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Quality assurance of Mo-99/Tc-99m radionuclide generators

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Abstract: *Gamma-ray spectrometry analyses of the radionuclide content of eluate from two Mo-99/Tc-99m radionuclide generators POLTECHNET have been performed. The relative activities of ^{99}Mo ^{103}Ru and ^{131}I radioisotopes with respect to the activity of ^{99m}Tc at different time intervals after the primary pertechnetate elution of the generators have been analyzed. The relative activities of the isotopes were determined and compared to the radionuclidic purity requirements for ^{99m}Tc.*

Keywords: *quality assurance, technetium generator, gamma-ray spectroscopy, nuclear medicine.*

Introduction

Technetium-99m (^{99m}Tc) radionuclide is one of the most commonly used radionuclides for diagnostic procedures in nuclear medicine. At present a great part of all morphological and dynamic images of individual organs and the whole body diagnostic procedures, are conducted using pertechnetate solutions containing ^{99m}Tc or using raiopharmaceuticals marked with it. Discovered in 1957 [1], this isotope is a metastable nuclear isomer of technetium-99 (^{99}Tc). The isotope of ^{99m}Tc has a relatively short half-life ($T_{1/2}$~6 hours); it is a unique source of gamma rays, and is a mono-energetic

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low-energy gamma-ray source suitable for imaging of biological [2]. The reason for its extremely widespread use is that technetium has outstanding properties important for medical applications - relatively small quantities of the chemical element in the body have no influence on its physiology. This also applies to a large part of the technetium chemical compounds. In addition, its property to easy bind the other organic and inorganic compounds make it very convenient for the synthesis of various types of radiopharmaceuticals [3,4].

Nowadays, the most exploited ^{99m}Tc fabrication method is based on the production of the longer-lived radionuclide molybdenum-99 (^{99}Mo) obtained by the fission of highly uranium-235 (^{235}U) enriched targets (including about 80% of uranium-235) in nuclear reactors. The ^{99}Mo isotope decays by isomeric transition to ^{99m}Tc with a half-life of 66 hours. It gives an opportunity to avoid the problem of the faster decay of ^{99m}Tc and the necesseity for rapid delivery to the sites where it is to be applied. Based on this principle, so-called ^{99}Mo/^{99m}Tc column generators (also called "Moly" generators) [5] are fabricated, which are easily transportable and very convenient to deliver the isotope directly to the destination sites. A main feature of these generators is that they contain aluminum oxide (Al_2O_3) loaded in a plastic or glass chromatographic column located in a lead container. The ^{99}Mo isotope is adsorbed to the aluminum oxide such as MoO_4^{2-} (molybdate). There ^{99}Mo decays to ^{99m}Tc and forms pertechnetate $^{99m}TcO_4^-$, which is single charged and hence is less tightly bound to the aluminum oxide. When normal saline (0.9% NaCl solution in water) passes the column it elutes the soluble ^{99m}Tc, resulting in a physiological solution containing ^{99m}Tc as pertechnetate ($Na^{99m}TcO_4$), with sodium as a counter balancing cation. The solution of sodium pertechnetate can be used directly for specific procedures requiring only $^{99m}TcO_4^-$, as a primary radiopharmaceutical without necessity of pharmaceutical tagging or it can be used to label an organ-specific pharmaceutical.

Because the ^{99m}Tc thus obtained is intended for medical applications, there are serious requirements about the presence of the accompanying radionuclides, especially ^{99}Mo. With respect to the presence of other gamma-ray emitting isotopes Moly generators yield some possible contaminates such as ^{99}Mo (Molybdenum breakthrough), as well as ^{131}I and ^{103}Ru. A control of these gamma-ray emitters is necessary in order to ensure that the ^{99}Mo/^{99m}Tc generator satisfies the safety standards for their clinical applications. In this study, we present the results of gamma spectroscopic analyses of several ^{99}Mo/^{99m}Tc generator eluates taken during a time interval comparable to the exploitation period of this type of generators.

