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Studies on the separation of ^{99m}Tc from large excess of molybdenum

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Abstract

BACKGROUND: Due to aging and unexpected prolonged shutdown of nuclear reactors producing ^{99}Mo for ^{99}Mo/^{99m}Tc generators it was necessary to explore the alternative methods of technetium-99m production. The first choice were the accelerators. Three years ago IAEA (International Atomic Energy Agency) initiated the Coordinated Research Project "Accelerator-based Alternatives to Non-HEU production of Mo-99 /Tc-99m" aimed at direct production of ^{99m}Tc in proton accelerators using the ^{100}Mo(p,2n)^{99m}Tc reaction. POLATOM is participating in this enterprise together with the Heavy Ion Laboratory of Warsaw University and the Institute of Nuclear Chemistry and Technology.
MATERIAL AND METHODS: ^{99}Mo/^{99m}Tc solutions and pure ^{99m}Tc used for generators production or milked from ready to use generators were used in experiments. Commercial chromatographic and laboratory-prepared columns were used for separation. The peristaltic pumps were used for solutions delivery onto the columns. Radioactivity of eluted ^{99}Mo and ^{99m}Tc was measured using high resolution gamma spectrometry or ionisation chamber in case of high radioactivity. For separation, three different chromatographic methods were used, one based on ion exchange and two on extraction.
RESULTS: Synthetic mixtures simulating the real solutions were used. ^{99m}Tc is quantitatively bound in the Dowex-1×8 column whereas molybdenum is only slightly retained and totally rinsed with 2M NaOH. ^{99m}Tc is eluted with TBAB. The elution yield has been reproducible and amounted to 78%. The AnaLig Tc-02 resin column was used for ^{99m}Tc retention. Residual Mo was removed by rinsing with 2M NaOH and ^{99m}Tc eluted using small volume of water. The recovery was equal to about 85%. Using C-18 column coated with PEG over 80% of ^{99m}Tc was recovered in about 50 mL of water. The reduction of volume was necessary.
CONCLUSIONS: The recovery of ^{99m}Tc was the highest using AnaLig Tc-02 resin. Time of ^{99m}Tc separation is the shortest for AnaLig Tc-02 resin and it is not higher than 100 minutes and it can further be shortened.

KEY words: ^{99m}Tc, molybdenum, Dowex-1×8, TBAB, AnaLig Tc-02, PEG, ^{99m}Tc separation

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Background

The ^{99m}Tc is the most frequently used isotope for medical diagnosis. From the about 30 million examination procedures performed yearly about 95% apply this isotope. Practically, till now the total supply comes from the ^{99}Mo/^{99m}Tc generators in which ^{99}Mo is the fission product of ^{235}U. There are worldwide no more than 6 nuclear reactors producing significant amounts of ^{99}Mo covering these needs. The reactors are mostly approaching the end of their production lives and the reliable delivery of ^{99}Mo can be seriously distorted in coming years. There are alternative methods of ^{99}Mo production. One of the most promising is the use of proton accelerators which are already quite widely used in hospitals for production of such isotopes as ^{18}F, ^{11}C, ^{13}N, ^{15}O. ^{99m}Tc can abundantly be produced in the nuclear reaction ^{100}Mo(p,2n)^{99m}Tc. This method of ^{99m}Tc production is known since 1971 [1]. A number of studies on the cross section of this reaction has been carried out [2–6]. The simultaneous production of undersirable Tc isotopes have also been taken into account [7]. The required ^{99m}Tc product using protons of energy in the range from 16 to 20 MeV can constitute about 80%. The rest is long lived ^{99}Tc ($T_{1/2} = 2.1 \times 10^5$ years).

First separations of Tc from other elements has been undertaken in 1960s [8, 9]. This topic still requires improvement. Good summary of separation methods is given in [10]. There is a number of patents on ^{99m}Tc separation [11–14].

In last few years several papers, mostly from Canadian laboratories, were published on experimental production of ^{99m}Tc and its separation, even in curie quantities [15–17]. The ^{99m}Tc with its half live of 6 hours must be quickly separated from the bulk of molybdenum. The irradiated ^{100}Mo has to be dissolved in the shortest possible time and ^{99m}Tc separated. It is expected that the cyclotron production of ^{99m}Tc will be implemented in Poland in near future.

