JP0450627

JAERI－Conf 2004－010

1.12 PERFORMANCE TESTS ON NEW CHROMATOGRAPHIC MATERIAL FOR ^{99}Mo-^{99m}Tc GENERATORS[1]

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ABSTRACT

Technetium-99m continues to be the main workhorse of nuclear medicine in the Philippines. Almost 13TBq of ^{99m}Tc was imported to the country in 2002 supplied as ^{99m}Tc-^{99}Mo generators. These generators make use of fission molybdenum adsorbed onto an alumina column. Problems associated with the alumina chromatographic generators arise due to safety and economic issues that would be remedied by gel-type generators using low specific activity reactor-produced molybdenum-99 adsorbed on a high capacity gel column material. The Philippine Nuclear Research Institute (PNRI) exerted efforts in this direction by developing a gel-type column, which showed satisfactory molybdenum adsorptive capacity. Likewise, Kaken Co. in Japan in cooperation with Japan Atomic Energy Research Institute (JAERI) developed a dried form of a gel-type polyzirconium compound (PZC). It is a ready-to-use high molybdenum capacity column material for adsorbing reactor-produced molybedum-99. The performance of this material is being tested under the framework of the FNCA project on Research Reactor Utilization.

Performance tests on four batches of PZC were performed using fission molybdenum eluted from a ^{99}Mo-^{99M}Tc generator. A total of 3.3 GBq ^{99}Mo was extracted from an alumina column of a commercial generator and mixed with carrier molybdenum solution. About 0.67 GBq was loaded into each of the 12 x 90 mm column. One batch was prepared and distributed in 1999 and tests showed very poor elution yield of 30%. Three recent batches of PZC (2002) gave elution yields of 71% (Range of 69-75). The adsorptive capacity is 99% with about 4% desorption rate. Elution volume is at 5-6 ml. Daily elution for five days gave from 1.6 to 5.5% variability. The tests were performed all at the same time and a trend of improving elution yield and consistency of daily elution yield was observed with the time of testing nearer to the sample preparation date.

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[1] *Paper presented during the 2002 FNCA Workshop on the Utilization of Reasearch Reactors, Serpong, Indonesia, 13-17 January 2003*

X-ray diffraction analysis showed an amorphous structure for all three batches although PZC020522 showed the presence of a small amount of crystalline structure in the sample. X-ray fluorescence analysis gave about 40% zirconium in the sample.

These results need to be compared with the results of tests obtained at higher activity of molybdenum-99 to determine any radiation effect that may affect the elution behavior of the column material. The rate of decomposition of the gel, which is affecting its performance characteristics, needs to be defined.

I. INTRODUCTION

Technetium-99m (^{99m}Tc) remains as the main workhorse of nuclear medicine in the country. Alone or conjugated with other ligands, it is being used to show the function of major organs and other tissues such as the lung, brain, kidney, liver and bone. A three-year profile of imports of radioisotopes used as radiopharmaceutical is shown in Table 1. In addition, radioactive sources like Ir-192, Cs-137, I-125 and Sr-90 have been used in brachytherapy.

Table 1. List of Radioisotopes used in Nuclear Medicine from 2000 to 2002, in GBq[2]

Radioisotope	2000	2001	2002
Tc-99m	9.76 x 10^3	10.76 x 10^3	12.78 x 10^3
I-131 (solution and capsule)	3.55 x 10^3	5.00 x 10^3	6.11 x 10^3
I-131 (mIBG)	-	1.0 x 10^{-1}	3.54 x 10^{-1}
I-125 (RIA kits)	2.45	1.3	1.27
Tl-201	1.52 x 10^2	1.54 x 10^2	2.5 x 10^2
Ga-67	1.9	2.12	4.14
In-111	3.22 x 10^{-1}	-	-
Sm-153	-	2.5	-

About 13 TBq of ^{99m}Tc was imported in bulk as ^{99}Mo-^{99m}Tc in 2002. There are 21 hospitals with nuclear medicine facilities including a gamma scanner, most of which are located in MetroManila. Last year, St. Luke's Medical Center in Metro Manila, launched the first and only Positron Emission Tomography Scanner (P.E.T.) in Southeast Asia. Unlike conventional scans like the Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) that only provide images of organ anatomy or structures, P.E.T. can provide a direct measure of biochemistry and functional activity. At present, a cyclotron-produced Fluorine-18 FDG is used as the radioactive tracer. However, the key benefits associated with the use of technetium-99m including its lower cost in relation to Fluorine-18 FDG (PET) will continue the increasing use of ^{99m}Tc in nuclear medicine applications.

