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PREPARATION OF PZC BASED ^{99m}TC GENERATOR TO BE AVAILABLE FOR CLINICAL APPLICATION

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ABSTRACT

The performance of PZC was investigated for chromatographic Tc-99m generator preparation. Mo-adsorption of PZC in different Mo-solutions and Tc-99m elution of ^{99}Mo-PZC column were studied. Mo- adsorption capacity of higher than 250mgMo/gPZC and Tc-99m elution yield of higher than 80% were achieved with PZC adsorbent. Mo-99 breakthrough of 0.02% and Molybdenum element breakthrough of around 5µg Mo/ml were found in Tc-99m eluate. A good relationship between the Mo-content of adsorption solution and the Mo-adsorption capacity, adsorption percentage, Mo-breakthrough and Tc-99m elution yield was found.

The column pre-loading procedure for the preparation of PZC based chromatographic Tc-99m generators were described in detail .

INTRODUCTION

Tc-99m is a mainstay radioisotope for nuclear medicine application. This radioisotope now-a-day is eluted routinely from a radionuclide chromatographic generator using a parent Mo-99 radionuclide produced by (n,γ) or (n , fission) nuclear reaction and a chromatographic column on which Mo-99 parent nuclide is adsorbed. The chromatographic column packing material can be Alumina adsorbent, zirconium-molybdate or titanium–molybdate gel powder [1] and a newly developed Polymer Zirconium Compound (PZC) [2]. Each column packing is specified for a particular case of Tc-99m generator type. The Tc-99m generator technology using a recently developed PZC column packing adsorbent is noted as a new alternative one. As a contribution ,our report is aimed to investigate and evaluate the performance of PZC

adsorbent for the preparation of a clinically available Tc-99m generator.

The column pre-loading procedure for the preparation of PZC based chromatographic Tc-99m generators was recently developed by us in Vietnam. This procedure seems to be safe and more comfortable in the operation .

EXPERIMENTAL

INVESTIGATION ON THE PERFORMANCE OF PZC FOR CHROMATOGRAPHIC TC-99m GENERATOR PREPARATION :

Polymer Zirconium Compound (PZC) adsorbent synthesized by us was used in all experiments. The PZC samples of different preparation batches were investigated and compared with each other. 15 ml radioactive Mo-99 solution of concentration of 13.316 mg Mo / ml, pH=7 were added to PZC samples of 0.75 g weight, then these samples were gently shaked in water bath of 50^{o}C overnight. After shaking the samples were let to stand and a portion of clear supernatant solution was taken out to measure Mo-99 radioactivity for Mo–adsorption capacity calculation and then the remained solution was decanted to get the solid PZC part. This solid PZC sample was packed in 8ml glass column and washed with 30 ml water followed by passing column with 10 ml saline. After this step first Tc-99m elution was started after 24 hours equilibration time and daily an elution was conducted. All experiments were carried out with PZC columns of Mo-99 radioactivity of 10 – 30 mCi. Each column was eluted for five to seven days (one elution a day). Elution yield, Mo-99 break-through , Mo element content were determined for each elution.

THE COLUMN PRE-LOADING PROCEDURE

(^{99m}Tc generator reparation by on- PZC column adsorption of Mo-99 using Mo-99 solution of low specific radioactivity):

This procedure was intended to be applied for the production of a generator of radioactivity ranging from 200 mCi to 1000 mCi Tc-99m which can be satisfactorily used in the clinical nuclear medicine application. A column of 4 gram PZC packing was chosen to prepare the Tc-99m generators of radioactivity changing from 100 mCi to 1000 mCi Mo-99 (see Table 1).

Table 1 : Tc-99m generator production capability using a PZC column of 4 gram weight and of 250 mg Mo/g PZC Mo-adsorption capacity in the nuclear reactors of different neutron flux . Irradiation time : 186 hours continuously

Thermal neutron flux ($n.cm^{-2}.sec^{-1}$)	10^{13}	2.5×10^{13}	5×10^{13}	10^{14}
Mo-99 radioactivity at E.O.B	164.88 mCi	412.2 mCi	824.4 mCi	1648.0 mCi
Mo-99 radioactivity after one day cooling time and one day of generator preparation .	100.10 mCi	250.2 mCi	500.4 mCi	1000.8 mCi

(The values in the Table 1 were calculated for one gram weight of Molybdenum equivalent to Mo content of 4 gram PZC column.)

