent; 3: extractor; 4: MEK evaporator; 5: saline; 6: MEK receiver; 7: condenser; 8: $^{99\text{m}}\text{Tc}$ solution receiver; 9: Millipore filter; 10: final $^{99\text{m}}\text{Tc}$ solution vial; 11: acidic alumina column; 12: 70°C water circulator; v: valve; V: vacuum line.

ketones, crown ethers, trioctylamine, tricaprlyl methyl ammonium chloride (Aliquat-336), liquid ion-exchangers, and ionic liquids) were investigated [35, 60, 87–91]. Among the extractant compounds investigated, methyl ethyl ketone (MEK) is the best for the extraction of $^{99\text{m}}\text{Tc}$ -pertechnetate in terms of high extraction yield, high radiation stability, and low boiling temperature. Generators based on MEK extraction of $^{99\text{m}}\text{Tc}$ -pertechnetate from alkaline aqueous molybdate solutions have been widely used for the production of $^{99\text{m}}\text{Tc}$. The extraction cycle consists of adding a mixture of MEK solvent containing 1% aqueous hydrogen peroxide to the 5 M NaOH solution of ^{99}Mo target and mechanically stirring the mixture to selectively extract the $^{99\text{m}}\text{Tc}$ from the aqueous phase into the MEK phase. The hydrogen peroxide is added to keep the ^{99}Mo and $^{99\text{m}}\text{Tc}$ in the appropriate oxidation state. After standing of the mixture to allow the phase separation, the supernatant MEK/ $^{99\text{m}}\text{Tc}$ solution/organic phase containing the extracted $^{99\text{m}}\text{Tc}$ is removed by sucking effected by a negative pressure and then it is passed through an acidic alumina to remove any ^{99}Mo that may be coextracted with $^{99\text{m}}\text{Tc}$ into the MEK solution. In the following, the MEK/ $^{99\text{m}}\text{Tc}$ solution is transferred to an evaporation vessel (evaporator). The evaporator is heated to $\sim 70^\circ\text{C}$ under a slight negative pressure to hasten the evaporation of the MEK. After the MEK has been completely removed, sterile saline is added to the evaporator to recover the $^{99\text{m}}\text{Tc}$ in the form of sodium- ($^{99\text{m}}\text{Tc}$) pertechnetate dissolved in the saline. This $^{99\text{m}}\text{Tc}$ saline solution is then sterilized by passing through a Millipore filter and transferred into a sterile vial for further processing at quality control and for formulating the radiopharmaceuticals.

The centralized solvent extraction-based $^{99\text{m}}\text{Tc}$ generator systems have been successfully performed for more than decade in Australia [92] and Czechoslovakia [6, 35, 93, 94].

Some other systems are routinely used in Russia, Peru, and in Asian countries where the fission ^{99}Mo -based chromatographic $^{99\text{m}}\text{Tc}$ generators do not enter the competition [60, 87, 95–97]. As an example, a centralized extraction-based $^{99\text{m}}\text{Tc}$ generator used for many years in a hospital in Vietnam is shown in Figure 4 [60].

The shortage in the fission ^{99}Mo supply today, however, has encouraged the $^{99\text{m}}\text{Tc}$ users over the world to use more effectively the solvent extraction-based $^{99\text{m}}\text{Tc}$ as well. So the less competitive solvent extraction-based $^{99\text{m}}\text{Tc}$ -generator systems developed several decades before should be upgraded to be used as a user-friendly prototype for a daily use in hospital environments. The update solvent extraction-based $^{99\text{m}}\text{Tc}$ generator systems under development are designed for an automated or semiautomated operation based either on the established extraction process [95, 98–100] as mentioned above or on the improved extraction technologies. The improvement in the removing of MEK from the extracted $^{99\text{m}}\text{Tc}$ -MEK organic phase to obtain $^{99\text{m}}\text{Tc}$ -pertechnetate is essential in the update MEK extraction technologies, because this will make the extraction being performed with $^{99\text{m}}\text{Tc}$ recovery into a aqueous solution without the complicated step of MEK evaporation, thus facilitating the process automation. This improved technology is based on the non-evaporation removing of MEK by passing the extracted $^{99\text{m}}\text{Tc}$ -MEK organic phase through a cation-exchange resin or basic alumina column coupled with an acidic alumina column, followed by a water wash to completely remove both ^{99}Mo contaminant and MEK. Then the $^{99\text{m}}\text{Tc}$ pertechnetate retained on the acidic alumina column will be eluted with a small volume of saline solution to achieve an injectable $^{99\text{m}}\text{Tc}$ pertechnetate solution. This approach has been developed in Japan in 1971 [71, 101, 102] and recently resurrected in India and Russia [95, 99, 100]. The process is pictorially described

in Figure 5. A computerized compact module for ^{99m}Tc separation based MEK extraction coupled with the MEK removing unit, which composes of a tandem of basic/acidic alumina columns, is developing in BRIT [100].

4.2. Sublimation Methods for $^{99}\text{Mo}/^{99m}\text{Tc}$ Separation and Sublimation-Based ^{99m}Tc Generator Systems. Three sublimation methods for $^{99}\text{Mo}/^{99m}\text{Tc}$ separation have been developed and commercially used in past decades [6, 35, 66, 70, 71, 92, 94, 112, 113]. The first is the high temperature sublimation method developed at the end of the sixties and used for many years in Australia, which is based on the heating a neutron-activated MoO_3 target on $>800^\circ\text{C}$ in a furnace with oxygen stream passed through. The sublimed ^{99m}Tc in the form of Tc_2O_7 is condensed in the cold finger at the end of the furnace and $^{99m}\text{TcO}_4^-$ is isolated by rinsing the cold finger with a hot 0.1 mM NaOH solution followed by purification on alumina. Some modified versions of this method were performed to achieve higher ^{99m}Tc recovery yield. The highest yield obtained was around 80% with a sublimation time of 20–30 minutes. The second method is the medium temperature sublimation. This method relies on heating a eutectic mixture of ^{99}Mo -molybdenum oxide and metal oxides on temperature between 500 and 750°C in an air flow and $\sim 90\%$ of ^{99m}Tc is recovered in the same way as applied in the first method. The third method is the low temperature sublimation. This method is based on the heating the solid powders of ^{99}Mo -molybdate of tetravalent metals such as titanium and zirconium molybdate on $380\text{--}450^\circ\text{C}$ in a water vapour flow and 40–65% of ^{99m}Tc is recovered in the saline in form of ready-to-use. Based on this method, the portable sublimation ^{99m}Tc generators were commercially produced in the nineteen eighties and used for years in several hospitals in Hungary [92, 94, 114, 115]. The thermochromatographic separation at an oven temperature of 1090°C has also been successfully utilized for the recovery of ^{94m}Tc from $^{94}\text{MoO}_3$ in the years 1990s [116]. This approach is expected to be used for the ^{99m}Tc separation from ^{99}Mo targets. From that time until now, no update version of the sublimation-based ^{99m}Tc recovery technology is found in the literature.

4.3. Electrochemical Methods for ^{99m}Tc Recovery. In the past the electrochemical separation of ^{99m}Tc from ^{99}Mo was performed for a radioanalytical purpose. Recently, Chakravarty et al. have further developed this method for seeking a ^{99m}Tc production capability using a low specific activity ^{99}Mo . The ^{99m}Tc electrodeposit and the followed pertechnetate recovery were performed at the voltage 5 V (current 500 mA and current density 300 mA/cm^2) and 10 V (reversed polarity), respectively. Postelectrolysis purification of ^{99m}Tc solution was also completed with an alumina column [117, 118].

4.4. Column Chromatographic Methods for ^{99m}Tc Recovery and Integrated ^{99m}Tc Generator Systems (Column Chromatography-Based ^{99m}Tc Generator Coupled with Postelution Purification/Concentration Process). The ^{99m}Tc recovery

technologies used in the separation of ^{99m}Tc from low specific activity ^{99}Mo , which are based on the column chromatographic method, are recognized as the best ways to bring the low SA ^{99}Mo -based ^{99m}Tc generators to the hospital users with minimal fission/nonfission Mo discrimination. Conventional chromatographic generators using alumina columns are not compatible with the loading with low SA ^{99}Mo due to its overwhelming excess of nonradioactive molybdenum. By rule of thumb, 1–2% of adsorption capacity of the alumina column loaded with molybdenum is tolerated to avoid a harmful ^{99}Mo breakthrough in the final ^{99m}Tc saline eluate. To produce a generator of acceptable activity using low SA ^{99}Mo a significantly large alumina column is required to be capable to adsorb 1–2 g of Mo target, because the capacity of alumina for Mo adsorption is limited ($\sim 20\text{ mg Mo/g}$ of alumina). A large alumina column requires large volume of the eluent to elute patient-dose quantities of ^{99m}Tc . As a consequence, large eluent volumes cause the radioactive concentration of the ^{99m}Tc -pertechnetate to become unacceptably low for use in most radiopharmaceutical diagnostic procedures. So, the postelution concentration process is required to increase the ^{99m}Tc -activity concentration. Although the recovery of ^{99m}Tc from enriched molybdenum target material has been applied in Uzbekistan and POLATOM, the ^{99m}Tc concentration of the eluate eluted from an enriched ^{98}Mo target-based generator is moderately improved with the use of high neutron flux reactor irradiation [2].

In principle, there is no impediment for simple in-line concentration of the ^{99m}Tc solution obtained from large alumina column generators using simple postelution concentration technologies. As examples, the large alumina column-based ^{99m}Tc generators using low specific activity ^{99}Mo , eluted with chloride (saline) or nonchloride (acetone) eluent and combined with a ^{99m}Tc concentration unit, were tested. The first low SA (7–15 GBq/g) ^{99}Mo -based ^{99m}Tc generator system using up to 80-gram alumina column (jumbo alumina column generator) was developed in India [52, 53]. 70 mL saline is used for ^{99m}Tc elution from this system and a concentration process with three consecutive processing steps (^{99m}Tc loading onto Dowex-1 \times 8 resin column; ^{99m}Tc elution from the resin column with 0.2 M NaI solution; removing of I^- ions from the effluent downstream with AgCl column) was applied. The second generator system was developed in Pakistan using a large alumina (16 g) column and acetone eluent (nonchloride organic eluent) [51]. ^{99m}Tc recovery in a small volume of saline was followed after removing acetone from the ^{99m}Tc /acetone eluate.

Despite the high recovery yield and good labelling quality of the highly concentrated ^{99m}Tc solution achieved, the time consumption for a large volume elution and the complexity in processing at concentration stage make large alumina column-based generator systems as described above inconvenient for a commercial scale production and for the convenient utilization in the hospital environment. So, the recovery of ^{99m}Tc from the low SA ^{99}Mo still requires further development to make it useful for nuclear medicine application. As a result of the development performed in many laboratories

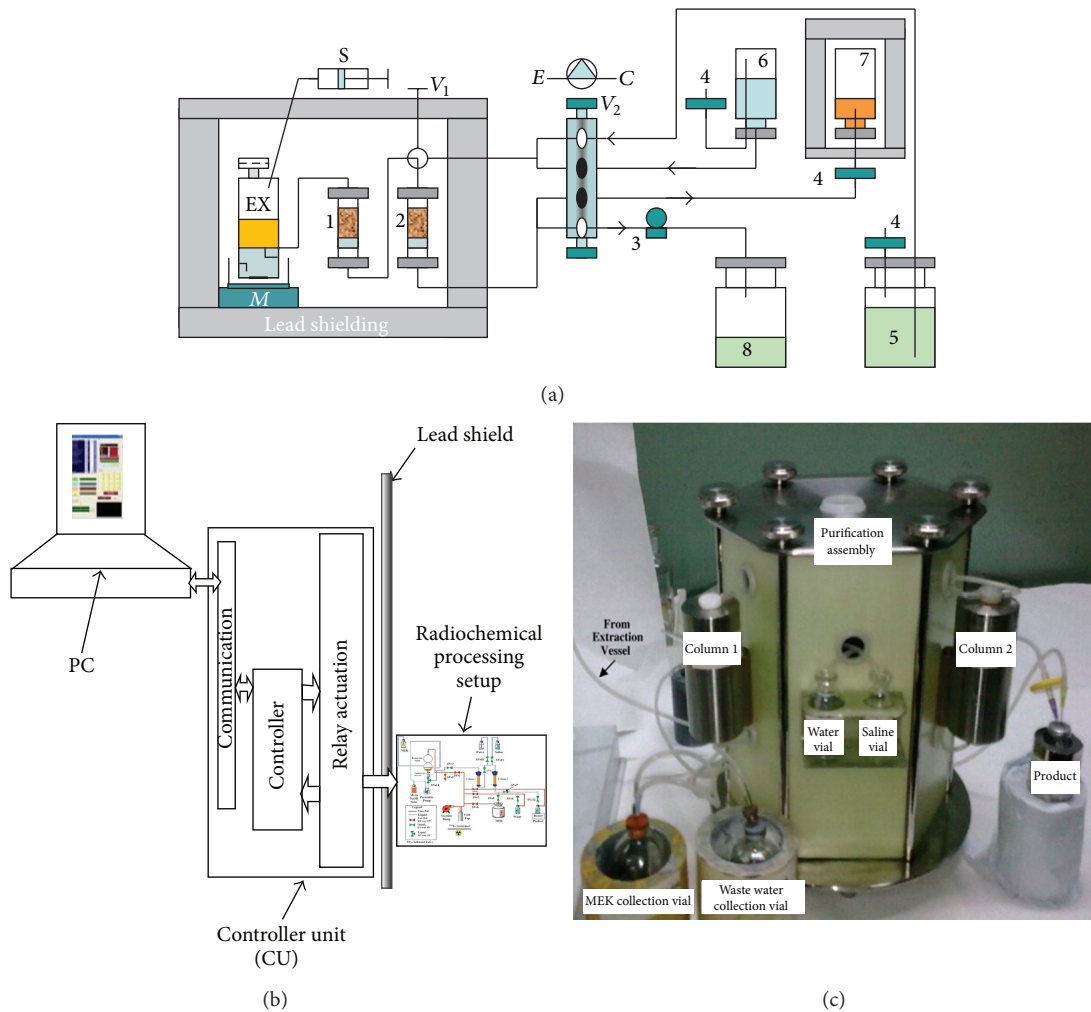


FIGURE 5: MEK extraction of ^{99m}Tc using a tandem sorbent column system for nonevaporation removing of MEK from the extracted ^{99m}Tc -MEK phase: (a) conceptual process diagram of ^{99m}Tc recovery by MEK extraction using a tandem cation-exchange resin/acidic alumina column system for nonevaporation removing of MEK (1: cation-exchange resin column; 2: alumina column; 3: peristaltic pump; 4: Milipore filter; 5: redistilled water; 6: saline; 7: final sterile ^{99m}Tc -pertechnetate solution; 8: waste container; V_1 and V_2 : solenoid valves; S: syringe for MEK addition; EX: extractor containing ^{99}Mo ; M: magnetic stirrer). The generator design is performed by author of this paper based on the processes reported in the literature [98, 102]. (b) Process diagram and (c) computerized module developed in BRIT for ^{99m}Tc separation based on the MEK extraction coupled with MEK-removing using a tandem basic/acidic alumina column system [99, 100].

around the world, some useful ^{99m}Tc recovery technologies developed up to date are described in the following.

It is the fact that the solution of high ^{99m}Tc concentration cannot directly be produced from the low specific activity ^{99}Mo source, except the ^{99m}Tc production based on the solvent extraction, sublimation, and electrochemical methods mentioned above. So, the technetium recovery technology based on the coupling a chromatographic ^{99m}Tc -generator column of high Mo-loading capacity with a postelution purification/concentration process/unit should be considered as an important solution. This technical solution is performed by an integrated system, so-called RADIGIS (radioisotope generator integrated system) to produce a medically useful ^{99m}Tc -pertechnetate solution of sufficiently

high ^{99m}Tc -concentration. In the following, different versions of RADIGIS developed to date are described.

4.4.1. *Technetium Selective Sorbent Column-Based ^{99m}Tc Recovery and Relevant Integrated ^{99m}Tc Generator System.* Several sorbents have been developed for selective adsorption of pertechnetate ions from aqueous solutions. Some of them, such as TEVA Spec resin (Aliquat-336 or tricaprlyl methyl ammonium chloride extractant impregnated in an inert substrate) and activated charcoal, adsorb TcO_4^- ions strongly in dilute nitric acid solutions. However, the strong acidic solution (8 M HNO_3) required for recovery of TcO_4^- ions is not preferred for practical application on the basis of daily use in nuclear medicine [119–123]. Some sorbents, such as

ABEC (aqueous biphasic extraction chromatographic) resin and strong anion-exchange (Dowex-1×8) resin, adsorb TcO_4^- ions from alkaline or neutral aqueous solutions. These resins are suitable for use in the production of $^{99\text{m}}\text{Tc}$ -generator by virtue of the fact that TcO_4^- ions can be easily desorbed from these sorbents by contacting with water or suitable organic solvent [124, 125].

(1) *Aqueous Biphasic System-Based $^{99\text{m}}\text{Tc}$ -Pertechnetate Recovery Method* [124, 126–131]. A $^{99\text{m}}\text{Tc}$ selective sorbent (ABEC-2000) column is recently developed to separate $^{99\text{m}}\text{Tc}$ from the alkaline solution of low specific activity ^{99}Mo . A new generator system developed by NorthStar Medical Radioisotopes (USA) using low specific activity ^{99}Mo is based on the ABEC-2000 resin column coupled with an alumina guard column. This system is shown in Figure 6.

The separation process is performed as follows. An alkaline ^{99}Mo solution in 5 M NaOH obtained from dissolution of molybdenum targets is fed onto the ABEC-2000 resin column which is specifically designed to adsorb pertechnetate. Once the column is loaded, it is first washed with 5 M NaOH solution to remove any molybdate that also may have been adsorbed on the column and then by a buffer solution of pH 8. Following the wash, the technetium is stripped from the column with a normal saline solution which is then passed through an alumina guard column to remove the residual ^{99}Mo impurities. The eluate is then passed through dual 0.22 micron sterility filters to achieve an injectable $^{99\text{m}}\text{Tc}$ -pertechnetate solution. The process can be repeated once a day as the $^{99\text{m}}\text{Tc}$ builds up in the ^{99}Mo solution. The $^{99\text{m}}\text{Tc}$ separation efficiencies for several consecutive days of operation were >90% with no detectable ^{99}Mo breakthrough. To date, the inherent disadvantage of this generator system reflected from the comment of user is that the elution process of this system takes a long time (about 40 minutes) and requires a 15-minute procedure for cleaning of column and tubing before the next elution is available. There is also some process to replace some components of the generator system that must be done after 5 elutions. Although the automated operation of this system facilitates the cumbersome elution-cleaning-replacing process, its being accepted as a user-friendly device may be challenged by the hospital user's community who is quite familiar to the simple operation of the current fission ^{99}Mo -based $^{99\text{m}}\text{Tc}$ generators.

The specific volume of $^{99\text{m}}\text{Tc}$ solution produced by this $^{99\text{m}}\text{Tc}$ recovery system is comparable to that of an alumina column generator loaded with the high SA fission. This new generator system is currently in the process of being validated for nuclear pharmacy use through a NDA on file with the US Food and Drug Administration [2, 130, 131].

(2) *Organic Solvent-Eluted Ion-Exchange Resin Column-Based $^{99\text{m}}\text{Tc}$ -Pertechnetate Recovery Method*. The chromatographic system of Dowex-1×8 resin column combined with tetrabutyl-ammonium-bromide (TBAB) eluent has been developed for separation of pertechnetate ions from aqueous ^{99}Mo -molybdate solution. Using commercially available anion-exchange resin Dowex-1×8 (25 mg) to selectively trap

and separate $^{99\text{m}}\text{TcO}_4^-$ from a low specific activity ^{99}Mo solution and then recovering $^{99\text{m}}\text{TcO}_4^-$ ions from the Dowex-1×8 column by elution with TBAB in CH_2Cl_2 were reported. After being purified by passing through a neutral alumina column and washing the resin column with water, the alumina column will be flushed with saline to strip $\text{Na}^{99\text{m}}\text{TcO}_4$. Subsequent quality control revealed no significant levels of trace metal contaminants or organic components. $^{99\text{m}}\text{Tc}$ recovery yields of greater than 90% were demonstrated, while radiochemical purity was consistently over 99% [125].

4.4.2. *High Mo-Loading Capacity Column-Based $^{99\text{m}}\text{Tc}$ Recovery and Relevant Integrated $^{99\text{m}}\text{Tc}$ Generator Systems*. The assessment on the capable utilisation of the high Mo-loading columns loaded with low specific activity (n, γ) ^{99}Mo for production of $^{99\text{m}}\text{Tc}$ -generator is performed based on the ^{98}Mo (n, γ) ^{99}Mo reaction yield ($A_{\text{Mo-99}}$) and Mo-loading capacity of column packing material (K). The relationship between the neutron flux Φ of the reactor used for the ^{99}Mo production and the Mo-loading capacity (K) of the column packing material is derived [69, 70, 103, 132].