The imported commercial ^{99}Mo-^{99m}Tc generator makes use of fission product molybdenum-99 immobilized on an alumina (Al_2O_3) column. Problems associated with the alumina chromatographic generators arise due to complex and expensive technology involved in the production of both fission molybdenum as well as the generators. Added to this is the complex management of toxic fission product wastes generated in the preparation of ^{99}Mo The safety and economic issues could be remedied by gel-type generators using low specific activity reactor-produced molybdenum-99 adsorbed on a high capacity column material.

[2] Import data provided by the Licensing Section, NRLSD, PNRI.

Alternatively, ^{99}Mo can be incorporated into a gel matrix and the gel is used as the column material from which Technetium-99m is eluted. This latter approach was explored at the Philippine Nuclear Research Institute (1).

Zirconium molybdate gel was prepared by mixing molybdenum oxide with tracer amounts of ^{99}Mo. Several procedures were tried (2,3) and the products were characterised mainly for crystal structure by x-ray diffraction analysis, Zr:Mo ratio and Zr and Mo contents by x-ray fluorescence spectrometry. It was noted that the products obtained varied in the ease with which the gel can be filtered, washed and dried. It was also observed that the structure of the zirconium molybdate gel depends on one or more critical factors most important of which is the pH of the reaction mixture. An amorphous structure was found desirable for good elution yield.

Kaken Co. in Japan in cooperation with Japan Atomic Energy Research Institute (JAERI) developed a dried form of a gel-type polyzirconium compound (PZC). It is a ready-to-use high molybdenum capacity column material for adsorbing reactor-produced molybedum-99.

II. PERFORMANCE TESTS ON PZC

Three batches of PZC, 5 grams each, were sent by mail to PNRI during the year 2002 (Table 2). The performance of these materials was tested under the framework of the Forum of Nuclear Cooperation in Asia (FNCA) project on Utilization of Research Reactor. This activity was agreed upon in the previous working group meeting held in China in November 2001.

Table 2. PZC samples received and tested in November 2002

Lot no.	Quantity, grams	Date received	Sample code used
99P-1007	5	October 1999	PZC1
PZC020319	5	April 2002	PZC2
PZC020522	5	August 2002	PZC3
PZC020806	5	October 2002	PZC4

The tests should have been conducted upon receipt of the material, but due to logistical problems associated with the availability and use of high activity molybdenum-99, the tests were conducted all at one time (November, 2002) and using fission molybdenum-99 extracted from a commercial generator. A batch of PZC sent in 1999 (table 2), although way past the expiration date, was included in the test. Molybdenum-99 activity put into each column was 6.7 MBq (18 millicurie).

Stock Molybdenum and Tracer Solution
Four grams of molybdenum oxide was dissolved in 10 ml of 6M NaOH and diluted to 20 ml (130 mg/ml). Fission molybdenum was extracted from the alumina column of an imported generator (Nexta, South Africa, 150 GBq at calibration date) using 10 ml of 1:1 NH_3 solution. The extract contains about 3.3 GBq (90 mCi) of ^{99}Mo.

Adsorption of molybdenum
Two (2) ml of the stock molybdenum solution and two (2) ml of the radioactive molybdenum solution with 0.67 GBq (18 mCi) were mixed with one (1) gram of PZC sample (one trial per

batch). The pH of the mixtures was adjusted to nearly neutral pH and then equilibrated in a 90°C water bath for three (3) hours. The mixtures were lightly mixed by shaking the flask by hand intermittently during equilibration. At the end of three hours one (1) ml of the solution from the mixture was taken for molybdenum gamma measurement. The corresponding same amount of the original Mo-99 solution was counted and used as reference value for calculating the amount of molybdenum taken up by the adsorbing material.

Packing of column
The floating fine particles were removed by decantation before packing into a propylene column (12mm x 90mm). The columns were washed five times with five 10-ml saline solutions to remove free molybdenum and zirconium.

