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PREPARATION OF A STERILE CLOSED SYSTEM ^{99m}Tc GENERATOR BASED ON ZIRCONIUM MOLYBDATE

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A procedure for preparation of a sterile closed system generator for ^{99m}Tc based on conversion to zirconium molybdate of ^{99}Mo produced by neutron activation is reported. The generator is sterilized by autoclaving. ^{99m}Tc is eluted using 0.9% NaCl with high yield and purity in successive elutions.

INTRODUCTION

^{99m}Tc labelled radiopharmaceuticals find extensive applications in diagnostic nuclear medicine[1,2]. ^{99m}Tc is supplied in the form of a generator in which it is separated from the parent ^{99}Mo, most commonly by column chromatography, over alumina and less widely by solvent extraction or sublimation[3]. Generators based on column chromatography have several advantages over the other methods for use in hospital radiopharmacy. These include:

- ability to incorporate in a closed system for maintenance of sterility,

- simple operation and hence little chances of bacterial contamination,
- less radiation dose to the operator,
- less time consuming and hence less decay losses of ^{99m}Tc and
- ^{99m}Tc can be obtained more than once in a day resulting in more efficient use.

However, the chromatographic generators based on adsorption of molybdate on substrates like alumina have a limited capacity for molybdate. Hence, they require high specific activity ^{99}Mo produced by neutron irradiation in high flux reactors or by the technologically complex process of separation from fission products. This has forced countries having low and medium flux reactors like India to opt for alternate methods like solvent extraction[4] which involves several steps and difficult to completely automate. The concept of converting directly the low and medium specific activity ^{99}Mo into insoluble substrates that can be eluted in a column was first tried by Levi et al.[5] in the form of ammonium phosphomolybdate and later more successfully by Evans et al. by conversion to zirconium molybdate[6]. The authors report here the preparation of a compact closed system sterile ^{99m}Tc generator based on conversion of ^{99}Mo produced by neutron irradiation, into an insoluble zirconium molybdate matrix.

Preparation of ^{99m}Tc generator

3 g of MoO_3 /E. Merck, GR/ was irradiated in the CIRUS reactor for a week at a flux 10^{13} n $cm^{-2}s^{-1}$. After irradiation it was dissolved in 20 cm^3 of 2M NaOH with slight warming. This was added dropwise to a solution of 6.5 g of zirconium oxychloride /$ZrOCl_2.8H_2O$/ /BDH, GR/ in 80 cm^3 water. The whole mixture was stirred with a

magnetic stirrer. A thick white jelly formed was kept stirred for about half an hour. The precipitate was filtered over a Whatman filter paper on a Buchner funnel, washed well with water and air dried. The precipitate along with the paper was rolled inside a thin aluminium foil and heated at 105 ^{o}C or 200 ^{o}C in a specially fabricated horizontal furnace controlled by a dimmer-stat. The dried zirconium molybdate /ZrM/-^{99}Mo was powdered to small grains in an agate mortar and pestle. This was transferred over an inactive bed of 5 g of hydrous zirconium oxide /100-200 mesh, Biorad Laboratories/ in a glass column. The glass column had a narrower end at the bottom to which a plastic tube with a needle was attached. A G-2 sintered disc was fitted close to the bottom to support the powdered material. The top end was finished like the mouth of 10 cm^3 serum vial so that it can be sealed with a rubber closure and aluminium cap. The elution of the column was carried out by attaching an evacuated vial to the needle and plastic tube at the bottom. The column loaded with ZrM was washed with about 15 cm^3 0.9% NaCl solution. It was then sealed in a polypropylene bag and sterilized by autoclaving in a steam steriliser at 15 psi for half an hour. After cooling, the column was housed in a lead shielding and eluted daily with 0.9% NaCl solution.

Performance checking of ^{99m}Tc generators

The ^{99}Mo activity in the column was measured directly in a dose calibrator on the first day and calculated on subsequent days using decay corrections. ^{99m}Tc activity eluted was measured in a dose calibrator and expressed as percentage of ^{99}Mo activity on the column. Elution profile of ^{99m}Tc was obtained by injecting 2 cm^3 volumes of 0.9% NaCl and individually eluting them in separate vials. The ^{99}Mo content was measured by counting 2 cm^3 ^{99m}Tc samples enclosed in a 4 mm lead container, integrating the count rate between 640 to 840 keV and comparing with standard ^{99}Mo samples. The radiochemical purity was measured by ascending paper chromatography with 85% methanol on a Whatman paper. The pH was measured with a pH meter using a combined electrode. The molybdenum content was measured by spectrophotometry as the thiocyanate complex[6]. The zirconium content was measured as the Arsenazo-III complex after extraction with thenoyl trifluoroacetone[7].