Based on the activation equation for the neutron capture reaction $^{98}\text{Mo}(n, \gamma)^{99}\text{Mo} \rightarrow ^{99\text{m}}\text{Tc}$, the ^{99}Mo activity/yield ($A_{\text{Mo-99}}$) and the relationship between $A_{\text{Mo-99}}$ and K are calculated as follows:

$$A_{\text{Mo-99}} = 1.628 \times 10^{-13} \left(\frac{\Theta \times G \times \sigma_{\text{act}} \times \Phi}{a} \right) \times (1 - e^{-0.693(t/T)}),$$

$$A_{\text{Mo-99}} = 2.055 \times 10^{-14} \times G \times \Phi \times (1 - e^{-0.0104 \times t}) \quad (10)$$

$$G = \frac{A_{\text{Mo-99}}}{2.055 \times 10^{-14} \times \Phi \times (1 - e^{-0.0104 \times t})},$$

$$K = \frac{G}{m} = \frac{A_{\text{Mo-99}}}{2.055 \times 10^{-14} \times m \times \Phi \times (1 - e^{-0.0104 \times t})}.$$

$K = G/m$ is the Mo-loading capacity of the packing material loaded in one generator column. $G(g)$ is the weight of molybdenum element target, which will be used for the production of one generator. $m(g)$ is the weight of column packing material packed in one generator column. $A_{\text{Mo-99}}(\text{Ci})$ is the given ^{99}Mo radioactivity of the generator, which is planned to be produced. t is the activation time, hour. $\Theta = 23.75\%$ is the natural abundance of ^{98}Mo . $a = 95.94$ is the molecular weight of molybdenum. $T = 66.7$ hours is the half-life of ^{99}Mo . $\sigma_{\text{act}} = 0.51$ barn is the normalised thermal and epithermal neutron activation cross-section of ^{98}Mo nuclide.

It is assumed that a generator column of the best performance for pertechnetate elution can be eluted with an eluent of volume $V(\text{mL}) = 2\text{ m}$, where $m(g)$ is the weight of the column packing material. The relationship between the $^{99\text{m}}\text{Tc}$ concentration in the eluate (C_{Tc}), the neutron flux, and K is also set up. This relationship shown in Figure 7 is for a given case of the following conditions. The weight of the column packing material is 5 g and corresponding elution volume is 10 mL. The activation time of natural Mo target is 100 hours.

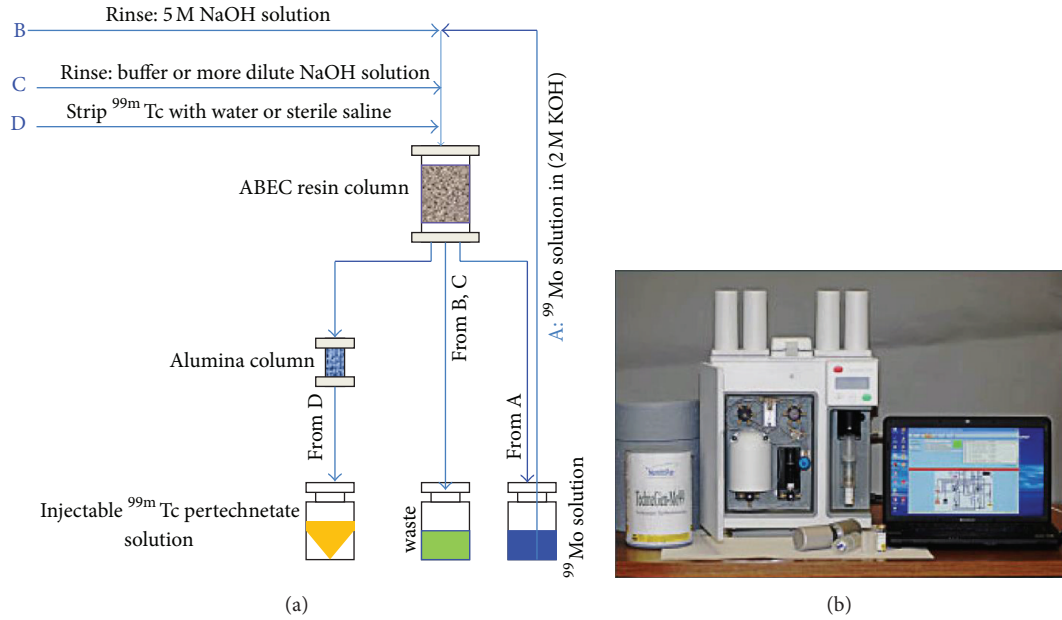


FIGURE 6: ^{99m}Tc recovery using ABEC resin column: (a) process diagram; (b) automated radionuclide separator ARSII developed by NorthStar Medical Radioisotopes (USA) using ABEC resin column [2].

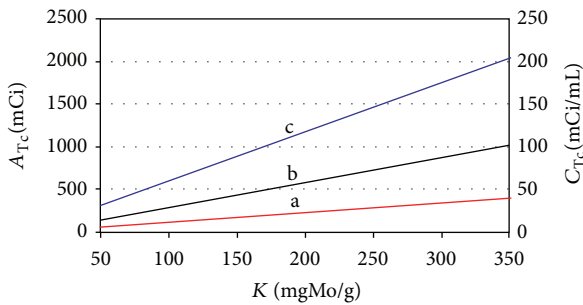


FIGURE 7: Assessment on the ^{99m}Tc -radioactivity (A_{Tc}) and ^{99m}Tc -concentration (C_{Tc}) of the eluate eluted from the generators of 5-gram weight column-packing materials of variable Mo-loading capacity K (low specific activity ^{99}Mo solutions used are produced in the nuclear reactors: (a) thermal neutron flux $\Phi = 2.1013 \text{ n} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$; (b) $\Phi = 5.1013 \text{ n} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$; (c) $\Phi = 1014 \text{ n} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$. The saline eluate volume is 10 mL).

With these conditions, the above mentioned K -equation is derived as follows:

$$K_{(5,100)} = \frac{1.72 \times 10^{13}}{\Phi} \times A_{\text{Tc}}. \quad (11)$$

$K_{(5,100)} = G/5$ is the Mo-loading capacity of the packing material used in the generator. $A_{\text{Tc}}(\text{mCi}) = (0.875 \times A_{\text{Mo-99}})$ is the radioactivity of ^{99m}Tc in this generator. $C_{\text{Tc}}(\text{mCi/mL})$ is the radioactive concentration of ^{99m}Tc in the eluate eluted from the generator.

This relationship shows a general assessment on the potential use of the column packing material of given Mo-loading capacity for the ^{99m}Tc -generator production using $(n, \gamma)^{99}\text{Mo}$ produced ex-natural molybdenum. As an

example, the result assessed by above equations indicates that the column packing material of molybdenum loading capacity $K \geq 172 \text{ mg Mo/g}$ could be used to produce a ^{99m}Tc generator of approximately 300 mCi at the generator calibration using a ^{99}Mo source of 500 mCi activity (at EOB) produced in a reactor of $\Phi = 5.1013 \text{ n} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$ and thus a ^{99m}Tc -pertechnetate solution of concentration $<30 \text{ mCi } ^{99m}\text{Tc} / \text{mL}$ could be achieved. This ^{99m}Tc solution could be used for limited numbers of organ imaging procedures due to its low ^{99m}Tc concentration as shown in Table 1. With the thermal neutron flux $\Phi > 5.1013 \text{ n} \cdot \text{cm}^{-2} \cdot \text{sec}^{-1}$ available in the majority of the research reactors around the world, it is justified that the column packing material of $K \geq 172 \text{ mg Mo/g}$ should be developed for the effective use in the process of ^{99m}Tc -generator production. Several sorbents, such as acidic/basic alumina, hydrous zirconium oxide, hydrous titanium oxide, manganese dioxide, silica gel, hydroxalclites, inorganic ion-exchange materials (zirconium-salt form of zirconium-phosphate ion exchanger), hydroxyapatite, mixed oxide of tetravalent metals, and diatomaceous earth, have been developed/investigated over the years [20, 133–141]. These sorbents are only used for the production of fission- ^{99}Mo -based ^{99m}Tc -generators but they are unsuitable for ^{99m}Tc -generators loaded with ^{99}Mo of low specific activity due to their low Mo-adsorption capacity ($<100 \text{ mg Mo/g}$).

Presently, there are the limitations in the available specific activity of ^{99}Mo produced from nuclear facilities: 1–6 Ci/g Mo (1–4 Ci/g at generator calibration day) of ^{99}Mo produced in the reactors of high neutron flux ($> 1014 \text{ n} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$) using both the natural molybdenum and enriched ^{98}Mo targets and $\sim 10 \text{ Ci/g Mo}$ of ^{99}Mo produced from the accelerators as mentioned above. The use of these ^{99}Mo sources and

the recently developed column packing materials of high Mo-loading capacity in the process of the ^{99m}Tc generator production, however, remain to be addressed. In order to reduce the ^{99m}Tc solution volume eluted from a column chromatographic generator using low SA ^{99}Mo to facilitate the postelution ^{99m}Tc -purification/concentration process, the columns of as high as possible Mo-loading capacity must be used. Although the Mo-loading capacity >0.25 g Mo per gram of column-packing material is achieved to date, the loading of this material with 1-2% of its capacity (similar to the loading regime of the alumina column in the fission ^{99}Mo -based generators) using a low specific ^{99}Mo available today will result in a generator of unacceptably low activity, because the $(n, \gamma)^{99}\text{Mo}$ produced in the majority of high neutron flux nuclear reactors and in the accelerators has a specific activity of 10000 times lower than that of the fission-based ^{99}Mo . So, the *fully Mo-loaded generator columns* should be used [57, 59, 60, 69, 70, 103–109, 112, 113, 132, 142–154]. As an example, the ^{99m}Tc generated in a 4-gram weight column of high Mo-loading capacity (250 mg Mo/g), which is fully loaded with 1.0 g Mo of low specific ^{99}Mo -activity to produce a generator of 1–4 Ci ^{99}Mo on generator calibration day, can be exhaustively eluted in 10 mL saline. This ^{99m}Tc eluate contains a higher ^{99}Mo breakthrough than that required for an injectable ^{99m}Tc solution due to the feature of the fully Mo-loaded generator column as mentioned above. This eluate needs to be purified to remove ^{99}Mo breakthrough contaminant by passing through a sorbent column such as alumina column of ~2-gram weight. Finally, an additional volume of the saline must be used to recover all ^{99m}Tc activity from the system. As a consequence, a low concentration ^{99m}Tc solution of approximately 20 mL volume is produced. This value means a double of saline volume used in a fission ^{99}Mo -based ^{99m}Tc generator column of 4 Ci activity loaded with 2 g alumina.

In case of the fully Mo-loaded generator columns used, the Mo affinity to the sorbent should be high enough to ensure a minimal Mo-breakthrough into the ^{99m}Tc eluate eluted from the generator, because the Mo breakthrough is directly proportional with the Mo amount loaded on the column and reversely with its affinity to the sorbent (known as distribution coefficient K_d). To achieve a maximal affinity for the adsorption process, the chemisorption with covalent bonding between molybdate ions and functional groups of the sorbent should be expected in the process of sorbent design.

Asif and Mushtaq [155] have tested to highly load alumina column with $(n, \gamma)^{99}\text{Mo}$ to produce a medically acceptable pertechnetate solution of higher ^{99m}Tc concentration. However, the high ^{99}Mo breakthrough in the ^{99m}Tc eluate and the moderate Mo-loading capacity of this fully Mo-loaded alumina column (150 mg/g) remain inconvincible for a practical application of this technique for the generator production.

The efforts of using a fully Mo-loaded column of high Mo-loading capacity and high adsorption affinity, however, are not the all to be done in this endeavour in the process

development of ^{99m}Tc -generator production, because the solution volume and ^{99}Mo breakthrough of the ^{99m}Tc eluate eluted from fully Mo-loaded generator columns loaded with low specific activity ^{99}Mo are still unacceptably higher compared with those obtained from the fission ^{99}Mo /alumina-based generators. All these issues suggest that the high Mo-loading capacity column-based ^{99m}Tc recovery should be combined with a postelution purification/concentration process to produce a ^{99m}Tc -pertechnetate solution of medically useful radioactive concentration for use in most radio-pharmaceutical diagnostic procedures.

With regard to the development of ^{99m}Tc generator using low SA ^{99}Mo , the column packing materials of high Mo-loading capacity developed in several laboratories are classified into two following groups. The first group includes the chemically formed solid powder materials containing molybdenum in the form of a chemical compounds such as polymolybdate compounds of tetravalent metals (in the form of solid gels) such as Zr-, Ti-, Sn-molybdates, and so forth [57, 59, 60, 69, 70, 103–106, 112, 113, 132, 142–147]. The second group composes of the sorbents of high Mo-adsorption capacity such as the functionalized alumina [156], the polymeric compounds of zirconium (PZC), titanium (PTC), and so forth [107, 108, 148–154, 157], the nanocrystalline mixed oxides of tetravalent metals [62–64, 109–111, 118, 158], the nanocrystalline zirconium/titanium-oxide and alumina [159–161], and recently multifunctional sorbents [40–42, 58]. Such materials, as discussed below, are shown to be suitable for ^{99m}Tc generator production. All these column-packing materials have a significantly higher Mo-loading capacity (>250 mg Mo per gram) than that of the alumina (10–20 mg Mo per gram). The ^{99m}Tc can be separated from these column packings by elution with a small volume of nonsaline or saline eluents. The choice of the eluent is subject to the postelution ^{99m}Tc -purification/concentration process preferred for the optimal design of an integrated system RADIGIS to produce the medically useful pertechnetate solution of sufficiently high ^{99m}Tc concentration.

The chemistry of molybdate ion sorption on hydrous metal oxides is a good guide in the process of sorbent development. It is established that there are 4 adsorption sites/groups on the alumina surface: basic OH group ($=\text{Al}-\text{OH}$), neutral OH group ($-\text{Al}-\text{OH}-\text{Al}-$), acidic OH group ($-\text{Al}-\text{OH}[-\text{Al}-]_2$), and coordinatively unsaturated site ($-\text{Al}^{3+}$). All these sites adsorb the molybdate ions to different extents depending on the pH of the solution and type of alumina sorbent used. Molybdate reacts irreversibly in a reaction (chemisorption) with the basic OH groups (at pH 8.5–6). However, as soon as these are protonated, molybdate also starts to be reversibly adsorbed by electrostatic interaction. The neutral OH groups, when protonated, also reversibly adsorb the molybdate ions. Molybdate is strongly adsorbed by the coordinatively unsaturated sites and by acidic OH groups via a physisorption/electrostatic interaction at pH <5 . For this reason, acidic alumina is used for the $^{99}\text{Mo}/^{99m}\text{Tc}$ generator production. Among tetravalent metal oxides, titania and zirconia are usually used in many studies for the ^{99m}Tc

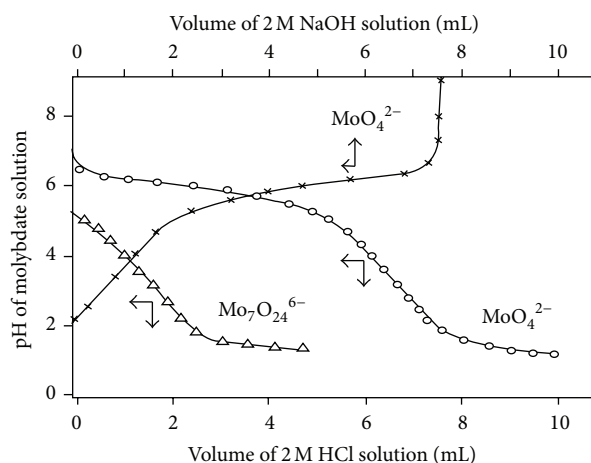
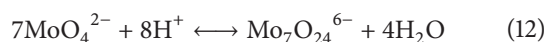


FIGURE 8: pH titration curves of molybdate solutions [57].

recovery from ^{99}Mo . Titania and possibly nanocrystalline tetragonal zirconia (calcined at 600°C , IEP at the pH 4.5 [62, 156, 161]) contain mainly coordinatively unsaturated sites, so these sorbents may adsorb molybdate ions via a physisorption/electrostatic interaction at pH <5. However, hydrous titanium oxide and zirconium oxide sorbents contain many acidic and basic OH groups, respectively. Consequently molybdate ions are adsorbed on the hydrous titanium oxide surface by a physisorption mechanism at pH <4 with a less adsorption affinity compared with that of hydrous zirconium oxide which adsorbs molybdate by an irreversible chemical reaction/chemisorption. Molybdate ions adsorb on the metal oxides in different forms depending on the pH of the solution because the molybdate polymerizes in weakly acidic solution as follows:



On the polymerization, the polymerized molybdate molecules have variable molecular weights depending on the pH. This property can be experienced from the results of the potentiometric titration of molybdate solutions shown in Figure 8. As shown the molybdate is in the form of polymolybdate $\text{Mo}_7\text{O}_{24}^{6-}$ at pH <5 [57].

When the titanium- and zirconium-molybdate gels are used as column packing materials in the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator preparation, the molybdate covalently bonds with Ti^{4+} and/or Zr^{4+} ions in the way of nonstoichiometry. So the residual charges of the polymolybdate ions will be neutralized by the positive charge of the protons and the gels will behave as a cation exchanger. Le (1987–1994) has found the polyfunctional cation-exchange property of the titanium- and zirconium-molybdate gels [59, 69, 104]. He has taken this advantage of the molybdate gels to design the water- and organic solvent (acetone)-eluted gel-type $^{99\text{m}}\text{Tc}$ generators as shown in Figures 14, 17, and 18 [57, 59, 60, 69, 103–106, 146]. The molybdate gels have two functional groups in their structure and the total ion-exchange capacity of approximately 10 meq/g was found as shown in Figure 9. The $^{99\text{m}}\text{TcO}_4^-$ anions, as the counter ions of the cation-exchange

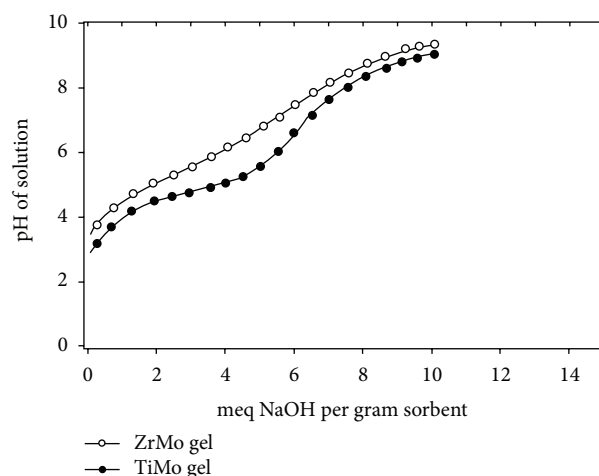


FIGURE 9: pH titration curves of molybdate gel sorbents [57, 59, 60, 69].

gel matrix, can be easily eluted with the water and water-soluble organic solvent from the column of gel-type $^{99\text{m}}\text{Tc}$ generator. Sarkar et al. (2004) also developed a water-eluted zirconium-molybdate gel-based $^{99\text{m}}\text{Tc}$ generator [49].

The cation exchange property can be found in all the sorbents which are fully loaded with molybdate ions. So the elution of $^{99\text{m}}\text{Tc}$ with water or with acetone (as nonsaline eluents) from the generator column fully loaded with ^{99}Mo will provide the advantages for a consecutive postelution purification/concentration process. Le (2011) has developed an automated system of the radioisotope generator coupled with purification/concentration process using PTC/PZC sorbent columns and an eluent composed of water containing small amount of NaCl (0.005%). This system called RADIGIS- $^{99\text{m}}\text{Tc}$ is shown in Figure 16 [62–64, 109, 109–111, 158].

The $^{99\text{m}}\text{TcO}_4^-$ anions are hardly eluted from a partly Mo-loaded sorbent column with nonsaline eluents due to its strong adsorption on the unoccupied residual OH groups of the sorbent. However, this elution can be achieved if the column is wetted with a sufficient amount of residual saline. This phenomenon has been experienced in the case of the $^{99\text{m}}\text{Tc}$ elution with acetone from an alumina column [51]. In this case the water in the aqueous saline phase existing on the sorbent surface plays a role of an ion transporter for $^{99\text{m}}\text{TcO}_4^-$ and Cl^- ions.

(1) Saline-Eluted Generator Systems Using High Mo-Loading Capacity Columns and Integrated Generator Systems

(i) *Saline-Eluted Molybdate-Gel Column-Based $^{99\text{m}}\text{Tc}$ -Generator Systems.* A zirconium-molybdate (ZrMo) and titanium-molybdate (TiMo) gels are the generator column packing materials used exclusively with low specific activity ^{99}Mo for $^{99\text{m}}\text{Tc}$ recovery. The molybdate gel column is considered as a fully Mo-loaded sorbent column as well. These materials were first developed by Evans et al. [143] and Evans and Matthews [162] and then further improved by several research groups around the world in the 1980s

[49, 57, 59, 60, 69, 70, 103–106, 132, 146, 147]. A comprehensive description of molybdate gel-based ^{99m}Tc generator systems using low specific activity ^{99}Mo is presented in IAEA-TECDOC-852 [70]. ZrMo and TiMo gels are prepared in the form of water insoluble solid powders containing molybdenum under a strictly controlled synthesis condition to ensure the best performance when used as a column packing material in chromatographic ^{99m}Tc generators. The conditions under which a molybdate (zirconium or titanium) is prepared will influence the nanostructure of the gels and thus the ^{99m}Tc generator's performance. Different ^{99m}Tc elution performances were found with the gels of amorphous or crystalline/semicrystalline structure [57, 59, 69, 132]. As a rule of thumb, the ^{99}Mo breakthrough from the generator column and the ^{99m}Tc elution yield are higher with the amorphous gels, while the performance of the crystalline structure gels reverses. The porosity of the solid gel particles is also an important factor influencing the out-diffusion of the pertechnetate ions and thus the ^{99m}Tc elution profile and ^{99m}Tc -elution yield of the generator column. So the gel synthesis conditions such as the molar ratios of zirconium (or titanium) to molybdenum, the solution concentrations, the order of reactive agent addition, the reaction temperature, the gel aging conditions (time and temperature), the acidity of reaction mixture, the drying conditions of the gel product (time, temperature, and atmosphere), and so forth must be properly controlled in order to consistently reproduce the properties of the gel.