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Materials and methods

Materials and instrumentation:

— sodium molybdate, ammonium carbonate, molybdenum trioxide, tetrabutyloammonium bromide (TBAB), hydrogen peroxide 30% solution, Dowex-1×8 resin (Cl^- form, 100–200 mesh); analitycal grade, Sigma-Aldrich;
— dichloromethane for HPLC, sodium hydroxide chemical grade; Merck;
— polyethylene glycols PEG-2000, PEG-3000, PEG-4000, PEG-6000, chemical grade; Fluka AG;
— C-18 column OASIS HB, Waters;
— AnaLig Tc-02 resin (60–100 mesh); IBC Advanced Technologies;
— 0.9% sodium chloride solution for injection; Polpharma;
— generator $^{99}Mo/^{99m}Tc$, (Polgentec, POLATOM);
— $Na_2{}^{99}MoO_4$ solution, NTP South Africa;
— acidic alumina column Pak Vacc 1cc (100 mg); Waters;
— Bond Elut Reservoir with two 20 μm polypropylene frits, volume 1.5 mL; Varian;
— Dose Calibrator CRC-55tR, Capintec;
— HPGe (High Purity Germanium) gamma spectometer GX1520, Canberra;
— MasterFlex Peristaltic Pump, Cole Palmer;
— Total Organic Carbon (TOC); Sievers 900 GE Healthcare.

Separation methods

Following three methods have been evaluated for ^{99m}Tc separation from large molybdenum excess:

1) anion exchange on Dowex-1×8 [15, 18];
2) adsorption on AnaLig Tc-02 resin [17];
3) C-18 column modified with PEG (ABEC procedure) [15, 19].

Separation on Dowex-1×8

After soaking of 100 to 140 mg of resin in 5 mL of 0.5 M NaOH, the suspension was introduced in a column. Before depositing the solution onto bed, the column was washed with 5 mL of 0.5 M NaOH. 10 mL of Na_2MoO_4 80 mg/mL solution containing 10 MBq of ^{99}Mo in equilibrium with ^{99m}Tc was introduced onto the column with a flow rate in the range from 0.6 to 1.0 mL/min. Eluate from column was collected in 1 mL portions. Activity of ^{99}Mo in collected aliquots was measured in a HPGe gamma spectrometer. Before the ^{99m}Tc elution the column was rinsed using 10 mL of 0.9% NaCl. As an eluent 5 mL of TBAB (tetrabutyloammonium bromide) solution of 0.2 mg/mL in CH_2Cl_2 was used. The eluate was collected as 1 mL aliquots and measured like ^{99}Mo fractions. The yield of adsorption and desorption processes was calculated as a ratio of measured activities of ^{99m}Tc in collected aliquots to the total activity of ^{99m}Tc loaded onto the column. Diagram of the process is shown in Figure 1.

Separation on AnaLig Tc-02

The columns were filled with about 100 mg of resin suspension. To 10 mL of Na_2MoO_4 solution of 120 mg/mL in 2 M NaOH, the tracers of ^{99}Mo (80 to 100 kBq) or $^{99m}TcO_4^-$ (170 to 240 MBq) were added. The solution was delivered on the column using a peristaltic pump with the flow rate of 0.2 mL/min. To the column outlet, a flexible tube was connected enabling the collection of eluate to vials for gamma spectrometry measurements of ^{99}Mo with the use of HPGe detector. In next step, the column was rinsed with 3 mL of 2M NaOH. For ^{99m}Tc elution 5 to 10 mL of water was used and the eluate was collected in 1 mL portions to 10 mL vials. The flow rate was 0.5 mL/min. Due to high activities of ^{99m}Tc the vials were measured in dose calibrator.

The diagram of the separation and desorption processes is shown in Figure 2.

