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The Use of Sodium Hypochlorite Solution for (n, γ)^{99}Mo/^{99m}Tc Generator Based on Zirconium-Based Material (ZBM)

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ABSTRACT

The many problems in preparing fission product ^{99}Mo led into this work to develop ^{99}Mo/^{99m}Tc generator using neutron-irradiated natural MoO_3 targets and, more specifically, to develop a zirconium-based material (ZBM) for chromatography columns that have an adsorption capacity of more than 100 mg Mo/g ZBM. This paper reports our recent experiments in the use of sodium hypochlorite solution of various concentrations to improve the yield of ^{99m}Tc in performance of (n,γ)^{99}Mo/^{99m}Tc generators based on the ZBM. The synthesized ZBM was coated with tetraethyl orthosilicate for improving the hardness of the material. The adsorption of [^{99}Mo]molybdate into ZBM was carried out by reacting ZBM into [^{99}Mo]molybdate solution at 90°C to form ZBM-[^{99}Mo] molybdate. ZBM-[^{99}Mo]molybdate was then packed into generator column, then eluted with 10 × 1 mL of saline followed by 1 × 5 mL of NaOCl solution. The NaOCl solution concentrations used were 0.5%; 1%; 3%; and 5% for each column, respectively. This study resulted in a ZBM which has a ^{99}Mo adsorption capacity of 167.5 ± 3.4 mgMo/g ZBM, as well as in a yield eluate of ^{99m}Tc of up to 70%, and the find that the optimum NaOCl concentration was 3%. The use of sodium hypochlorite solution affected ^{99}Mo breakthrough. The higher sodium hypochlorite concentration used, the more ^{99}Mo breaktrough exist on ^{99m}Tc eluate.

INTRODUCTION

A radionuclide generator of ^{99}Mo/^{99m}Tc is a commonly used device for effective separation of a daughter radionuclide of ^{99m}Tc from a decaying parent radionuclide of ^{99}Mo. This radionuclide generator is a convenient in-house radionuclide production systems that allow the obtention of ^{99m}Tc species without on-site reactor or accelerator [1-4]. ^{99m}Tc is the most widely used diagnostic radionuclide in nuclear medicine practice, in the form of ^{99m}Tc-radiopharmaceuticals, due to its short half-life of 6 hours and its emitted gamma ray energy of 140.5 keV which is ideal for the gamma camera of Single Photon Emission Computed Tomography (SPECT) [3-7]. ^{99m}Tc-radiopharmaceuticals are organ-specific diagnostics and available to delineate blood flow in organs such as the lungs (embolism), heart, and brain; to evaluate the functional state of thyroid, liver, kidney, or the hepatobiliary system; and to detect tumor and metastatic growths in bone structures and more specifically, somatostatin receptor-expressing tumors [8]. ^{99}Mo loaded into a generator column can be produced by two different nuclear reactions, i.e. fission reaction of uranium-235 (^{235}U (n,f) ^{99}Mo) and neutron activation reaction of molybdenum-98 (^{98}Mo (n,γ) ^{99}Mo) [3,9,10]. Various types of ^{99}Mo/^{99m}Tc generator systems have been developed

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over the last few years due to increasing needs for technetium-99m [4,11-13].

Currently, many types of $^{99}Mo/^{99m}Tc$ generator system have been developed. Those systems are based on various separation techniques, such as: the use of an electrochemical cell system through selective electrodeposition on an electrode surface under the influence of controlled applied potential to separate ^{99m}Tc from the solution consisting of ^{99}Mo, ^{99}Tc and other metal ions [4]; a solvent extraction technique based on extraction of ^{99m}Tc using methyl ethyl ketone (MEK) from low-medium specific acticity (n,γ) ^{99}Mo [3]; a chromatographic gel-type generator that contains molybdenum [2,14]; and column chromatography with alumina [14,15]. Today, column chromatography system with alumina as an adsorbent is a popular $^{99}Mo/^{99m}Tc$ generator system. The adsorption capacity of alumina to molybdate ion is unfortunately limited to about 2-20 mg Mo/g alumina [3,4]. On the other hand, the production of high-specific-activity ^{99}Mo is generally only possibly through fission reactions. Nevertheless, the separation of ^{99}Mo fission product is a complex processing technology which is highly costly and also generates large quantities of high-radiotoxicity and long-life radioactive waste and requires extensive purification prior to use. Furthermore, there are few suppliers of ^{99}Mo fission product from both high- and low-enriched uranium (HEU/LEU) targets available in the world [4,16,17].