The ^{99m}Tc -elution performance of the gels is assessed based on the following important factors: the ^{99m}Tc elution efficiency, the ^{99}Mo breakthrough in the ^{99m}Tc eluate, mechanical stability, and the uniformity/size of the gel particles, and the capability of thermal (steam) autoclaving.

The dried gel contains about 25% by weight of molybdenum (0.25 g Mo per gram of gel) and has the characteristics of a cation exchanger as discussed above. The passage of an aqueous eluent (typically either water or normal saline) through a molybdate-gel column releases the ^{99m}Tc . However, an additional small column of alumina is required to remove ^{99}Mo -impurities from the ^{99m}Tc eluate.

As in the case of the alumina-based ^{99m}Tc generator system, the radiochemical purity of the ^{99m}Tc eluted from a molybdate gel-type generator can be impacted by the effects of radiation, changes in temperature or pH, and the presence of reducing/oxidizing agents. Finished product quality control testing clearly demonstrates that the radiochemical purity is equivalent to that of the traditional alumina column/fission ^{99}Mo -based ^{99m}Tc generator.

TiMo and ZrMo gels are prepared in two different forms: the post-irradiation synthesized ^{99}Mo -containing molybdate gel and the preformed nonradioactive Mo-containing molybdate gel. In contrast to postirradiation gels which is chemically synthesized from the ^{99}Mo solution of neutron-activated Mo target, the preformed gel target is synthesized under nonradioactive conditions and the gel powders are loaded into the generator column after being activated with neutron in the reactor to perform $^{98}\text{Mo}(n, \gamma)^{99}\text{Mo}$ reaction. However,

the disadvantage of the preformed gel is that this gel powder material requires a thoughtful neutron irradiation condition to avoid any adverse effects on the change of gel structure and chemical properties, which is caused by high temperature and extremely high radiation dose during reactor irradiation. In consequence the ^{99m}Tc elution performance of the neutron-activated gels will be degraded. So, a special design of the irradiation container and specific radical scavenger have been used to save the original properties of the pre-formed gel during its long time irradiation in the reactor [69, 70, 104, 132]. A great care should be taken during the synthesis of TiMo gel to avoid any contaminants which may generate the radionuclidic impurities during neutron activation of the TiMo gel targets [163].

Originally, the molybdate gel-column-based generators (Figure 10) are specifically designed to use low specific activity ^{99}Mo to provide the ^{99m}Tc solution for diagnostic imaging the limited numbers of the organs due to low activity concentration of ^{99m}Tc solution eluted from these generators. Typical elution profiles of the molybdate-gel column-based ^{99m}Tc -generator are presented in Figure 11. The technical maturity of this chromatographic gel-based ^{99m}Tc recovery system has advanced significantly in the last decades.

(ii) Saline-Eluted High Mo-Loading Capacity Sorbent Column-Based ^{99m}Tc Generator Systems

(a) *Polymeric Zirconium Compound and Polymeric Titanium Compound Sorbents.* Polymeric zirconium-oxychloride or polymeric zirconium compound (PZC) and polymeric titanium-oxychloride or polymeric titanium compound (PTC) sorbent materials were first developed for use in $(n, \gamma)^{99}\text{Mo}$ -based ^{99m}Tc generators. These titanium/zirconium-based inorganic polymers exhibit both excellent ^{99}Mo -adsorption capacity and ^{99m}Tc -elution. The main constituents of this sorbent material are zirconium, oxygen, and chlorine. The adsorption capacity of PZC and PTC for ^{99}Mo was reported to be much higher than that of the conventional alumina. Many research activities were performed in JAEA (Japan), in NRI (Vietnam), and in other countries in Asia on the use of PTC and/or PZC materials as high Mo-loading capacity sorbent materials for packing of various radionuclide-generator columns [62–64, 107–111, 148–154, 158]. The PTC/PZC sorbent of high Mo-adsorption capacity serves as a ^{99}Mo -loaded column from which the ^{99m}Tc can be eluted in patient-dose quantities. In contrast to a traditional alumina of low Mo-adsorption capacity currently used in a commercial chromatographic generator system loaded with high specific activity ^{99}Mo solution, the high adsorption capacity of PTC and PZC sorbent for ^{99}Mo (270–275 mg Mo/g) is useful in reducing the size of the generator column and thus the daughter nuclide eluate volume, when these columns are used for low specific radioactivity ^{99}Mo -based generator production.

PZC and PTC sorbents were synthesized from isopropyl alcohol (iPrOH) and the relevant anhydrous metallic chloride under strictly controlled reaction conditions. A given amount



FIGURE 10: Typical chromatographic gel-type ^{99m}Tc generators (dual column systems compose of a ZrMo (^{99}Mo) gel column coupled with a purification acidic-alumina column): (a) Gelutec-A ^{99m}Tc -generator manufactured by NRI (Vietnam); (b) Geltech ^{99m}Tc -generator by BRIT (India). (Note: no ^{99m}Tc -concentration is available in these generator systems. In Gelutec-A system, two alumina columns are installed in parallel and a selector/valve is inserted between them to direct the ^{99m}Tc eluate from the gel column being passed over each column for 5 consecutive purification/elutions) [2, 57, 59, 60, 103].

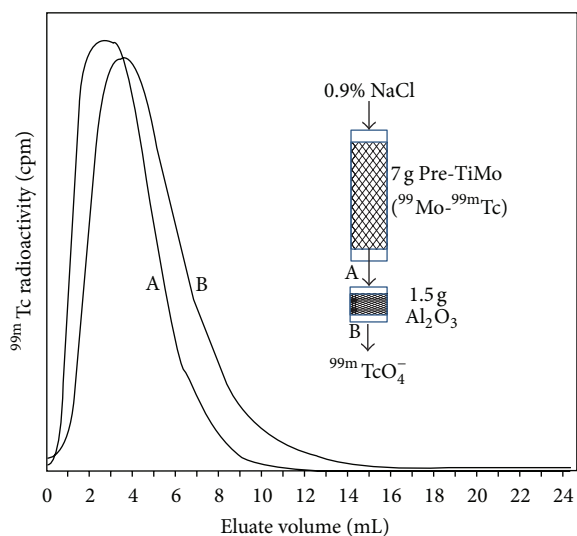


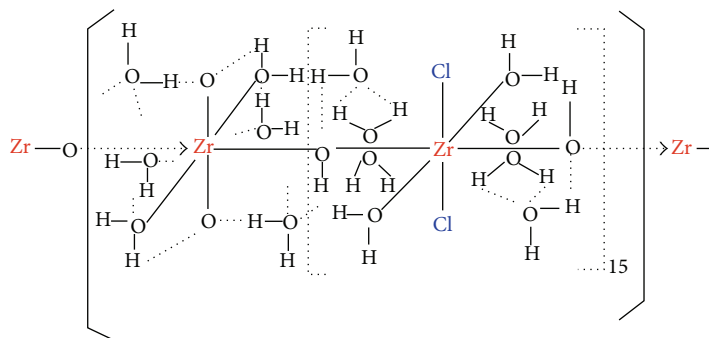
FIGURE 11: ^{99m}Tc elution profiles of Gelutec-A generator. A: the generator column without coupling with alumina purification column; B: the generator column coupled with alumina purification column [57, 59, 60, 103–106].

of relevant anhydrous metallic chloride (ZrCl_4 for PZC or TiCl_4 for PTC) was carefully added to different amounts of $i\text{PrOH}$. The temperature of the reaction mixture immediately reached $96\text{--}98^\circ\text{C}$ for the $i\text{PrOH-ZrCl}_4$ mixture and $92\text{--}94^\circ\text{C}$ for $i\text{PrOH-TiCl}_4$. The temperature of solution was maintained

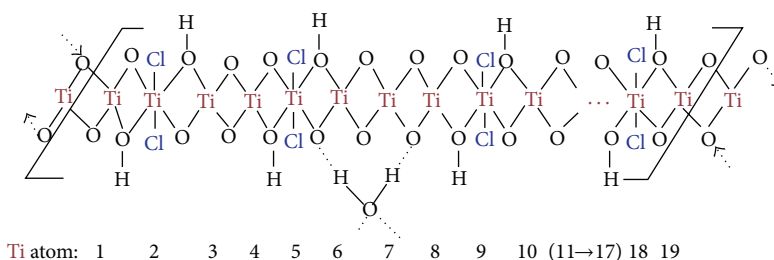
at these values and stirred gently by magnetic stirrer in open air until the solution became viscous. As the reaction temperature increased, a water-soluble PZC or PTC gel (the intermediate precursors) was formed at $129\text{--}131^\circ\text{C}$ for PZC and at $111\text{--}113^\circ\text{C}$ for PTC sorbent. The water-insoluble, solid PZC or PTC materials of particle size of 0.10 mm to 0.01 mm were split out by keeping the reaction temperature at $141\text{--}142^\circ\text{C}$ (30 minutes) for PZC and at $124\text{--}126^\circ\text{C}$ (45 minutes) for PTC. These were the finished products of PZC and PTC sorbents. The characterizations of the PZC and PTC materials synthesized and their preparation conditions are summarised in the literature [62, 107–109, 149–154].

The molecular formula of PZC sorbent was also estimated. The actual molecular weight (organic residue included) was determined to be $M = 5901.3$, where X is the organic molecules in one PZC molecule which was equivalent to 9.63% of PZC molecular weight as seen at thermal analysis. Because the organic substance in this formula was attributed to a residual organic by-product of chemical synthesis reaction and was completely being released from polymer matrix in aqueous solution, the segment unit of real polymer compound is of the following formula: $\text{Zr}_{15}(\text{OH})_{30}\text{Cl}_{30}(\text{ZrO}_2)\cdot 126\text{H}_2\text{O}$. The steric arrangement of atoms in this molecule is shown as Scheme 1.

The molecular weight of PZC sorbent is 5333.02. Chlorine content is 5.63 millimol Cl per gram PZC sorbent. Ion exchange capacity is 5.63 meq per gram PZC sorbent. The ion exchange capacity derived from the above chemical formula offers an adsorption capacity of 270.0 mg Mo/g PZC or



SCHEME 1



SCHEME 2

517.1 mg W/g PZC by assuming molybdate or tungstate ions adsorbed on PZC in the form of MoO_4^{2-} or WO_4^{2-} , respectively. In addition it is assumed that one molarity of MoO_4^{2-} or WO_4^{2-} ion consumes 2 equivalents of ion-exchange capacity of PZC and PTC sorbents (one equivalent of MoO_4^{2-} ion is 48 g molybdenum and one equivalent of WO_4^{2-} ion is 91.925 g). This type of strong adsorption suggests a covalent bond between molybdate or tungstate ions and zirconium metal atom.

The segment unit of real polymer compound is of the following formula $\text{Ti}_{40} \text{Cl}_{80} (\text{OH})_{80} (\text{TiO}_2)_{97} \cdot 60\text{H}_2\text{O}$. The steric arrangement of atoms in this molecule is shown as Scheme 2.

The molecular weight of PTC sorbent is 14939.56. The chlorine content of PTC sorbent is 5.35 millimol/gram PTC sorbent (18.965% of chlorine element in one gram PTC). This is equivalent to the ion exchange capacity of 5.35 meq/g PTC sorbent and consequently offers very high adsorption capacities of 257.0 mg Mo/g PTC or 491.8 mg W/g PTC by assuming molybdate or tungstate ions adsorbed on PTC in the form of MoO_4^{2-} or WO_4^{2-} , respectively, and one molarity of MoO_4^{2-} or WO_4^{2-} ion consuming 2 equivalents of ion-exchange capacity of PTC sorbent. This type of strong adsorption gives a covalent bond between molybdate or tungstate ions and titanium metal atom. The theoretical values of adsorption capacity calculated from the molecular formula of PZC and PTC compounds detailed above are in good agreement with the practical values achieved at the potential titration and at the Mo and/or W adsorption experiments. The adsorption capacity of both sorbents was variable depending on the temperature, reaction time, and gel aging process before forming the solid PZC and PTC polymers. The actual molybdenum adsorption of PZC and

PTC sorbents, which is to some extent higher than the above mentioned values, accounted for the noncovalently adsorbed molybdate ions and/or for adsorption of small amounts of poly-molybdate ions. These polyanions could form at the beginning stage of adsorption in the strongly acidic solution which resulted from the hydrolysis of $-\text{Zr}-\text{Cl}$ (or $-\text{Ti}-\text{Cl}$) groups of the back-bone of PZC or PTC molecules.

The PZC sorbents in its original forms, which are developed in Japan and Vietnam, contain so much HCl content in their structure and are subject to hydrolysis in an aqueous solution resulting a strong acidity. So the "in-pot" adsorption process should be applied to load ^{99}Mo -molybdate onto the sorbent before packing it into the generator column. This process is performed automatically using a smart machine (Figure 12(a)) developed by Japan Atomic Energy Agency (JAEA) and Kaken Co. Ltd. (Japan).

The PZC/PTC sorbents modified by further physico-chemical treatments performed in ANSTO and NRI, which are used for different radionuclide generator developments, are used for packing the generator column, so-called the prepacked column. This prepacked PZC/PTC column is then loaded with ^{99}Mo -molybdate solution to produce the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators in the same manner as that used for the production of the traditional alumina-based $^{99\text{m}}\text{Tc}$ generators (Figure 12(b)). Although the ^{99}Mo -adsorption capacity of the modified/prepacked PZC/PTC sorbent column is to some extent lower than that of original form of PZC sorbent, the former is preferred due to an easy-to-load property of the nonradioactive column loading procedure [108].

The saline-eluted high Mo-adsorption capacity PZC/PTC column (fully Mo-loaded column)-based $^{99\text{m}}\text{Tc}$ generator systems have been developed and the pertechnetate eluates of



(a)



(b)

FIGURE 12: Loading of ^{99}Mo solution on the PZC/PTC sorbents for $^{99\text{m}}\text{Tc}$ -generator production: (a) automatic machine developed by Kaken Co. Ltd. (Japan) for the in-pot ^{99}Mo -adsorption on PZC sorbent followed by packing of ^{99}Mo -loaded PZC into the generator column in the process of PZC sorbent-based $^{99\text{m}}\text{Tc}$ -generator production [107]; (b) the $^{99\text{m}}\text{Tc}$ -generators installed with prepacked PZC/PTC sorbent columns are in-line loaded with low specific activity ^{99}Mo solution in the process of PZC/PTC-based $^{99\text{m}}\text{Tc}$ -generator production at NRI [108].

$^{99\text{m}}\text{Tc}$ concentration suitable for a limited numbers of SPECT imaging procedures were obtained. The design of this type of the generator is similar to the molybdate gel-type generator described in Figure 10.

(b) *Nanocrystalline Sorbents.* Le (2009) has recently developed a group of nanocrystalline tetravalent metal oxide and mixed oxide sorbents for the radionuclide generator technology and radiochemical separation development [62–64, 109–111]. The tetravalent metal is each selected from the group consisting of Zr, Ti, Sn, and Ge. The chemical composition of the sorbents are described as $\text{Zr}_x\text{M}_y\text{O}_z(\text{OH})_{(2x+2y-z)}$, where x and y value pairs (x, y) are (1.0, 0.0), (0.75, 0.25), (0.5, 0.5), and (0.0, 1.0) and the value z is variable depending on heating of the powder so as to form the sorbent at the last step of synthesis process. Each M is, independently, Ti, Sn, or Ge. The process for making the sorbent comprises several steps: reacting a metal halide or a mixture of metal halides and an alcohol to form a gel and heating the gel to activate the condensation and/or polymerisation reaction for the formation of a particulate material. This solid polymer gel material in powder form with particle sizes from 0.10 to 0.01 mm is then left to cool at room temperature overnight before starting further chemical treatment. The solid polymer gel powder is treated in an alkali solution which contains oxidizing agent NaOCl : about 10 mL 0.5 M NaOH solution containing 1%

by weight NaOCl is used per gram of solid polymer gel powder. The solid powder/oxidant solution mixture is gently shaken using a mechanical shaker for at least 4 h so as to convert the gel structure solid powder into a macroporous solid powder and to convert any lower-valence metallic ions to their original 4^+ valence. The volume of solution required per gram of solid gel powder is determined so that the pH of solution at the process end is between 2 and 5. The solid matter is then separated by filtering through a sintered glass filter, washed several times with double-distilled water to remove all dissolved sodium and chloride ions, and dried at 80°C for 3 h to dryness to obtain a white solid powder. The resulting white solid powder is calcined at a temperature in the range from 500°C to 700°C for a time of about 3 h (the actual temperature depending on the particular sorbent being prepared) (the actual temperature depending on the particular sorbent being prepared). The calcinations are to complete the crystallization/recrystallization of the nanoparticles so as to form the sorbent. At the end of this heating process, the resulting powder is sieved. In particular, the fraction of particle size between about 50 and about $100\ \mu\text{m}$ may be collected to be used as a sorbent for chromatographic column packing applied to chemical separation processes. The initially formed solid is commonly in the form of white solid powder particles composed of different clusters of greater than about 100 nm in size. The clusters are aggregates of amorphous and semicrystalline nanoparticles (less than about 5 nm). The clusters appear to be held together by weak hydrogen bonds and van der Waals bonds. Consequently, the aggregate particles are macroporous and soft. During high-temperature calcining the amorphous and semicrystalline nanoparticles (less than about 5 nm) crystallize to form crystalline nanoparticles inside clusters. Simultaneously, these crystalline nanoparticles partially melt and combine with other nanoparticles inside the same cluster with interfacial coordinatively bond/ordered structure to form larger porous crystalline particles. Because there is longer distance between the clusters than that between nanoparticles within a single cluster, the nanoparticles belonging to different clusters do not combine with each other to form a single mass. Adjacent nanoparticles on the surface of clusters fuse into a limited area of the cluster surface to form a bridge to crosslink the clusters (at this stage, the clusters have already become larger crystalline particles) to form sorbent particles. In this way, meso/macroporosity formed between the former clusters may be maintained. The partial fusion and surface coordinative connection are thought to cross-link the particles to create a hard porous matrix of solid material. The high chemical and mechanical stability of the product is thought to result at least in part from the formation of stable crystalline monophase in the solid material. The crystalline structure of the product is stable when exposed to high radiation doses from radioactive materials. The powders obtained using the above process have high stability and high porosity (average pore size $\sim 120\ \text{\AA}$) and may be used as a state-of-the-art sorbent for different chemical separation processes, for example, for the separation of highly radioactive materials. The doping by different amounts of metal ions (e.g., Ti, Sn, or Ge) added to zirconium chloride solution in the synthesis is thought to