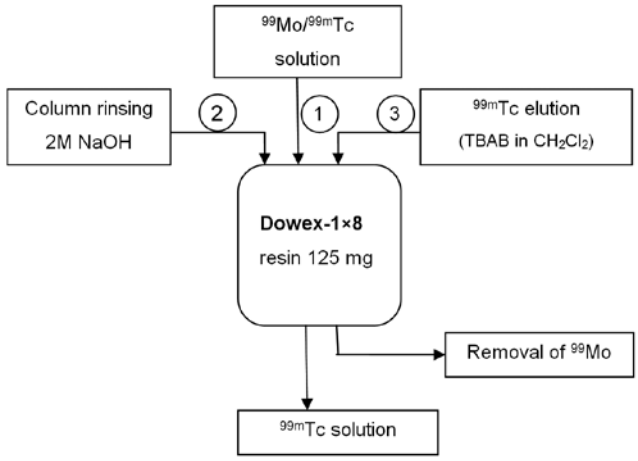

Figure 1. Diagram of sorption and elution process on Dowex-1×8

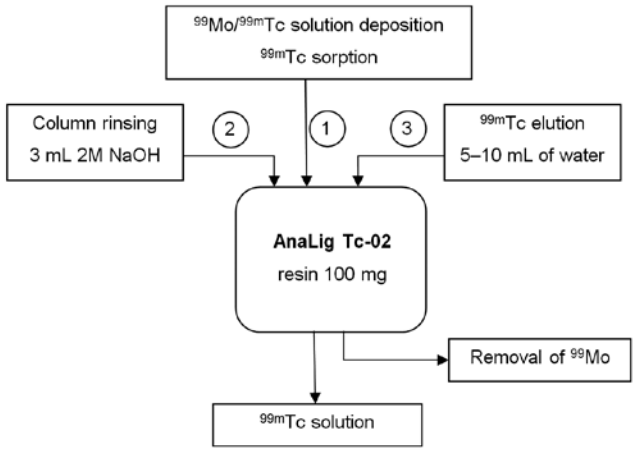

Figure 2. Diagram of separation process using AnaLig Tc-02 resin

Separation on C-18 column modified with PEG

The aqueous biphasic extraction chromatography (ABEC) with C18 (OASIS HB) column coated with polyethylene glycol as extractant was used. Around tenfold excess of polyethylene glycol with molecular weight in the range from 2000 to 6000 was loaded on the column containing 0.1 g of C-18 resin in water. The excess of PEG unbound with resin was washed with water. The solution of ammonium molybdate (0.05 g of Mo) with about 2 MBq of ^{99}Mo in 10 mL of 3M ammonium carbonate solution was loaded on the column. The column was washed with 10 mL 3M ammonium carbonate and then ^{99m}Tc was eluted with ten 5 mL fractions of water. Elution yield and content of ^{99}Mo in technetium fraction were determined by gamma spectrometry with HPGe detector. The content of polyethylene glycol in ^{99m}Tc fraction was measured by TOC method.

Results and disscusion

Separation on Dowex-1×8

In four experimental runs using Dowex resin, the ^{99m}Tc yield was above 77%. Total retention of ^{99m}Tc was achieved for the flow rate of 0.6 mL/min. Increasing flow rate to 2 mL/min during column loading and elution resulted in decreasing the elution yield for more than 10%. The elution is fastest at the beginning and more than 90% of ^{99m}Tc is contained in the first 5 mL of TBAB solution. The elution yield was higher when the contact of TBAB solution with Dowex resin was increased to about 10 minutes. On the other hand this has no effect on the amount of ^{99m}Tc retained on the column. Results of ^{99m}Tc recovery are presented in Table 1.

Separation on AnaLig Tc-02

Table 2 shows the results of ^{99m}Tc retention on column from 2M NaOH solution and ^{99m}Tc recovery from this column after elution with water. ^{99m}Tc is retained almost completely on the column. Only 0.025 % of technetium is lost in these steps of separation. The recovery of ^{99m}Tc amounted to approximately 85% and all technetium was contained in 2 mL of water solution.

The ^{99}Mo activity distribution from the AnaLig Tc-02 column loaded with ^{99}Mo in equlibrium with technetium is shown in Table 3. It can be seen from this table and Figure 3 that all molybdenum was found in eluate and in rinsing solutions. The activity of ^{99}Mo measured in ^{99m}Tc water fractions was from 1 to 8 Bq.

