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ELUTION EFFICIENCY OF MO-99/TC-99M GENERATORS

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Abstract. *Elution efficiency of 99mTc from 99Mo/99mTc generators was examined in dependance on the kind of adsorbent and eluence. The generators contained either pure alumina or alumina modified by addition of silica gel or by adsorption of divalent copper. For elutions, besides pure saline solution (0.9% NaCl), saline modified by addition of 100 μg of ascorbic acid per ml was tested. High and stable 99mTc elution yield ensures only the adsorbent modified by addition of copper (0.2-0.3 mg Cu(II)/g alumina), both in the "dry" and the "wet" mode of the generator operation. It was found that, under the given experimental conditions, ascorbic acid has no significant influence on 99mTc elution efficiency.*

Key words: *technetium-99m, molybdenum-99/technetium-99m generator, elution efficiency*

1. INTORODUCTION

Radioisotope ^{99m}Tc is an artificial element which does not exists in nature. Perrier and Segre [1] discovered it in 1937 in the scraps of a deflektor lip made of molybdenum which have been irradiated by deuterons in the cyclotron of the University of California at Berkeley. It remained more or less only a scientific curiosity till the late sixties when its potential for the use in nuclear medicine was recognized. The decay photons of 140,5 keV, 6,01 h half-life and practically no corpuscular radiation were found to be almost ideal for *in vivo* diagnostics.

However, for the routine praxis a reliable production route was needed. The relatively short half-life, favourable in the application, is a drawback in the supply of the users distant from the production site. This logistic problem is solved by the introduction of the ^{99}Mo/^{99m}Tc generators.

The concept of the radionuclide generators is not new. Already in 1920 Failla patented the first one (^{226}Ra/^{222}Rn) for the production of ^{222}Rn. Principally, it is based on the effective separation of a decaying, longer-lived, parent and the daughter of shorter half life. The obtained daughter radioisotope should be in a pure radionuclidic and

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radiochemical form. After the separation, the precursor, by decay, generates a new supply of the daughter. So, instead of a short lived daughter, the longer-lived parent, bond onto a suitable substrate, is transported. The separation is performed by the end user, often very distant from the production site. In the literature the generators are often named as "cows" as the daughter is "milked" from its parent.

In an $^{99}Mo/^{99m}Tc$ generator, the daugher ^{99m}Tc ($T_{1/2} = 6.01$ h) is separated from its parent radioisotope ^{99}Mo ($T_{1/2}$ = 66,0 h). Thus an easy and inexpensive access of ^{99m}Tc was created. Its use has grown dramatically ever since, with an expected growth of about 5-10% per year. At present, about 90% of all scintigraphic examinations is performed by ^{99m}Tc. It is also used in conjuction with some therapeutic treatments as well as in *in vitro* diagnostics.

There are several routes for the production of ^{99}Mo which apply nuclear reactions both in nuclear reactor and cyclotron. The separation of ^{99m}Tc is performed by using ion exchange, extraction, sublimation, etc. These topics, covered by several reviews [2,3], are beyond the scope of this article.

The current ^{99m}Tc production system is based on the chromatographic $^{99}Mo/^{99m}Tc$ generator in which ^{99}Mo is obtained by uranium fission via the nuclear reaction $^{235}U(n,f)^{99m}Zr \rightarrow \ldots ^{99}Mo$. For practical reasons it is sometimes denoted as $(n,f)^{99}Mo$ and is, in the form of molybdate ions ($^{99}MoO_4^{2-}$), loaded on alumina in the generator column. ^{99m}Tc produced by the decay passes readily into the saline solution (0.9% NaCl) and is thus in the form of pertechnetate $^{99m}TcO_4^-$ separated from molybdenum as the solution is drawn out of the column.

The generator should fulfil certain requirements for the use in nuclear medicine. One of the most important is the efficiency of the separation of ^{99m}Tc from ^{99}Mo. To ensure the high and stable elution yield, several procedures were tested based on the modifications of the adsorbent layer. In this paper the influence of the addition of ascorbic acid to the eluence saline solution on the ^{99m}Tc elution yield is also examined. The latter method could be of further practical interest as ascorbic acid, present in ^{99m}Tc eluate, could stabilize ^{99m}Tc-radiopharmaceuticals during preparation.

