



INTERNATIONAL ATOMIC ENERGY AGENCY

1

INTERNATIONAL SYMPOSIUM ON MODERN TRENDS IN RADIOPHARMACEUTICALS FOR
DIAGNOSIS AND THERAPY

Lisbon, Portugal, 30 March - 3 April 1998

IAEA-SM-355/35

CONF-980348--

Use of a New Tandem Cation/Anion Exchange System with Clinical-Scale
Generators Provides High Specific Volume Solutions of Technetium-99m and
Rhenium-188

§ F. F. (Russ) Knapp, Jr., § A. L. Beets, § S. Mirzadeh, and §,¶ S. Gohlke, § Nuclear Medicine
Group, Oak Ridge National Laboratory (ORNL), Oak Ridge, TN, U.S.A. and ¶ Clinic for
Nuclear Medicine, University of Bonn, Germany.

19980422 070

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

ph

MASTER

*The submitted manuscript has been authored
by a contractor of the U.S. Government under
contract No. DE-AC05-96OR22464.
Accordingly, the U.S. Government retains a
nonexclusive, royalty-free license to publish or
reproduce the published form of this
contribution, or allow others to do so, for U.S.
Government purposes.*

DTIC QUALITY INSPECTED

This is a preprint of a paper intended for presentation at a scientific meeting. Because of the provisional nature of its content and since changes of substance or detail may have to be made before publication, the preprint is made available on the understanding that it will not be cited in the literature or in any way be reproduced in its present form. The view expressed and the statements made remain the responsibility of the named author(s); the views do not necessarily reflect those of the government of the designating Member State(s) or of the designating organization(s). *In particular, neither the IAEA nor any other organization or body sponsoring this meeting can be held responsible for any material reproduced in this preprint.*

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

ABSTRACT

In this paper we describe the first application of our simple and inexpensive post-elution tandem cation/anion exchange column system which is based on generator elution with salts of weak acids such as ammonium acetate instead of saline solution to provide very high specific volume solutions of technetium-99m and rhenium-188 from clinical-scale molybdenum-99/technetium-99m generator prepared from low specific activity (n,y) molybdenum-99, and tungsten-188/rhenium-188 generators, respectively. Initial passage of the bolus through a strong cation exchange cartridge converts the ammonium acetate to acetic acid which is essentially not ionized at the acidic pH, allowing specific subsequent amine-type (QMA SepPak™) anion exchange cartridge column trapping of the microscopic levels of the pertechnetate or perrhenate. Subsequent elution of the anion cartridge with a small volume (< 1 mL) of saline then provides high specific volume solutions of technetium-99m by concentration of the high eluant volumes obtained by elution of clinical-scale (1 Ci) generators. This new approach also works very effectively to obtain high specific volume solutions of rhenium-188 (> 500 mCi/mL) from the alumina-based tungsten-188/rhenium-188 generator.

INTRODUCTION

Nuclear reactors play an important role in providing radioisotopes for both diagnostic and therapeutic applications in nuclear medicine and radionuclide generator systems [1-3] prepared from reactor-produced parent radioisotopes are attractive to obtain the daughter products at facilities remote from the production site. The availability of radionuclide generator systems continues to represent an important source of radioisotopes for applications in both diagnostic and therapeutic radioisotopes nuclear medicine. Chromatographic-type molybdenum-99/technetium-99m generators fabricated from fission-produced molybdenum-99 are widely used to obtain high specific volume solutions of technetium-99m. For therapeutic applications, the rhenium-188 radioisotope (half-life 16.9 hours; β_{max} 2.12 MeV ; 15% gamma 155 keV) has many attractive properties, since it is obtained carrier-free from the reactor-produced tungsten-188 parent (half-life 69 days). The tungsten-188/rhenium-188 generator is thus an attractive candidate for use in isolated clinical sites, in less developed countries and in a centralized radiopharmacy.

1. MATERIALS AND METHODS

General. All chemicals and reagents were analytical grade unless otherwise indicated. The > 86% enriched tungsten-186 was purchased from the ORNL Isotope Distribution Office. BioRad alumina was used as the generator adsorbant. Cation-exchange cartridges (IC-H Plus) were purchased from Alltech Associates (Deerfield, IL) and the QMA "Light" SepPak™ anion-exchange columns were obtained from Waters Corporation (Milford, MA). Generator columns were fitted with a coarse glass frit at the bottom under the alumina column. The columns were fitted with machined Teflon plugs on both top and bottom which were fitted with Luer locks for attachment to short lengths of arterial extension tubing. The molybdenum-99/technetium-99m generators (1 Ci) were purchased from Mallinckrodt Medical (St. Louis, MO).