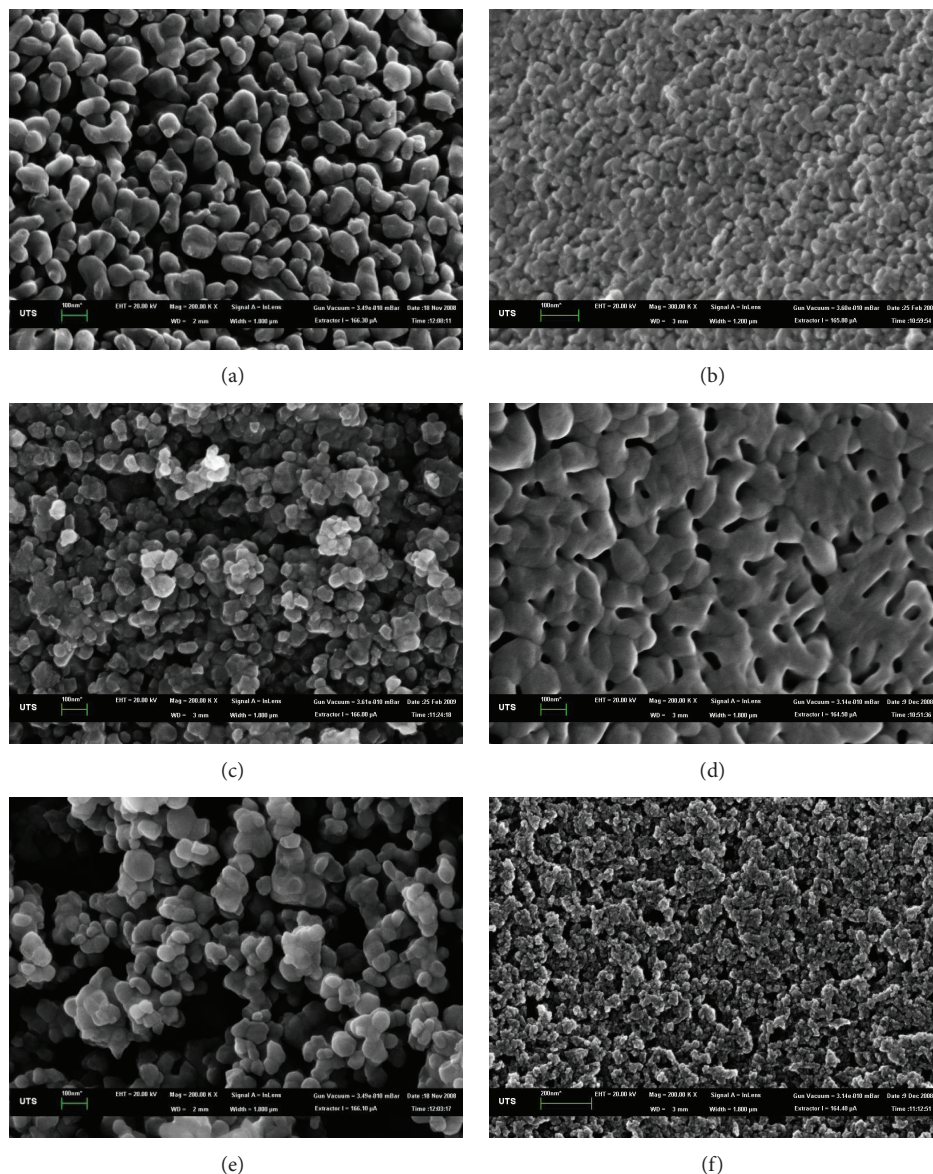


FIGURE 13: SEM picture of the nanocrystalline sorbents used for packing radionuclide generator columns. Sorbents: (a) ZiSorb, (b) TiSorb, (c) SnSorb, (d) ZT-11, (e) ZT-31, and (f) organic-polymer resin OASIS-HLB (Waters) of average pore diameter 80 Å (for a comparison purpose) [62].

be responsible for a stabilized crystalline phase which makes the product chemically and mechanically stable. The doping of smaller ions, Ge^{4+} (radius 0.53 Å), Ti^{4+} (radius 0.605 Å), and Sn^{4+} (radius 0.69 Å), onto the matrix of larger ions Zr^{4+} (radius 0.80 Å) facilitates isomorphism-based adsorption of the parent nuclides such as $^{68}\text{Ge}^{4+}$, $^{113}\text{Sn}^{4+}$, and $^{44}\text{Ti}^{4+}$ ions from its acidic solution for the preparation of the $^{68}\text{Ge}/^{68}\text{Ga}$, $^{113}\text{Sn}/^{113\text{m}}\text{In}$, $^{110}\text{Sn}/^{110\text{m}}\text{In}$, and $^{44}\text{Ti}/^{44}\text{Sc}$ generators, respectively. Moreover, the doping process is also to increase the numbers of covalently unsaturated sites ($= \text{M}^{-}$) and to reduce the isoelectric point (IEP) of zirconia (at pH ~8) to a value (at pH ~4–6), which are suitable to the adsorption of parent nuclide ions and to the elution of daughter isotope in the process of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$

and $^{188}\text{W}/^{188}\text{Re}$ generator production. The Mo-adsorption capacity of these sorbents is in the range 200–240 mg Mo/g and saline-eluted $^{99\text{m}}\text{Tc}$ -pertechnetate recovery is satisfied with medical use requirement. Scanning electron microscopy (SEM) images showing the micro- and mesoporosity of the sorbent materials synthesized above are presented in Figure 13. X-ray diffraction patterns of these sorbents showed a monophasic structure of the nanocrystalline structure [62, 64].

The nanocrystalline zirconia (tetragonal phase, $t\text{-ZrO}_2$), nanocrystalline titania, and nanocrystalline alumina sorbents of high Mo-adsorption capacity were also developed in Bhabha Atomic Research Center, Mumbai (India), for use in the $^{99\text{m}}\text{Tc}$ generator production [160, 161, 164, 165]. The sorbents were synthesized by controlled hydrolysis of 0.17 M

zirconium chloride solution in a well stirred 2.5 M ammonia solution at pH 9–11. The formed hydrogel was washed with deionized water until free of chloride ions. Subsequently the hydrogel was then refluxed at 96°C for 24 h in an ammonia solution of pH 12 and then filtered, washed with water, dried at 100°C overnight, calcined at 600°C for 5 h, and ground and sieved to get particles of 50–100 mesh for chromatographic column packing. The specific area of these materials (100–340 m²/g) is in the range of that reported for alumina (150 m²/g). These sorbents have high Mo-adsorption capacity and good ^{99m}Tc elution properties. The static ⁹⁹Mo-adsorption capacity >250 mg Mo per gram sorbent was reported. The breakthrough capacity was 100 mg/g. The column loaded with 25% of its total static Mo-adsorption capacity was investigated on the ^{99m}Tc elution performance. The ^{99m}Tc elution yield of >90% was achieved with saline eluent. The ^{99m}Tc elution performance of fully Mo-loaded nanocrystalline sorbent columns was not tested. The long time of 50 min is needed to attain the adsorption equilibrium of molybdate and tungstate ions in the static adsorption process. The kinetics of ⁹⁹Mo-adsorption process is rather slow using these materials, probably; because their pore size is smaller than the size of the molybdate/tungstate ions (pore size of ~0.4 nm for the sorbent compared with the ion size of 0.646 nm for MoO₄²⁻ and 0.648 nm for WO₄²⁻). This fact may reduce the practical application of this sorbent due to high potential of particle cracking when it is highly loaded with Mo/W. The utilisation of these sorbents for loading of low specific activity ⁹⁹Mo in the process of the production of ^{99m}Tc/¹⁸⁸Re generators needs more experimental investigations for improvement in the porosity and dynamic loading capacity. Continuing the developments of nanomaterial-based sorbents for ^{99m}Tc and ¹⁸⁸Re-generator production, the above mentioned scientist group also reported the capability of mesoporous nanocrystalline alumina in the production of ^{99m}Tc/¹⁸⁸Re generators [164, 165]. Although the Mo-adsorption capacity (230 mg/g) is in the similar range as that achieved by the above-mentioned sorbents (PZC/PTC sorbents and nanocrystalline zirconia), the effort was made to use this new alumina in a tandem system of double columns for ^{99m}Tc-generator preparation. Despite the use of double columns for increasing the Mo-loading capacity of the generator, this configuration requires the (*n*, *γ*)⁹⁹Mo of improved specific activity produced in a high neutron flux (10¹⁴–10¹⁵ n·cm²·s⁻¹) to produce a clinical scale ⁹⁹Mo/^{99m}Tc generator.

(c) *Functionalized Sorbents*. Functional alumina sorbents (sulfated alumina and alumina sulphated zirconia) developed in Korea [156] have a ⁹⁹Mo-adsorption capacity >200 mg Mo per gram of sorbent. The sorbents were synthesized by the reaction of aluminium-tri-sec butoxide, zirconium-propoxide, and anhydrous H₂SO₄ in mixture of HCl and alkyl alcohol. The obtained precipitate was dried at 100°C to get the final sorbent product. This sorbent material was used for the ^{99m}Tc generator production. The ^{99m}Tc-pertechnetate was eluted by saline with 60–85% elution yield.

The multifunctional sorbents were also developed by MED-ISOTEC (Australia) for the ^{99m}Tc generator production and for several radiochemical separations including the uses in ⁹⁹Mo/^{99m}Tc and ¹⁸⁸W/¹⁸⁸Re generator production [58]. These sorbent materials may comprise porous silica having a plurality of groups of formula -O_{4-z}(M)A_iX_{z-i-k}R_k'' on the surface thereof, wherein each M is, independently, Ti, Zr, Hf, Sn, Th, Pb, Si, or Ge; each A is, independently, either OH or R (where R is an alkyl group C_nH_{2n+1} and *n* is from 1 to 18); each R'' is an aminoalkyl group [(CH₂)_m-(Amino group1)], where *m* is from 1 to 6; each X is a [M'(oxo-hydroxyl-alkyl-aminoalkyl)M''(oxo-hydroxyl-alkyl-aminoalkyl)] group of formula [(OM')_j{(OH)_a(C_bH_{2b+1})_c[(CH₂)_d-(Aminogroup2)]_e}{(OM'')_f(OH)_g(C_hH_{2h+1})_p[(CH₂)_q-(Amino group3)]_v}, where each M' is, independently, Si, Ti, Zr, or Hf and each M'' is, independently, Si, Ti, Zr, or Hf; *z* is from 1 to 3; *i* is from 0 to 3; (*i* + *k*) is from 0 to 3; *j* is 0 or 1; *a* is from 0 to 3; *b* is from 1 to 6; *c* is from 0 to 3; *d* is from 1 to 6; *e* is from 0 to 3; (*a* + *c* + *e*) is 3; *f* is 0 or 1; *g* is from 0 to 3; *h* is from 1 to 6; *p* is from 0 to 3; *q* is from 1 to 6; *v* is from 0 to 3; and (*g* + *p* + *v*) is 3. The ⁹⁹Mo-adsorption capacity of these materials (>600 mg Mo/g) is significantly higher than that of the sorbents developed up to date. The kinetics of ⁹⁹Mo-adsorption process is fast with these materials due to their high porosity (pore size 2–10 nm) and high surface area (>700 m²/g). The excellent ^{99m}Tc elution properties of these sorbents are well confirmed when used with saline eluent. The functional sorbent generator columns can be sterilized by a normal steam process in the autoclave. A commercial production of the ^{99m}Tc generators using these sorbents for loading of low specific activity ⁹⁹Mo is well promising.

(2) *Nonsaline Eluent-Eluted Generator Systems Using High Mo-Loading Capacity Columns and Integrated Generator Systems*. In contrast to the saline-eluted generator systems using high Mo-loading capacity columns which are used for a limited number of SPECT imaging procedures due to a rather low ^{99m}Tc concentration of ^{99m}Tc eluate obtained, the nonsaline aqueous solution-eluted ^{99m}Tc generators or ^{99m}Tc recovery processes are mainly developed to couple with the ^{99m}Tc-purification/concentration process to set up the ⁹⁹Mo/^{99m}Tc generator systems which are suitable for a routine production of ^{99m}Tc solution of medically useful radioactivity concentration effectively used in all the diagnostic SPECT imaging procedures.

(i) *Nonsaline Aqueous Solution-Eluted ^{99m}Tc Generator Systems Using Molybdate-Gel Columns*. Recent advances in radiopharmaceutical diagnostic applications using the ^{99m}Tc-pertechnetate of moderate to high activity concentration (as shown in Table 1) require the development of the integrated generator system RADIGIS which composes of a molybdate-gel column-based ^{99m}Tc generator coupled with a postelution ^{99m}Tc concentrator to produce a medically useful pertechnetate solution of sufficiently high ^{99m}Tc concentration.

A version of RADIGIS developed in the 1980s is presented in Figure 14. The operation of this system is semiautomated.

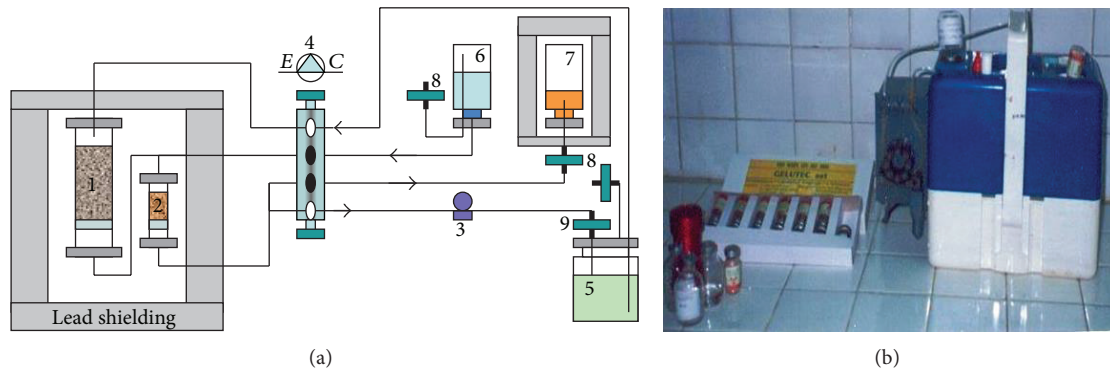


FIGURE 14: Integrated ^{99m}Tc -generator system (RADIGIS): (a) process diagram and design; (b) photo of GELUTEC-C system used for years in Vietnam which composes of a ZrMo (^{99}Mo) gel column coupled with a zirconia/alumina column-based purification/concentration unit: 1: gel column; 2: zirconia/alumina column; 3: peristaltic pump; 4: selector valve; 5: circulating eluent container (water containing 0.005% NaCl); 6: saline vial; 7: final ^{99m}Tc solution; 8: Milipore filter; 9: coarse filter. (Specifications: Semi-automated operation based on the circulating elution with an eluent of redistilled water containing 0.005% NaCl; Processing time 20 min; Final ^{99m}Tc solution of 100–200 mCi/mL concentration depending on the activity of ^{99}Mo -loading) [57, 103].

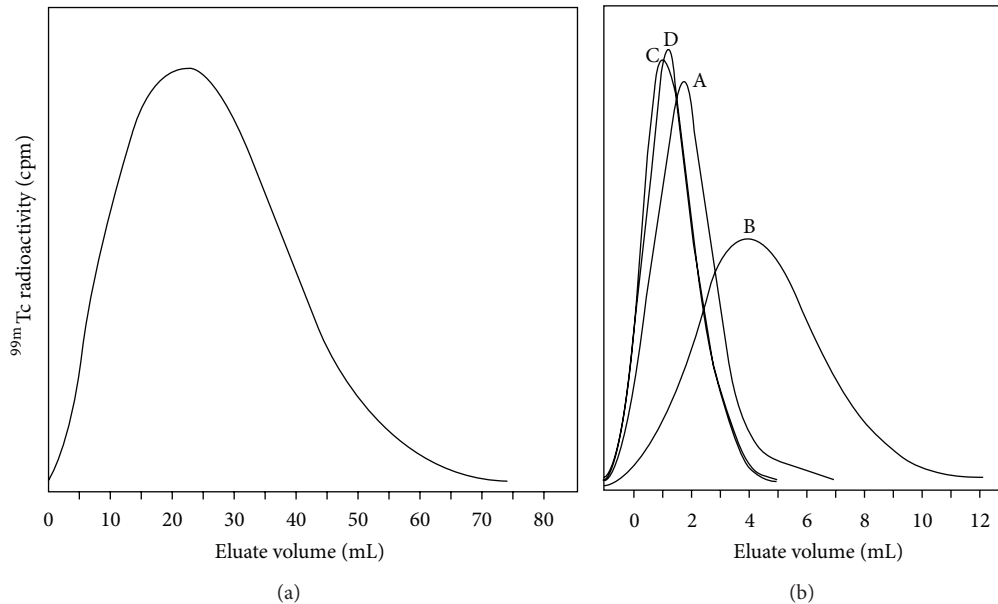


FIGURE 15: ^{99m}Tc elution profiles of the system GELUTEC-C (ZrMo(^{99}Mo) gel column coupled with a metal-oxide sorbent column-based purification/concentration unit): (a) the elution profile of the generator column of 50 g weight of titanium-molybdate gel eluted with redistilled water; (b) the elution profiles of the concentration columns of 1.5 g weight eluted with saline: A: alumina; B: zisorb; C: titania; D: MnO_2 [57].

This integrated generator system has been used for years in the hospitals in Vietnam [57, 59, 60, 103]. The low-cost automation of the generator elution using a simple electronic time-sequence-based control unit provides the convenience in operation and preference for use in a daily hospital environment. The ^{99m}Tc elution profile of the molybdate gel-column-based generator is shown in Figure 15. TiMo and ZrMo gel columns are prepared as described in the previous section “Saline-eluted molybdate-gel column. Both the post-irradiation synthesized gel and preformed gel columns are equally used for the preparation of nonsaline aqueous solution-eluted ^{99m}Tc generator systems. Redistilled water is

used as eluent for both TiMo and ZrMo gel columns, while the water containing 0.005% NaCl is more effectively used for ZrMo gel column [57, 59, 60, 69, 70, 103–106, 132, 146]. Similarly, the zirconium-molybdate gel-based ^{99m}Tc generator which is eluted with water is developed in India [49].

(ii) *Nonsaline Aqueous Solution-Eluted ^{99m}Tc Generator Systems Using High Mo-Loading Capacity Sorbent Columns*

(a) *PZC/PTC Sorbent Column-Based Generators.* Research is in progress at MEDISOTEC (Australia) on the use of the high Mo-adsorption capacity PTC/PZC sorbent materials for the

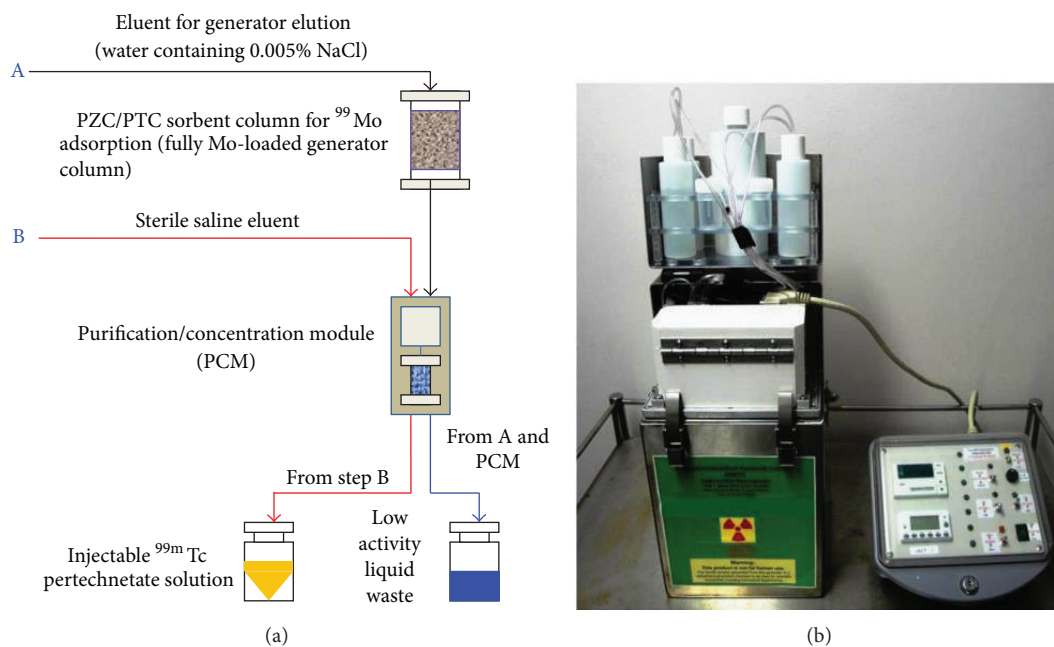


FIGURE 16: Integrated radioisotope generator system (radionuclide generator column coupled with an automated purification/concentration unit of the programmable time sequence control): (a) process diagram; (b) photo of the system recently developed at MEDISOTEC and ANSTO [58, 62–64, 109–111].

production of a nonsaline aqueous solution-eluted $^{99\text{m}}\text{Tc}$ generator system. These sorbents are prepared as described in the previous section “Saline-eluted high Mo-adsorption capacity sorbent columns”. The PTC and PZC sorbent columns are loaded with a low specific activity ^{99}Mo solution and the $^{99\text{m}}\text{Tc}$ -pertechnetate eluted with redistilled water containing 0.005% NaCl is consecutively concentrated using a small alumina concentration column.

The automated purification/concentration unit coupled with $^{99\text{m}}\text{Tc}$ generator column is shown in Figure 16. This device is a versatile radionuclide generator system which can be used for the production of different daughter nuclide solutions (such as $^{99\text{m}}\text{Tc}$, ^{188}Re , ^{90}Y , and ^{68}Ga) of high activity concentration using low specific radioactivity parent nuclides [63]. The chemical process applied in this system is based on the selective adsorption of $^{99\text{m}}\text{Tc}$, which is eluted from a large ^{99}Mo -PZC/PTC column, onto a significantly smaller concentration column. In the following step the technetium is stripped from the column with a small volume of injectable saline solution. Optionally, this small sorbent column is washed to remove any parent nuclide ions and metallic impurities that also may have been adsorbed on the column. Following the wash, the daughter nuclide is stripped from the column with a small volume of solution suitable for injection or for investigational purposes.

The process of the daughter radionuclide elution from the generator followed by the postelution purification/concentration process was performed using a low-cost automated bench-top system [62–64]. This system was designed based on the timing sequence of several processing steps without feedback control. The variable flow rate of eluents

used for elution/purification in this system also ensures the optimisation of operating times with respect to different adsorption/desorption kinetics of daughter radionuclide ion species, which is controlled by the sorbents used in the generator and the purification columns.