Other techniques for ^{99}Mo production are also developed in order to reduce the fission-produced ^{99}Mo dependencies. ^{99}Mo can be produced by thermal neutron activation of natural or enriched MoO_3 in a nuclear reactor. The advantages of this route include less radioactive waste and by-products and simpler post irradiation process. The disadvantage is that the produced ^{99}Mo has a low specific radioactivity.

Accordingly, for $^{99}Mo/^{99m}Tc$ generator application, using ^{99}Mo neutron activation is preferred to using ^{99}Mo fission product. The low specific radioactivity of ^{99}Mo can be overcome with the use of materials having high adsorption capacity of molybdate ion. Tanase et al. reported that a titania organic polymer (Poly Zirconium Compound) adsorbent is able to adsorb more than 250 mg Mo of 1 g adsorbent with low activity of ^{99}Mo [18]. The weaknesses of this material was that it is fragile and less hard, and it reduces the ^{99}Mo adsorption capacity if the activity of the ^{99}Mo used is high.

Since a few years ago, the Centre for Radioisotopes and Radiopharmaceuticals Technology (CRRT), National Nuclear Energy Agency (BATAN) has been developing the synthesis of Zirconium-Based Material (ZBM), as an adsorbent for $^{99}Mo/^{99m}Tc$ generator, using a modified synthesis method that was previously developed by Tanase et al. [18]. Rohadi et al. [19] reported that the synthesized ZBM was able to absorb ^{99}Mo with a capacity of up to ~ 183 mg Mo/g ZBM. However, the synthesized ZBM was still fragile and a small amount of the material was dissolved when reacted with [^{99}Mo]-molybdate solution. To increase the hardness of the adsorbent and the ^{99}Mo adsorption capacity, the material was coated with tetraethyl orthosilicate (TEOS). It appears that while the coated ZBM is a harder material, its capacity to absorb ^{99}Mo decreased from 183 to 79.8 mg Mo/g ZBM [20]. Further improvements of the preparation method increase the adsorption capacity to ~ 193 mg Mo/g ZBM [21]. The next step is to obtain ^{99m}Tc from ^{99}Mo which has been adsorbed into ZBM. Rohadi et al. [22] have investigated influence of a oxidizing agent addition to elution yield of ^{99m}T on ZBM adsorbent. NaOCl solution is used as oxidizing agent for treating the column. The solution acts as oxidant that can be used to increase ^{99m}Tc eluted from the Mo/Tc generator column [22,23].

This paper reports our recent improvement on the performance of Zirconium-Based Material (ZBM) as $^{99}Mo/^{99m}Tc$ column generator. The hypothesis is the NaOCl solution can increase the yield of ^{99m}Tc optimally. The purpose of this paper is to obtain a ZBM which can adsorb ^{99}Mo radioisotope and eluate ^{99m}Tc optimally from the column generator.

EXPERIMENTAL METHODS

The chemicals used in this experiment were high grade commercial reagents without further purification, namely: molibdenum (VI) oxide (MoO_3), zirconium (IV) chloride ($ZrCl_4$), tetrahydrofuran (THF), isopropyl alcohol (iPrOH), sodium hydroxide (NaOH), methanol (CH_3OH), and sodium hypochlorite (NaOCl), which were purchased from E Merck; tetra ethyl ortho silicate (TEOS) which was supplied by Aldrich; and aquabidest (H_2O) and saline which were ordered from IPHA-Indonesia. The ^{99}Mo radioisotope was obtained from MoO_3 irradiated with neutron in the G. A. Siwabessy nuclear reactor in Serpong.

The equipment used in this study comprised of a magnetic stirrer (Acculab ALC-110.4), a stirring hot plate (Health magnetic stirrer), a furnace (Ceramco Vulcan A-130), and a single-channel analyzer (Bioscan). The ^{99m}Tc radioactivity was measured using a dose calibrator

(Biodex Atomlab 100 plus) whereas the ^{99}Mo breaktrough was evaluated using a multi-channel analyzer (Ortec X-COOLER MCA).

