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Development of $^{99}Mo/^{99m}Tc$ Generator System for Production of Medical Radionuclide ^{99m}Tc using a Neutron-activated ^{99}Mo and Zirconium Based Material (ZBM) as its Adsorbent

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ABSTRACT

Molybdenum produced from fission of U-235 is the most desirable precursor for $^{99}Mo/^{99m}Tc$ generator system as it is non-carrier added and has high specific activity. However, in the last decade there has been short supply of ^{99}Mo due to several constrains. Therefore, there have been many works performed for development of $^{99}Mo/^{99m}Tc$ generator system using ^{99}Mo which is not produced from either LEU or HEU. This report deals with development of $^{99}Mo/^{99m}Tc$ generator system where zirconium-based material (ZBM) is used as adsorbent of neutron-activated ^{99}Mo. The system was prepared by firstly irradiating natural Mo in the G. A. Siwabessy reactor to produce neutron-activated ^{99}Mo. The target was dissolved in NaOH 4N and then neutralized with 12 M HCl. The ^{99}Mo solution was then mixed with a certain amount of ZBM followed by heating at 90°C for three hours to allow the ^{99}Mo adsorbed on ZBM. The ^{99}Mo-ZBM (9.36 GBq of ^{99}Mo was Mo/ 4.2 g ZBM) was packed on a fritz-glass column. This column was then fitted serially with an alumina column for trapping ^{99}Mo breakthrough. The columns were then eluted daily with saline solution for up to one week. The yield of ^{99m}Tc was found to be between 53.7 – 74% (n= 5). All ^{99m}Tc eluates were clear solutions with pH of 5. Breakthrough of ^{99}Mo in ^{99m}Tc eluates was found to be 0.031 ± 0.019 µCi ^{99}Mo/ mCi ^{99m}Tc (n= 5) which was less than the maximum activity of ^{99}Mo allowed in ^{99m}Tc solution (< 1 µCi ^{99}Mo/mCi ^{99m}Tc). Aluminum breakthrough in ^{99m}Tc eluates was found to be less than 10 ppm. The radiochemical purity of ^{99m}Tc in form of $Na^{99m}TcO_4$ was > 99%. Radiolabeling of this ^{99m}Tc towards methylene diphosphonate (MDP) kit gave a radiolabelling efficiency of 99%. In summary, a new $^{99}Mo/^{99m}Tc$ generator system that used neutron-activated ^{99}Mo and ZBM as its adsorbent has been successfully prepared. The ^{99m}Tc produced from this new $^{99}Mo/^{99m}Tc$ generator system attained the quality of ^{99m}Tc required for medical purposes.

INTRODUCTION

Radiopharmaceuticals based on technetium-99m (Tc-99m or ^{99m}Tc) are the most common radiopharmaceuticals used in nuclear medicine procedures [1]. Nearly 85% of diagnostic imaging procedures in nuclear medicine use ^{99m}Tc-labeling [2]. This is due to the versatile physical properties of ^{99m}Tc. It has a physical half-life ($T_{1/2}$) of 6 h and emits pure gamma ray with energy of 140 keV that is suitable to be imaged by Single Photon Emission Computed Tomography (SPECT) [3]. ^{99m}Tc is the daughter of beta decay of parent nuclide of molybdenum-99 (Mo-99 or ^{99}Mo) with an efficiency of 87.5% [2,4]. ^{99m}Tc is commonly obtained from a

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chromatography-based generator (well known as ^{99}Mo/^{99m}Tc generator system) where ^{99}Mo is adsorbed in an alumina column. ^{99}Mo decays periodically to ^{99m}Tc and it is then retrieved by eluting the ^{99}Mo/^{99m}Tc generator system with physiological saline solution.