Materials and Methods

An object of a special interest in the analysis of the quality of Moly generators is to determine the activity of the ^{99}Mo isotope in the sodium pertechnetate since this is the main isotope contained in the chromatographic column of the generator. According to the International Atomic Energy Agency (IAEA) safety standards concerning the radionuclidic purity of the sodium pertechnetate containing ^{99m}Tc, any elution for clinical use should not contain more than 0.15 μCi (5.55 kBq) of ^{99}Mo per 1 mCi (37 MBq) of ^{99m}Tc per administered dosage at the time of administration [5, 6, 7]. In other words, the molybdenum breakthrough (MBT) should be less than 0.15 % of the activity of ^{99m}Tc. It worth noting that the requirements of the European Pharmacopoeia about the maximum of MBT are even stronger, limiting its relative value up to 0.1% [8, 9]. The reason for such a limitation of MBT is twofold. Generator elution with higher level of MBT is not suitable for imaging because the image produced would have poor spatial resolution and contrast due to the higher-energy emission passing through the septa of detectors' collimators. However, more important consequence of the presence of ^{99}Mo in the pertechnetate, is the fact that it causes a higher radiation dose to the patients.

The aim of the present study was to analyze the quantities of contaminant radioactive isotopes in the eluate from two Moly generators and to check if their activity remains below the limits determined by the safety standards. A matter of a particular interest was to verify also whether the measured relative activity of ^{99}Mo remains unchanged with respect to the activity of ^{99m}Tc during the

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exploitation period of the generators. A second goal of the experiment was to verify whether, as a result of the multiple passages of the physiological solution through the chromatographic column during the elution processes, the washout of MoO_4^{2-}_4 (2) ions changed significantly in time, thus giving rise the probability of ^{99}Mo MBT. This could be a consequence of kind of erosion processes causing column defect, such as channeling in the adsorbent bed, or could be an effect of autoradiolysis, resulting in a change of the chemical form of ^{99m}Tc, caused by the high radioactivity [5].

Two POLTECHNET 8,0 Moly generators with activity of 175 GBq, produced by POLATOM were studied. The generators have been produced in 17.03.2017 and 12.05.2017 and referred to as Generator 1 ad Generator 2 correspondingly. Both generators have been supplied to the Department of nuclear medicine at the Complex Oncology Center of Ruse, Bulgaria. Four samples from each generator were prepared, eluting the pertechnetate solution at different days after the primary elution of the generator as it is shown in Table 1 and Table 2. To analyze the content of radionuclides in the eluate, gamma-ray spectra of the samples were collected at the low-background gamma-ray spectrometric setup of the Laboratory of Nuclear Physics and Radioecology at the "Konstantin Preslavsky" University of Shumen.

The eluted samples were stored in suitable thin-walled glass vials and the total gamma-ray activity of the samples was measured immediately after the elution. The vials were held in a lead shielded storages for a certain amount of time (up to several days) in order to sufficiently reduce the ^{99m}Tc gamma-ray activity. This was necessary to prevent additional experimental error due to the pulse overlap during the spectra acquisition as well as to reduce the experimental uncertainty due to the dead time corrections. Moreover, when sufficiently longer samples' storage times were used the gamma-ray intensity of the shorter-half-life ^{99m}Tc isotope was reduced giving rise the possibility to better measure the activities of the lower-activity isotopes, which normally were hidden in the high background, created by ^{99m}Tc in the freshly obtained eluate.

The main purpose of this work was to measure the activities of ^{99}Mo isotope in the eluate at different moments after the primary eluate date of the generators and to compare the values obtained with the limits according to the requirements for the quality control of the eluate. The activities of other two isotopes ^{103}Ru and ^{131}I, which are inevitably present due to the production/extraction procedure of ^{99m}Tc [10], were controlled too, analyzing the spectra from the same samples, collected after longer storage times.

Table 1. Elution dates and sample activities measured from Generator 1, primary eluate obtained at 20.03.2017

Sample number	Date of the eluton	Days passed after the primary elution	Sample total activity measured after the elution (MBq)
1	29.03.2017	9	0.408
2	01.04.2017	12	564.4
3	06.04.2017	17	154.6
4	10.04.2017	21	61.63

Table 2. Elution dates and sample activities measured from Generator2, primary eluate obtained at 15.05.2017

Sample number	Date of the elution	Days passed after the primary elution	Sample total activity measured after the elution (MBq)
1	15.05.2017	0	1086
2	18.05.2017	3	331.1

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3	23.05.2017	8	270.0
4	26.05.2017	11	550.7

The limits of the activities of ^{99}Mo and the other radionuclides in Moly Generators according to the European Pharmacopeia safety regulations [8], and to the certificates issued by POLATOM are shown in Table 3.