Synthesis of ZBM [21]

First, 0.21 mol of zirconium (IV) chloride powder was added into a mixture of 0.27 mol of tetrahydrofurane and 0.43 mol of isopropyl alcohol in a 100 mL beaker glass. The mixture was stirred for several minutes at room temperature until dissolved. Then 7.6 mL of water and 20 g of tetrahydrofurane were added. The stirring continued and the reaction mixture was heated up to 95°C. It was dried overnight. The ZBM precursor granules as reaction product were converted to ZBM by heating for 1 h at a specific temperature in the atmosphere. The ZBM was coated with tetraethyl orthosilicate to harden the material.

Adsorption of ^{99}Mo into ZBM

Based on the reactor operation schedule, the treatments of ^{99}Mo adsorption into ZBM were performed with interval time of 6 months. Experiment A was performed in February 2014, whereas experiment B in August 2014. The same batch of ZBM was used for both experiments on the same treatment of adsorption process. ^{99}Mo was obtained by irradiating 5 grams of natural MoO_3 target (abundance ratio of ^{98}Mo ~ 23.75 %) through nuclear activation reaction ^{98}Mo (n,γ) ^{99}Mo for 120 h in Central Iradiation Position (CIP) of the G.A. Siwabesy nuclear reactor, the thermal neutron flux was 1.2 x 10^{14} n/cm^{2}s [24]. The irradiated target was dissolved in 20 ml of 6 M NaOH solution. The solution was spiked to measure the radioactivity of ^{99}Mo. After bulk solution radioactivity is known, 150 mCi of the solution (A_{loaded}) was transferred from the bulk solution into erlenmeyer flask and then adjust pH up to 7 by adding 1 M HCl and water until 10 ml volume (~ 300 mg of total Mo per 10 ml).

To each solution was added ~ 1.5 grams of ZBM at 90°C. The mixture was kept for 3 h in a water bath. Next, the mixture was decanted to obtain ZBM-[^{99}Mo]-molybdate. The radioactivity of ^{99}Mo in ZBM-[^{99}Mo]-molybdate (A_{zbm}) was measured with a dose calibrator.

Preparation of the column of ZBM

Two ZBM columns (A-1 and A-2) were prepared in experiment A, whereas two other ZBM columns (B-1 and B-2) were prepared in experiment B. After Mo was adsorbed into the ZBM, the ZBM was transferred and packed into a glass column (diameter 7 mm; length 50 mm; equipped with cotton wool in the bottom side and fitted with stopcock). The packed ZBM column was washed with 20 mL of saline solution to remove the excess Mo. To determine the optimization of the yield of ^{99m}Tc, it was eluted with saline solution containing four different concentrations of NaOCl, i.e. 0.5%, 1%, 3%, 5%, and saline solution only

Elution of ^{99m}Tc

^{99m}Tc was eluted from ZBM-[^{99}Mo]molybdate columns with various solutions which are shown in Table 1. After 24 h, each column was eluted with 10 × 1 mL of saline (NaCl 0.9%) at flow rate of 0.7 mL/min followed by elution of 1 × 5 mL of NaOCl solution. The NaCl solution was used to elute ^{99m}Tc from the column as sodium pertechnetat (TcO_4^-). The fractional elution activities of ^{99m}Tc in every 1 mL of the eluate were measured. The ^{99m}Tc elution yield was determined by measuring the ^{99m}Tc activity using dose calibrator. The ^{99}Mo breakthrough was determined by measuring ^{99}Mo activity at gamma energies of 740 keV and 780 keV using a multi-channel analyzer. Further, the elution of ^{99m}Tc was repeated every day for a week.

Table 1. Various solutions used to elute ^{99m}Tc from ZBM columns

ZBM-[^{99}Mo]-molybdate column	NaCl solution concentration	NaOCl solution concentration
A-1	0.9 %	0.5 %
A-2	0.9 %	3 %
B-1	0.9 %	1 %
B-2	0.9 %	5 %

RESULTS AND DISCUSSION

Adsorption of ^{99}Mo into ZBM

The adsorption yield of ^{99}Mo to the adsorbent column was determined by equation (1);

$$Adsorption\ yield\ of\ ^{99}Mo = \frac{A_{ZBM}}{A_{loaded}} x100 \quad (1)$$

The percentage of ^{99}Mo adsorption yield and ^{99}Mo adsorption capacity of ZBM is shown in Table 2. The adsorption capacity of ^{99}Mo in experiment A and B are significantly different (examined by t-test, 95 % confidence level).