2. EXPERIMENTAL

The ^{99m}Tc elution yield is determined by the following relation:

$$\text{Elution yield (\%)} = A_{Tc(measured)} / A_{(Tc\ theoteritcal)} \times 100$$

where:

$A_{Tc(measured)}$ is activity of ^{99m}Tc measured in the eluate, and

$A_{Tc(theoretical)}$ is the activity of ^{99m}Tc calculated according to the activity of ^{99}Mo adsorbed on the column and time elapsed after adsorption or previous elution

The ^{99m}Tc elution yield was determined under the following experimental conditions:

1. Generator columns

a) Fission-produced ^{99}Mo adsorbed on the top of the column containing 1 g Al_2O_3 (ICN R)

b) Fission-produced ^{99}Mo adsorbed in the upper layer consisting of 0.2 g Al_2O_3xCu containing 0.2-0.3 μg Cu(II)/g Al_2O_3 (ICN N); under layer 0.5 g Al_2O_3 (ICN R)

c) Fission-produced ^{99}Mo adsorbed in the upper layer consisting of 0.2 g Al_2O_3 (ICN N) + 0.3 g SiO_2 (Merck); under layer 0.5 g Al_2O_3 (ICN R)

2. Eluence
a) The columns were eluted by 10 ml of home-made saline (0.9% NaCl)
b) The columns were eluted by 10 ml of home-made saline containing 20-120 μg ascorbic acid (Fluka) per ml
3. Mode of generator operation
a) "Dry" mode – after each elution the column was dried by passing about 20 ccm of air through it (by using another vacuum vial)
b) "Wet" mode – after each elution the column was filled with pure saline

Fission-produced ^{99}Mo (Nordion, Canada) is purchased as molybdate in 2 N NaOH. The solution is acidified by diluted HCl and the aliquots of desired activity are adsorbed in the columns. The generators are eluted daily (interval between two subsequent elutions: 22-24 h).

The ^{99m}Tc activity measurements were performed by using dose calibrator (Capintec CRC-15R).

3. Results and discussion

The constructions of ^{99}Mo/^{99m}Tc generators differ from one producer to another. Common to them all is the column containing alumina with adsorbed (n,f)^{99}Mo. The elutions of ^{99m}Tc are performed by saline (0.9% NaCl) which is passed through the column by the action of vacuum. In principle, the generators are designed to operate either in the "dry" or "wet" mode of operation. The first mode presumes that after each elution the rest of saline is removed by passing air through the column. The "wet" generators comprise a reservoir of eluence sufficient for all elutions during the whole life time of the generator (about 10 days). The desired volume is passed by the action of vacuum and the column remains filled with saline till the next elution.

The problem of low or reduced elution yield is one of the major problems with the generators based on (n,f)^{99}Mo. It happens that the elution yield (i.e. the retention of ^{99m}Tc on the column) varies for no obvious reason. It occurs random but it is most probable in the first days of the use, i.e. when it contains the highest activities. The probability of its occurrence is also high in the case when the generator was not eluted for several days (so-called "Monday" eluate).

There are several reasons that could cause the retention of ^{99m}Tc on the column (mechanical defects, insufficient volume of the eluence, etc). For example, it is known that disinfectants or extracts from the plastic parts of the generator can influence the yield.

However, the main reason are the complex chemical, physicochemical and radiochemical processes in the column. ^{99}Mo/^{99m}Tc generator is a heterogeneous system. Due to its very high specific activity, fission-produced ^{99}Mo is adsorbed in a very limited volume of the adsorbent. The self irradiation doses due to the decay of ^{99}Mo could be very high. In the presence of water, highly reactive oxidation and reduction agents are formed. A lot of investigations was devoted to this problem but still it is not completely understood.

Cifka [5] showed that the elution yield depends on the valence state of technetium. Heptavalent technetium is readily eluted, but reduced forms remain firmly bond to alumina. It is supposed that the hydrated electrons are the species responsible for the reduction and thus for the decrease of the elution yield. Therefore, any method of ensuring stable and high elution yields should be based on the prevention of the reduction of Tc(VII).

The first attempts were the introduction of some strong oxidizing agent (like hydrogen peroxide) into the column or into the eluence. The drawbacks were the need for high concentrations of such agents and their probable interferences with the stainless steel parts of the generator and particularly with the subsequent uses of the eluate.

In our experiments two attempts of maintaining high ^{99m}Tc elution efficiency were tried. They involved either the modifications of the adsorbent layer or of the eluence.