RESULTS AND DISCUSSION

The performance of PZC in different solutions

In table 2-3 the results of studies on the adsorption and Tc-99m elution performance of ^{99}Mo- PZC in different solutions were presented. It is found that the oxidizing agent added Mo-solution did not affect the Mo-adsorption and Tc-99m elution performance of ^{99}Mo- PZC columns. The conditioning ^{99}Mo- PZC columns with solution containing agent of higher Zirconium-adsorption power such as PO_4^{3-} and with a solution of high Cl^- concentration will affect the performance of ^{99}Mo- PZC column. This effect brought about higher Mo-breakthrough in Tc-99m eluate and reduced to some extent the Tc-99m elution yield.

Table 2: The Mo adsorption of PZC in different solutions

Lot. No. of PZC	Sample	pH after adsorption	Adsorption capacity (mg Mo/g PZC)	Weight of discarded fine PZC powder (%)	Weight of PZC powder in generator column (%)
A1	I	5	249.7	8.5	91.5
	II*	5	249.7	12.5	87.5
	III*	5	252.1	15.8	84.2

	IV*	5	250.2	13.8	86.2
A2	I	4.5	239.5	6.2	93.8
	II	5.5	208.4	4.5	95.5
	III	5.5	196.0	4.6	95.4
	IV	5.5	214.9	5.0	95.0
A3	I	4.5	252.3	7.7	92.3
	II	5.5	207.1	5.4	94.6
	III	5.5	209.8	5.6	94.4
	IV	5.5	202.2	5.5	94.5

Table 3: The Tc-99m elution t of PZC in different solutions

Lot No of PZC	Sample	First elution			Second to fifth elution		
		Elution Yield of Tc-99m (%)	Mo breakthrough		Elution Yield of Tc-99m (%)	Mo-breakthrough	
			µg Mo (*)	(%) (**)		µg Mo (*)	(%) (**)
A1	I	77.8	27.4	0.023	92.5 ± 0.5	27.8	0.020
	II*	80.7	196.6	0.168	94.5 ± 0.7	184.8	0.134
	III*	90.1	60.1	0.024	90.2 ± 0.5	34.3	0.014
	IV*	92.5	55.5	0.022	93.1 ± 0.3	31.2	0.012
A2	I	92.5	50.4	0.036	94.5 ± 0.5	25.1	0.017
	II	94.2	49.6	0.040	98.4 ± 0.6	22.5	0.017
	III	99.2	50.4	0.042	97.1 ± 0.6	21.4	0.018
	IV	99.5	52.8	0.039	98.2 ± 0.3	24.0	0.018
A3	I	92.4	43.2	0.035	92.8 ± 0.5	12.2	0.010
	II	96.4	40.0	0.033	97.5 ± 0.3	13.4	0.011
	III	98.0	35.2	0.028	98.5 ± 0.3	11.7	0.010
	IV	97.0	40.0	0.034	98.2 ± 0.3	16.2	0.013

Sample symbol:

(I) With normal condition of Mo-adsorption in water solution of Molybdate and Column washing with 50 ml distilled water, eluted with saline.

(II) With normal condition of Mo-adsorption in Acetate buffer solution of Molybdate and column washing with 50 ml distilled water, eluted with saline.

(III) With normal condition of Mo-adsorption in Acetate buffer solution of Molybdate added with H_2O_2 and column washing with 50 ml distilled water, eluted with saline.

(IV) With normal condition of Mo-adsorption in Acetate buffer solution of Molybdate added with CrO_4^{2-} and column washing with 50 ml distilled water, eluted with saline.

(II*) With normal condition of Mo-adsorption in water solution of Molybdate and Column washing with 20 ml solution of 0.2M KH_2PO_4, pH=6.2 followed by washing with 30 ml distilled water, eluted with saline

(III*) With normal condition of Mo-adsorption in water solution of Molybdate and Column washing with 20 ml solution of 9% NaCl followed by washing with 30 ml distilled water, eluted with saline

(IV*) With normal condition of Mo-adsorption in water solution of Molybdate and Column washing with 20 ml solution of Acetate buffer solution of 0.2M Acetic acid, pH=5, followed by washing with 30 ml distilled water, eluted with saline

(*) Total Molybdenum content in 8 ml eluate.

(**) Percentage of Mo-99 radioactivity in the eluate of Tc-99m.