The adsorption capacity of ^{99}Mo in experiment A is higher than in experiment B. Based on Table 2, it appears that storage time and storage conditions of ZBM are the main cause of decreasing the quality of ZBM in terms of ^{99}Mo adsorption yield and ^{99}Mo adsorption capacity of ZBM. In order to obtain high ^{99}Mo adsorption yield and ^{99}Mo adsorb capacity, in the future ZBM must be stored in lower-humidity areas and in dark containers/vials to prevent light exposure.

Table 2. Percentage of ^{99}Mo adsorption yield and ^{99}Mo adsorption capacity of ZBM

Parameter	Experiment A		Experiment B	
	A-1	A-2	B-1	B-2
Volume of Mo solution (ml)	10	10	10	10
^{99}Mo activity loaded (mCi)	155.6	158.9	160	159.7
pH before adsorption	6	6	6	6
pH after adsorption	1	1	1	1
^{99}Mo Adsorption yield (%)	85.04	84.62	70.36	70.55
^{99}Mo adsorption capacity of ZBM (mg Mo/g ZBM)	170.37	169.34	164.3	164.74

The mechanism of Mo adsorption into zirconium material has been explained by several sources as occuring through an ion exchange reaction between molybdate ion and chloride ion on the surface of the material as depicted in Fig. 1 [18,22].

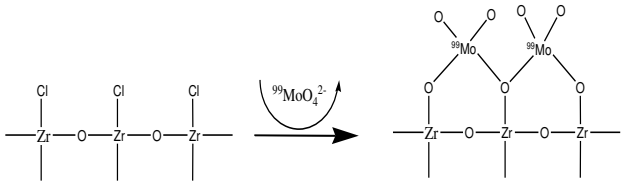

Fig. 1. Proposed mechanism of Mo adsorption into ZBM.

The amount of Mo adsorbed into the ZBM depends on the number of Cl atoms bound into the zirconium atom in the molecule. Substitution reaction between Cl and Mo occurs at the bound Zr-Cl molecules which are close to each other. The mass ratio of the element in the ZBM before [19] and after ^{99}Mo adsorption was determined using SEM-EDX (see Table 3 and Fig. 2). The significant decrease in the number of Cl atoms after Mo adsorption was shown. Based on Table 3, after adsorption ^{99}Mo, the mole ratio of the zirconium (Zr) to molybdenum (Mo) is 2:1 in which 2 zirconium atoms able to bonded of 1 molybdenum atoms on the ZBM.

Table 3. Mass element ratio of ZBM

Element	Before adsorption of Mo(%)	After adsorption of Mo (%)
Cl	10.7	1
O	38.9	39.3
C	0.6	0.9
Zr	43.9	37.5
Si	5.9	2
Mo	-	19.3