(b) *Alumina Column-Based Generator Systems.* Several research groups reported on using different nonsaline aqueous eluents for elution of $^{99\text{m}}\text{Tc}$ from alumina-based generator systems which couple with a concentration unit for increasing the pertechnetate concentration of the $^{99\text{m}}\text{Tc}$ solution. The eluents used are the following: the mixture of 0.7 M acetic acid and 0.0225 M NaCl solution [50], the solution of the salt of weak acids such as ammonium acetate, citrate, titrate, and so forth, and the mixture of acetic acid and ammonium acetate solution [43–48]. Although the elution performance of these eluents is excellent and suitable for the concentration processes using an anion exchange materials such as QMA Sep-Pak Cartridge, NH_2 Amberlite, BondElut SAX, Dowex-1, DEAE Cellulose, and so forth, the large volume of the eluents used for the $^{99\text{m}}\text{Tc}$ elution from large alumina column-based generators is the main issue for the routine use of all these methods. The details of $^{99\text{m}}\text{Tc}$ concentration techniques will be reviewed in the next sections.

(c) *New Sorbent-Based Generator Systems.* No work on using nonsaline aqueous eluents for the elution of $^{99\text{m}}\text{Tc}$ from recently developed high Mo-adsorption capacity sorbent materials (such as nanocrystalline zircona (tetragonal phase, t-ZrO_2), nanocrystalline titania, nanocrystalline alumina,

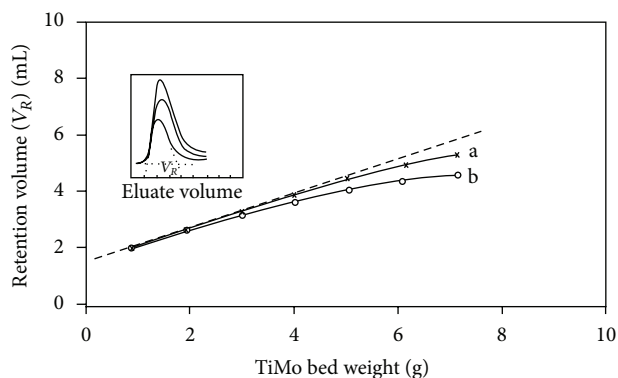


FIGURE 17: Retention volume V_R versus TiMo-column-bed weight (TiMo particle size 100–200 mesh; column size 10 mm i.d.). a: acetone as eluent; b: 0.9% NaCl solution as eluent [59, 106].

and functional alumina sorbents (sulfated alumina and alumina sulphated zircona)) was performed until now. The integrated ^{99m}Tc -generator systems (integration of elution, purification, concentration, and column-generation) using a column containing multifunctional sorbent materials of high Mo-adsorption capacity and an acetate solution as circulating eluent are recently developed by MEDISOTEC [58].

(iii) *Nonsaline Organic Solvent-Eluted ^{99m}Tc Generator Systems Using Molybdate-Gel Columns and Acetone Eluent (Solid-Liquid Extraction ^{99m}Tc Generator).* ^{99m}Tc can be eluted from a zirconium/titanium-molybdate gel-type generator column and from ^{99}Mo -loaded diatomaceous earth sorbent using organic solvents (so-called “solid-solvent” extraction) [57, 59, 60, 103–106, 141, 146]. The results of investigations on the elution of ^{99m}Tc from TiMo and ZrMo-gel columns using organic solvents such as methyl ethyl ketone (MEK), acetone, ethyl ether, chloroform, and so forth showed that the separation yield of ^{99m}Tc was around 80% for acetone eluent and <40% for the others. The ^{99m}Tc elution profile of the acetone elution is very similar to that of saline eluent (Figure 17). So the acetone can be used as a useful eluent for a solid-solvent extraction-based generator using zirconium/titanium-molybdate-gel columns of high Mo-loading capacity.

The solid-liquid extraction-based ^{99m}Tc generator system using acetone as eluent operates as follows. First the ^{99}Mo -molybdate gel (TiMo or ZrMo) columns are prepared as described in the previous section “Saline-eluted molybdate gel columns”. Then the ^{99m}Tc is eluted with acetone eluent. In the following steps the ^{99m}Tc -acetone eluate is evaporated to dryness and the recovery of ^{99m}Tc pertechnetate into a small volume of saline is followed. The ^{99m}Tc pertechnetate is then passed through a small alumina and Millipore filter giving a sterile pertechnetate solution of high ^{99m}Tc concentration. The generator flowchart is shown in Figure 18.

Acetone is a less toxic volatile solvent. Low boiling temperature and low risk of polymerization of the acetone offers the advantages of economical low temperature evaporation

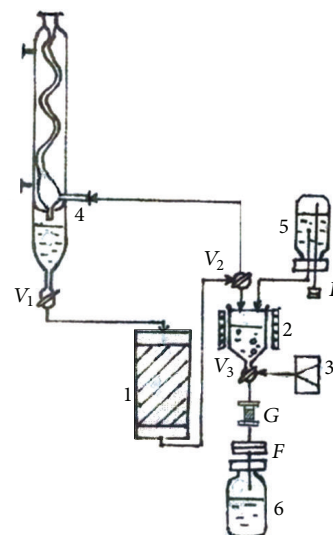


FIGURE 18: Process diagram of the solid-liquid extraction-based ^{99m}Tc -generator system GELUTEC-B developed in NRI. 1: ^{99}Mo -loaded molybdate-gel column; 2: acetone evaporator; 3: air pump; 4: acetone reservoir/condenser; 5: saline for recovery of ^{99m}Tc -pertechnetate; 6: ^{99m}Tc -pertechnetate injectable solution; V_{1-3} : valves; G: alumina guard column; MF: Millipore filter [57, 59, 60, 103, 105, 106].

of ^{99m}Tc /acetone eluate of small volume, which is performed faster using a less elaborated apparatus as compared with MEK extraction-based ^{99m}Tc generator system described above. Thus the generator system based on solid-solvent extraction using acetone as eluent is found to meet the requirements of an effective method of ^{99m}Tc recovery from low specific activity ^{99}Mo . The quality of pertechnetate solution obtained from this generator system was found to meet all the requirements of ^{99m}Tc pertechnetate injection as specified in various pharmacopeia [36, 37].

^{99m}Tc elution from an alumina column-based generator using acetone eluent was also tested and reported with a positive result [51].

(iv) *Nonsaline Organic Solvent-Eluted ^{99m}Tc Generator Systems Using High Mo-Loading Capacity Sorbent Columns.* No work on using organic eluent for ^{99m}Tc elution from the recently developed sorbent materials of high Mo-adsorption capacity (such as nanocrystalline zircona $t\text{-ZrO}_2$, nanocrystalline titania, nanocrystalline alumina, and functional alumina sorbents (sulfated alumina and alumina sulphated zircona), polyfunctional sorbents) was performed until now.

4.4.3. ^{99m}Tc Concentration Methods Used in the ^{99m}Tc Recovery from Low Specific Activity ^{99}Mo

(1) *Characterization and Performance Assessment of Chromatographic Column Concentration Process.* Le (2003) has developed a method for assessment of concentration factor

values which are achievable in different concentrating processes. This method rely on the basic parameters currently used in the chromatographic processes such as the retention time/volume and the distribution coefficient of the solute [103]. This evaluation is an important guide for designing of the concentrator with optimal operation conditions. In his further development, as being reported in this review, a standardization method of concentration factor evaluation is developed using a standard elution, which is performed with normal saline solution (0.9% NaCl), as a reference. In this case, the normal saline may play both the role of a generator eluate containing solute (^{99m}Tc), which is fed/loaded onto the concentration column to be concentrated, and the role of the eluate of final concentrated ^{99m}Tc -product which is stripped from the concentration column. This approach is useful for the researchers in the process of concentration method development to evaluate the effectiveness of one concentration system (sorbent-eluent system) in comparison with others which could or would be performed under the similar (normalized) conditions of the experiments.

In general, the performance of the concentration process is characterized with the concentration factor n :

$$n = \frac{c_2}{c_1}. \quad (13)$$

For a concentration process of solute recovery yield (k), the following mass balance is established:

$$V_2 \times c_2 = k \times c_1 \times V_1. \quad (14)$$

Relating the above equations, the following is derived:

$$n = \frac{c_2}{c_1} = k \times \frac{V_1}{V_2}, \quad (15)$$

where V_1 and V_2 are the solution volumes before and after concentration, respectively. c_1 is the solute concentration in the solution before the concentration and c_2 is the solute concentration in the solution after the concentration using a given concentration process.

In individual case of ^{99m}Tc concentration, c_1 is the ^{99m}Tc radioactivity concentration in the eluate eluted from the ^{99m}Tc generator and c_2 is the ^{99m}Tc radioactivity concentration in the ^{99m}Tc solution concentrated using a given concentration process.

Except being concentrated by the evaporation of solvent or by the electrolysis, all the chromatographic column concentration processes are described by the following basic equations.

For a sorbent (e.g., ion-exchange resin) characterized with a volume of solid substrate used in the concentration column,

$$V_1 = V_m + K_V \times V_S. \quad (16)$$

For a sorbent (e.g., alumina) characterized with a specific surface area of solid substrate used in the concentration column,

$$V_1 = V_m + K_S \times S, \quad (17)$$

where

$$S = m_c \times \bar{S}$$

$$V_S = m_c \times \bar{V}_S = m_c \times \frac{1}{\rho_{\text{Re}}}, \quad (18)$$

$$K_V = \rho_{\text{Re}} \times K_W$$

(more details about these equations for refer to [166]).

The following is received by relating (16) and (17):

$$K_V \times V_S = K_S \times S. \quad (19)$$

K_S value is calculated by putting the value of K_V, V_S , and S into this equation:

$$K_S = \frac{K_W}{\bar{S}}, \quad (20)$$

where K_S (mL/m²), K_V (mL/mL), K_W (mL/g) are the area, volume, and weight distribution coefficient of the solute ($^{99m}\text{TcO}_4^-$) in a given sorbent-solution system, respectively; S is the surface area of the sorbent (m²); V_S is the volume of the dry resin (mL); m_c is the weight of the dry resin/sorbent loaded in the column (g); \bar{S} is the specific surface area of the sorbent (m²/g); \bar{V}_S is the specific volume of the resin (mL/g); ρ_{Re} is the weight density of the resin (g/mL).

Based on the above equations (assuming the dead volume of the concentration column $V_m \ll V_2$), the concentration factor (n) is assessed for the designing of the concentrator column as follows.

For the ion-exchange resin column,

$$n = k \times \frac{V_1}{V_2} = k \times \left[\frac{V_m}{V_2} + K_V \times \left(\frac{V_S}{V_2} \right) \right] = k \times K_V \times \left(\frac{V_S}{V_2} \right). \quad (21)$$

For the sorbent column,

$$n = k \times \frac{V_1}{V_2} = k \times \left[\frac{V_m}{V_2} + K_S \times \left(\frac{S}{V_2} \right) \right] = k \times K_S \times \left(\frac{S}{V_2} \right). \quad (22)$$

If V_2 is given as a designed value, the concentration factor (n) only depends on the value of k, K_S , and S (or K_V and V_S).

As an example, the design of the generator systems, which are composed of the molybdate gel (Figure 14) or PZC/PTC nanocrystalline sorbent (Figure 16) generator column coupled with a alumina concentrator column described above, was based on the following parameters calculated using the above equations: $K_S = 2.0$, $V_2 = 5.0$ mL, and $k = 0.95$; the available concentration factor for a bolus elution (with $V_1 = 460$ mL for a generator TiMo (or PZC/PTC)-column of 375–380 g weight, $V_2 = 7.5$ mL and $k = 1$) is $n = 55.7$; the elution-by-elution (with $V_1 = 65$ mL for each elution from a 53 g weight-sorbent column, Mo-breakthrough of $<40 \mu\text{g/mL}$, $V_2 = 5.0$ mL and $k = 0.95$) concentration factor is $n = 11.2$. The design is also performed with a conservation of the influence of MoO_4^{2-} breakthrough in the primary solution eluted

from the generator column. The above-described calculation method was also successfully applied for the evaluation and designing of a compact concentrator ULTRALUTE using a more effective new sorbent concentration-column as shown in Figure 3.

Due to the diversity of the eluents of variable volume used for the elution of ^{99m}Tc -generators, the evaluation of concentration factor of the integrated generator systems (integrated elution-concentration processes) should be harmonized using a common language for communication/justification on the elution/concentration performance of the given systems. When a nonsaline solvent-eluted process is applied for the ^{99m}Tc generator elution and consecutively the eluate of this elution is concentrated using a chromatographic column concentration method, we need a tool to assess/justify the effectiveness of each elution-concentration process in comparison with others. So we need a reference to be used for the comparison. The saline-eluted process of the ^{99m}Tc generator is considered as a gold standard/reference elution due to its suitability for clinical use. The reference is set up as follows.

V_{Eqv} (equivalent volume) is the volume of nonsaline eluent used for the elution of ^{99m}Tc from a generator (with a nonspecified activity) giving a ^{99m}Tc elution yield f_E which is equal to the yield achieved by an elution performed with the volume V_{S1} of saline.

V_E is the volume of nonsaline eluent (containing ^{99m}Tc) actually passed through the concentration column of the weight m , in which the ^{99m}Tc will be retained with adsorption yield (x) from its total amount present in the volume V_E .

At the stage of the elution of the concentration column with a small volume of saline, V_{S2} is the volume of the saline used to recover the ^{99m}Tc from the concentration column to achieve a concentrated ^{99m}Tc solution and the elution yield of this concentration column is y . The yield of the overall concentration process k is composed of the adsorption yield x and recovery elution yield y , as follows:

$$k = x \times y. \quad (23)$$

The normalized concentration factor will be set up as follows:

$$n = k \times \frac{V_{S1}}{V_{\text{Eqv}}} \times \frac{V_E}{V_{S2}}. \quad (24)$$

With introduction of the weight of the sorbent (m) used in the concentration column, the further analysis of the above equation is shown as follows:

$$\bar{V} \times m = V_{S2}, \quad (25)$$

$$n = \frac{V_{S1}}{V_{\text{Eqv}}} \times \frac{x}{\bar{V}} \times \frac{y \times V_E}{m}, \quad (26)$$

where \bar{V} (mL/g) is the specific elution volume of the concentration column eluted with saline to get a concentrated ^{99m}Tc solution of volume V_{2S} .

Equation (26) composes four components characterizing the system involved.

The term (V_{S1}/V_{Eqv}) characterizes the relation of the saline elution versus alternative nonsaline elution of a given generator column.

The term $(1/\bar{V})$ characterizes the saline elution of the concentrator column.

(V_E/m) and K characterize the adsorption/elution capability of the sorbent for the pertechnetate ions with an alternative nonsaline eluent.

The equations described above can be used for both the theoretical and practical evaluations of the normalized concentration factor:

$$n_T = k_T \times \frac{V_{S1}}{V_{\text{Eqv}}} \times \frac{V_{E-T}}{V_{S2-T}}. \quad (27)$$

Equation (27) is used for theoretical assessment of the normalized concentration factor, where $k_T = 1$; V_{E-T} and V_{S2-T} are obtained from the practical determination of retention time/retention volume using an established standard chromatographic procedure performed with the same column or are calculated from the distribution coefficient K as described above. K_W is determined as described in the literature [166]. n_T value is used for the evaluation of the effectiveness of the concentration system (sorbent-eluent)/method of interest, while n_P value is to evaluate the performance of a practical procedure/concentrator device designed using this concentration system/method. n_P value is calculated as follows:

$$n_P = k_P \times \frac{V_{S1}}{V_{\text{Eqv}}} \times \frac{V_{E-P}}{V_{S2-P}}, \quad (28)$$

where V_{E-P} and V_{S2-P} are the volume of nonsaline eluent and saline actually used in the concentration procedure/device, respectively.

Note that the overall ^{99m}Tc recovery yield of the integrated generator-concentration system will be

$$Y = f_E \times k, \quad (29)$$

where f_E is the elution yield of the generator column and k is the purification/concentration yield.

Table 3 shows the majority of the concentration methods developed up to date and the normalized concentration factor values assessed by the approach described above using the process performance parameters extracted from the literatures. It may be interesting to note that in many cases the optimal design of a practical procedure/concentrator device was not performed to match the inherent effectiveness of the method developed.

(2) *Chemistry and Methods of ^{99m}Tc Concentration.* The chemistry of pertechnetate ions should be reviewed herein in regard to the development of the ^{99m}Tc concentration methods. Except for the materials containing cyclic compounds of π -electrons, almost all the anion-exchange materials reversibly adsorb the pertechnetate ions in aqueous solutions. Unfortunately the chloride ions compete strongly with pertechnetate ions in the adsorption on these sorbents. This fact makes the concentration of ^{99m}Tc -pertechnetate from a saline solution very hard. The following parameters are useful to justify a proper selection of the sorbent and suitable eluent to develop an effective process for ^{99m}Tc concentration.

TABLE 3: Assessment of normalized concentration factor of the concentration methods (electrolysis- and solvent-evaporation-based concentration methods are not included herein.).

Method and concentration column (CC)/(generator column)	Generator elution volumes		Adsorption: Retention volume of nonsaline eluent passed over CC		Elution: volume of saline eluted from concentration column		Values calculated using K_w or retention volume (V_{E-T})		Values calculated based on experiment parameters (exp. result)		Reference
	V_{Eg}	V_{G1}	V_{E-T}	V_{E-P}	V_{S2-T}	V_{S2-P}	k_T	n_T	k_p	n_p	
0.3 M NH_4OAc + 0.01 M NH_4NO_3 QMA-SepPak (130 mg)/ (alumina)	20**	10**	—	20	—	0.5	1.0	—	0.69	13.8 (40)	Knapp et al. (1998) [43–45]
0.7 M $AcOH$ + 0.132% (0.025 M) $NaCl$ QMA-SepPak (130 mg)/ (alumina)	10	10	10	10	1.5	2.0	1.0	6.6	0.9	4.5 (4.5)	Mushfaq (2004) [50]
0.5 M $AcOH$ + 0.025% $NaCl$ QMA-SepPak (130 mg)/ (alumina)	25	10	13	13	1.5	1.5	1.0	3.5	0.9	3.2 (3.1)	Le (2013) (for this report)
0.7 M $AcOH$ + 0.025 M NH_4OAc DEAE-cellulose (300 mg)/ (alumina)	40	45	40	40	6.0	6.0	1.0	7.5	0.8	6.0 (5-7)	Sarkar et al. (2001) [47, 48]
0.1 M $AcOH$ + 0.05% $NaCl$ DEAE-cellulose (0.25 mL)/ (alumina)	40	10	120	120	6.0	6.0	1.0	5.0	0.95	4.75 (4.5)	Le (2013) (for this report)
0.3 M $AcOH$ + 0.05% $NaCl$ DEAE-cellulose (0.25 mL)/ (alumina)	27	10	108	108	6.0	6.0	1.0	6.7	0.95	6.3 (6.0)	Le (2013) (for this report)
0.3 M $AcOH$ + 0.05% $NaCl$ DEAE-cellulose (0.25 mL)/ (alumina)	27	10	108	108	4.0*	3.5*	1.0	10.0	0.85	9.7 (9.4)	Le (2013) (for this report)
0.5 M $AcOH$ + 0.1% $NaCl$ DEAE-sephadex (0.125 mL) (alumina)	15	10	20	20	4.0	4.0	1.0	3.3	0.9	3.0 (3.0)	Le (2013) (for this report)
0.5 M $AcOH$ + 0.05% $NaCl$ Isosorb-MOX-01 (100 mg)/ (alumina)	20	10	18	16	1.5	1.5	1.0	6.0	0.95	5.0 (4.5)	Le and Le (2013) [58]
0.1 M $AcOH$ + 0.05% $NaCl$ Isosorb-FS-01 (100 mg)/ (alumina)	40	10	40	35	1.5	1.5	1.0	6.6	0.90	5.25 (5.0)	Le and Le (2013) [58]
H_2O alumina (2.0 g)/ (ZrMo molybdate gel)	16	16	—	20	—	3.0	1.0	—	0.9	6.0 (4.0)	Sarkar et al. (2004) [49]

TABLE 3: Continued.