Effect of the solution Mo-content on the Mo-adsorption capacity of PZC and on the Tc-99m elution yield and Mo-breakthrough of Tc-99m eluate.

The variable volumes of the radioactive Mo-99 solution of concentration of 13.316 mg Mo / ml , pH=7 were added to PZC samples of 0.2 g weight, then these samples were gently shaked in water bath of 50^{o} C overnight. After shaking the samples were let to stand and a portion of clear supernatant solution were taken out to measure Mo-99 radioactivity for Mo–adsorption capacity calculation and then the remained solution was decanted to get the solid PZC part. This solid PZC was washed with 10 ml water followed by passing column with 10 ml saline. After this step first Tc-99m elution was started after 24 hours equilibration time and daily an elution was conducted.

The experimental results presented on Figs: 1-2 revealed the fact that the Mo-adsorption capacity of PZC and Mo-breakthrough of Mo-PZC column decreased with the increasing Mo-content of adsorption solution. This is attributed to the excess of weakly bound Molybdate ion on the surface of PZC. This excess of Molybdate ion may block

the pathway of Tc-99m Pertechnetate ion out- diffusion and cause the lower Tc-99m elution yield observed on the right side of curve in fig. 2.

The lower Mo-content of adsorption solution has caused the unsaturated adsorption and left to some extent free active groups of high anion-affinity on PZC surface. The action of these groups may contribute a retention power to reduce Tc-99m elution yield and Mo-breakthrough in Tc-99m eluate. In our experiment the adsorption percentage of around 90% was chosen as an optimal value for Mo-adsorption to give a ^{99}Mo- PZC column of highest performance.

Fig.1 : Effect of Mo-content of adsorption solution on Mo-Adsorption and Adsorption percentage of PZC

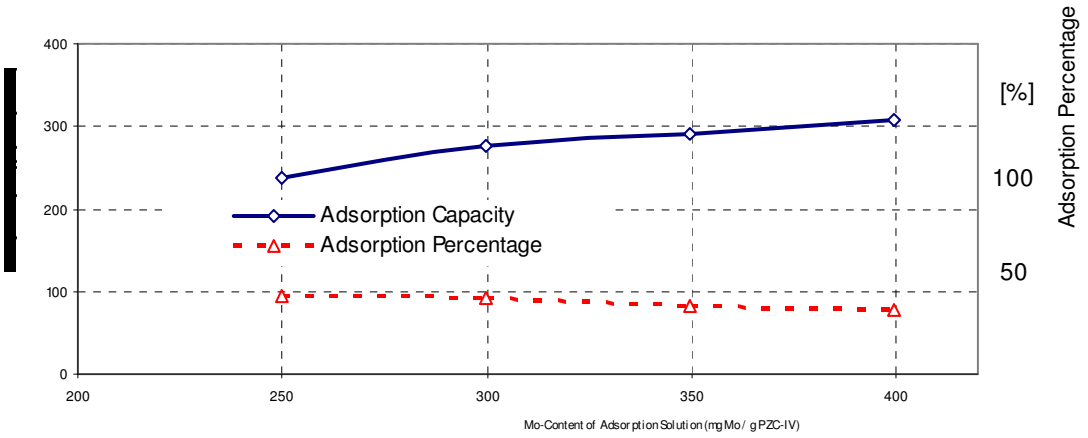
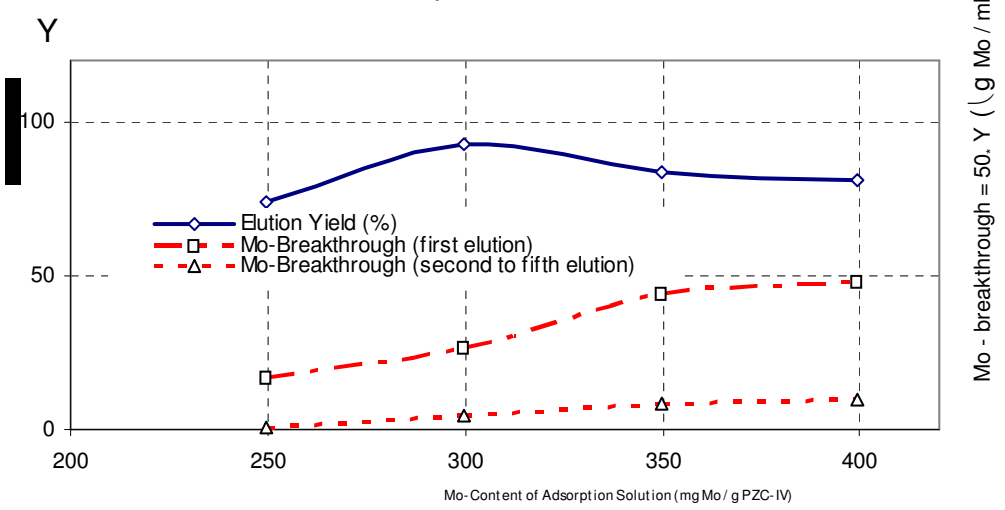