Radionuclide Analyses. Radionuclide measurements were determined using a calibrated HpGe solid state detector (EG&G ORTEC, Oak Ridge, TN) coupled to a PC-based MCA (Nuclear Data/Canberra, Inc.). Samples of constant geometry were counted with low (< 5 %) deadtime. Data were analyzed using Nuclear Data Accu-Spec Spectroscopy software. Nuclear data were taken from Lederer and Shirley [4] and the radioisotope levels were determined by quantification of the following photo peaks: ¹⁸⁸Re, 155 keV (15%); ¹⁹²Ir, 316 keV (82.8%); ¹⁹¹Os 129 keV (25.9%), ^{99m}Tc 140 keV (89 %), ⁹⁹Mo 739.6 keV (12.1 %). The tungsten-188 levels were usually quantified by measurements of the 155 keV γ -ray from decay of the ¹⁸⁸Re daughter in the ¹⁸⁶W/¹⁸⁸Re equilibrium mixtures. Molybdenum-99 breakthrough was directly measured by analysis of the 739.6 keV photopeak. In some cases, direct measurement of the 227 keV (0.22%) and 290 keV (0.39%) γ -rays from decay of ¹⁸⁶W was possible after post elution "trapping" of the ¹⁸⁶W generator column breakthrough on an alumina (neutral) SepPak® as described earlier [5]. Routine generator elution yields were determined using a calibrated Capintec dose calibrator.

Reactor Production and Processing of Tungsten-188. Tungsten-188 was produced by irradiation of enriched tungsten-186 oxide targets in the ORNL High Flux Isotope Reactor (HFIR) at a thermal neutron flux of $2\text{-}2.5 \times 10^{15}$ neutrons per $\text{cm}^{-2}\text{sec}^{-1}$. The targets were processed by dissolution in 1 N NaOH solution in the presence of hydrogen peroxide as described earlier [6-7]. The specific activity of W-188 averaged 4-5 mCi/mg W-186 for a one cycle, 24-day irradiation.

Fabrication and Performance of the Tungsten-188/Rhenium-188 Generator. Following dissolution,

the sodium tungstate solution was acidified to pH 2-3 with 1 N HCl and adsorbed on a column of acid-washed BioRad alumina housed in a lead shield [7]. Generators were then conditioned by washing thoroughly with 100-200 mL of 0.9% saline by elution with a peristaltic pump at a flow rate of 1-2 mL/min and were then eluted with saline to determine the baseline elution yields. The generator system housed in a lead shield is illustrated in FIG. 1.

Generator Elution. Prior to elution of the generators with the ammonium acetate solutions, the generators were equilibrated with eluant by elution at a constant flow rate of 1-2 mL/min using a peristaltic pump.

Concentration of Technetium-99m and Rhenium-188 Generator Eluants Using the Tandem Cation/Anion Columns System. The typical set-up of the generator and elution and concentration systems are illustrated in FIG. 2. In order to minimize exposure, the system is used behind a leaded glass and/or Lucite shield. A short length of disposable extension tubing is attached to the lower Luer outlet connection of the generator. Inclusion of an in-line 0.22 micron Millipore filter ensures trapping of any alumina fines or other particles which may be eluted from the generator. The in-line alumina SepPak™ traps the low levels of tungsten-188 parent breakthrough [5]. The tandem cation/anion concentration system (FIG. 2) consists of a commercially available cation exchange cartridge with a capacity of 2-4 milliequivalents attached to a three-way stopcock connected at the outlet to the QMA SepPak® anion-exchange column. Another length of extension tubing then connects the outlet of the anion exchange column to the rhenium-188 collection vessel which is housed in a lead or Lucite shield. With the stopcock open the generator is eluted with 12-15 mL of 0.9% saline. The eluant collected from the QMA column contains only low levels of radioactivity and is discarded. The stopcock is then adjusted to permit elution of technetium-99m Na-pertechnetate or rhenium-188 Na-perrhenate from the QMA anion trapping column with 0.9 mL of 0.9% saline.