Method and concentration column (CC)/(generator column)	Generator elution volumes		Adsorption: Retention volume of nonsaline eluent passed over CC		Elution: volume of saline eluted from concentration column		Values calculated using K_w or retention volume (V_{E-T})		Values calculated based on experiment parameters (exp. result)		Reference
	V_{Eq}	V_{SI}	V_{E-T}	V_{E-P}	V_{S2-T}	V_{S2-P}	k_T	n_T	k_p	n_p	
H ₂ O alumina (1.5 g)/ (TiMo/ZrMo molybdate gel)	11	10	460	65****	7.5	5.0	1.0	55.7	0.95	11.2 (10.5)	Le (1990) [57]
H ₂ O MnO ₂ ·xH ₂ O (1.5 g)/ (TiMo/ZrMo molybdate gel)	11	10	440	62****	7.0	5.0	1.0	62.8	0.95	11.8 (10.4)	Le (1990) [57]
H ₂ O TiO ₂ ·xH ₂ O (1.5 g)/ (TiMo/ZrMo molybdate gel)	11	10	400	55****	6.5	5.0	1.0	61.5	0.95	10.5 (10.1)	Le (1990) [57]
H ₂ O ZrO ₂ ·xH ₂ O (1.5 g)/ (TiMo/ZrMo molybdate gel)	11	10	660	95****	12.0	10.0	1.0	55.0	0.8	7.6 (7.0)	Le (1990) [57]
Saline → H ₂ O Ag-resin-alumina (0.25 mL; ~260 mg)/ (alumina)	10	10	—	20	3.0	—	1.0	—	0.98	6.53 (6.57)	Ruddock (1978) [38]
Saline → H ₂ O Ag-resin-alumina (0.5 g)/ (alumina)	10	10	150	150	2.5	2.5	1.0	60	0.90	54.0 (50.0)	Le et al. (2013) [40]
Saline → H ₂ O Ag-resin-MnO ₂ (0.5 g)/ (alumina)	10	10	145	145	2.2	2.2	1.0	65.9	0.90	59.3 (53.0)	Le and Le (2013) [58]
Saline → H ₂ O Ag-resin-TiO ₂ (0.5 g)/ (alumina)	10	10	140	140	2.0	2.0	1.0	70	0.90	63.0 (57.0)	Le and Le (2013) [58]
Saline → H ₂ O Ag-resin-microcrystalline ZT-11 sorbent (0.5 g)/ (alumina)	10	10	155	155	2.75	2.5	1.0	56.3	0.90	55.8 (55)	Le (2010-2013) [63, 64]
Saline → H ₂ O Ag-resin-microcrystalline ZT-31 sorbent (0.5 g)/ (alumina)	10	10	200	200	5.0	5.0	1.0	40.0	0.8	32.0 (31.0)	Le (2010-2013) [63, 64]
Saline → H ₂ O Ag-resin-isosorb-FS-01 (0.5 g)/ (alumina)	10	10	275	275	5.0	5.0	1.0	55.0	0.95	52.2 (50)	Le and Le (2013) [58]
Saline → H ₂ O Ag-resin-QMA SepPak (130 mg)/ (alumina)	10	10	—	10	—	1.0	1.0	—	0.82	8.2	Knapp et al. (1998) [43, 44]

TABLE 3: Continued.

Method and concentration column (CC)/(generator column)	Generator elution volumes		Adsorption: Retention volume of nonsaline eluent passed over CC		Elution: volume of saline eluted from concentration column		Values calculated using K_w or retention volume (V_{E-T})		Values calculated based on experiment parameters (exp. result)		Reference
	V_{Eg}	V_{S1}	V_{E-T}	V_{E-P}	V_{S2-T}	V_{S2-P}	k_T	n_T	k_p	n_p	
Saline \rightarrow H ₂ O Ag-resin-BondElut-SAX (100 mg/ alumina)	10	10	25	10	2.0	2.0	1.0	12.5	0.95	4.75 (4.7)	Blower (1993) [39]
Saline \rightarrow 0.2 M NaI Dowex 1 \times 8-resin (10 mg) \rightarrow AgCl, 1.0 g/ (alumina)	10	10	66	70	5.5	7.5	1.0	12.0	0.8	7.5 (7.7)	Chattopadhyay et al. (2002) [53]
0.02 M Na ₂ SO ₄ \rightarrow H ₂ O Pb-resin-alumina (300 mg/ alumina)	45	60	45	45	1.5	1.0	1.0	40	0.9	54 (38)	Bokhari et al. (2007) [54]

* Concentrator column is eluted with 0.15 M NaOH and followed by passing over a cation-exchange resin column.

** Value is assumed based on different data sources.

*** Values are designed for a useful life (14 elution cycles) of the generator without replacement of the concentrator column.

TABLE 4: Details of the methods of ^{99m}Tc -pertechnetate concentration from the saline eluate of ^{99m}Tc -pertechnetate (dual column concentration methods).

Scheme	Concentration process			^{99m}Tc -generator column	References
	Elution	Interfering ions remover	^{99m}Tc concentrator		
1A	Step A: saline Step B: saline	Cation exchange resin (Ag form)	Alumina, zircona, and MnO_2 columns	Alumina	Ruddock (1978) [38]
1A	Step A: saline Step B: saline	Cation exchange resin (Ag form) OnGuard-AG	BondElut-SAX column	Alumina	Blower (1993) [39]
1A	Step A: saline Step B: saline	Cation exchange resin (Ag form) OnGuard-AG	QMA-SepPak column	Alumina	Knapp et al. (1998) [43, 44]
1A	Step A: saline Step B: saline	Cation exchange resin (Ag form)	Functional sorbent (isosorb-FS-01) columns	Alumina	Le and Le (2013) [58]
1A	Step A: saline Step B: saline	Cation exchange resin (Ag form)	MnO_2 , TiO_2 , ZrO_2 , ZT-11, ZT-31 sorbent columns	Alumina	Le et al. (2013) [40]
2A	Step A: saline Step B: NaI solution	AgCl powder column	Anion exchange resin (Dowex-1 \times 8) column	Large alumina	Chattopadhyay et al. (2002) [53]
3A	Step A: saline Step B: Tetrabutylammonium bromide in methylene chloride	Not needed	Anion exchange resin (Dowex-1 \times 8) column combined with solvent evaporator	Large alumina	Chattopadhyay and Das (2008) [52]

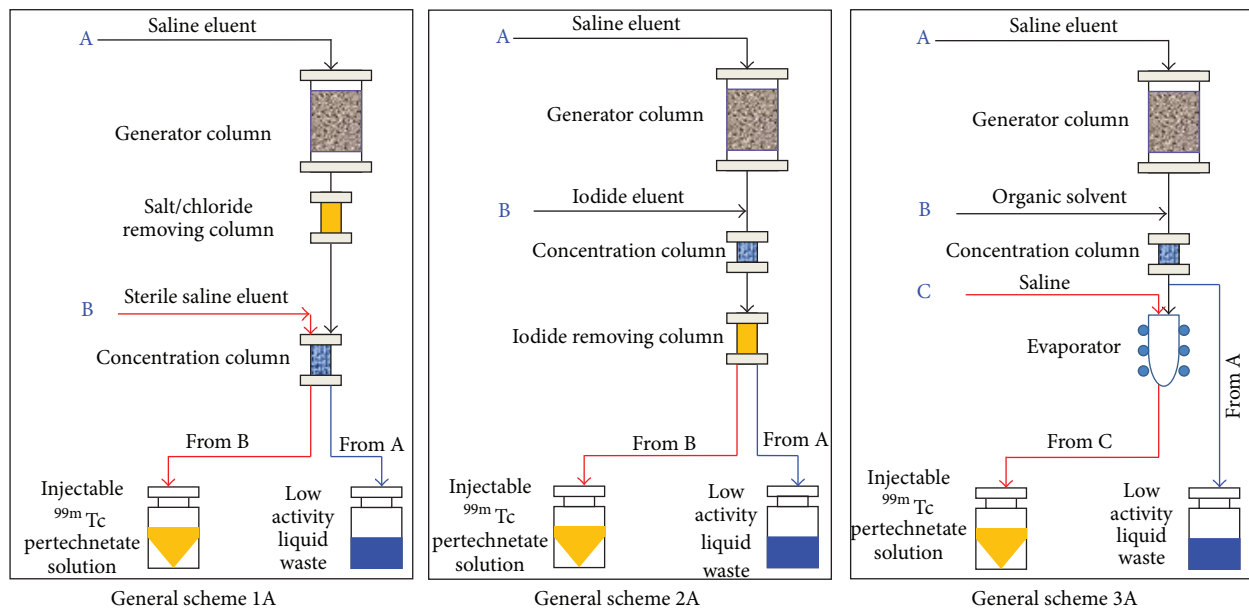


FIGURE 19: Group 1 of concentration methods: ^{99m}Tc -pertechnetate concentration from the saline eluate of the ^{99m}Tc generator.

Techneium has an electron configuration with presence of d-orbital electrons, ($\text{K L M } 4s^2 4p^6 4d^5 5s^2$), while that of chlorine is ($\text{K L } 3s^2 3p^5$) and oxygen $\text{K } 2s^2 2p^4$. The energy of outer electrons of these atoms is in the range of $2p_{\text{oxygen}} \sim 3p_{\text{chlorine}} \sim 4d_{\text{technetium}} < 5s_{\text{technetium}}$. The ion radius of TcO_4^- is 3.2 Å, while that of Cl^- ion is 1.81 Å. This big difference in the ion radius justifies a strong competition of

chloride in the adsorption with pertechnetate ions when the anion exchange resin is applied for $\text{TcO}_4^-/\text{Cl}^-$ separation.

In the aqueous solutions, pertechnic acid (HTcO_4) has an ionization constant $pK_a = 0.3$. So the weak acid of $pK_a > 0.3$ should be used as eluent in the process of ^{99m}Tc pertechnetate elution from the generator/concentration system. The weak acid used must also have a pK_a value below that of the sorbent

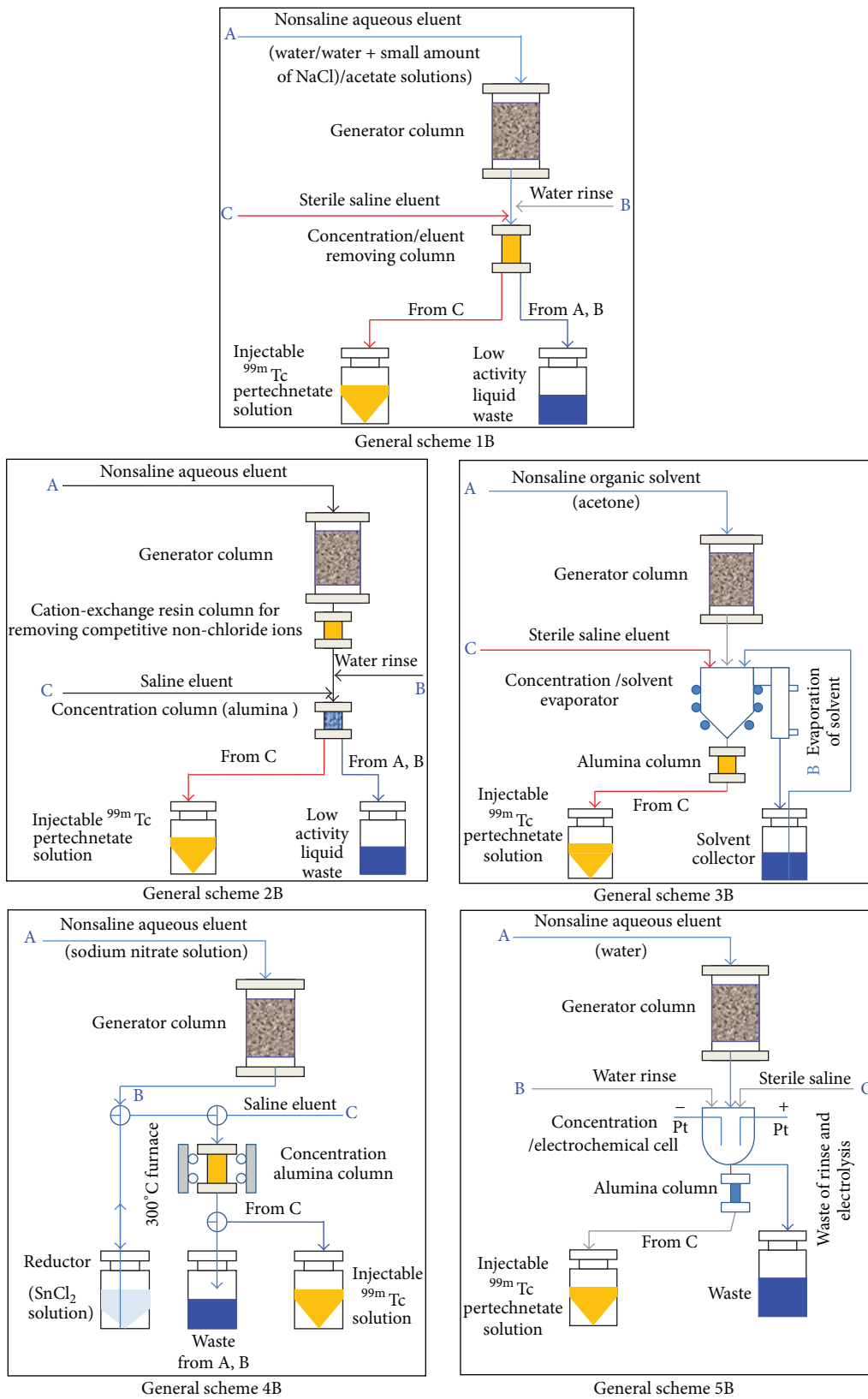


FIGURE 20: Group 2 of concentration methods: ^{99m}Tc -pertechnetate concentration from nonsaline eluate of the ^{99m}Tc generator.

TABLE 5: Details of methods of ^{99m}Tc -pertechnetate concentration from the nonsaline eluate of ^{99m}Tc -pertechnetate (single and dual column concentration methods).

Scheme	Concentration process		Generator column	References
	Elution	^{99m}Tc concentrator		
1B	A: H_2O B: saline	Alumina and/or TiO_2 , MnO_2 , zircona	TiMo/ZrMo molybdate gel	Le (1990) [57]
1B	A: H_2O B: saline	Alumina	ZrMo molybdate gel	Sarkar et al. (2004) [49]
1B	A: $\text{NH}_4\text{OAc} + \text{NH}_4\text{NO}_3$ B: water C: saline	QMA SepPak	Alumina	Knapp et al. (1998) [43–45]
1B	A: acetic acid + NaCl B: water C: saline	QMA SepPak	Alumina	Mushtaq (2004) [50] Le (2013) (for this review)
1B	A: acetic acid + ammonium-acetate B: water C: saline	DEAE-cellulose	Alumina	Sarkar et al. (2001) [47, 48]
1B	A: acetic acid + NaCl B: water C: saline	DEAE-cellulose	Alumina	Le (2013) (for this review)
1B	A: acetic acid + NaCl B: water C: saline	DEAE-sephadex	Alumina	Le (2013) (for this review)
1B	A: acetic acid + NaCl B: water C: saline	Isosorb-FS-01	Alumina	Le and Le (2013) [58]
2B	A: Na_2SO_4 B: H_2O C: saline	Pb-resin-alumina	Alumina	Bokhari et al.(2007) [54]
3B	Step A: acetone Step C: saline	Evaporator	TiMo/ZrMo gel	Le (1987–1994) [57, 59, 60, 104]
3B	Step A: acetone Step C: saline	Evaporator	Alumina	Mushtaq (2003) [51]
4B	A: NaNO_3 B: $\text{NaNO}_3 + \text{SnCl}_2$ C: saline	Redox agent + alumina	Alumina	Seifert et al. (1994) [55]
5B	A: H_2O B: H_2O C: saline	Electrochemical cell with Pt electrodes	ZrMo molybdate gel	Chakravarty et al. (2012) [56]

used in a consequent pertechnetate-concentration process to ensure the reversible adsorption of TcO_4^- ions in a sorbent column of reasonably small volume.

The conflict exists between the conventional/convenient use of saline in the elution of medical isotope generator and the challenge of chloride ions in the process of ^{99m}Tc concentration. So, the ^{99m}Tc concentration methods developed up to date in different laboratories are dedicated to the ^{99m}Tc concentration from the saline eluate or from nonsaline eluate of the generators. Accordingly, they are classified in two following groups and described as follows.

(i) *Group 1: ^{99m}Tc -Pertechnetate Concentration from the Saline Eluate of the ^{99m}Tc Generator.* In the first group of concentration methods are briefly described in Table 4.

The general process diagrams are shown in Figure 19. The main characteristic of this group is the increase of ^{99m}Tc -pertechnetate concentration from a saline eluate of the ^{99m}Tc generator. As an example, in one of the dual column purification/concentration processes (Scheme 1 in Figure 19), the saline eluate of the generator is first passed through a small silver ions loaded sorbent (or an ion exchange resin in Ag^+ form) column which traps the chloride anions allowing subsequent in-tandem passage through a sorbent cartridge (concentration column) with specific trapping of the TcO_4^- ions. The pertechnetate anion is subsequently easily removed with a small volume of normal saline ready for “kit” radiolabeling. The concentration factors can be as high as 10–60, with the silver ion stoichiometry based on the volume of the saline eluant. Among concentrator prototypes developed using this

postelution concentration concept the commercially available concentrator device ULTRALUTE is shown in Figure 3 [40–42].

(ii) *Group 2: ^{99m}Tc -Pertechnetate Concentration from the Nonsaline Elution of the ^{99m}Tc Generator.* In the second group of concentration methods are briefly described in Table 5. The general process diagrams are shown in Figure 20. The main characteristic of this group is the increase of ^{99m}Tc -pertechnetate concentration from a nonsaline eluate of the ^{99m}Tc generator. These methods are generally known as the single column concentration methods developed in years 1980s for the purification/concentration of the dilute solution of ^{99m}Tc , which is eluted from the low specific activity (n, γ) ^{99}Mo column generator [57, 59, 60]. Recently, many alternatives have been further developed and improved with an automated operation, as shown in Figures 5, 14, and 16. This process is based on the selective adsorption of ^{99m}Tc eluted from the ^{99}Mo column onto a significantly smaller sorbent column (concentration column). In the following step, the technetium is stripped from the column with a small volume of injectable saline solution. Optionally, this small sorbent column can be washed to remove any parent nuclide ions and metallic impurities that may also have been adsorbed onto the column. Following the wash, the daughter nuclide is stripped from the column with a small volume of solution suitable for injection or for other investigational purposes. The automated purification/concentration unit coupled radionuclide generator shown in Figure 16 is a versatile system which can be used for production of different daughter nuclides (such as ^{99m}Tc , ^{188}Re , ^{90}Y and ^{68}Ga) giving solutions of high radioactive concentration from low specific radioactivity parent nuclides.

5. Summary

^{99m}Tc plays an important role in diagnostic nuclear medicine imaging. Demographic and medical trends suggested that in the near future, the global demand for ^{99m}Tc will grow at an average rate between 3% and 8% per year as new markets. So, there is a need for diversity in all aspects of the ^{99m}Tc production using different specific activity ^{99}Mo sources to provide important supplements for increasing reliability of $^{99}\text{Mo}/^{99m}\text{Tc}$ generator supply. Accordingly, ^{99m}Tc recovery should be performed by suitable technologies to make them acceptable for nuclear medicine uses. Several alternative/supplementary technologies for producing high and low specific activity ^{99}Mo solutions and for ^{99m}Tc recovery therefrom have been developed and proposed. Some of them are not yet commercially proven or still require further development. To provide the researchers/producers a look into up-to-date $^{99}\text{Mo}/^{99m}\text{Tc}$ technologies, a review on the ^{99}Mo sources available today and on the ^{99m}Tc generators developed up to date for increasing the effectiveness of ^{99}Mo utilization is performed in the format of detailed description of the features and technical performance of the technological groups of the

^{99}Mo production and ^{99m}Tc recovery. Presently, the technologies of ^{99m}Tc recovery from low specific activity ^{99}Mo are playing an increasing role in ensuring the security of supplies of ^{99m}Tc to users worldwide. Various ^{99m}Tc recovery processes using low specific activity ^{99}Mo have been reported. Besides the low specific volume of ^{99m}Tc eluate obtained, the problem of complexity in operation of ^{99m}Tc -generator and of the high cost for automation/computerization of ^{99m}Tc -recovery process remain to be solved regarding cheaper, better, safer, and faster supply of ^{99m}Tc solution for SPECT imaging use in a daily hospital environment. Definitely, each technology developed may have some limitation. However the indispensable criteria of ^{99m}Tc production technology, which reflect the acceptance of the hospital users, are the reliability/reproducibility, the simplicity and safety in operation, and the proven capability to provide the ^{99m}Tc -pertechnetate solution which is safe for human use and effective for a wide range of the ^{99m}Tc -labeled radiopharmaceutical preparations. In terms of compliance with the requirements of human use, the technologies developed should not contain any materials of high toxicity for human use, which will make the registration process complicated and thus the delay in the technological product delivery.

Conflict of Interests

The author declares no conflict of interests.

Acknowledgments

The author would like to thank MEDISOTEC and Cyclopharm Ltd. (Australia) for financial support for the Radionuclide Development Project which includes the activity of this paper. The author also acknowledges Professor Nabil Morcos, Ms. Hien Do, and Minh Khoi Le for their valuable supports.

References

- [1] P. Richards, W. D. Tucker, and S. C. Srivastava, "Technetium-99m: an historical perspective," *International Journal of Applied Radiation and Isotopes*, vol. 33, no. 10, pp. 793–799, 1982.
- [2] *Non-HEU Production Technologies for Molybdenum-99 and Technetium-99m*, IAEA Nuclear Energy Series no. NF-T-5.4, International Atomic Energy Agency, Vienna, Austria, 2013.
- [3] Expert Review Panel on Medical Isotope Production, *Report of the Expert Review Panel on Medical Isotope Production*, Ministry of Natural Resources of Canada, Ottawa, Canada, 2009.
- [4] National Research Council of the National Academies, *Medical Isotope Production without Highly Enriched Uranium*, The National Academies Press, 2009.
- [5] OECD Nuclear Energy Agency, *The Supply of Medical Radioisotopes: Review of Potential Molybdenum-99/Technetium-99m Production Technologies*, OECD, Paris, France, 2010.
- [6] IAEA-TECDOC-1065, *Production Technologies for Molybdenum-99 and Technetium-99m*, International Atomic Energy Agency, Vienna, Austria, 1999.