Table 3. Limits of the activities of radionuclide impurities in Moly Generators according to the safety regulations [8] and the certificates issued by POLATOM.

Radionuclide	Acceptance criteria (not more than)	Applied method
^{99}Mo	0.1%	Gamma spectrometry (Eur. Pharmacopeia chapter 2.2.26)
^{131}I	5×10^{-3} %	
^{103}Ru	5×10^{-3} %	
Other impurities	0.01 %	

Determination of the activity of ^{99}Mo and isotopes ^{103}Ru and ^{131}I of the obtained spectra was performed using the formula

$$A = \frac{S}{t_{sp}\varepsilon I\omega}, \quad (1)$$

where: A is the activity of the corresponding radionuclide; S is the area of the radionuclide peak in the gamma-ray spectrum; t_{sp} is the spectrum acquisition time; ε is the efficiency of the gamma-ray radiation detector for the corresponding peak energy in the spectrum; I represents the intensity of the corresponding gamma line or the probability of emission of gamma ray with the corresponding energy; ω is the solid angle corresponding to the detector position for the given distance from the sample to the detector.

Table 4 shows the main features of ^{99}Mo, ^{103}Ru and ^{131}I radionuclides used for peak spectrum identification and activity calculation.

All the values obtained for the activities of the radionuclides were recalculated for the corresponding initial moments when the eluate was obtained from the generators according to the formula

$$A_0 = A \exp(\lambda t), \quad (2)$$

where A_0 is the activity of the radionuclide at the moment of elution of the generator, λ is the radioactive decay constant for the corresponding radionuclide, and t is the time elapsed prior the acquisition of the corresponding gamma spectrum.

Since ^{99}Mo decay results in an increase of the quantity of ^{99m}Tc in the pertechnetate solution, this would contribute in elevated initial ^{99m}Tc activity values when (2) is used to calculate the ^{99m}Tc activity at the time of draining. To avoid this problem, the calculated activity of ^{99m}Tc from (2) was corrected by subtracting the contribution of ^{99}Mo using the formula [5]:

$$A_{Tc} = \frac{\lambda_{Tc}}{\lambda_{Tc}-\lambda_{Mo}}(A_{Mo})_0.[\exp(-\lambda_{Mo}t) - \exp(-\lambda_{Tc}t)], \quad (3)$$

where: A_{Tc} is the ^{99m}Tc activity produced by the decay of ^{99}Mo; λ_{Tc} and λ_{Mo} are the radioactive decay constants of ^{99m}Tc and ^{99}Mo; $(A_{Mo})_0$ is ^{99}Mo activity at the moment of elution of the generator.

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Table 4. Radionuclide data of the analysed nuclides in the technetium eluate.

No	Nuclide	Half-life $T_{1/2}$	Gamma ray energy (keV)	Intensity of the emitted gamma ray (%)
1	^{99m}Tc	6.0067 h	140.511	89
2	^{99}Mo	65.976 h	181.0.68	6.14
			366.421	1.204
			739.50	12.26
			777.921	4.30
3	^{103}Ru	39.242 d	497.085	91
4	^{131}I	8.052 d	364.489	81.5

Experimental

Gamma-ray spectra of the samples from Mo-99/Tc-99m radionuclide generators Generator 1 and Generator 2, obtained at different days, as it is shown in Table 1 and Table 2, have been collected in the low background gamma-ray spectrometry system and analyzed using ANGES program [11]. A typical gamma-ray spectrum in semi-logarithmic scale of the sodium pertechnetate of Sample 4 from Generator 1, made 57 hours after the elution, is shown in Figure 1. In the figure are identified the peaks of ^{99m}Tc (140.5keV), ^{99}Mo (181.1keV, 366.4keV, 739.5keV and 777.9keV). The peaks of ^{103}Ru (497keV) and ^{131}I(364.5keV), as it can be seen from the figure, are somewhat hidden and need to be measured after a longer storage period.