There are three methods of ^{99}Mo production reported so far, namely: via fission reaction of uranium-235 (U-235 or ^{235}U), using accelerated particles, and through ^{98}Mo neutron capture [5-7]. The production of ^{98}Mo via fission reaction of ^{235}U using both high- and low-enriched uranium (HEU/LEU) targets results in a high specific activity (Ci/ mass Mo) of the produced ^{98}Mo. High-specific-activity ^{99}Mo can be adsorbed on a relatively small alumina column of ^{99}Mo/^{99m}Tc generator system. Therefore, ^{99m}Tc from this system can be retrieved efficiently which results in a high concentration of ^{99m}Tc [7]. However, the separation process of ^{99}Mo form fission reaction of ^{235}U is very complex and expensive. In addition, this separation process also produces extremely large amounts of radioactive wastes with very long $T_{1/2}$ which are difficult to contain [8]. Another problem is that there is a restriction on distribution of HEU-235 imposed by the Congress of the United States in order to prevent its abuse [4].

Researchers have also been trying to develop accelerator-based methods for producing ^{99}Mo/^{99m}Tc in order to solve the supply problem of ^{99}Mo. These include the use of accelerated-proton, -electron, or -deuteron. The primary accelerated charged particles are used to produce energetic secondary particles (photon/neutron) which then interact with the target material, producing ^{99}Mo [9]. Production of ^{99m}Tc using electron LINAC is reported to be technically simple and economically and ecologically feasible [10]. Similar research also reveals that ^{99}Mo can be produced via nuclear reaction of ^{100}Mo(n,2n)^{99}Mo using neutrons with energy of 14 MeV resulting from bombarding Be or C with 40 MeV deuteron beam [11]. Other researchers report concerning evaluation of experimental data for production of ^{99}Mo from nuclear reaction via ^{100}Mo(p,d+pn)^{99}Mo and ^{100}Mo(p,2n)^{99m}Tc conducted using code STAPRE. The result reported was that the atomic ratio of of long-lived ^{98g}Tc and ^{98}Tc to ^{99m}Tc is higher in cyclotron product. As a consequence, radiolabelling of radiopharmaceutical kits/chelates with the former will be more effective than in generator production of ^{99m}Tc [12]. However, currently the abovementioned technologies are still at their basic concepts and experimental stages. It will need some time for these technologies to be available for production of either ^{99}Mo or ^{99m}Tc commercially.

Neutron activation of ^{98}Mo in a nuclear reactor via the nuclear reaction of ^{98}Mo(n,γ)^{99}Mo could be a solution for small-scale production of ^{99}Mo in developing countries. This method is relatively simple in terms of postirradiation process, safety, and waste management. However, this method produces relatively low specific activity ^{99}Mo when natural ^{98}Mo (abundance of 24.2%) is used as a target. Awaludin *et al*. have investigated the ability of zirconium-based material (ZBM) as adsorbent of ^{99}Mo for use as ^{99}Mo/^{99m}Tc generator system column [13]. ZBM was found to be a good adsorbent for Mo with an average of 177 mg Mo/g ZBM [13]. Therefore, the objective of this work was to produce ^{99}Mo/^{99m}Tc generator system using ^{99}Mo produced from neutron activation of ^{98}Mo and ZBM as adsorbent of Mo. The ^{99m}Tc from this ^{99}Mo/^{99m}Tc generator system was expected to conform to the quality standard for ^{99m}Tc for nuclear medicine purposes.

THEORY

^{99}Mo and ^{99m}Tc radionuclides are important in the ^{99}Mo/^{99m}Tc generator system. Figure 1 shows the radionuclide decay scheme on a ^{99}Mo/^{99m}Tc generator system. It could be seen that ^{99}Mo, as the parent nuclide, decays to ^{99m}Tc (branching percentage 87.5%) and to ^{99}Tc (12.5%) nuclides. These radionuclides eventually decay to stable ^{99}Ru [3].

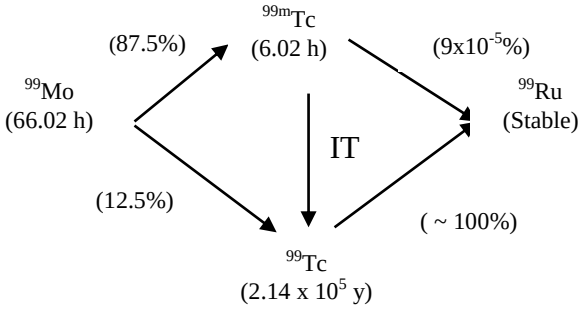


Fig 1. The decay of ^{99}Mo [3].