- [7] IAEA TECDOC-515, "Fission molybdenum for medical use," in *Proceedings of the Technical Committee Meeting*, International Atomic Energy Agency, Karlsruhe, Germany, October 1987.
- [8] A. A. Sameh and H. J. Ache, "Production techniques of fission molybdenum-99," *Radiochimica Acta*, vol. 41, pp. 65–72, 1987.
- [9] H. Arino, H. H. Kramer, J. J. McGovern, and A. K. Thornton, "Production of high purity fission product molybdenum-99," U.S. patent no. 3799883, March 1974.
- [10] D. Novotny and G. Wagner, "Procedure of small scale production of Mo-99 on the basis of irradiated natural uranium target," in *Proceedings of the IAEA Consultancy Meeting on Small Scale Production of Fission Mo-99 for Use in Tc-99m Generators*, Vienna, Austria, July 2003.
- [11] A. A. Sameh and A. Bertram-Berg, "HEU and LEU as target materials for the production of fission molybdenum," in *Proceedings of the International Meeting on Reduced Enrichment for Research and Test Reactors*, pp. 313–333, RERTR, Roskilde, Denmark, 1992, TM19, Conf-9209266.
- [12] T. N. van der Walt and P. P. Coetzee, "The isolation of ^{99}Mo from fission material for use in the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator for medical use," *Radiochimica Acta*, vol. 92, no. 4–6, pp. 251–257, 2004.
- [13] A. Perkins, A. Hilson, and J. Hall, "Global shortage of medical isotopes threatens nuclear medicine services," *The British Medical Journal*, vol. 337, article a1577, 2008.
- [14] N. Ramamoorthy, "Commentary: supplies of molybdenum-99—need for sustainable strategies and enhanced international cooperation," *Nuclear Medicine Communications*, vol. 30, no. 12, pp. 899–905, 2009.
- [15] R. O. Marque's, P. R. Cristini, H. Fernandez, and D. Marziale, "Operation of the installation for fission Mo-99 production in Argentina," IAEA-TECDOC 515, 1989.
- [16] P. R. Cristini, H. J. Cols, R. Bavaro, M. Bronca, R. Centurio'n, and D. Cestan, "Production of molybdenum-99 from low enriched uranium targets," in *Proceedings of the International Meeting on Reduced Enrichment for Research and Test Reactor*, Bariloche, Argentina, November 2002.
- [17] ANSTO Media Releases, "ANSTO to help supply the world with nuclear medicine," http://www.ansto.gov.au/AboutANSTO/News/ACSTEST_039937.
- [18] IAEA TECDOC-1601, *Homogeneous Aqueous Solution Nuclear Reactors for the Production of Mo-99 and Other Short Lived Radioisotopes*, International Atomic Energy Agency, Vienna, Austria, 2008.
- [19] A. J. Ziegler, D. C. Stepinski, J. F. Krebs, S. D. Chemerisov, A. J. Bakel, and G. F. Vandegrift, "Mo-99 recovery from aqueous-homogeneous-reactor fuel- behavior of termoxid sorbents," in *Proceedings of the International RERTR Meeting*, Washington, DC, USA, October 2008.
- [20] D. C. Stepinski, A. V. Gelis, P. Gentner, A. J. Bakel, and G. V. Vandegrift, "Evaluation of radisorb, isosorb (Thermoxid) and PZC as potential sorbents for separation of ^{99}Mo from a homogenous-reactor fuel solution," IAEA-TECDOC-1601, September 2009.
- [21] S. Khamyanov and S. Voloshin, "A proposed international project of low-enriched uranium salt solution reactor for medical isotope production," in *Proceedings of the International Meeting on Reduced Enrichment for Research and Test Reactors*, Lisbon, Portugal, October 2010.
- [22] F. Stichelbaut and Y. Jongen, " ^{99}Mo production by proton-induced fission with LEU," in *Proceedings of the CNS Workshop on the Production of Medical Radionuclides*, Ottawa, Canada, 2009.
- [23] F. Y. Tsang, "Techniques for on-demand production of medical isotopes such as Mo-99/Tc-99m and radioactive iodine isotopes including I-131," World Intellectual Property Organization, WO, 2011/093938 A2, August 2011.
- [24] S. Lapi, T. Ruth, and J. D'Auria, "The MoRe Project: an alternative route to the production of high specific activity ^{99}Mo ," in *Proceedings of the International Symposium on Technetium and Other Radiometals in Chemistry and Medicine*, Brixen, Italy, 2010.
- [25] A. Fong, T. I. Meyer, and K. Zala, *Making Medical Isotopes: Final Report of the Task Force on Alternatives for Medical-Isotope Production*, TRIUMF, Vancouver, Canada, 2008.
- [26] V. S. Le, "Automated modular fission Mo-99 production process," Project Proposal, ANSTO Life Sciences, Australian Nuclear Science and Technology Organisation, 2010.
- [27] V. S. Le and C. D. Nguyen, "Separation of Tungsten from LEU fission-produced ^{99}Mo solution to improve technological performance in both the processes of ^{99}Mo and $^{99\text{m}}\text{Tc}$ generator production," in *Proceedings of the 5th Asia-Pacific Symposium on Radiochemistry*, p. 197, Kanazawa, Japan, September 2013.
- [28] V. S. Le, "Specific radioactivity of neutron induced radioisotopes: assessment methods and application for medically useful ^{177}Lu production as a case," *Molecules*, vol. 16, no. 1, pp. 818–846, 2011.
- [29] W. C. Eckelman, "Unparalleled contribution of technetium-99m to medicine over 5 decades," *JACC: Cardiovascular Imaging*, vol. 2, no. 3, pp. 364–368, 2009.
- [30] P. Gould, "Medical isotopes: time to secure supplies?" *The Lancet Oncology*, vol. 9, no. 11, p. 1027, 2008.
- [31] *Technetium-99m Radiopharmaceuticals: Manufacture of Kits*, IAEA Technical Report Series no. 466, International Atomic Energy Agency, Vienna, Austria, 2008.
- [32] W. C. Eckelman and B. M. Coursey, "Technetium-99 m generators, chemistry and preparation of radio-pharmaceuticals," *The International Journal of Applied Radiation and Isotopes*, vol. 33, pp. 793–950, 1982.
- [33] J. J. M. de Goeij, "Routes for supply of technetium-99m for diagnostic nuclear medicine," *Transactions of the American Nuclear Society*, vol. 77, p. 519, 1997.
- [34] K. Bremer, "Large-scale production and distribution of Tc-99 m generators for medical use," *Radiochimica Acta*, vol. 41, pp. 73–81, 1987.
- [35] V. J. Molinski, "A review of $^{99\text{m}}\text{Tc}$ generator technology," *International Journal of Applied Radiation and Isotopes*, vol. 33, no. 10, pp. 811–819, 1982.
- [36] United States Pharmacopeial Convention, *Official Monographs: USP 28, Sodium Pertechnetate Tc $^{99\text{m}}$ Injection*, United States Pharmacopoeia (USP) 28- National Formulary (NF) 23, 2005.
- [37] British Pharmacopoeia Commission, *British Pharmacopoeia*, The Stationery Office, Norwich, UK, 2008, <http://www.pharmacopoeia.org.uk/>.
- [38] C. F. Ruddock, "Purification of Technetium-99m pertechnetate solution," U.S. patent no. 4123497, October 1978.
- [39] P. J. Blower, "Extending the life of a $^{99\text{m}}\text{Tc}$ generator: a simple and convenient method for concentrating generator eluate for clinical use," *Nuclear Medicine Communications*, vol. 14, no. 11, pp. 995–997, 1993.
- [40] V. S. Le, J. McBrayer, and N. Morcos, "A radioisotope concentrator device for use with a radioisotope source, a system, and a process for capturing at least one radioisotope from a radioisotope solution obtained from a radioisotope source," Australia patent application, AU2012904683, October 2012.

- [41] V. S. Le, N. Morcos, J. McBrayer, Z. Bogulski, C. Buttigieg, and G. Phillips, "Disposable cartridge-based radioisotope concentrator device for increasing ^{99m}Tc and ^{188}Re concentration of commercial radionuclide generator eluates," *Journal of Labelled Compounds and Radiopharmaceuticals*, vol. 56, supplement 1, p. S190, 2013.
- [42] V. S. Le and N. Morcos, "An in-line, cartridge-based radioisotope concentrator device for use with multiple elutions from ^{99m}Tc and ^{188}Re generators," *Journal of Nuclear Medicine*, vol. 54, supplement 2, p. 609, 2013.
- [43] F. F. Knapp Jr., A. L. Beets, S. Mirzadeh, and S. Gluhlke, "Use of a new tandem cation/anion exchange system with clinical-scale generators provides high specific volume solutions of technetium-99m and rhenium-188," IAEA-TECDOC-1029, 1998.
- [44] F. F. Knapp, "The development and use of radionuclide generators in nuclear medicine: recent advances and future perspectives," in *Modern Trends in Radiopharmaceuticals for Diagnosis and Therapy*, IAEA-TECDOC-1029, pp. 485–495, International Atomic Energy Agency, Vienna, Austria, 1998.
- [45] F. F. Knapp Jr., A. L. Beets, S. Mirzadeh, and S. Guhlke, "Concentration of perrhenate and pertechnetate solutions," U.S. patent no. 5729821, March 1998.
- [46] S. Mirzadeh, F. F. Knapp Jr., and E. D. Collins, "A tandem radioisotope generator system for preparation of highly concentrated solutions of Tc-99m from low specific activity Mo-99," U.S. patent no. 5774782, June 1998.
- [47] S. K. Sarkar, G. Arjun, P. Saraswathy, and N. Ramamoorthy, "Post-elution concentration of $^{99m}\text{TcO}_4^-$ by a single anion exchanger column I: feasibility of extending the useful life of column chromatographic ^{99m}Tc generator," *Applied Radiation and Isotopes*, vol. 55, no. 4, pp. 561–567, 2001.
- [48] S. K. Sarkar, G. Arjun, P. Saraswathy, and N. Ramamoorthy, "Post-elution concentration of $(\text{TcO}_4^-)^{-}$ ^{99m}Tc by a single anion exchanger column: II. Preparation and evaluation of jumbo alumina column chromatographic generator for ^{99m}Tc ," *Nuclear Medicine Communications*, vol. 22, pp. 389–397, 2001.
- [49] S. K. Sarkar, P. Saraswathy, G. Arjun, and N. Ramamoorthy, "High radioactive concentration of ^{99m}Tc from a zirconium [^{99}Mo]molybdate gel generator using an acidic alumina column for purification and concentration," *Nuclear Medicine Communications*, vol. 25, no. 6, pp. 609–614, 2004.
- [50] A. Mushtaq, "Concentration of $^{99m}\text{TcO}_4^-/^{188}\text{ReO}_4^-$ by a single, compact, anion exchange cartridge," *Nuclear Medicine Communications*, vol. 25, no. 9, pp. 957–962, 2004.
- [51] A. Mushtaq, "Preparation of high specific-volume solutions of technetium-99m and rhenium-188," *Applied Radiation and Isotopes*, vol. 58, no. 3, pp. 309–314, 2003.
- [52] S. Chattopadhyay and M. K. Das, "A novel technique for the effective concentration of ^{99m}Tc from a large alumina column loaded with low specific-activity (n,γ) -produced ^{99}Mo ," *Applied Radiation and Isotopes*, vol. 66, no. 10, pp. 1295–1299, 2008.
- [53] S. Chattopadhyay, M. K. Das, S. K. Sarkar, P. Saraswathy, and N. Ramamoorthy, "A novel ^{99m}Tc delivery system using $(n,\gamma)^{99}\text{Mo}$ adsorbed on a large alumina column in tandem with Dowex-1 and AgCl columns," *Applied Radiation and Isotopes*, vol. 57, no. 1, pp. 7–16, 2002.
- [54] T. H. Bokhari, A. Mushtaq, and I. U. Khan, "Lead (Pb) column for concentration of ^{99m}Tc -pertechnetate," *Radiochimica Acta*, vol. 95, no. 11, pp. 663–667, 2007.
- [55] S. Seifert, G. Wagner, and A. Eckardt, "Highly concentrated [^{99m}Tc]pertechnetate solutions from $(n,\gamma)^{99}\text{Mo}/^{99m}\text{Tc}$ generators for nuclear medical use," *Applied Radiation and Isotopes*, vol. 45, no. 5, pp. 577–579, 1994.
- [56] R. Chakravarty, S. K. Sarkar, M. Venkatesh, and A. Dash, "An electrochemical procedure to concentrate ^{99m}Tc availed from a zirconium [^{99}Mo] molybdate gel generator," *Applied Radiation and Isotopes*, vol. 70, no. 2, pp. 375–379, 2012.
- [57] V. S. Le, "Preparation of gel type chromatographic ^{99m}Tc generators using Titanium and Zirconium Molybdate columns containing $(n,\gamma)\text{Mo-99}$," in *Proceedings of the IAEA Research Coordination Meeting*, Bombay, India, March 1990.
- [58] V. S. Le and M. K. Le, "Multifunctional sorbent materials and uses thereof," Australia patent application, AU2013903629, September 2013.
- [59] V. S. Le, "Production of ^{99m}Tc isotope from chromatographic generator using zirconium-molybdate and titanium-molybdate targets as column packing materials," in *Proceedings of the IAEA Research Coordination Meeting*, Bandung, Indonesia, October 1987.
- [60] V. S. Le, "The radioisotope and radiopharmaceutical production in Vietnam," in *Proceedings of the 2nd Asian Symposium on Research Reactors (ASRR '89)*, vol. 2, pp. 1–19, Jakarta, Indonesia, May 1989.
- [61] V. S. Le, N. Morcos, J. McBrayer et al., "Development of the in-line, multiple elution cartridge-based radioisotope concentrator device for increasing ^{99m}Tc and ^{188}Re concentration of commercial radionuclide generator eluates and effectiveness of ^{99}Mo utilisation," in *Proceedings of the 5th Asia-Pacific Symposium on Radiochemistry (APSORC '13)*, Kanazawa, Japan, September 2013, abstract ID 23-RPP-01.
- [62] V. S. Le, "Sorbent material," U.S. patent application publication, US, 2013/0048568 A1, February 2013, World Intellectual Property Organization, WO, 2011/106847 A1, September 2011, Australia patent application, AU2010900902, March 2010.
- [63] V. S. Le, "Gallium-68 purification," U.S. patent application publication, US, 2013/0055855 A1, March 2013, World Intellectual Property Organization, WO, 2011/106846 A1, September 2011, Australia patent application, AU2010900900, March 2010.
- [64] V. S. Le, "Gallium-68 generator integrated system: elution-purification-concentration integration," in *Theranostics, Gallium-68, and Other Radionuclides, Recent Results in Cancer Research 194*, R. P. Baum and F. Rösch, Eds., pp. 43–75, Springer, Berlin, Germany, 2013.
- [65] V. S. Le, "Identifying optimal conditions for the production of next generation radiopharmaceuticals," in *Research Selections*, pp. 71–73, ANSTO, 2011, <http://apo.ansto.gov.au/dspace/handle/10238/3886>.
- [66] T. Genka, "Needs and current status of Mo-99/Tc-99m production in Japan," in *Proceedings of the Meeting on Mo-99 Production by (n,γ) Method*, Tokyo, Japan, March 2012.
- [67] A. Mushtaq, "Producing radioisotopes in power reactor," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 292, pp. 793–802, 2012.
- [68] V. S. Le, "Utilisation of nuclear research reactor in Vietnam," in *Proceedings of the IAEA Advisory Group Meeting on Optimisation of Research Reactor Utilisation for Production of Radioisotopes*, JAERI, Tokai-Mura, Japan, October 1995.
- [69] V. S. Le, "Development of alternative technologies for a gel-type chromatographic ^{99m}Tc generator," in *Proceedings of the IAEA Research Coordination Meeting*, Vienna, Austria, May 1994.

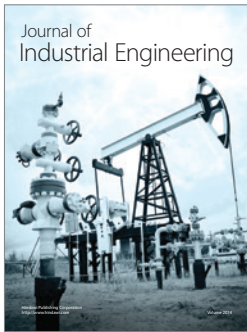
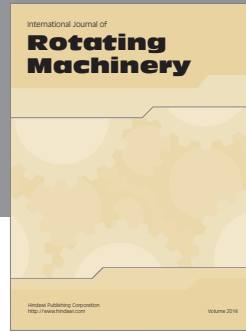
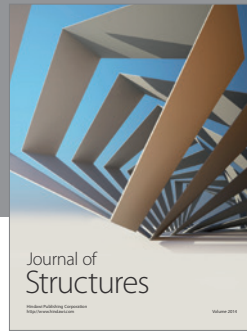
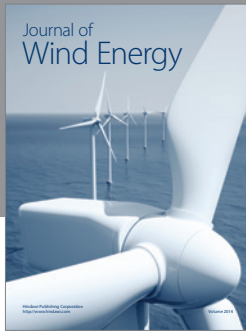
- [70] IAEA-TECDOC-852, *Alternative Technologies for ^{99m}Tc Generators*, International Atomic Energy Agency, Vienna, Austria, 1995.
- [71] K. Tsuchiya, "Atatus of ^{99}Mo - ^{99m}Tc production development by (n,γ) reaction in Japan," in *Proceedings of the Specialist Meeting on Mo-99 Production by (n,γ) Method*, Tokyo, Japan, March 2012.
- [72] E. Ishitsuka and K. Tatenuma, "Process for producing radioactive molybdenum," World Intellectual Property Organization, WO, 2008/047946, April 2008.
- [73] B. J. Jun, M. Tanimotor, A. Kimura, N. Hori, H. Izumo, and K. Tsuchiya, "Feasibility study on mass production of (n,γ) ^{99}Mo ," JAEA-Research Report 2010-046, Japan Atomic Energy Agency, 2011.
- [74] Y. Inaba, K. Iimura, J. Hosokawa, H. Izumo, N. Hori, and E. Ishitsuka, "Status of development on ^{99}Mo production technologies in JMTR," *IEEE Transactions on Nuclear Science*, vol. 58, no. 3, pp. 1151–1158, 2011.
- [75] C. Ross, R. Galea, P. Small et al., "Using the ^{100}Mo photonuclear reaction to meet Canada's requirement for ^{99m}Tc ," *Physics in Canada*, vol. 66, pp. 19–24, 2010.
- [76] M. C. Lagunas-Solar, P. M. Kiefer, O. F. Carvacho, C. A. Lagunas, and Y. P. Cha, "Cyclotron production of NCA ^{99m}Tc and ^{99}Mo . An alternative non-reactor supply source of instant ^{99m}Tc and $^{99}\text{Mo} \rightarrow ^{99m}\text{Tc}$ generators," *Applied Radiation and Isotopes*, vol. 42, no. 7, pp. 643–657, 1991.
- [77] M. C. Lagunas-Solar, "Accelerator production of ^{99m}Tc with proton beams and enriched ^{100}Mo targets," in *IAEA-TECDOC-1065, Production Technologies for Molybdenum-99 and Technetium-99m*, International Atomic Energy Agency, Vienna, Austria, 1999.
- [78] B. Scholten, R. M. Lambrecht, M. Cogneau, H. V. Ruiz, and S. M. Qaim, "Excitation functions for the cyclotron production of ^{99m}Tc and ^{99}Mo ," *Applied Radiation and Isotopes*, vol. 51, no. 1, pp. 69–80, 1999.
- [79] S. Takács, Z. Szücs, F. Tárkányi, A. Hermanne, and M. Sonckz, "Evaluation of proton induced reactions on ^{100}Mo : new cross sections for production of ^{99m}Tc and ^{99}Mo ," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 257, no. 1, pp. 195–201, 2003.
- [80] Y. Nagai and Y. Hatsukawa, "Production of ^{99}Mo for nuclear medicine by $^{100}\text{Mo}(n, 2n)^{99}\text{Mo}$," *Journal of the Physical Society of Japan*, vol. 78, no. 3, Article ID 033201, 2009.
- [81] J. E. Beaver and H. B. Hupf, "Production of ^{99m}Tc on a medical cyclotron: a feasibility study," *Journal of Nuclear Medicine*, vol. 12, no. 11, pp. 739–741, 1971.
- [82] M. B. Challan, M. N. H. Comsan, and M. A. Abou-Zeid, "Thin target yields and Empire: II. predictions on the accelerator production of technetium-99m," *Journal of Nuclear and Radiation Physics*, vol. 2, no. 1, pp. 1–12, 2007.
- [83] K. Gagnon, F. Bénard, M. Kovacs et al., "Cyclotron production of ^{99m}Tc : experimental measurement of the $^{100}\text{Mo}(p,x)^{99}\text{Mo}$, ^{99m}Tc and ^{99g}Tc excitation functions from 8 to 18 MeV," *Nuclear Medicine and Biology*, vol. 38, no. 6, pp. 907–916, 2011.
- [84] H. T. Wolterbeek and P. Bode, "A process for the production of no-carrier added ^{99}Mo ," European Patents EP, 2131369 (A1), December 2009, Worldwide Patent 2009148306, December 2009, EP, 2301041 (A1), March 2011, U.S. patent US, 2011118491 (A1), May 2011.
- [85] B. S. Tomar, O. M. Steinebach, B. E. Terpstra, P. Bode, and H. T. Wolterbeek, "Studies on production of high specific activity ^{99}Mo and ^{90}Y by Szilard Chalmers reaction," *Radiochimica Acta*, vol. 98, no. 8, pp. 499–506, 2010.
- [86] T. J. Ruth, "Two routes to solving the Mo/Tc isotope crisis: direct production of ^{99m}Tc and isotope separation," in *Proceedings of the CNS Workshop on the Production of Medical Radionuclides*, Ottawa, Canada, 2009.
- [87] E. P. Belkas and D. C. Perricos, "Technetium-99m production based on the extraction with methyl-ethyl ketone," *Radiochimica Acta*, vol. 11, p. 56, 1969.
- [88] G. D. Robinson, "A simple manual system for the efficient, routine production of ^{99m}Tc by methyl-ethyl-ketone extraction," *Journal of Nuclear Medicine*, vol. 12, p. 459, 1971.
- [89] M. P. Zykov, V. N. Romanovskii, D. W. Wester et al., "Use of extraction generator for preparing a ^{99m}Tc radiopharmaceutical," *Radiochemistry*, vol. 43, no. 3, pp. 297–300, 2001.
- [90] T. le Minh and T. Lengyel, "On the separation of molybdenum and technetium crown ether as extraction agent," *Journal of Radioanalytical and Nuclear Chemistry Letters*, vol. 135, no. 6, pp. 403–407, 1989.
- [91] M. Maiti and S. Lahiri, "Separation of ^{99}Mo and ^{99m}Tc by liquid-liquid extraction using trioctylamine as extractant," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 283, no. 3, pp. 661–663, 2010.
- [92] R. E. Boyd, "Technetium-99m generators—the available options," *International Journal of Applied Radiation and Isotopes*, vol. 33, no. 10, pp. 801–809, 1982.
- [93] K. Svoboda, "Survey of solvent extraction ^{99m}Tc -generator technologies," *Radiochimica Acta*, vol. 41, pp. 83–89, 1987.
- [94] "Radionuclide generator technology," *Radiochimica Acta*, vol. 41, no. 2-3, 1987.
- [95] A. A. Kuznetsov, A. A. Kudrin, and G. E. Kodina, "Semi-automatic ^{99m}Tc solvent extraction system," in *Proceedings of the 7th International Symposium on Technetium and Rhenium-Science and Utilization*, Moscow, Russia, July 2011, abstract book 4.P13.
- [96] E. Taskaev, M. Taskaeva, and P. Nikolov, "Extraction generator for [^{99m}Tc]sodium pertechnetate production," *Applied Radiation and Isotopes*, vol. 46, no. 1, pp. 13–16, 1995.
- [97] O. P. D. Noronha, "Solvent extraction technology of ^{99}Mo - ^{99m}Tc generator system," in *Proceedings of the Conference on Radiopharmaceuticals and Labelled Compounds*, Tokyo, Japan, 1984.
- [98] Y. N. Reshetnik, A. N. Bykov, G. E. Kodina, and A. O. Malysheva, "Sorption removal of $\text{Na } ^{99m}\text{TcO}_4$ from extracts of extraction generator $^{99}\text{Mo}/^{99m}\text{Tc}$," in *Proceedings of the 7th International Symposium on Technetium and Rhenium-Science and Utilization*, Moscow, Russia, July 2011, abstract book 4.P12.
- [99] S. Chattopadhyay, S. S. Das, and L. Barua, "A simple and rapid technique for recovery of ^{99m}Tc from low specific activity $(n,\gamma)^{99}\text{Mo}$ based on solvent extraction and column chromatography," *Applied Radiation and Isotopes*, vol. 68, no. 1, pp. 1–4, 2010.
- [100] S. Chattopadhyay, L. Barua, A. De et al., "A computerized compact module for separation of ^{99m}Tc -radionuclide from molybdenum," *Applied Radiation and Isotopes*, vol. 70, no. 11, pp. 2631–2637, 2012.
- [101] M. Tanase, A. Kimura, Y. Morikawa et al., "R&D in on extraction and concentration of ^{99m}Tc : a preliminary study using Re instead of ^{99m}Tc ," in *Proceedings of the Specialist Meeting on Mo-99 Production by (n,γ) Method*, Tokyo, Japan, March 2012.