Separation on C-18 column modified with PEG

Typical elution profile of ^{99}Mo and ^{99m}Tc from C-18 column coated with PEG is presented in Figure 4. Blue line represents the ^{99}Mo eluted during solution loading on the column while the red line represents ^{99m}Tc eluted from the column with water after successful ^{99}Mo loading. The ^{99m}Tc elution profile improves with decrease of PEG molecular weight as can be seen in Figure 5.

Using the C-18 column in-house modified with polyethylene glycol allowed to separate ^{99m}Tc from excess of Mo with over 80% yield. The highest elution yield of ^{99m}Tc > 80% were obtained for polyethylene glycol with low molecular weight (PEG-2000 and PEG-3000). With increasing the molecular weight of PEG, elution yields of ^{99m}Tc drops to around 70% for PEG-6000 as can be seen in Table 4.

Assuming that TOC method quantifies the level of PEG residue in ^{99m}Tc solution, the PEG contamination was lower than 0.005% and significantly decreased with increasing PEG molecular weight. The contamination of ^{99m}Tc with ^{99}Mo was lower than 0.01% for all experiments. Despite the high separation yield, the volume of ^{99m}Tc eluate is rather high and further post-elution concentration might be required.

Conclusion

The separation yield of ^{99m}Tc for all 3 resins used is above 75%. In comparison to technetium-99m half-life the separation times were relatively short and were not higher then 100 minutes.

Table 1. Elution efficiency of ^{99m}Tc

Dowex-1×8 mass [mg]	^{99m}Tc in 0.9% NaCl solution	^{99m}Tc eluted [%]	^{99m}Tc retained on column [%]
125	nd	77.5	22.5
133	nd	78.6	21.4
139	nd	78.5	21.5
140	nd	79.1	20.9

nd — not detected

Table 4. Elution yield of ^{99m}Tc and TOC content in ^{99m}Tc solution obtained from OASIS HLB Plus column coated with PEG

PEG	Elution yield of ^{99m}Tc (50 mL of water) [%]	TOC content in ^{99m}Tc solution [μg/mL]
PEG-2000	82.5	25.7 ± 2.6
PEG-3000	80.1	22.1 ± 1.9
PEG-4000	73.6	9.8 ± 1.3
PEG-6000	71.3	3.0 ± 0.3

Table 2. ^{99m}Tc activity distribution in retention and elution process using AnaLigTc-02 resin

Experiment	^{99m}Tc in solution loaded on column [MBq]	^{99m}Tc in solution		^{99m}Tc eluted from column [MBq]	^{99m}Tc recovery [%]
		Leaving column [kBq]	2 M NaOH rinsing [kBq]		
1	172	10	20	144	83.7
2	235	20	30	204	86.5
3	176	10	20	149	84.6
4	235	20	20	203	86.3

Table 3. ^{99}Mo activity distribution in ^{99m}Tc recovery process

^{99}Mo in solution loaded on column [kBq]	^{99}Mo not retained on [kBq]	^{99}Mo in 2M NaOH rinsing solution [kBq]	^{99}Mo in water eluted ^{99m}Tc 1 mL fractions [Bq]			
			1	2	3	4
94	90.0	3.80	1	nd	nd	nd
96	92.6	3.35	5	nd	nd	nd
89	86.0	2.86	nd	nd	nd	nd
102	97.8	4.10	8	nd	nd	nd