2. CONCEPT OF THE TANDEM CATION/ANION CONCENTRATION OF SOLUTIONS OF SALTS OF WEAK ACIDS

Because tungsten-188 is produced [6-7] with relatively low specific activity in most research reactors (typically < 5 mCi/mg W-186), the large amounts of alumina required to bind the low specific activity tungsten-188 parent results in high elution volumes and low specific volume

solutions of rhenium-188. Simple effective methods are thus required for concentration of the generator eluant to the high specific volumes required for radiopharmaceutical labeling and for other applications. Our development of a very new simple method using a tandem cation/anion exchange column concentration system (FIG. 1) for the efficient concentration of rhenium-188-perrhenate and technetium-99m-pertechnetate makes the availability of high specific volume solutions of carrier-free rhenium-188 feasible and extends the generator shelf-life to several months. Our preliminary results [8] have demonstrated that concentration is readily feasible on an experimental scale and we now demonstrate the effectiveness of this new approach for the multiple elution of clinical-scale tungsten-188/rhenium-188 (500 mCi) and molybdenum-99/technetium-99m (1 Ci) generators.

3. CONCENTRATION OF RHENIUM-188 SOLUTIONS FROM THE TUNGSTEN-188/ RHENIUM-188 GENERATOR

For these studies, the generators were initially eluted with 0.9% saline for control elution yields, and then equilibrated with the ammonium acetate (NH_4OAc) eluant solution. Yield values were determined using a dose calibrator. Following elution of a clinical-scale tungsten-188/rhenium-188 generator (Table 1) with a salt of a weak acid such as ammonium acetate, the eluant is passed through a tandem ion exchange system consisting of an initial strong cation exchange column which transform the ammonium acetate to acetic acid, which is essentially unionized at this pH. Since the macroscopic levels of the acetate anion eluant have been transformed to an unionized form, subsequent elution through an anion column specifically traps the microscopic levels of the perrhenate anions with the principal non-radioactive volume passing through as waste. After adjustment of the intermediary three-way valve, and subsequent washing of the QMA anion column with water, the rhenium-188 perrhenate is then eluted from the anion column in < 1 mL of isotonic saline. This method provides high specific volume solutions of rhenium-188 sodium perrhenate over several weeks (Table 1).

4. CONCENTRATION OF TECHNETIUM-99m SOLUTIONS FROM THE MOLYBDENUM-99/TECHNETIUM-99m GENERATOR

We have now demonstrated that this approach also works well with clinical-scale 1 Curie molybdenum-99/technetium-99m generators (Table 1). Although fission-produced molybdenum-99

is exclusively used in western developed countries, the use of low specific activity molybdenum-99 to obtain technetium-99m has been known for many years with sublimation and solvent extraction methods for use when fission-produced molybdenum-99 is not available [9]. Our new concentration method, however, allows the use of alumina-based chromatographic generator methods for separation of carrier-free technetium-99m from low specific activity molybdenum-99. Data from a typical study are summarized in Table 1. In contrast to the ease of oxidation of reduced rhenium species to Re(VII), reduced technetium-99m species are apparently retained on the alumina column, and we have thus determined that the 0.3 M NH_4OAc generator eluant for elution of the molybdenum-99 generator must also contain low levels of a mild oxidizing agent such as 0.01 M NH_4NO_3 to maintain the reproducibly high elution yields of technetium-99m. Another advantage of our tandem concentration system is that the shelf-life of the molybdenum-99 generators can be extended indefinitely essentially until the molybdenum-99 parent has decayed. The obvious advantages of using neutron-activated molybdenum-99 include the absence of large amounts of highly radioactive waste and no need for highly enriched uranium-235.

Although elution yields are somewhat lower, this approach permits very good routine yields. Generator eluant volumes as high as 20 mL are readily concentrated to < 0.5 mL (40:1) and concentration factors are essentially unlimited, based on the size of the anion column and void volume of the tubing system, etc. By using this new method for simple eluant concentration, many reactors throughout the world can now be used for production of both tungsten-188 by double neutron capture on enriched tungsten-186 targets and molybdenum-99 by neutron activation of enriched molybdenum-98, making these generators routinely available at remote clinical sites in less developed regions to obtain the versatile rhenium-188 therapeutic radioisotope and technetium-99m for preparation of diagnostic agents.