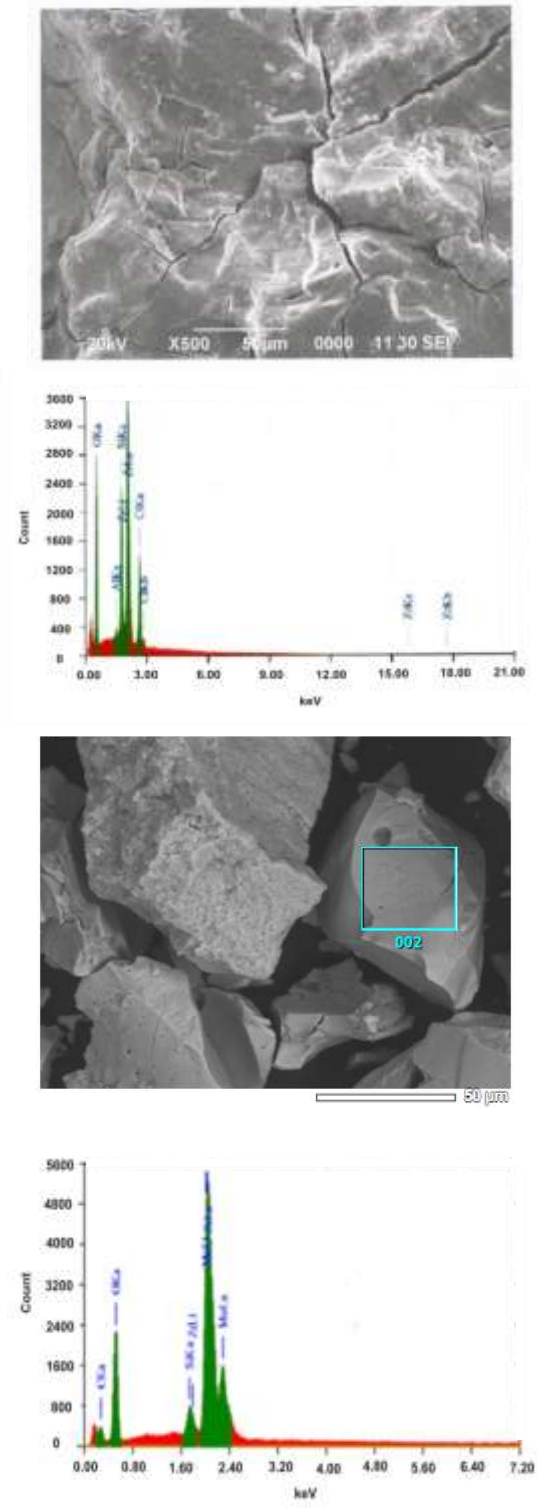

Fig. 2. Microscopic picture of SEM and EDX analysis of ZBM before and after Mo adsorption.

During the process of Mo adsorption into ZBM, the pH of the molybdate solution decreased from 6 to 1. The ZBM contains -ZrO- and ZrO^+Cl^- groups which are easily hydrolized at high pH values or in water. The formation of hydrochloride resulting from hydrolysis will decrease the solution's pH or create an acidic solution [25] (see equation (2)).

$$-ZrO^+Cl^- + H_2O \leftrightarrow -ZrOOH + HCl \quad (2)$$

Effect of NaOCl concentration variations on ^{99m}Tc yield.

Figure 3 shows the yield of ^{99m}Tc obtained from the columns eluted with saline solution (0.9% NaCl) only and the yields obtained from columns where NaOCl solution was added to the saline solution. The concentration of the NaOCl solution was varied at 0 %, 0.5 %, 1 %, 3 %, and 5 %. Column elution with saline solution only resulted in a small amount of ^{99m}Tc, whereas column elution with additional NaOCl solution resulted in yield of ^{99m}Tc > 70 %. NaOCl solution has a role as an oxidizing agent to remove solvated electrons resulting from the β^- emission from ^{99}Mo. The solvated electrons are capable of reducing TcO_4^- to insoluble TcO_2 which is subsequently retained in the column. The NaOCl solution used can oxidize Tc into Tc(VII), the highest oxidation state, as TcO_4^- which was then easily released from the column when eluted by saline solution. After the use of NaOCl solution, the yield of ^{99m}Tc increased to over 70 %. The optimum yield of ^{99m}Tc was achieved at NaOCl concentration of 3%. The yield of elution achieved in this study is higher than in the previous study [22].

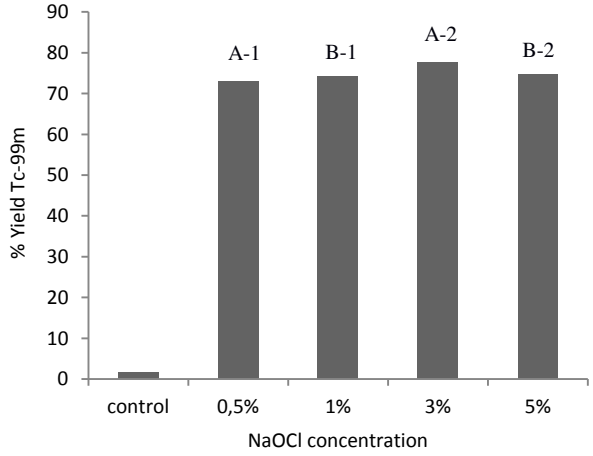

Fig. 3. NaOCl concentration vs yield of ^{99m}Tc. Control = saline solution only without NaOCl