The column with the modified adsorbent consisted of two layers. The upper layer, in which (n,f)^{99}Mo is adsorbed, was in the first case the mixture of alumina and silica gel. So the volume containing (n,f)^{99}Mo is much larger causing the reduction of the radiation doses. In the second modification, a radical scavenger was introduced into the generator column. We have chosen divalent copper adsorbed on alumina [5]. In both cases the under layer was pure alumina which should retain ^{99}Mo which eventually passes the upper layer.

The modification of the saline eluence consisted of addition of ascorbic acid. This acid is a well known antioxidant which can be efficiently applied in the stabilization of several radiopharmaceuticals [6]. By using such a modification ascorbic acid would be present already in ^{99m}Tc eluate. In was found in the literature that this approach improves the elution yield in the case of ^{188}W/^{188}Re generator which is similar to ^{99}Mo/^{99m}Tc generator (adsorbent alumina, eluence saline solution) [7]. So, the aim of the present paper was also to determine if the presence of ascorbic acid in quantities sufficient for the stabilization of radiopharmaceuticals, influences ^{99m}Tc elution yield.

In the experiments the test generators were eluted both with pure or modified 0.9% NaCl solution. The content of ascorbic acid varied from 20 – 120 μg/ml but no dependance on the concentracions was observed. So the Tables contain only the results obtained by using saline containing 100 μg ascorbic acid per ml.

The ^{99m}Tc elution yields in the columns with pure alumina and the modified adsorbent layers in the "dry' mode of the generator operation are shown in Table 1. The elutions were performed by the modified eluence (100 μg ascorbic acid per ml of saline).

Table 1. Dependance of ^{99m}Tc elution efficiency on the composition of the adsorbent in the "dry" mode of ^{99}Mo/^{99m}Tc generator operation
Generator column: 1 g Al_2O_3
Modified generator columns:
a) Upper layer: 0.2 g Al_2O_3 + 0.3 g SiO_2; Under layer: 0.5 g Al_2O_3
b) Upper layer: 0.2 g Al_2O_3 xCu (0.3-0.4 mg Cu/g Al_2O_3; Under layer: 0.5 g Al_2O_3
Eluence: 0.9% NaCl + 100μg ascorbic acid per ml (pH = 6-6.7)
Volume of eluence: 10 ml
^{99}Mo activity at calibration: 8-10 GBq

Number of elution (days)^x	^{99m}Tc elution efficiency (%)		
	Al_2O_3	$Al_2O_3 + SiO_2$	Al_2O_3xCu
1	75.2	84.8	95.2
2	79.2	85.3	91.2
3	78.4	84.0	91.4
4	80.1	84.5	90.2
5	80.1	83.9	90.2

x- interval between two subsequent elutions 22-24 h

The data given in Table 1 show that "dry" mode of generator operation ensures stable elution efficiencies. The best results are obtained when copper is present. Almost all ^{99m}Tc activity, present in the column, is eluted.

The same test generators were examined also in the "wet" mode of operation. Namely, it often happens that some saline remains in the column despite drying. The causes could be insufficient vacuum in the vial or simply a mistake of the user who omitted to dry the column after the elution. These results are shown in Table 2. The elutions are performed by using the modified eluence (100 µg ascorbic acid per ml).

Table 2. Dependance of ^{99m}Tc elution efficiency on the composition of the adsorbent in the "wet" mode of $^{99}Mo/^{99m}Tc$ generator operation
Generator column: 1 g Al_2O_3
Modified generator columns:
a) Upper layer: 0.2 g Al_2O_3 + 0.3 g SiO_2 Under layer: 0.5 g Al_2O_3
b) Upper layer: 0.2 g Al_2O_3xCu (0.3-0.4 mg Cu/g Al_2O_3 ;Under layer: 0.5 g Al_2O_3
Eluence: 0.9% NaCl + 100µg ascorbic acid per ml (pH = 6-6.7)
Volume of eluence: 10 ml
^{99}Mo activity at calibration: 8-10 GBq

Number of elution (days)^x	^{99m}Tc elution efficiency (%)		
	Al_2O_3	$Al_2O_3 + SiO_2$	Al_2O_3xCu
1	15.2	20.3	90.2
2	66.3	29.2	89.9
3	11.8	65.7	90.1
4	42.9	12.8	89.6
5	3.5	9.9	90.1

x- interval between two subsequent elutions 22-24 h

The obtained results show that the "wet" mode of generator operation is not suitable for the routine generator production. Alumina and the mixture of $Al_2O_3 + SiO_2$ perform low and very variable elution efficiencies. Only the method of doping alumina with copper has shown good results both in the "dry" and "wet" mode of operation.