The measured activities of ^{99m}Tc, ^{99}Mo, ^{103}Ru and ^{131}I from the obtained gamma-ray spectra were recalculated back to the time when the corresponding samples have been eluted using formula (2). The values of the activity of ^{99m}Tc were corrected according to (3) and finally the calculated isotope activities of ^{99}Mo, ^{103}Ru and ^{131}I as a percentage of the activity of ^{99m}Tc were calculated. The relative activities of ^{99}Mo, ^{103}Ru and ^{131}I, calculated for the prepared samples from both Moly generators Generator 1 and Generator 2, are shown in Table 5 and Table 6 correspondingly.

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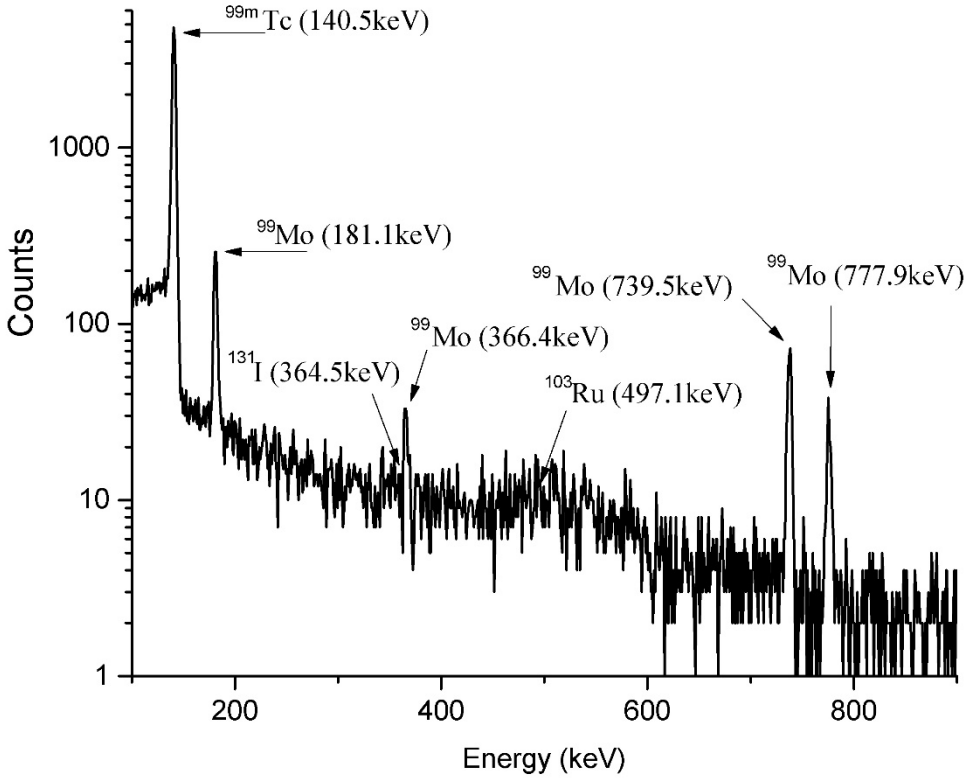

Figure 1. A spectrum of gamma-ray emission from elution of Sample 4 from Generator 1, made 57 hours after the elution

Table 5. Measured relative activities of ^{99}Mo, ^{103}Ru and ^{131}I in the eluate of Generator 1 recalculated for the time of elution.

Sampe	Elution date	Measured relative activity (%)		
		^{99}Mo	^{131}I	^{103}Ru
1	29.03.2017	0.0026 ± 0.0006	NA	NA
2	01.04.2017	0.00084 ± 0.00003	1.23E-05 ± 5.1E-06	1.98E-06 ± 1.2E-06
3	06.04.2017	0.0011 ± 0.00003	1.36E-05 ± 2.7E-06	
4	10.04.2017	0.00083 ± 0.00003	1.17E-05 ± 1.05E-06	2.9E-06 ±1.9E-06

Table 6. Measured relative activities of ^{99}Mo, ^{103}Ru and ^{131}I in the eluate of Generator 2 recalculated for the time of elution.