The activity of ^{99m}Tc can be determined by using the following equation:

$$A(^{99m}Tc) = 0.875\,[Z.\,[X-Y] + Ao(^{99m}Tc).Y] \quad (1)$$

X, Y, and Z were determined from

$X = \exp(-\lambda(^{99}Mo).\,t)$

$Y = \exp(-\lambda(^{99m}Tc).\,t)$

$$Z = \frac{Ao(^{99}Mo)}{\lambda(^{99}Mo) - \lambda(^{99m}Tc)}$$

where A(^{99m}Tc) is the activity of ^{99m}Tc, Ao(^{99}Mo) is the actvity of ^{99}Mo present when t = 0, λ(^{99}Mo) is the decay constant of ^{99}Mo, λ(^{99m}Tc) is the decay constant of ^{99m}Tc, Ao(^{99}Tc) is the actvity of ^{99m}Tc present when t = 0, and t is the elapsed time. The value of 0.875 in (1) is the 87.5% branching percentage of the ^{99}Mo decay to ^{99m}Tc.

Figure 2 shows the decay-growth of the ^{99}Mo/^{99m}Tc generator system. It is created by using equation (1). It can be seen that maximum activity of ^{99m}Tc is obtained from ^{99}Mo decay after 22.89 hours of growing time. Therefore, in order to obtain ^{99m}Tc with maximum radioactivity, the ^{99}Mo/^{99m}Tc generator system is eluted every ~ 23 hours.

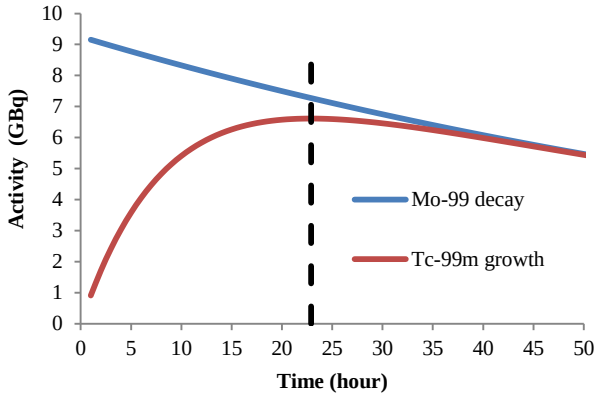


Fig. 2. The Decay –growth of the ^{99}Mo/^{99m}Tc generator system.

EXPERIMENTAL METHODS

Preparation of ZBM

ZBM as ^{99}Mo adsorbent was synthesized in similar manner to the one reported by Rohadi *et al* [13]. In short, 0.21 mol of zirconium(IV) chloride powder was added into a mixture of 0.27 mol of tetrahydrofurane and 0.43 mol isopropyl alchohol. The solution was stirred for several minutes at room temperature until dissolved. An aliquot of water and 0.3 mol tetrahydrofurane was then added to the solution. The solution was stirrred and heated to 95°C. The resulted ZBM was then treated by tetraethylorthosilicate (TEOS).

Preparation of ^{99}Mo solution

^{98}Mo was prepared by iradiating natural Mo in the form of MoO_3 in the G. A. Siwabessy Reactor, BATAN, Serpong, Indonesia. The target material (MoO_3) placed in a quartz ampoule was irradiated in the reactor (with a thermal neutron flux of 1.26×10^{14} neutron $cm^{-2}.s^{-1}$) for five days. After irradiation, the target was transferred to a hot cell and dissolved in 4 M NaOH. The specific activity of ^{99}Mo at the end of irradiation (EOI) was 20.17 MBq/mg MoO_3. The ^{99}Mo solution was neutralized with 12 M HCl which was then pipetted out to a 5 mL flask. The solution was then diluted to 15 mL with aquabidest which was followed by addition of ZBM (4.2 g). The mixture heated at 90°C for three hours, followed by decantation of the remaining solution. Filtrate and ZBM which absorbed ^{99}Mo (ZBM-^{99}Mo) were then measured for their radioactivity's using a dose calibrator (Atom Lab 100 plus).