Fig. 2 : Effect of Mo-content of adsorption solution on Molybdenum element breakthrough and Tc-99m elution yield of Mo-99 PZC column



The column pre-loading procedure : ^{99m}Tc generator preparation by on- PZC column adsorption of Mo-99 using Mo-99 solution of low specific radioactivity.

The procedure described hereby is specified for a generator column packed with 4 gram PZC coupled with an Alumina column of 2 g weight. In the case of a generator column packed with smaller weight of PZC an Alumina column of proportionally smaller weight can be used and all calculation equations described in the following paragraphs must be adjusted to harmonize with a selected value of PZC weight, the volume of original Mo-99 solution for adsorption, the volume of conditioning and eluting solution.

I. Solution preparation

- Activate 2 g MoO_3 by thermal neutron in a nuclear reactor, then dissolve the irradiated MoO_3 in 5 ml 6M NaOH solution. Adjust pH of the solution to pH =7 with 1N HCl (or with 1N NaOH). Dilute the solution with water to 25 ml to get a ^{99}Mo solution of concentration of C_{Mo} = 53.4 mg Mo/ml. This resulting solution is called the Original ^{99}Mo Solution.

- Pipette out 5 ml of original ^{99}Mo solution and put into a penicillin type vial of 10 ml volume for ^{99}Mo radioactivity measurement. Measure the ^{99}Mo radioactivity of this solution (noted as $\mathbf{a_o}$)using a radioisotope dose calibrator and calculate the ^{99}Mo radioactivity of 20 ml original ^{99}Mo solution (noted as $\mathbf{A_o}$) which will be used for the Molybdenum adsorption on PZC adsorbent in the following steps.

- ^{99}Mo radioactivity of 20 ml original ^{99}Mo solution (calibrated at time of radioactivity measurement of the original ^{99}Mo solution)

$$\mathbf{A_o} = 20 \text{ x } \mathbf{a_o} : 5 \qquad (1)$$

- Specific radioactivity of original ^{99}Mo solution (noted as S_o)

$$S_o\left(\frac{mCi\,^{99}Mo}{mg\,Mo}\right)=\frac{A_o}{20\,x\,53.4} \qquad (2)$$

II. Cold assembling of generator spare-parts

All assembling operation steps should be carried out in a clean room of class C-100. The connection of the sterilized alumina column with outlet needle and of the millipore airfilter with one of the inlet needles will be completed under aseptic condition. After

connection , the needles , alumina column and millipore filter will be assembled into a generator's adapter for further hot assembling of Mo-99 PZC column.

III . ^{99}Mo adsorption on PZC column and Conditioning ^{99}Mo-PZC generator column

1. PZC column preparation

- Mix 90ml of distilled water with 5ml 0.1M NaOH solution and 5ml 1.5% NaOCl solution to get a solution for PZC column preparation.Add 4g PZC to the above prepared solution and shake mixture gently for 2 hours at room temperature then let it stand for one minute and remove the fine PZC powder from solution mixture by the decantation of the supernatant solution. Wash PZC powder and decant supernatant twice with 100 ml bi-distilled water. Check-up the acidity of solution. pH around pH = 2 should be chosen. Pack gently PZC powder into a glass column of 12 mm in diameter and 80mm in length with G3 fritted glass filter on one of its ends. Place a small piece of fine glass wool on the surface of PZC bed and apply the column stopper on the column ends.