Effect of NaOCl concentration to elution profile

Figure 4 shows the effect of NaOCl concentration to elution profiles. From the elution profiles at fractions of 1 to 4, it appear there are significant differences between the profiles resulting from the use of high concentration NaOCl solution (3% - 5%) and those low concentration (0.5% - 1%). However, for the range of fractions 4 to 10, the elution profiles for all concentration of NaOCl solution are quite similar. It is plausible that the use of high concentration NaOCl (3% - 5%) at the initial step elution will yield high specific radioactivity of ^{99m}Tc due to its ability to simultaneously remove solvated electrons and oxidize low-valence $^{99m}TcO_2$ to $^{99m}TcO_4^-$. When low-concentration NaOCl solution is used, incomplete removal of solvated electrons occurs and reduced $^{99m}TcO_2$ still remains in the column. However, in general, the yield of ^{99m}Tc from fraction 1 to 10 in every NaOCl concentration variations resulted in the same total activity of ^{99m}Tc.

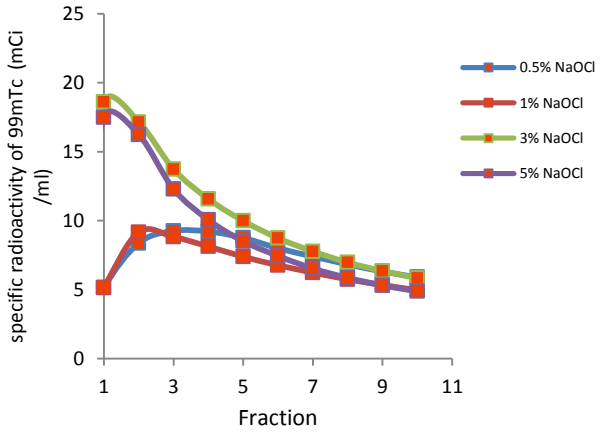

Fig. 4. Elution profile of MBZ column eluted with 0.9 % NaCl solution and addition of NaOCl solution

Effect of NaOCl concentration variations to ^{99}Mo breakthrough in ^{99m}Tc eluate

The ^{99}Mo breakthrough associated with radionuclide purity in the ^{99m}Tc eluate is one of the most important requirements before labeling radiopharmaceutical kits with ^{99m}Tc for clinical uses. The effect of the use of variations of NaOCl concentration to ^{99}Mo breakthrough is shown in Fig. 5. Based on the data, the highest ^{99}Mo breakthrough in ^{99m}Tc eluate due to the 5% NaOCl concentration. The higher NaOCl concentrations used, the higher ^{99}Mo breakthrough resulted. It is presumed that NaOCl in high concentration could break the bonding between Mo and ZBM. It is suggested to use tandem column for reduce ^{99}Mo breaktrough.

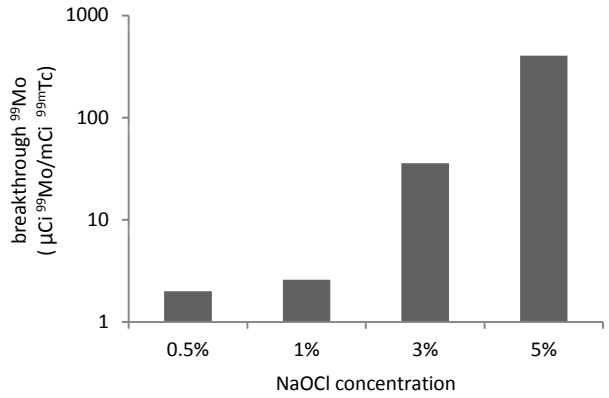

Fig. 5. ^{99}Mo breakthrough profile.

CONCLUSION

The synthesized ZBM could be used as adsorbent of neutron-irradiated natural molybdenum in ^{99}Mo/^{99m}Tc generators. Although the present ZBM has a lower ^{99}Mo adsorption capacity (167.5 ± 3.4 mg/g ZBM) than the one in an earlier study (~193 mg/g ZBM), the ZBM yielded eluate of ^{99m}Tc up to 70% optimally using NaOCl 3%. The future prospect of ZBM adsorbent for ^{99}Mo/^{99m}Tc column using NaOCl is good, but the effects of NaOCl to the quality of the obtained ^{99m}Tc needs to be investigated. Furthermore, the quality of ^{99m}Tc and its suitability for radiopharmaceuticals must be checked.