Preparation of a ^{99}Mo/^{99m}Tc generator system using ZBM as adsorbent of ^{99}Mo

ZBM-^{99}Mo (4.2 g) with radioactivity of 9.36 GBq was transferred to a fritz glass column (2 cm × 8 cm, inner diameter 1.3 cm). The column (ZBM-^{99}Mo) was then packed by covering its top and bottom with a slice of glass wool and then sealed with silicone rubber septa cap and finally crimped with aluminum crimper. The top and bottom of the column were then fitted with syringes. A second column (1.3 cm × 7.5 cm, inner diameter 0.7 cm) was filled with alumina (one gram) and serially attached to the ZBM-^{99}Mo column. The purpose of the alumina column was for trapping the ^{99}Mo breakthrough. The columns were washed with 20 ml normal saline and the effluent was checked to ensure that its pH was 5. The ZBM-^{99}Mo column was treated using with a 3% NaOCl solution and the columns were left for 23 hours for allowing the ^{99m}Tc to accumulate. The columns were then eluted with saline solution in order to obtain ^{99m}Tc in the form of Na^{99m}TcO$_4$. The eluate (Na^{99m}TcO$_4$) was retrieved in 10 fractions (1 mL/fraction) and the radioactivity of each fraction was then measured with a dose calibrator.

Measurement of radionuclide impurity in Na^{99m}TcO$_4$

^{99}Mo is an impurity in Na^{99m}TcO$_4$ product solution. An aliquot of sample from each eluate fraction was spotted on a piece of filter paper which was then measured with a gamma spectrometer coupled with a calibrated HPGe detector and multichannel analyzer (MCA). A lead container was used to clearly remove 140 keV photon of ^{99m}Tc. The activity ^{99}Mo breaktrough was measured at 740 keV gamma ray peak.

Measurement of radiochemical purity of $Na^{99m}TcO_4$

Paper chromatographic strips (Whatman No. 1, 10 cm × 2 cm) were used to examine the radiochemical purity of the $Na^{99m}TcO_4$ solution. An aliquot of sample was applied on chromatographic strips and then developed in methanol-water (80% v/v) as mobile phase. The strips were then scanned by autoradioghrapy scanner.

Measurement of chemical impurity $Na^{99m}TcO_4$

The alumunium breakthrough (chemical impurity) in the $Na^{99m}TcO_4$ solution was determined by a spot test using Al breakthrough standard kits (Tec-Control Alumminium breakthrough kit, Biodex Medical systems).

Radiolabeling of radiopharmaceutical kits using $Na^{99m}TcO_4$

Radiolabeling of radiopharmaceutical kits by using the $Na^{99m}TcO_4$ produced from the $^{99}Mo/^{99m}Tc$ generator system using ZBM as the adsorbent of ^{99}Mo was performed in order to confirm the ability of $Na^{99m}TcO_4$ (^{99m}Tc) to form complexes with its ligands (radiopharmaceutical kits). An aliquot of $Na^{99m}TcO_4$ was added to reconstituted-radiopharmaceutical kits of methylene-diphosphonate (MDP). The radiochemical of the complex was measured by two systems of paper chromatography, namely: 1) Whatman paper No. 1 strip as stationary phase/metyl ethyl ketone as mobile phase; and: 2) Whatman paper No. 1 strip as stationary phase/saline solution as mobile phase.

RESULTS AND DISCUSSION

A new $^{99}Mo/^{99m}Tc$ generator system using ZBM as adsorbent of ^{99}Mo has been prepared. The ^{99}Mo used in this system was a low specific activity ^{99}Mo solution which was obtained by neutron activation of natural MoO_3. Therefore, an adsorbent with high absorption capacity must be used if the aforementioned ^{99}Mo was going to be used in a ^{99m}Tc on $^{99}Mo/^{99m}Tc$ generator system. Awaludin *et al*. reported that ZBM has a high ability to adsorb ^{99}Mo; therefore, in this project, ZBM is used as the adsorbent of ^{99}Mo in this new $^{99}Mo/^{99m}Tc$ generator system [13]. As a system that produces ^{99m}Tc, a new $^{99}Mo/^{99m}Tc$ generator must produce ^{99m}Tc that conforms the quality standard of ^{99m}Tc used in nuclear medicine.