Elution yield determination
After allowing radioactive growth for 24 hours, ^{99m}Tc was eluted with 10-ml saline solution. The ^{99m}Tc activity was measured using an isotope calibrator (Victoreen CALRAD). The elution yield was calculated by comparing the activity of ^{99m}Tc with the theoretical amount of ^{99m}Tc resulting from the decay of ^{99}Mo adsorbed in the column. (Check calculations). The elution yield was measured for 5 consecutive days.

Desorption rate (molybdenum breakthrough)
The desorption rate was measured using one (1) ml of the technetium eluate. Molybdenum activity at 739 KeV was measured by gamma spectrometry using a germanium detector. The molybdenum activity corrected for PZC absorption factor was used as reference.

Elution volume
The elution profile for each column was determined by successive elution of 10 one-ml portions.

Structural analysis and zirconium content determination
Using a Xray diffractometer (Cu anode, Siemens x-ray generator, Phillips goniometer) the structure of the material was determined. The zirconium content was measured by XRF method (Kevex EDX-771)

III. RESULTS AND DISCUSSIONS

The results of the tests performed on the four batches of PZC samples are summarised in Table 3. Due to logistical limitations, only one trial for each batch had been performed. The tests were performed all at the same time and a trend of improving elution yield and consistency of daily elution yield was observed with the time of testing nearer to the sample preparation date.

The elution yield is presented graphically in Figure 1 for the four samples while Table 4 gives the daily elution yield values for the PZC samples. Figure 2 shows graphically the elution volume for each sample.

Table 3. Column properties of the PZC samples

Sample ID (Code)	% Mo Absorption	% Mo Desorption	%Elution Yield 5 days avg.	Elution Volume,ml
99P-1007 (PZC1)	97	ND	30 ± 2	6
PZC020319 (PZC2)	99	3.8	69 ± 3	5
PZC020522 (PZC3)	99	4.0	72 ± 3	5
PZC020806 (PZC4)	99	4.2	75 ± 1	5

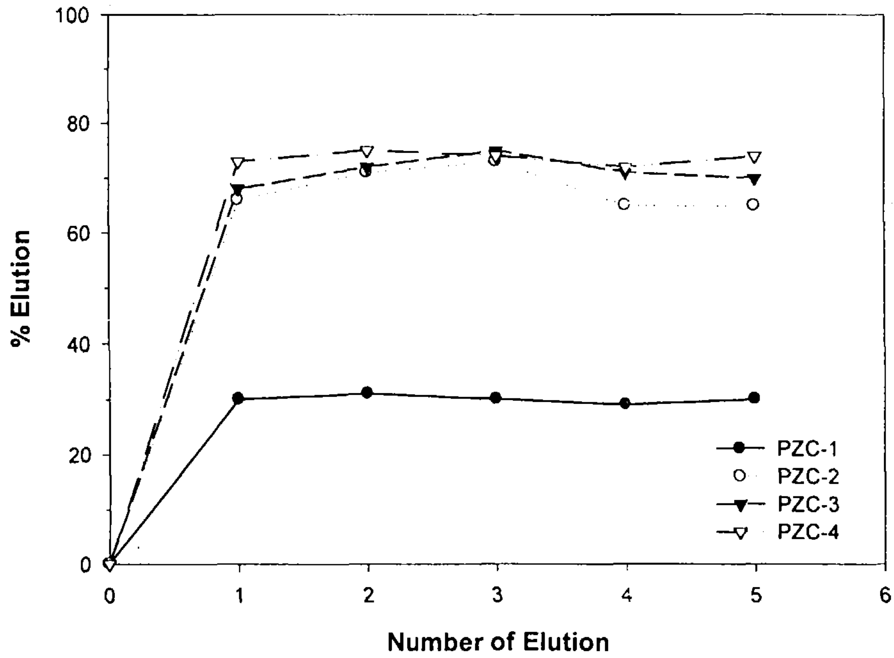

Figure 1. The elution yield of the PZC generators (2002) averages at 72%.