SUMMARY AND CONCLUSIONS

The availability of our new simple and inexpensive tandem cation/anion exchange system in conjunction with use of salts of a weak acid such as 0.3 M ammonium acetate for elution of clinical-scale molybdenum-99/technetium-99m generators prepared from low specific activity (n,γ) molybdenum-99 and with tungsten-188/rhenium-188 generators is effective in providing high specific volume solutions of technetium-99m and rhenium-188. Although the yields are somewhat lower in comparison to use of the traditional 0.9 % (0.15 M) sodium chloride eluant, this new method can be

used indefinitely with no apparent decrease in daughter yields with time and continued low parent breakthrough and should allow the widespread use of these generators.

ACKNOWLEDGMENTS

Research at ORNL sponsored by the U.S. Department of Energy under contract AC05-96OR22464 with Lockheed Martin Energy Research Corporation.

REFERENCES

- [1] KNAPP, F. F., Jr., MIRZADEH, S., The Continuing Important Role of Radionuclide Generator Systems for Nuclear Medicine, *Eur. J. Nucl. Med.* 21 (1994) 1151-1166.
- [2] MIRZADEH S. AND KNAPP F. F. JR., Biomedical Radioisotope Generator Systems," *J. Radioanalyt. Nucl. Chem.* 203 (1996) 471-488.
- [3] LAMBRECHT R. M., TOMIYOSHI K., SEKINE T., Radionuclide Generators," *Radiochim. Acta* 77 (1997) 103-121.
- [4] LEDERER C. M. AND SHIRLEY V. S. (Editors), "Table of Isotopes," 7th Edition, Wiley Pub., New York (1978).
- [5] CALLAHAN A. P., RICE D. E., MCPHERSON D. W. AND KNAPP F. F. JR., The Use of Alumina SepPaks™ As a Simple Method for the Removal and Determination of Tungsten-188 Breakthrough from Tungsten-188/Rhenium-188 Generatoes, *Int. J. Appl. Radiat. Isot.* 43 (1992) 801-804.
- [6] CALLAHAN A. P., RICE D. E., AND KNAPP F. F. JR., Rhenium-188 for Therapeutic Applications from an Alumina-Based Tungsten-188/Rhenium-188 Generator, *NucCompact* 20 (1989) 3-6.

- [7] KNAPP, F. F., Jr., CALLAHAN, A. P., BEETS, A. L., MIRZADEH, S. AND HSIEH, B.-T., Processing of Reactor-Produced Tungsten-188 for Fabrication of Clinical Scale Alumina-Base Tungsten-188/Rhenium-188 Generators, *Appl. Radiat. And Isot.* 45 (1994) 1123-1128.
- [8] GUHLKE, S., BEETS, KNAPP, F. F., JR. AND BIRSACK, H.-J., Elution of Re-188 from W-188/Re-188 Generators with Salts of Weak Acids Permits Efficient Concentration to Low Volumes Using a New Tandem Cation/Anion Exchange System, *J. Nucl. Med.* 38 (1997) 125P (Abstract).
- [9] BOYD, R. E., Molybdenum-99:Technetium-99m Generator, *Radiochim. Acta* 30 (1982) 123-145.

FIGURE LEGENDS

FIG 1. Schematic of the generator elution and tandem concentration system.

FIG 3. Detailed schematic of the tandem cation/anion tandem system used for concentration of low specific volume solutions of technetium-99m and rhenium-188 illustrating the chemical transformations on which the concept of using the salt of a weak acid for generator elution is based.

Table 1. Average yields of rhenium-188 and technetium-99m obtained by elution of clinical-scale generators with 0.3 M ammonium acetate solution.

Tungsten-188/Rhenium-188 Generator		Molybdenum-99/Technetium-99m Generator	
0.9 % NaCl Eluant	0.3 M NH ₄ OAc Eluant, pH 5.5	0.9% NaCl Eluant	0.3 M NH ₄ OAc Containing 0.01 M NH ₄ NO ₃ Eluant, pH 5.2
n = 3 Elutions Yield = 70.9±9.9 %	n = 31 Elutions Over > 3 Month Period Yield = 62.6±14.4 %	n = 8 Elutions Yield = 84.2±1.2%	n = 20 Elutions Over > 7 Day Period Yield = 69.±1.2%

M98003387



Report Number (14) ORNL/CP-96890
CONF-980348 --

Publ. Date (11) 199803
Sponsor Code (18) DOE/ER, XF
UC Category (19) UC-400, DOE/ER

DOE