A new $^{99}Mo/^{99m}Tc$ generator system using ZBM as adsorbent of ^{99}Mo was prepared in a series of steps which consisted of: (1) adsorption process of ^{99}Mo on ZBM; (2) packing of ZBM-^{99}Mo on the fritz-glass column; and: (3) serial fitting of ZBM-^{99}Mo column with an alumina column. The new $^{99}Mo/^{99m}Tc$ generator system was then tested for its performance which included elution profile and quality of the eluted ^{99m}Tc.

It is reported that the ^{99}Mo adsorption and ^{99m}Tc release on the ZBM occurred through ion exchange cycle mechanism as shown in Fig. 3 [13]. The Mo in a NaOH solution exists as a molybdate (MoO_4^{2-}). Based on the surface functionality of the adsorbent, MoO_4^{2-} will replace chloride ions (Cl^-) from the pore surface of the adsorbent when MoO_4^{2-} is adsorbed. Based on the greater ion affinity strength of MoO_4^{2-} than Cl^-, the Cl^- position can be easily replaced by MoO_4^{2-} [14,15]. The $^{99}MoO_4^{2-}$ ions transmute to pertechnetate ions (in form of $^{99}TcO_4^{2-}$) as ^{99}Mo decays to ^{99m}Tc. When the ZBM (containing $^{99}TcO_4^{2-}$) is eluted with saline solution, Cl^- ions from saline will replace pertechnetate ions and as a consequence the sodium pertechnetate (Na_2TcO_4) is then releasead.

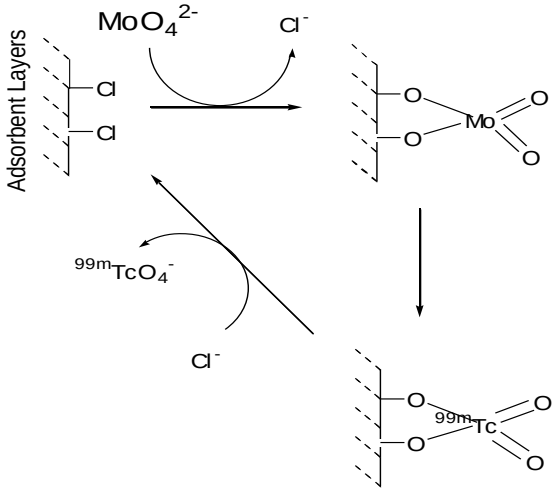


Fig 3. An ion exchange cycle mechanism on the adsorbed site ZBM [13].

Table 1 shows the yield (the percentage of radioactivity obtained/radioactivity expected) of ^{99m}Tc eluted or recovered from the $^{99}Mo/^{99m}Tc$ generator system (with ZBM-based column). It can be seen that the yield of this system ranged with is 53.7-74% (n=5). These yields are lower than the yields obtained by alumina molybdate gel technology. El-Absy *et al.* conducted research on $^{99}Mo/^{99m}Tc$ generators based on alumina molybdate gel technology and reported that they gave a ^{99m}Tc

yield of greater than 86% [15]. Therefore, improvements of the ZBM are clearly needed for the ZBM-based ^{99}Mo/^{99m}Tc generator systems to increase the yield.