- [102] S. Tachimori, H. Amano, and H. Nakamura, "Preparation of Tc-99m by direct adsorption from organic solution," *Journal of Nuclear Science and Technology*, vol. 8, pp. 357–362, 1971.
- [103] V. S. Le, "99mTc generator preparation using (n,γ)99Mo produced ex-natural molybdenum," in *Proceedings of the FNCA Workshop on the Utilization of Research Reactors*, pp. 216–223, Japan Atomic Energy Research Institute, 2003, JAERI-Conf 2003-004.
- [104] V. S. Le and R. M. Lambrecht, "Development of alternative technologies for a gel-type chromatographic 99mTc generator," *Journal of Labelled Compounds and Radiopharmaceuticals*, vol. 35, pp. 270–272, 1994.
- [105] V. S. Le, "Recent progress in radioisotope production in Vietnam," in *Proceedings of the Workshop on the Utilization of Research Reactors*, pp. 308–314, Japan Atomic Energy Research Institute, 1998, JAERI-conf 98-015.
- [106] V. S. Le, "Preparation of chromatographic and solid-solvent extraction 99mTc generator using gel-type targets," in *Proceedings of the Workshop on the Utilization of Research Reactors*, pp. 187–192, Japan Atomic Energy Research Institute, 2000, JAERI-conf 2000-017.
- [107] T. Genka, "Development of PZC-based Tc-99m Generator," *Forum for Nuclear Cooperation in Asia (FNCA)*, no. 2, March 2007.
- [108] V. S. Le, "Procedures for the production of poly-zirconium-compound (PZC) based chromatographic 99mTc generator to be available for clinical application," in *Proceedings of the FNCA Workshop on the Utilization of Research Reactors*, pp. 229–256, Japan Atomic Energy Agency, 2006, JAEA-Conf 2006-001.
- [109] V. S. Le, C. D. Nguyen, P. Pellegrini, and V. C. Bui, "Polymeric titanium oxychloride sorbent for 188W/188Re nuclide pair separation," *Separation Science and Technology*, vol. 44, no. 5, pp. 1074–1098, 2009.
- [110] V. S. Le, "Medical radioisotope development, radionuclide development group, project no. RRI-0168," Report at ANSTO's Board Review Panel, ANSTO, 2009.
- [111] V. S. Le, "68Ga PET-radionuclide generator development," in *Proceedings of the Seminar on Radiopharmaceutical Development*, Radiopharmaceutical Research Institute, ANSTO, June 2009.
- [112] R. E. Boyd, "99Mo/99mTc generator," *Radiochimica Acta*, vol. 30, no. 3, pp. 123–146, 1982.
- [113] R. E. Boyd, "Technetium generators—status and prospects," *Radiochimica Acta*, vol. 41, no. 2-3, pp. 59–63, 1987.
- [114] J. Gerse, J. Kern, J. Imre, and L. Zsinka, "Examination of a portable 99Mo/99mTc isotope generator /SUBLITECH(R)," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 128, no. 1, pp. 71–80, 1988.
- [115] L. Zsinka, "99mTc sublimation generators," *Radiochimica Acta*, vol. 41, pp. 91–96, 1987.
- [116] F. Rösch, A. F. Novgorodov, and S. M. Qaim, "Thermochromatographic separation of 94mTc from enriched molybdenum targets and its large scale production for nuclear medical application," *Radiochimica Acta*, vol. 64, pp. 113–120, 1994.
- [117] R. Chakravarty, M. Venkatesh, and A. Dash, "A novel electrochemical 99Mo/99mTc generator," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 290, no. 1, pp. 45–51, 2011.
- [118] R. Chakravarty, A. Dash, and M. Venkatesh, "A novel electrochemical technique for the production of clinical grade 99mTc using (n,γ)99Mo," *Nuclear Medicine and Biology*, vol. 37, no. 1, pp. 21–28, 2010.
- [119] K. Tagami and S. Uchida, "Elution behavior of Tc and Re through a Tc-selective chromatographic resin column," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 239, p. 643, 1999.
- [120] X. Hou, M. Jensen, and S. Nielsen, "Use of 99mTc from a commercial 99Mo/99mTc generator as yield tracer for the determination of 99Tc at low levels," *Applied Radiation and Isotopes*, vol. 65, no. 5, pp. 610–618, 2007.
- [121] M. Fikrle, J. Kučera, and F. Šebesta, "Preparation of 95mTc radio-tracer," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 286, no. 3, pp. 661–663, 2010.
- [122] A. Bartosova, P. Rajec, and M. Reich, "Preparation and characterization of an extraction chromatography column for technetium separation based on Aliquat-336 and silica gel support," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 261, no. 1, pp. 119–124, 2004.
- [123] E. Akatsu, R. Ono, K. Tsukuechi, and H. Uchiyama, "Radiochemical study of adsorption behavior of inorganic ions on zirconium-phosphate, silica gel and charcoal," *Journal of Nuclear Science and Technology*, vol. 2, pp. 141–148, 1965.
- [124] R. Rogers, P. E. Horwitz, and A. H. Bond, "Process for recovering pertechnetate ions from an aqueous solution also containing other ions," U.S. patent no. 5603834, February 1997.
- [125] S. Chattopadhyay, S. S. Das, M. K. Das, and N. C. Goomer, "Recovery of 99mTc from Na2[99Mo]MoO4 solution obtained from reactor-produced (n,γ)99Mo using a tiny Dowex-1 column in tandem with a small alumina column," *Applied Radiation and Isotopes*, vol. 66, no. 12, pp. 1814–1817, 2008.
- [126] R. D. Rogers, A. H. Bond, J. Zhang, and E. Philip Horwitz, "New technetium-99m generator technologies utilizing polyethylene glycol-based aqueous biphasic systems," *Separation Science and Technology*, vol. 32, no. 1-4, pp. 867–882, 1997.
- [127] S. K. Spear, S. T. Griffin, J. G. Huddleston, and R. D. Rogers, "Radiopharmaceutical and hydrometallurgical separations of perrhenate using aqueous biphasic systems and the analogous aqueous biphasic extraction chromatographic resins," *Industrial and Engineering Chemistry Research*, vol. 39, no. 9, pp. 3173–3180, 2000.
- [128] J. E. Young and J. J. Hines, "Compact automated radionuclide separator," U.S. patent no. 6770195, August 2004.
- [129] H. Bond, J. J. Hines, J. E. Young, and E. P. Horwitz, "Automated radionuclide separation system and method," U.S. patent no. 67870427, September 2004.
- [130] E. P. Horwitz and A. H. Bond, "Multicolumn selectivity inversion generator for production of ultrapure radionuclides," U.S. patent no. 6998052, February 2006.
- [131] D. R. McAlister and E. P. Horwitz, "Automated two column generator systems for medical radionuclides," *Applied Radiation and Isotopes*, vol. 67, no. 11, pp. 1985–1991, 2009.
- [132] V. S. Le, "Development of alternative technologies for a gel-type chromatographic 99mTc generator," IAEA-TECDOC 852, December 1995.
- [133] J. J. Pinajian, "A technetium-99m generator using hydrous zirconium oxide," *The International Journal of Applied Radiation and Isotopes*, vol. 17, no. 11-12, pp. 664–670, 1966.
- [134] Q. M. Qazi and A. Mushtaq, "Preparation and evaluation of hydrous titanium oxide as a high affinity adsorbent for molybdenum (99Mo) and its potential for use in 99mTc generators," *Radiochimica Acta*, vol. 99, no. 4, pp. 231–235, 2011.
- [135] S. Meloni and A. Brandone, "A new technetium-99m generator using manganese dioxide," *The International Journal of Applied Radiation and Isotopes*, vol. 19, no. 2, pp. 164–166, 1968.

- [136] J. Serrano Gómez and F. Granados Correa, “ ^{99m}Tc generator with hydrated MnO_2 as adsorbent of ^{99}Mo ,” *Journal of Radioanalytical and Nuclear Chemistry*, vol. 254, no. 3, pp. 625–628, 2002.
- [137] Y. Maki and Y. Murakami, “ ^{99m}Tc generator by use of silica gel as adsorbent,” *Nippon Kagaku Zasshi*, vol. 92, pp. 1211–1212, 1971.
- [138] J. Serrano, H. González, H. López, N. Aranda, F. Granados, and S. Bulbulian, “Sorption of $^{99}\text{MoO}_4^{2-}$ ions on commercial hydrotralcites,” *Radiochimica Acta*, vol. 93, no. 9-10, pp. 605–609, 2005.
- [139] V. S. Le, *Investigation on inorganic ion exchangers supported on silica matrix [Ph.D. thesis]*, Isotope Institute, Hungarian Academy of Sciences, 1985.
- [140] F. Monroy-Guzman, V. E. Badillo Almaraz, J. A. Flores de la Torre, J. Cosgrove, and F. F. Knapp Jr., “Hydroxyapatite-based $^{99}\text{Mo}/^{99m}\text{Tc}$ and $^{188}\text{W}/^{188}\text{Re}$ generator systems,” in *Trends in Radiopharmaceutical (ISTR-2005)*, vol. 1, IAEA, Vienna, Austria, 2007.
- [141] T. Braun, H. Imura, and N. Suzuki, “Separation of ^{99m}Tc from parent ^{99}Mo by solid-phase column extraction as a simple option for a new ^{99m}Tc generator concept,” *Journal of Radioanalytical and Nuclear Chemistry Letters*, vol. 119, no. 4, pp. 315–325, 1987.
- [142] V. S. Le, “Study on the titanium- and zirconium-molybdate gel-type ^{99m}Tc generators,” Annual Report, Vietnam Atomic Energy Committee, 1984.
- [143] J. V. Evans, P. W. Moore, M. E. Shying, and J. M. Sodeau, “Zirconium molybdate gel as a generator for technetium-99m—I. The concept and its evaluation,” *International Journal of Radiation Applications and Instrumentation A*, vol. 38, no. 1, pp. 19–23, 1987.
- [144] P. W. Moore, M. E. Shying, J. M. Sodeau, J. V. Evans, D. J. Maddalena, and K. H. Farrington, “Zirconium molybdate gel as a generator for technetium-99m—II. High activity generators,” *International Journal of Radiation Applications and Instrumentation A*, vol. 38, no. 1, pp. 25–29, 1987.
- [145] R. E. Boyd, “The gel generator: a viable alternative source of ^{99m}Tc for nuclear medicine,” *Applied Radiation and Isotopes*, vol. 48, no. 8, pp. 1027–1033, 1997.
- [146] V. S. Le, “Development of alternative technologies for a gel-type chromatographic ^{99m}Tc generator,” in *Proceedings of the IAEA Research Coordination Meeting*, Budapest, Hungary, February 1993.
- [147] J. A. Osso Junior, A. L. V. P. Lima, N. C. da Silva, R. C. Nieto, and A. C. de Velosa, “Preparation of a gel of zirconium molybdate for use in the generators of ^{99}Mo — ^{99m}Tc prepared with ^{99}Mo produced by the $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$ reaction,” in *Proceedings of the International Meeting on Reduced Enrichment for Research and Test Reactors*, San Paulo, Brazil, October 1998.
- [148] V. S. Le, “Investigation on the performance of polymer zirconium compound (PZC) for chromatographic ^{99m}Tc generator preparation,” in *Proceedings of the FNCA Workshop on the Utilization of Research Reactors*, pp. 90–104, Japan Atomic Energy Research Institute, 2004, JAERI-Conf 2004-010.
- [149] Y. Hasegawa, M. Nishino, T. Takeuch et al., “Mo adsorbent for ^{99}Mo - ^{99m}Tc generators and manufacturing thereof,” US patent no. 5681974, October 1997.
- [150] M. Tanase, K. Tatenuma, K. Ishikawa, K. Kurosawa, M. Nishino, and Y. Hasegawa, “A ^{99m}Tc generator using a new inorganic polymer adsorbent for $(n,\gamma)^{99}\text{Mo}$,” *Applied Radiation and Isotopes*, vol. 48, no. 5, pp. 607–611, 1997.
- [151] V. S. Le, “Preparation of PZC based ^{99m}Tc generator to be available for clinical application,” in *Proceedings of the IAEA Research Coordination Meeting on Development of Generator Technologies for Therapeutic Radionuclides*, ANSTO, Vienna, Austria, October 2004, <http://apo.ansto.gov.au/dspace/handle/10238/3713>.
- [152] V. S. Le, “Chemical synthesis and application of zirconium and titanium polymer compounds for the preparation of Tc-99m and Re-188 chromatographic generators,” in *Proceedings of the 2nd Research Coordination Meeting on Development of Generator Technologies for Therapeutic Radionuclides*, ANSTO, Milan, Italy, April 2006, <http://apo.ansto.gov.au/dspace/handle/10238/3714>.
- [153] V. S. Le, C. D. Nguyen, V. C. Bui, and C. H. Vo, “Synthesis, characterization and application of PTC and PZC sorbents for preparation of chromatographic ^{99m}Tc and ^{188}Re generators,” in *Proceedings of the IAEA Research Coordination Meeting on Development of Generator Technologies for Therapeutic Radionuclides*, ANSTO, Daejeon, Republic of Korea, October 2007, <http://apo.ansto.gov.au/dspace/handle/10238/3715>.
- [154] V. S. Le, C. D. Nguyen, V. C. Bui, and C. H. Vo, “Preparation of inorganic polymer sorbents and their application in radionuclide generator technology,” in *Therapeutic Radionuclide Generators: $^{90}\text{Sr}/^{90}\text{Y}$ and $^{188}\text{W}/^{188}\text{Re}$ Generators*, IAEA Technical Report Series no. 470, chapter 20, International Atomic Energy Agency, Vienna, Austria, 2009.
- [155] M. Asif and A. Mushtaq, “Evaluation of highly loaded low specific activity ^{99}Mo on alumina column as ^{99m}Tc generator,” *Journal of Radioanalytical and Nuclear Chemistry*, vol. 284, no. 2, pp. 439–442, 2010.
- [156] J. S. Lee, H. S. Han, U. J. Park et al., “Adsorbents for radioisotopes, preparation method thereof, and radioisotope generators using the same,” U.S. patent application publication, US, 2009/0277828 A1, November 2009.
- [157] A. Mushtaq, “Inorganic ion-exchangers: their role in chromatographic radionuclide generators for the decade 1993–2002,” *Journal of Radioanalytical and Nuclear Chemistry*, vol. 262, no. 3, pp. 797–810, 2004.
- [158] V. S. Le, M. Izard, P. Pellegrini, and M. Zaw, “Development of ^{68}Ga generator at ANSTO,” in *Proceedings of the 1st World Congress on Ga-68 and Peptide Receptor Radionuclide Therapy (THERANOSTICS '11)*, ANSTO, Bad Berka, Germany, June 2011, *World Journal of Nuclear Medicine*, vol. 10, no. 1, pp. 73–89, P-023, <http://apo.ansto.gov.au/dspace/handle/10238/3701>.
- [159] R. Chakravarty, R. Shukla, S. Gandhi et al., “Polymer embedded nanocrystalline titania sorbent for ^{99}Mo - ^{99m}Tc generator,” *Journal of Nanoscience and Nanotechnology*, vol. 8, no. 9, pp. 4447–4452, 2008.
- [160] R. Chakravarty, R. R. Shukla, R. Ram, A. K. Tyagi, A. Das, and M. Venkatesh, “Nanocrystalline zirconia: a new sorbent for the preparation of ^{99}Mo - ^{99m}Tc generators,” *Journal of Labelled Compounds and Radiopharmaceuticals*, vol. 52, supplement 1, p. S500, 2009.
- [161] R. Chakravarty, *Development of radionuclide generator for biomedical applications [Ph.D. thesis]*, Homi Bhabha National Institute, 2011.
- [162] J. V. Evans and R. W. Matthews, “Technetium-99m generators,” U.S. patent no. 4280053, July 1981.
- [163] V. H. Tran and V. S. Le, “Activation analysis of trace elements in titanium-molybdate gel target used for pre-formed TiMo-gel-based ^{99m}Tc generator production and radionuclidic impurity of ^{99m}Tc pertechnetate eluate,” in *Proceedings of the FNCA Workshop on the Utilization of Research Reactors*, pp. 105–111,

Japan Atomic Energy Research Institute, June 2004, JAERI-Conf 2004-010.

- [164] R. Chakravarty, R. Ram, R. Mishra et al., "Mesoporous Alumina (MA) based double column approach for development of a clinical scale $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator using $(n,\gamma)^{99}\text{Mo}$: an enticing application of nanomaterial," *Industrial & Engineering Chemistry Research*, vol. 52, no. 33, pp. 11673–11684, 2013.
- [165] A. Dash, F. F. (Russ) Knapp Jr., and M. R. A. Pillaia, " $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ separation: an assessment of technology options," *Nuclear Medicine and Biology*, vol. 40, no. 2, pp. 167–176, 2013.
- [166] V. S. Le and N. Morcos, "New SPE column packing material: retention assessment method and its application for the radionuclide chromatographic separation," *Journal of Radioanalytical and Nuclear Chemistry*, vol. 277, no. 3, pp. 651–661, 2008.
- [167] I. Zolle, Ed., *Technetium-99m Radiopharmaceuticals: Preparation and Quality Control in Nuclear Medicine*, Springer, Berlin, Germany, 2007.



Hindawi

Submit your manuscripts at
<http://www.hindawi.com>