nd — not detected

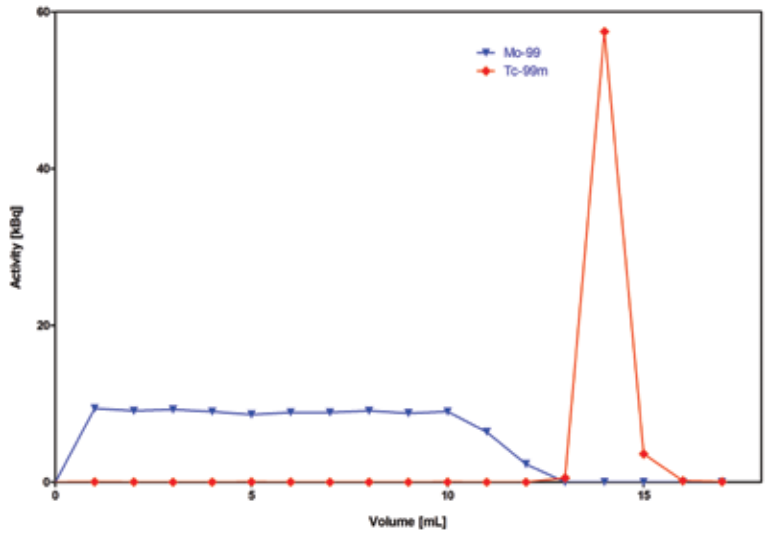

Figure 3. ^{99m}Tc separation process on AnaLig Tc-02 resin

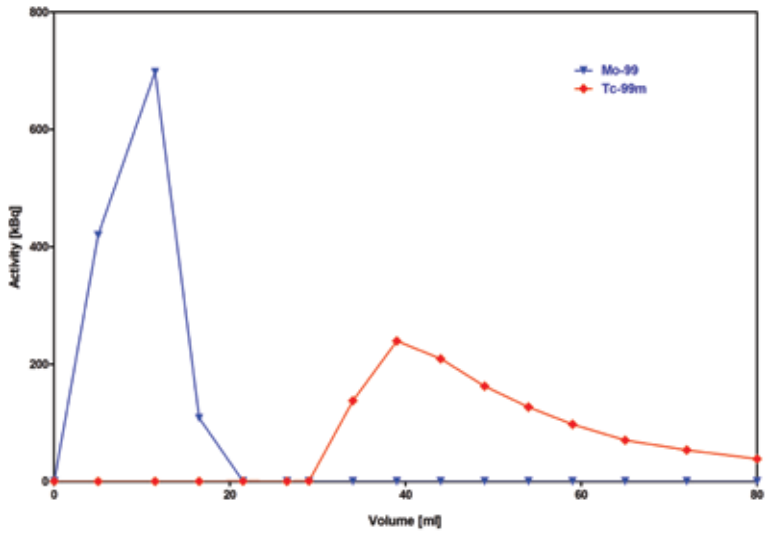

Figure 4. Typical elution profile of ^{99}Mo and ^{99m}Tc from OASIS HLB Plus column coated with PEG

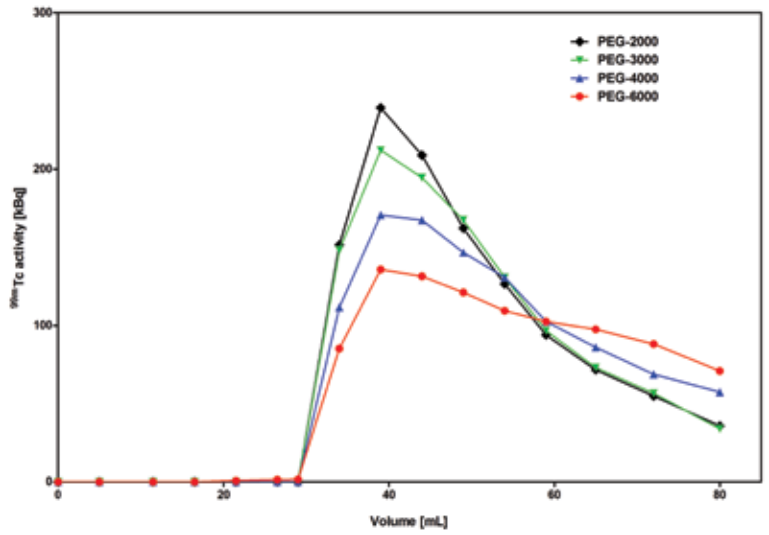

Figure 5. Influence of PEG molecular weight on the elution profile of ^{99m}Tc from OASIS HLB Plus column coated with PEG

The highest concentration of ^{99m}Tc has been achieved with the use of AnaLig Tc-02 resin. The concentration of ^{99}Mo in recovered ^{99m}Tc is below 0.01 % using AnaLig Tc-02 and C-18 column modified with PEG resins.

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