Table 3 presents the results obtained when the experimental columns were eluted by pure 0.9% NaCl and by the modified eluence. As shown in Table 2 in the "wet" mode pure alumina and its mixture with silica gel perform unstable and highly variable results. So, these data could not be included. The results given in Table 3 are obtained by ten subsequent elutions of the generators under the given experimental conditions.

Table 3. Dependance of ^{99m}Tc elution efficiency on the composition of the adsorbent in the "dry" and "wet" mode of $^{99}Mo/^{99m}Tc$ generator operation
Generator column: 1 g Al_2O_3
Modified generator columns:
a) Upper layer: 0.2 g Al_2O_3 + 0.3 g SiO_2 ; Under layer: 0.5 g Al_2O_3
b) Upper layer: 0.2 g Al_2O_3xCu (0.3-0.4 mg Cu/g Al_2O_3 ;Under layer: 0.5 g Al_2O_3
Eluence: 0.9% NaCl or 0.9% NaCl + 100µg ascorbic acid per ml (pH = 6-6.7)
Volume of eluence: 10 ml
^{99}Mo activity at calibration: 8-10 GBq

Composition of the column	Mode of operation	^{99m}Tc elution efficiency (%) (0.9% NaCl)	^{99m}Tc elution efficiency (%) (0.9% NaCl+asc.acid)^x
Al_2O_3	"Dry"	79.1 ± 2.4	78.6 ± 2.9
$Al_2O_3 + SiO_2$	"Dry"	92.3 ± 3.2	84.5 ± 0.5
Al_2O_3xCu	"Dry"	90.7 ± 3.5	91.6 ± 1.8
	"Wet"	95.0 ± 2.1	89.7 ± 0.5

x- content of ascorbic acid: 100 µg/ml saline

Table 3 presents the reliability of the examined protection methods. It can be seen that only the generators based on the introduction of Cu(II) as the radical scavenger into the adsorbent layer give high and stable ^{99m}Tc elution yields, regardless the mode of operation. Ascorbic acid neither protects the columns in the "wet" mode of operation nor, under the given experimental conditions, influences ^{99m}Tc elution yield. So, in principle, ascorbic acid could be added to the eluence solution for the intended purposes (stabilization of radiopharmaceuticals). However, for the routine use, further investigations are needed.

4. CONCLUSION

The results show that the generators containing pure alumina as adsorbent are not reliable. The ^{99m}Tc elution yields vary, particularly when the eluence is present in the column ("wet" mode). In the experiments two modifications of the adsorbent were tested. Fision-produced ^{99}Mo was adsorbed either in the mixture of Al_2O_3 + SiO_2 or in alumina on which divalent copper has been adsorbed. The latter solution gives the best results, both in te "dry" and "wet" mode of the generator operation. The addition of ascorbic acid was found not to interfere with the elution efficiency. Therefore such an eluence could be used as on this way sufficient quantity of this antioxidant is provided in ^{99m}Tc eluate for the effective stabilization of radiopharmaceuticals. However, for a possible routine use of this procedure further investigations are needed.

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PRINOS ELUIRANJA MOLIBDEN-99/TEHNECIJUM-99M GENERATORA

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Ispitivana je zavisnost prinosa eluiranja ^{99m}Tc u ^{99}Mo/^{99m}Tc generatorima u zavisnosti od vrste adsorbensa i eluensa. Pored čistog korišćen je i Al_2O_3 modifikovan dodavanjem silika gela ili adsorpcijom dvovaletnog bakra. Za eluiranje korišćeni su čist fiziološki rastvor (0,9% NaCl) ili fiziološki rastvor koji je sadržavao 100 μg askorbinske kiseline po ml. Visoki i stabilni prinosi eluiranja ^{99m}Tc i u "suvom" i u "mokrom" režimu rada generatora, dobijeni su samo korišćenjem Al_2O_3 sa adsorbovanim Cu(II). Nadjeno je da pod datim experimentalnim uslovima askorbinska kiselina ne utiće na prinos eluiranja ^{99m}Tc.