RESULTS

The precipitation of ^{99}Mo as zirconium molybdate under the conditions described /1:1 mole ratio/ was found to be quantitative. With other ratios of Zr:Mo, the precipitation of ^{99}Mo was found to be poorer. It was also affected by slight changes in the precipitation conditions such as alkalinity, total volume etc and these had to be strictly controlled to reduce loss of ^{99}Mo activity.

The ^{99m}Tc yield obtained from the generator under optimum conditions was better than 85%. The yield of ^{99m}Tc was found to depend almost entirely on the drying conditions. It was found that the drying could be carried out either at 105 ^{o}C or 200 ^{o}C for getting optimum ^{99m}Tc yield. However, duration of heating had to be carefully monitored to avoid overheating which resulted in poor yields. When heating at 105 ^{o}C even though it took longer time for drying slightly prolonged heating did not significantly reduce the ^{99m}Tc yields. On the other hand, heating at 200 ^{o}C considerably reduced the time of drying but to get a good ^{99m}Tc yield, the duration of drying had to be carefully monitored. Even slightly prolonged heating was found to result in drastically reduced ^{99m}Tc yields. The ^{99m}Tc yield initially obtained, which was largely dependent on the drying temperature and duration, was found to remain almost constant throughout the subsequent elutions. Sterilizing the column by autoclaving at 15 psi for 30 min did not significantly reduce the ^{99m}Tc yield. The ^{99m}Tc yield, radiochemical purity, pH, Mo content and Zr content on seven successive elutions of a typical sterile ^{99m}Tc generator prepared as described earlier are given in Table 1.

The ^{99m}Tc yields are comparable to alumina column type generators and are better than solvent extraction generators. The radiochemical purity was always higher than 98%, comparable to that of alumina column type generators and better than in solvent extraction generators. The pH of the ^{99m}Tc was about 7. The pH was found to depend on the amount of HZO used as an inactive bed, the amount of ZrM and the volume and pH of eluent. However, unlike in case of alumina type generators, the ^{99m}Tc yield or purity was not affected by the initial pH of the 0.9% NaCl. So by changing the pH of 0.9% NaCl used for elution suitably, the desired final pH can be obtained. The elution profiles of both ^{99m}Tc and ^{99}Mo are given in Fig. 1. The elution profile of ^{99m}Tc was sharp with a peak at 4 to 6 cm^3. The ^{99}Mo breakthrough per cm^3 was more or less constant indicating that it is due to the definite solubility of ZrM. The ^{99}Mo level could be reduced well below the permissible level of 0.015% /Ref. 9/ by using an inactive bed of HZO. Alumina also could be used for bringing down the level of ^{99}Mo. However, HZO was found to have a higher capacity than alumina to retain MoO_4^{2-} and be effective on repeated elutions.

TABLE 1

Performance checking of sterile ^{99m}Tc generator based on zirconium molybdate

Time since previous elution, d	^{99}Mo activity on the column, mCi	^{99m}Tc eluted, mCi	Yield, %	^{99}Mo content, %	pH	Zr content, cm^3	Mo content, cm^3	Rc purity, %
1	54	45.9	85	0.0001	7.0	<1 μg	<1 μg	99.2
1	42.12	36.2	81	0.0001	7.1	<1 μg	<1 μg	98.9
1	32.85	27.9	85	0.0003	6.9	<1 μg	<1 μg	99.5
2	19.99	17.6	88	0.0005	7.1	<1 μg	<1 μg	99.8
1	15.59	13.3	85	0.0003	7.0	<1 μg	<1 μg	99.8
1	12.16	10.5	86	0.0004	7.1	<1 μg	<1 μg	99.3
1	9.49	8.4	88	0.0003	7.0	<1 μg	<1 μg	99.5