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REFERENCES

1. Anonymous, *Production of Long Lived Parent Radionuclides for Generators : ^{68}Ge, ^{82}Sr, ^{90}Sr and ^{188}W*, IAEA, IAEA-TECDOC-1436 (2010).
2. V.S. Le., Science and Technology of Nuclear Installations **2014** (2014) 41.
3. S. Chattopadhyay, S.S. Das and L. Barua, Nucl. Med. Biol. **37** (2010) 17.
4. R. Chakravarty, A. Dash and M. Venkatesh, Nucl. Med. Biol. **37** (2010) 21.
5. B.J. Jun, M. Tanimoto, A. Kimura *et al*., Feasibility Study on Mass Production of (n , γ) ^{99}Mo, JAEA-Research, Japan **046** (2011).
6. M. Mostafa, M.A. Motaleb and T.M. Sakr, Appl. Radiat. Isot. **68** (2010) 1959.
7. V.S. Le, Z.P. Do, M.K. Le *et al*., Molecule **19** (2014) 7714.
8. I. Zolle, Technetium-99m Pharmaceuticals Preapration and Quality Control in Nuclear Medicine, Springer Berlin Heidelberg, New York (2007) 7.
9. M. Raghavan, A. Pillai, A. Dash *et al*., J. Nucl. Med. **54** (2014) 2.
10. V.S. Le, J. Radioanal. Nucl. Chem. **301** (2014) 3.
11. Anonymous, Accelerator-based alternatives to Non-HEU Production of 99Mo/99mTc, http://www.naweb.iaea.org/napc/iachem/working_materials/RC-1212-1-report/. Retrieved in March (2014).
12. J. Nolen, Current and Possible New Methods for Accelerator-Based Production of Medical Isotopes, http://epaper.kek.jp/LINAC2010/talks/fr201_talk/ 2010. Retrieved in June (2014)
13. Lokhov, The Supply of Medical Radioisotopes: Review of Potential Molybdenum-99/Technetium-99m Production Technologies, https://www.oecd-nea.org/medradio/reports/Med-Radio-99Mo-Prod-Tech. Retrieved in March (2014).
14. M.A. El-Absy, M.A. El-Amir, T.W. Fasih *et al*., J. Radioanal. Nucl. Chem. **299** (2014) 1859.
15. A. Dash, R. Chakravarty, R. Ram *et al*., Appl. Radiat. Isot. **70** (2012) 51.
16. M.A. Brown, J.L. Jerden, A.V. Gelis *et al*., Development of Frontend Processing to Allow Use of High-Density LEU Foil Targets in Current Mo-99 Production Facilities, http://mo99.ne.anl.gov/2014/pdfs/papers/. Retrieved in April (2014)
17. P.H. Liem, H.N. Tran and T.M. Sembiring, Prog. Nucl. Energy **82** (2015) 191.
18. M. Tanase, K. Tatenuma, K. Ishikawa *et al*., Appl. Radiat. Isot. **48** (1997) 607.
19. R. Awaludin, Sriyono and Herlina, J. Radioisot. and Radiopharm. **13** (2010) 23. (in Indonesian)

20. R. Awaludin and Sriyono, J. Sains Nucl. Technol. Indonesia **12** (2011) 1. (in Indonesian)

21. I. Saptiama, Sriyono and Herlina, JFN **6** (2012) 114. (in Indonesian)

22. R. Awaludin, M. Tanase, M. Ishihara *et al*., J. Radioanal. Nucl. Chem. **303** (2014) 1481.

23. H.G. Adang, A. Mutalib, L. Hotman *et al*., *Performanced of $^{99}Mo/^{99m}Tc$ Generator Based PZC (Poly Zyrconium Compound) using ^{99}Mo via Natural Molybdenum-Neutron Activated with 5 Ci ^{99}Mo activity*, Proceeding of National Conference on Basic Research and Nuclear Technology, BATAN (2011) 44.

24. R. Awaludin, Makara **13** (2009) 42. (in Indonesian)

25. L. Van So, N.C. Duc, B. Van Cuong *et al*., Synthesis, Characterization and Application of Zirconium and Titanium Inorganic Polymer Sorbent for The Preparation of Chromatographic ^{99m}Tc and ^{188}Re Generator, http://apo.ansto.gov.au/dspace/handle/10238/3715 Retrieved in April (2014).