- The loss of the fine PZC powder (noted as σ) is determined by carrying out a parallelly separated experiment: treat 0.5g PZC powder in a solution mixture (prepared as above) of proper volume proportional with the 0.5g weight of PZC. After decanting to get a PZC portion of larger particles, we centrifuge the collected supernatant solution to get a PZC portion of smaller particles. Dry these PZC portions at the same temperature and balance their weight to calculate

$$\sigma(\%) = \left[100\, x \frac{weight\ of\ PZC\ portion\ of\ smaller\ particles}{total\ weight\ of\ two\ PZC\ portion} \right] \qquad (3)$$

- Calculate the weight of PZC packed on column (noted as m_c)

$$m_c\,(g) = \frac{100-\sigma}{100}\, x\, 4 \qquad (4)$$

2. ^{99}Mo adsorption solution preparation

Pipette 20ml of the original ^{99}Mo solution of radioactivity A_o, which contains 1068 mg Mo into a flash, add 3.3ml 1.5% NaOCl solution and adjust the volume of this solution with water to 100ml. Adjust pH of the above solution to pH = 2.

3. ^{99}Mo adsorption on PZC column

- By passing the above prepared ^{99}Mo adsorption solution through PZC column with flow rate of 1.5 ml/min and repeating this three times by recycling we will finish the ^{99}Mo adsorption step. After adsorption, 350ml of bi-distilled water will be passed through the ^{99}Mo – PZC column to remove the non-adsorbed ^{99}Mo solution from PZC column. Lastly, the ^{99}Mo – PZC column will be conditioned with 50ml 0.9% NaCl solution.

- Collect all used ^{99}Mo solution, column washing water and saline in one waste vessel. Pipette 5ml of this mixed solution into 10ml penicillin type vial and then measure the ^{99}Mo radioactivity of this solution (noted as a_1) with a radioisotope dose calibrator (using a lead pot of 5mm in thickness to attenuate 140 keV gamma ray of Tc-99m) and calculate total ^{99}Mo radioactivity non-absorpted on PZC-column (noted as A_1).

- Measure the ^{99}Mo radioactivity of ^{99}Mo-PZC column (noted as A_{mc}) with a radioisotope dose calibrator of reference time t=0 (using a lead pot of 5mm in thickness to attenuate 140keV gamma ray of Tc-99m).

- Sterilize the ^{99}Mo-PZC column by steaming in an autoclave at 124^{o}C for 30 minutes.

4. Calculation of ^{99}Mo radioactivity of ^{99}Mo-PZC column

- Non-adsorbed ^{99}Mo content (at reference time t=0)

$$A_1\,(mCi\ ^{99}\mathrm{Mo}) = \frac{a_1}{5}\,x\,500 \qquad (5)$$

- Calculated ^{99}Mo radioactivity of ^{99}Mo-PZC column (noted as A_{cc}) at the reference time t=0

$$A_{cc}\ (\mathrm{mCi}\ ^{99}\mathrm{Mo}) = (A_o \times f_o) - A_1 \qquad (6)$$

(f_o: ^{99}Mo decay factor for the time period from ^{99}Mo radioactivity measurement of the ^{99}Mo original solution to the reference time t=0)

- ^{99}Mo-PZC column radioactivity deviation between measured and calculated values (noted as δ)

$$\delta(\%) = \left[100\, x \frac{(A_{mc} - A_{cc})}{A_{cc}} \right] \quad (7)$$

- ^{99}Mo adsorption percentage (noted as p)

$$p(\%) = \frac{A_{cc}}{A_o . f_o} x100 \quad (8)$$

- Specific radioactivity of PZC (noted as S) at the time of radioactivity measurement of original Mo-99 solution.

$$S\left(\frac{mCi\ ^{99}Mo}{g\ PZC} \right) = \frac{A_{cc}\ x100}{4(100-\sigma).f_o} \quad (9)$$

- Molybdenum adsorption capacity of PZC (noted as $K_{c(Mo)}$)

$$K_{c(Mo)} \left(\frac{mg\ Mo}{g\ PZC}\right) = \frac{A_{cc}}{A_o . f_o} x \frac{20\, x\, 53.4\, x100}{4(100-\sigma)} \quad (10)$$

- Factor of the effective adsorption capacity of PZC column :

$$Fc = K_{c(Mo)}/K_{Mo} \quad (11)$$

(Measurement of K_{Mo} was described in Reference (6))

IV. Hot assembling of generator

(See paragraph VI , " Generator Design")

By connecting the outlet of ^{99}Mo-PZC column with inlet of a pre-prepared and sterilized 2 gram Alumina column and the inlet needle of saline solution vial with inlet of ^{99}Mo-PZC column under aseptic conditions and assembling these connected columns into a generator body , we have a **^{99}Mo – PZC – Alumina based ^{99m}Tc generator system.**

After assembling, condition the generator column system two times with 20 ml of sterilized isotonic saline by sucking the eluate completely into two evacuated sterilized bottles of 30 ml volume.