Sampe	Elution date	Measured relative activity (%)		
		^{99}Mo	^{131}I	^{103}Ru
1	15.05.2017	0.00022 ± 0.00002	1.63E-06 ± 2.33E-07	NA
2	18.05.2017	0.00035 ± 0.00003	3.39E-06 ± 1.52E-07	NA
3	23.05.2017	0.00013 ± 0.00002	9.9E-07 ± 7.72E-8	NA

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4	26.05.2017	0.00088 ± 0.0002	1.41E-05 ± 1.26E-06	2.86E-06 ±1.9E-06

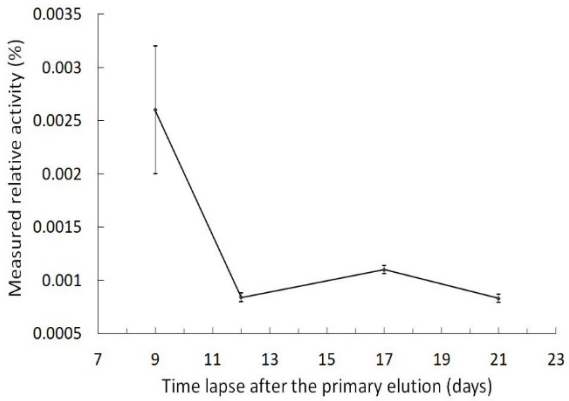

Fig. 2 Relative ^{99}Mo activity in the eluate of Generator 1 as a function of the time elapsed since the primary elution

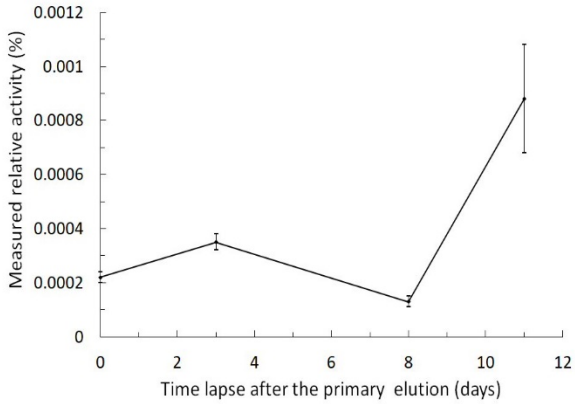

Fig. 3. Relative ^{99}Mo activity in the eluate of Generator 2 as a function of the time elapsed since the primary elution

Figure 2 and figure 3 show the measured relative Relative ^{99}Mo activity in the eluate of Generator 1 and Generator 2 as a function of the time elapsed since the primary elution.

Conclusion

The comparison of the measured ^{99}Mo activity data in Table 5 and Table 6 with the corresponding certificate values in Table 3 gives the reason to conclude that both Polatom Mo-99/Tc-99m Generators (Generator 1 and Generator 2) have values below the limits of the activities to the certificates issued by POLATOM. Tracking the ^{99}Mo relative activity in the pertechnetate from Generator 1, measured as a function of the time elapsed after the primary elution, demonstrates a value of 0.0025% at the ninth day followed by a slight decrease and remains almost constant with an average value around 0.001% for a period even beyond the twentieth day. Measurements of the ^{99}Mo relative activity in the pertechnetate from Generator 2 started sooner after the primary elution, so it shows of a different behavior: after almost constant values around 2.5×10^{-3} % it slightly increases up to 8.8×10^{-3} %. However, in general the variations of both measured relative activities remain far below the limits shown in table 3, which gives us the reason to reject the assumption of alteration of the molybdate properties in the chromatographic column.

The relative activities of the other two isotopes ^{103}Ru and ^{131}I shown in Table 5 and Table 6 are of several orders of magnitude lower than the limits in Table 3 demonstrating a high radionuclidic purity of both Moly generators.

The general results from the conducted analyses of the radionuclidic purity of both generators confirmed their compliance with the requirements of the European Pharmacopoeia concerning the radionuclidic purity of the sodium pertechnetate.

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