Table 1. The recovery of Na^{99m}TcO$_4$ from ^{99}Mo

^{99}Mo activity (GBq)	^{99m}Tc growth time (h)	^{99m}Tc expected (GBq)	^{99m}Tc obtained (GBq)	^{99m}Tc yield (%)
9.40	17.05	7.43	3.99	53.7
7.80	18.92	6.37	3.32	52.0
6.41	24.15	4.86	2.49	51.3
4.96	22.8	3.83	2.40	65.0
3.89	72.72	1.72	1.26	74

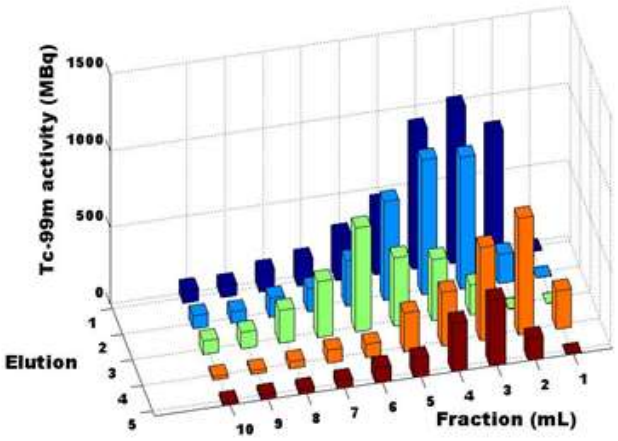


Fig 4. Profile of ^{99m}Tc radioactivity.

The elution profile of ^{99m}Tc from the ^{99}Mo/^{99m}Tc generator system (with ZBM-based column), eluted with saline solution, was investigated for up to 7 days (during which five rounds of elutions occurred) after its assembly process. Figure 4 shows the elution profile of the ^{99}Mo/^{99m}Tc generator system (the ZBM-based column). In general, 47.4-70.6% yields of ^{99m}Tc (1^{st}-5^{th} elution), can be eluted or collected in 7 mL (fraction 2-8) of their effluents.

The radioactivities of ^{99m}Tc from fractions 2-6 were relatively higher than those of the other fractions. The elution profile of ^{99m}Tc (1^{st}-5^{th} elution) seemed to follow a similar trend. The elution profile also showed there was no ^{99m}Tc eluted from the ^{99}Mo/^{99m}Tc generator system (the ZBM-based column) in the first fraction (1 mL) which might be due to uniform distribution of ^{99}Mo in the ZBM column [16].

The smaller the ^{99}Mo activity is, the weaker its influence of β- emission in reducing ^{99m}Tc is, so the easier it is for ^{99m}Tc to be released from the column [17]. This effect is showed in ^{99m}Tc yields for ^{99}Mo activities of lower than 6.41 GBq in which the lower the ^{99}Mo activity is, the higher the ^{99m}Tc yield is.

The ^{99m}Tc retrieved from a ^{99}Mo/^{99m}Tc generator system must conform to the quality standard for ^{99m}Tc used in nuclear medicine as shown on Table 2. ^{99m}Tc eluted from the ^{99}Mo/^{99m}Tc generator system (the ZBM-based column) was found to be a clear solution with a pH of 5. The measured radionuclide impurity or breaktrough of ^{99}Mo in Na^{99m}TcO$_4$ product solution was found to be 0.031 ± 0.019μCi ^{99}Mo/mCi ^{99m}Tc (n=5). This value is lower than the maximum ^{99}Mo breakthrough permitted for ^{99m}Tc used in nuclear medicine (<1 μCi ^{99}Mo/mCi ^{99m}Tc) [14]. This might be the result of the use of aluminum column which was serially fitted to ZBM column.

The use of aluminum column in order to hold the ^{99}Mo breakthrough might result in a breakthrough of aluminum in Na^{99m}TcO$_4$ solution. Therefore the aluminum content in Na^{99m}TcO$_4$ solution has to be determined. The aluminum content is 10 ppm in the Na^{99m}TcO$_4$ solution used in nuclear medicine [14]. The alumina content in Na^{99m}TcO$_4$ solution was determined by spot test using 10 ppm standard solution. Figure 5 shows the result of the spot test of alumina content in in Na^{99m}TcO$_4$ solution compared to the standard solution. It can be seen that the sample of Na^{99m}TcO$_4$ gave a colorless spot while the standard (10 ppm standard solution) showed a pinkish spot. This results indicates that the Al content in the Na^{99m}TcO$_4$ solution was under 10 ppm or lower than the maximum allowed by the standard for Na^{99m}TcO$_4$ used in nuclear medicine