Table 4. Per cent elution yield and elution volume for each of the samples

Sample Code	Elution day					Avg. Elution Yield (%)	Elution Volume, ml
	1	2	3	4	5		
PZC1	30	30	30	29	30	30 ± 2	6
PZC2	66	73	73	65	65	69 ± 3	5
PZC3	68	75	75	71	70	72 ± 3	5
PZC4	73	74	74	72	74	75 ± 1	5

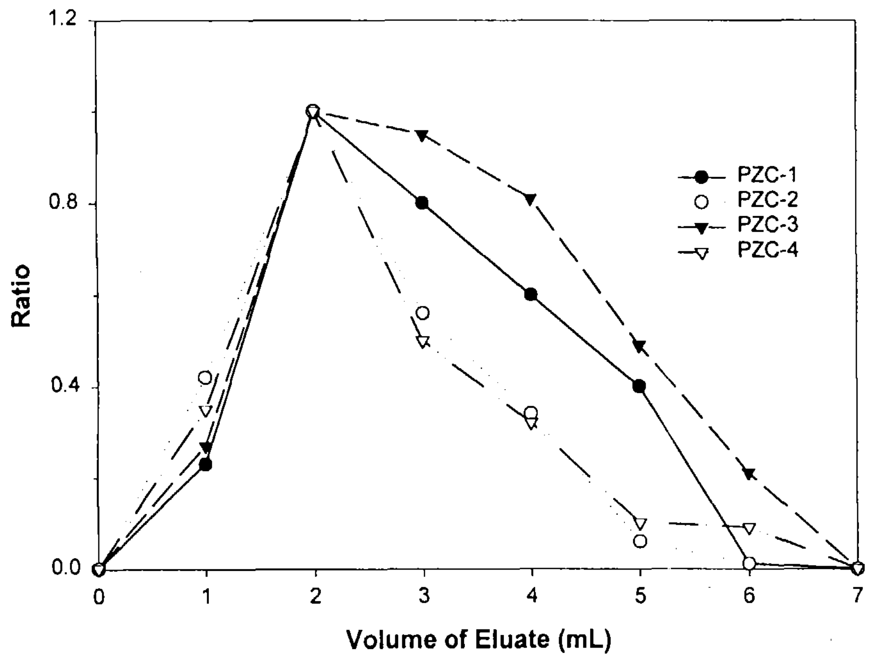

Figure 2. A five-ml saline is generally sufficient to elute the available technetium-99m from the column

The tests results of the first sample received by PNRI and which was distributed and tested in 1997 gave similar results (1). The average cumulative yield obtained (5 trials) was 73.5 ± 3.6% and the average day-to-day elution yield is 70.2 ± 1.7 %. Radiochemical assays (%pertechnetate) were performed by paper chromatography in methanol:water (75:15). The radiochemical purity of the eluate was >97%. The molybdenum-99 tracer was at nanocurie level and was also obtained from a commercial generator.

The zirconium content and structure of the samples are summarised in Table 5. Figure 3 shows the XRD patterns of the samples including that of pure ZrO. The samples were amorphous. PZC3 showed some unidentified peaks.

Table 5. Structure and zirconium content of the PZC samples

Sample ID (Code)	% Zirconium	Structure
99P-1007 (PZC1)	42	amorphous
PZC020319 (PZC2)	42	amorphous
PZC020522 (PZC3)	43	amorphous
PZC020806 (PZC4)	38	amorphous