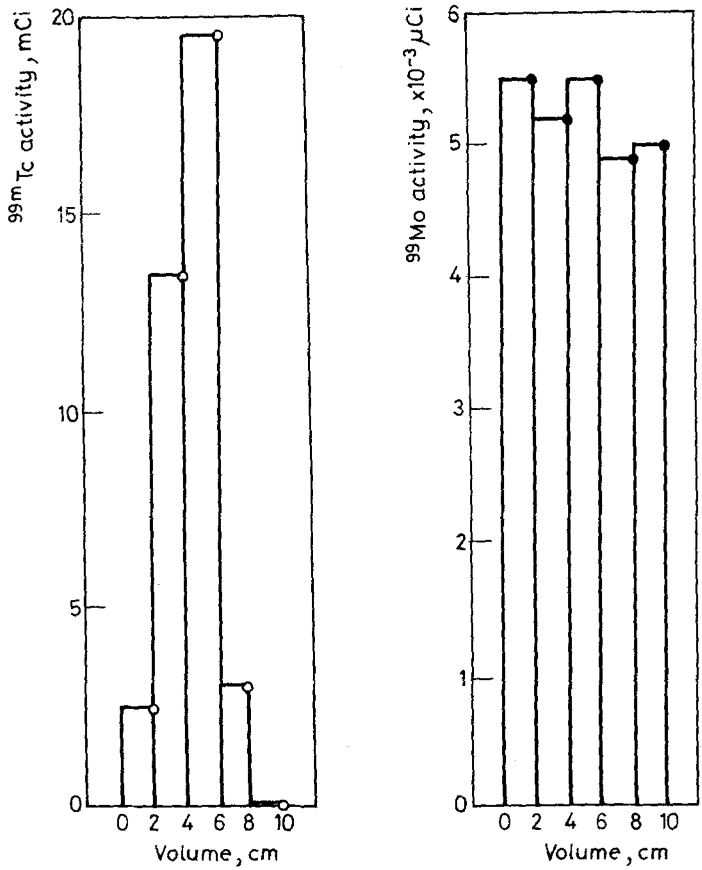

Fig. 1. Elution profile of ^{99m}Tc and ^{99}Mo from zirconium molybdate column

Alumina in the form of a disposable cartridge, one for each elution can be used with the same result. HZO probably retains MoO_4^{2-} by a mechanism different from simple adsorption as in case of PO_4^{3-} /Ref. 10/. It is the usual practice in case of other chromatographic generators to wash the column extensively to remove loosely bound activity. In case of the ZrM column washing was found unnecessary. On the contrary extensive washing may saturate the sites on HZO inactive bed and results in excess ^{99}Mo contamination in ^{99m}Tc. The Mo content of the eluent before passing through HZO was in the range of 100 ppm which reduced to less than 5 ppm after passage through HZO. The zirconium content was also less than 5 ppm estimated colorimetrically. This level of zirconium is tolerated in intravenous injections of ^{113m}In /Ref. 11/. The sterility of ^{99m}Tc samples tested by pharmacopeal methods was found satisfactory. In conclusion, the quality of ^{99m}Tc obtained from this compact sterile ^{99m}Tc generator was found to meet all the requirements of ^{99m}Tc pertechnetate injection obtained from other generators as specified in various pharmacopea[9,12].

DISCUSSION

Zirconium molybdate is reported to be a cation exchanger[10] and its gel forming systems are reported[13]. It is reported to have a layered structure with the interlayer hydrogen bonds formed through the interagency of water molecules. The interlayer distances are reported to vary with the water content and hence with drying conditions. The ^{99m}Tc formed by decay of ^{99}Mo can be expected to be in the highest valence state as TcO_4^-. So the essential requirement to get high yield of ^{99m}Tc is to have an interlayer distance which will allow free diffusion of $^{99m}TcO_4^-$ ion. The drying conditions, which determine the water content and hence the interlayer distance, were found to be the main factors affecting the ^{99m}Tc yield[14] and hence have to be very carefully controlled.

While incorporating the simplicity and safety of an alumina column type generator, the ZrM column overcomes the problem of limited capacity of alumina. For a 0.01% ^{99}Mo breakthrough an alumina capacity of 2 mg of Mo per gram of alumina is reported at neutral pH[15]. Assuming a practical size column of 15 g of alumina, 30 mg Mo can be loaded safely. If 1 curie ^{99}Mo generators have to be prepared with such a system, a ^{99}Mo specific activity of greater than 30 Ci per gram is required. ^{99}Mo of such high specific activity can be produced by irradiation of molybdenum greater than 95% enriched in ^{98}Mo at a neutron flux of greater than 10^{15} n $cm^{-2}s^{-1}$ or by separating carrier-free ^{99}Mo from fission products. Use of fission product ^{99}Mo seems to be the general trend in various centres even though it requires special remote processing and waste disposal facilities. Control of alpha contamination and long lived fission product contamination in the ^{99}Mo is also a difficult problem. ^{99m}Tc generators based on ZrM seem to be a simpler alternative well within the reach of countries possessing medium and low flux reactors. Using ^{99}Mo of specific activity 200-300 mCi per gram produced in the CIRUS reactor /maximum flux 6.5×10^{13}/ sterile column type ^{99m}Tc generators of 1 curie ^{99}Mo activity can be produced using the zirconium molybdate process.

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