V. Elution of ^{99m}Tc

1. Elution process:

After 24 hours of standing from the reference time t=0 (from the end of loading and

conditioning step) , elute the build- up Tc-99m from above assembled ^{99}Mo – PZC – Alumina based ^{99m}Tc generator system with 20 ml sterilized 0.9% saline by sucking Tc-99m eluate completely into an evacuated sterilized bottle of 30 ml volume or by passing exhaustively with gravity force and collecting Tc-99m eluate in a 30 ml bottle.

Pipette 5 ml Tc-99m eluate into 10 ml penicillin type vial under aseptic conditions and measure the Tc-99m radioactivity (noted as $\mathbf{a_{Tc}}$) and the Mo-99 radioactivity (noted as $\mathbf{a_{Mo}}$) of this portion of Tc-99m eluate with a radioisotope dose calibrator (using a lead pot of 5 mm thickness to attenuate 140 KeV gamma ray of Tc-99m for Mo-99 radioactivity measurement) .

Repeat this elution process every twenty-four hours and collect all measured data for calculation.

2.Calculation of Tc-99m radioactivity, Tc-99m elution yield, Mo-99 breakthrough and Molybdenum content in Tc-99m eluate.

- Total ^{99m}Tc radioactivity of Tc-99m eluate (noted as $\mathbf{A_{Tc}}$):

$$\mathbf{A_{Tc} = (a_{Tc} \times 20): 5} \quad (12)$$

- ^{99m}Tc elution yield of Tc-99m generator system (noted as **Y %**):

$$\mathbf{Y\ (\%) = (100 \times A_{Tc}): (Acc\ x0.86 \times f_e)} \quad (13)$$

($\mathbf{f_e}$: ^{99}Mo decay factor for the time period from present Tc-99m elution of generator to the Reference time t=0)

- ^{99}Mo breakthrough in Tc-99m eluate (noted as **B %**) :

$$\mathbf{B\ (\%) = [100 \times (a_{Mo} \times 20: 5) : (A_{Tc})]} \quad (14)$$

- Molybdenum content in Tc-99m eluate [noted as **M (µgMo/ml)]** ,

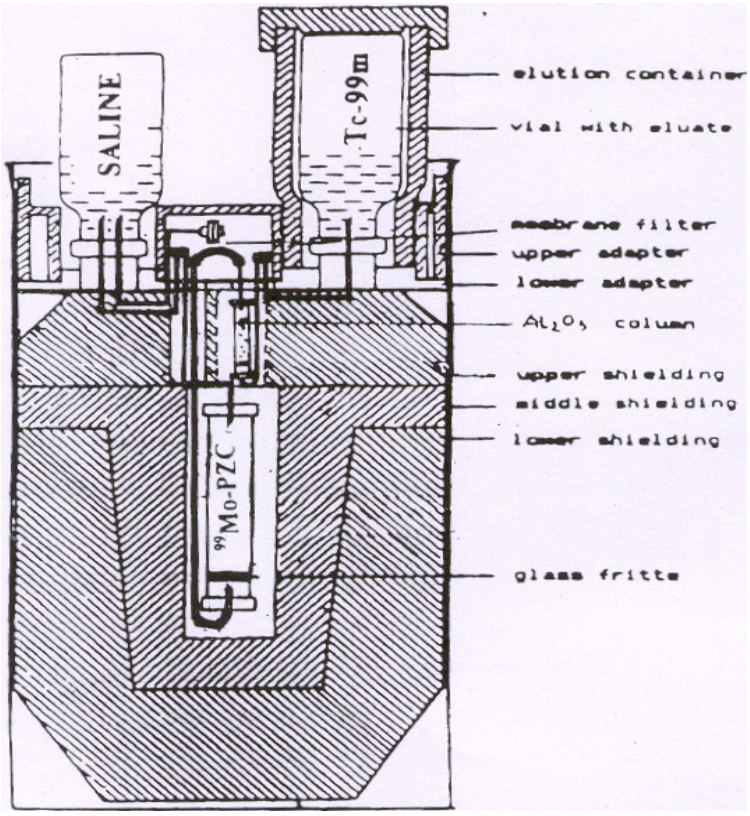
$$\mathbf{M\ (\mu gMo/ml) = [1068000 : Ao] \times [a_{Mo} : (f_t \times 5)]} \quad (15)$$

($\mathbf{f_t}$ = ^{99}Mo decay factor for the time from ^{99}Mo radioactivity measurement of ^{99}Mo original solution to present Tc-99m elution of generator.)