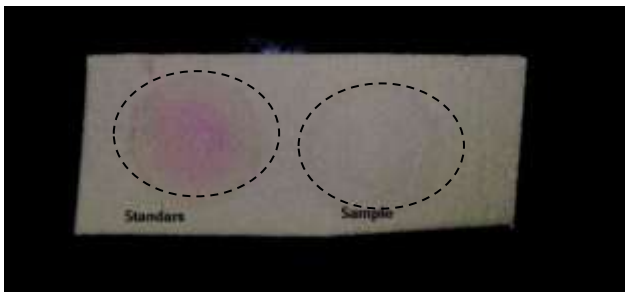


Fig. 5. Aluminium breaktrough test

Table 2. Standard quality of ^{99m}Tc nuclear medicine used in nuclear medicine [14] and experimental result

Propeties	Standard	Experimental
Clarity	Clear	Clear
pH	4-8	5
^{99}Mo breakthrough	< 1 uCi ^{99}Mo/mCi ^{99m}Tc	0.013 ± 0.019 uCi ^{99}Mo/mCi ^{99m}Tc
Radiochemical purity	> 95%	> 99%
Al breaktrough	< 10 ppm	< 10 ppm

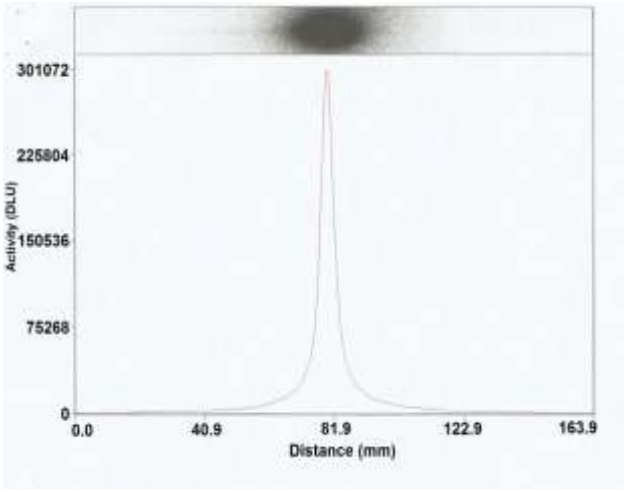
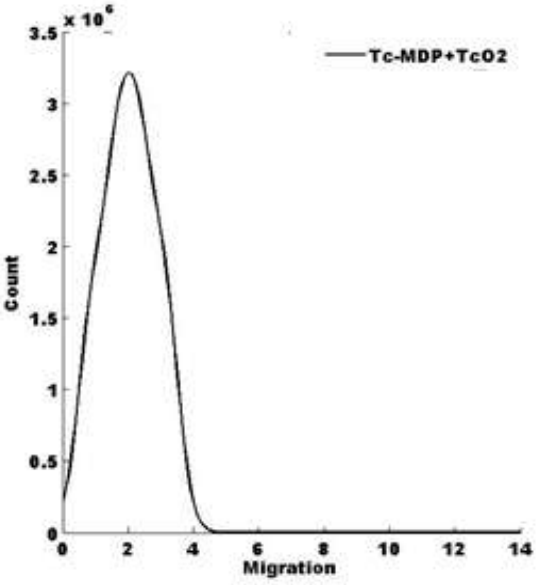


Fig. 6. Radiochromatogram of $Na^{99m}TcO_4$(Whatman paper No. 1 strip/ methanol-water 80% v/v).