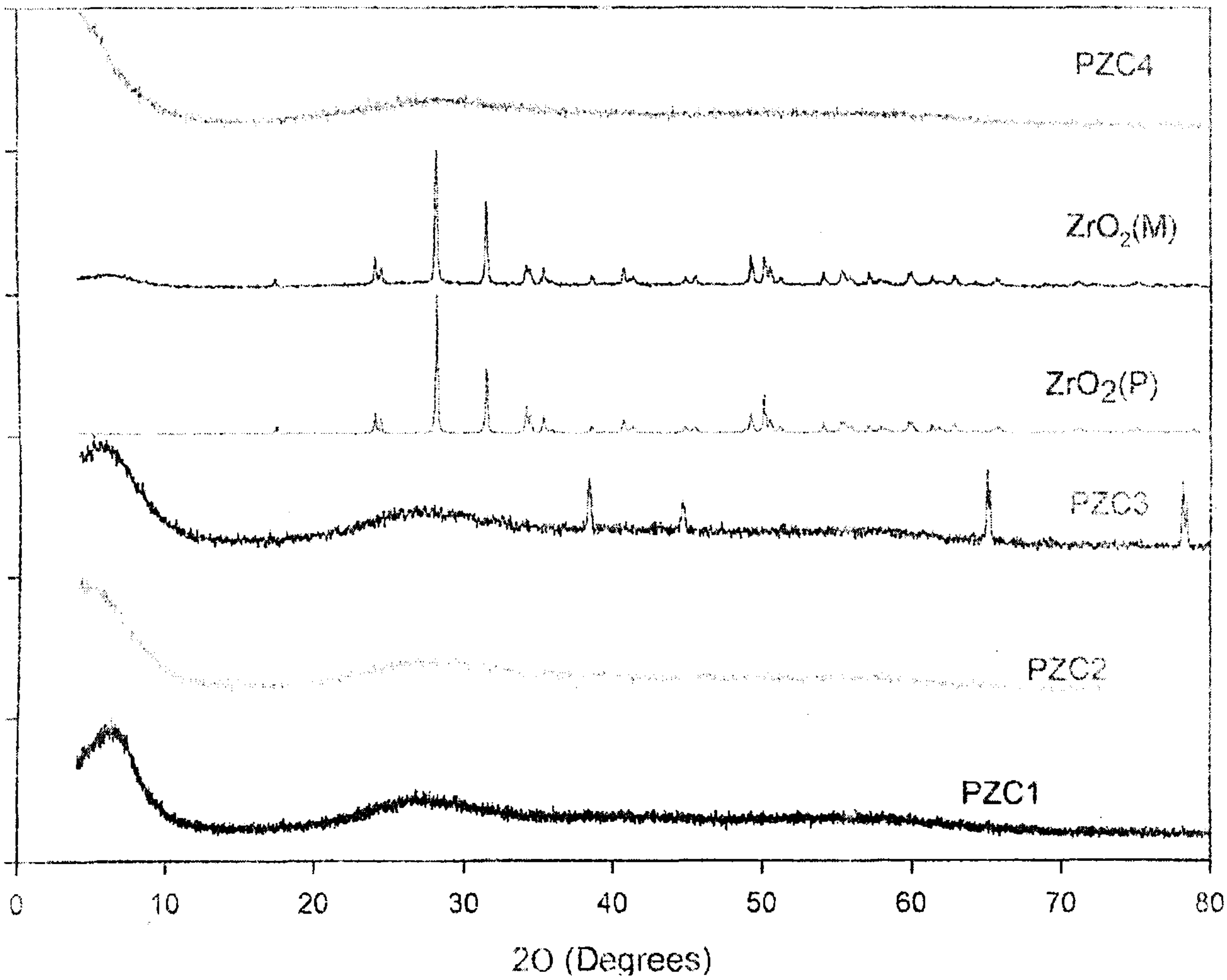

Figure 3. The PZC samples are amorphous although PZC3 exhibits some unidentified peaks.

IV. CONCLUSION

Recognizing the importance of ^{99m}Tc and ^{99m}Tc-based radiopharmaceuticals in nuclear medicine, the Philippine Nuclear Research Institute has initiated research on the development of column-type generators for ^{99m}Tc using reactor-produced ^{99}Mo. The concept is to incorporate low specific activity ^{99}Mo produced by the n,gamma reaction (with natural molybdenum as target material) into a zirconium molybdate gel matrix. This gel will serve as the column material from which the ^{99m}Tc is eluted. The advantage lies in the larger amount of molybdenum in the column material (40%maximum) compared with that of alumina currently in use (2%). This compensates for the lower specific activity attainable in the irradiation of natural molybdenum.

Although the process has been found useful for the preparation of commercial generators in some countries, the gel technology, as described, has several disadvantages: cumbersome procedures of filtering and drying of the gel, greater radiation hazard, dependence on operator skill, and long time required for the preparation. The availability of a pre-formed gel column material on which molybdenum can be adsorbed and from which technetium-99m can be eluted consistently and at high yield is a better option.

The results obtained for PZC, although limited in number of trials and the level of molybdenum activity loaded into the column, showed that the column holds promise as molybdenum column material for the generator. If the generator using this column can be available at lower cost, it is reasonable to project an increasing utilization of technetium-99 in medical applications in the country.

ACKNOWLEDGMENT
We wish to thank Syncor, Philippines for providing us with the spent commercial generators that we used for this study, the Irradiation Services Section for allowing the use of their isotope calibrator, the Applied Physics Research Section for the XRD analysis and the Analytical Measurement Research Section for the XRF analysis.

V. REFERENCES

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