VI. Generator design ^{99}Mo – PZC – Alumina based ^{99m}Tc generator system for "Column pre-loading procedure"

The ^{99m}Tc generator system must be designed correctly to fulfill QA & GMP requirements for the production of radiopharmaceuticals.These ^{99}Mo – PZC – Alumina based ^{99m}Tc generator systems were successfully designed as below:

Scheme of the Tc-99m generator:



VII. Quality control

The radionuclidic purity , radiochemical purity , pH , sterility , the pyrogenity of Tc-99m Pertechnetate solution were investigated in accordance with 21 st US Pharmacopoeia.

VIII. Results of practical application

Measured data	Calculated data
m_{PZC} = 4.0 gPZC	C_{Mo} = 53.4 mgMo/ml
σ = 6.10 %	m_c = 3.756 g
a_o = 80.10 mCi^{99}Mo/5ml	A_o = 320.40 mCi^{99}Mo
S_o = 0.30 mCi^{99}Mo/mgMo	A_1 = 82.00 mCi^{99}Mo
a_1 = 0.82 mCi^{99}Mo/5ml	A_{cc} = 228.46 mCi^{99}Mo
K_{Mo}= 250.9 mgMo/ g PZC (***)	K_{cMo} = 209.20 mgMo/g PZC
A_{mc} = 225.30 mCi^{99}Mo	F_c = 0.83

a_{Tc} = 37.75 mCi^{99m}Tc/5ml	S = 62.77 mCi^{99}Mo/gPZC
a_{Mo} = 0.004 mCi^{99}Mo/5ml	P = 73.6 %
f_o = 0.9690 (t= 3 hours)	δ = 1.40 %
f_e = 0.7772 (t=24 hours)	A_{Tc} = 151.00 mCi^{99m}Tc
f_t = 0.7531 (t=27 hours)	C_{Tc} = 7.55 mCi^{99m}Tc/ml (*)
	Y = 98.8 %
	B = 0.011 %
	M = 3.54 μgMo/ml
	Radionuclidic purity: > 99.99% (**)
	Radiochemical purity: > 99.5% (**)

(*): For the first elution of ^{99m}Tc

(**): Results from "Quality control" of ^{99m}Tc pertechnetate solution described hereafter.

(***) Measurement of K_{Mo} was described in Reference (6).

CONCLUSION

The experimental results reveal the fact that PZC adsorbent has good performance for the preparation of chromatographic Tc-99m generator.

The Molybdenum adsorption capacity of PZC and its Tc-99m elution yield were not strongly affected by the column treatment conditions and composition of adsorption solution. The Molybdenum breakthrough of Tc-99m eluate eluted from PZC column was sensitive to Mo-adsorption and PZC column treatment conditions. A good relationship between the Mo-content of adsorption solution and the Mo-adsorption capacity , adsorption percentage , Mo-breakthrough and Tc-99m elution yield was found. So the optimal parameters for Mo-99 adsorption and Tc-99m generator column preparation were successfully found for the production of a Tc-99m generator giving a Tc-99m pertechnetate solution reaching the requirements of the International pharmacopoeia.

The main parameters of PZC based Tc-99m generator were stated as follows: Mo-adsorption capacity of higher than 250 mgMo/g PZC and Tc-99m elution yield of higher than 80% were found with PZC adsorbent. Mo-99 breakthrough of lower than

0.015% for a generator system of Mo-99 PZC column coupled with a clean-up

Alumina column and Molybdenum element breakthrough of around 5 µg Mo/ml were found in Tc-99m eluate.

The procedures and relevant Tc-99m generator designs for the preparation of PZC based Tc-99m generators were successfully set up.The columns of from 1.0 gram to 4.0 gram weight of PZC and from 200 mCi to 1000 mCi Mo-99 can be used to produce portable , chromatographic type Tc-99m generators which have a good performance for application in clinical investigations.

Among the established procedures the column pre-loading procedure was highly evaluated , because it proved to be prominent figures for easy and safe operation , for low cost of technology facilities and equipment and for the capability to match the traditional technology of the fission Mo-99 based Tc-99m generator production.

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