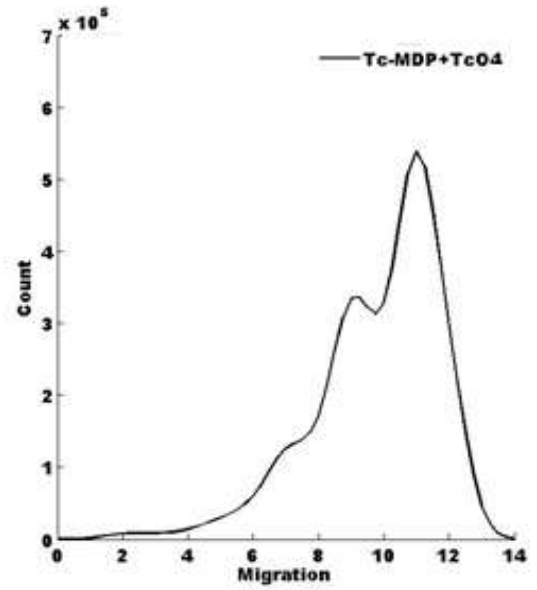
The radiochemical purity of the eluted $Na^{99m}TcO_4$ solution from the $^{99}Mo/^{99m}Tc$ generator system (the ZBM-based column) was measured by paper chromatography by using Whatman paper No. 1 strip as stationary phase and methanol-water (80% v/v) as mobile phase. The radiochromatogram from this chromatograph is shown in Fig. 6. It can be seen that there is only one peak with R_f of 0.48 which indicates that only one species exists in the solution, corresponding to $Na^{99m}TcO_4$ [14].

The results of several tests that had been performed on $Na^{99m}TcO_4$ solution retrieved from $^{99}Mo/^{99m}Tc$ generator system (the ZBM-based column) are summarized in Table 2. The $Na^{99m}TcO_4$ produced from the abovementioned $^{99}Mo/^{99m}Tc$ generator system was found to conform to the requirements of the quality standard of $Na^{99m}TcO_4$ for nuclear medicine purposes (see Table 2). In general, the $^{99}Mo/^{99m}Tc$ generator system (the ZBM-based column) was found to be reliable in producing $Na^{99m}TcO_4$. The only downsides of this $^{99}Mo/^{99m}Tc$ generator system (the ZBM-based column) were : 1) the adsorption process of ^{99}Mo toward ZBM for formation of ^{99}Mo-ZBM was time consuming; and 2) the activity was much lower compared to the $^{99}Mo/^{99m}Tc$ generator system where the ^{99}Mo used was obtained from the fission of HEU/LEU.

In addition to the aforementioned tests, radiolabeling test of $Na^{99m}TcO_4$ produced from $^{99}Mo/^{99m}Tc$ generator system (the ZBM-based column) toward radiopharmaceutical kits MDP was also performed. The ^{99m}Tc-MDP was tested with two chromatography systems: 1) Whatman paper No.1 strip/ metyl ethyl ketone and Whatman paper No.1 strip/saline solution. The resulting chromatograms are shown in Fig. 7(a) and Fig. 7(b), respectively. It can be seen on Fig. 7(a) that there is only one peak, with an R_f of 0.0 (99.9%), correlating with the presence of ^{99m}Tc-MDP and TcO_2. The peak with R_f = 1.0 in this chromatogram correlates with free $^{99m}TcO_4^{2-}$. Figure 7(b) shows a radiochromatogram with several peaks at $R_f > 0.5$ that correlate with the existence of ^{99m}Tc-MDP and free $^{99m}TcO_4^{2-}$ and a peak with R_f = 0.0 that correlates with the existence of TcO_2 colloids. The radiochemical purity of ^{99m}Tc-MDP was calculated by deducting the percentage of peak with R_f = 0 from Fig. 7(a) with the percentage of peak with R_f = 0 from Fig. 7(b). The results showed that the radiochemical purity of ^{99m}Tc-MDP was 99%.



(a)



(b)

Fig. 7. Radiochromatogram of ^{99m}Tc-MDP.
(a) Whatman paper No. 1 strip/ Metyl Ethyl Ketone
(b) Whatman paper No. 1 strip/ Saline solution

CONCLUSION

Development of $^{99}Mo/^{99m}Tc$ generator system (ZBM based column) has been conducted. The performance of $^{99}Mo/^{99m}Tc$ generator system (ZBM based column) was found to be reliable. It produced $Na^{99m}TcO_4$ with a quality which conform to the quality standard of $Na^{99m}TcO_4$ for uses in nuclear medicine. Further tests such as sterility test, pyrogenicity test, and clinical studies have to be performed before this $^{99}Mo/^{99m}Tc$ generator system (the ZBM-based column) can be used clini

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