TECHNICAL REPORTS SERIES no. 470

Therapeutic Radionuclide Generators: ^{90}Sr/^{90}Y and ^{188}W/^{188}Re Generators

IAEA
International Atomic Energy Agency

THERAPEUTIC RADIONUCLIDE GENERATORS: ^{90}Sr/^{90}Y AND ^{188}W/^{188}Re GENERATORS

The following States are Members of the International Atomic Energy Agency:

AFGHANISTAN	GREECE	OMAN
ALBANIA	GUATEMALA	PAKISTAN
ALGERIA	HAITI	PALAU
ANGOLA	HOLY SEE	PANAMA
ARGENTINA	HONDURAS	PARAGUAY
ARMENIA	HUNGARY	PERU
AUSTRALIA	ICELAND	PHILIPPINES
AUSTRIA	INDIA	POLAND
AZERBAIJAN	INDONESIA	PORTUGAL
BAHRAIN	IRAN, ISLAMIC REPUBLIC OF	QATAR
BANGLADESH	IRAQ	REPUBLIC OF MOLDOVA
BELARUS	IRELAND	ROMANIA
BELGIUM	ISRAEL	RUSSIAN FEDERATION
BELIZE	ITALY	SAUDI ARABIA
BENIN	JAMAICA	SENEGAL
BOLIVIA	JAPAN	SERBIA
BOSNIA AND HERZEGOVINA	JORDAN	SEYCHELLES
BOTSWANA	KAZAKHSTAN	SIERRA LEONE
BRAZIL	KENYA	SINGAPORE
BULGARIA	KOREA, REPUBLIC OF	SLOVAKIA
BURKINA FASO	KUWAIT	SLOVENIA
BURUNDI	KYRGYZSTAN	SOUTH AFRICA
CAMEROON	LATVIA	SPAIN
CANADA	LEBANON	SRI LANKA
CENTRAL AFRICAN	LIBERIA	SUDAN
REPUBLIC	LIBYAN ARAB JAMAHIRIYA	SWEDEN
CHAD	LIECHTENSTEIN	SWITZERLAND
CHILE	LITHUANIA	SYRIAN ARAB REPUBLIC
CHINA	LUXEMBOURG	TAJIKISTAN
COLOMBIA	MADAGASCAR	THAILAND
COSTA RICA	MALAWI	THE FORMER YUGOSLAV
CÔTE D'IVOIRE	MALAYSIA	REPUBLIC OF MACEDONIA
CROATIA	MALI	TUNISIA
CUBA	MALTA	TURKEY
CYPRUS	MARSHALL ISLANDS	UGANDA
CZECH REPUBLIC	MAURITANIA	UKRAINE
DEMOCRATIC REPUBLIC	MAURITIUS	UNITED ARAB EMIRATES
OF THE CONGO	MEXICO	UNITED KINGDOM OF
DENMARK	MONACO	GREAT BRITAIN AND
DOMINICAN REPUBLIC	MONGOLIA	NORTHERN IRELAND
ECUADOR	MONTENEGRO	UNITED REPUBLIC
EGYPT	MOROCCO	OF TANZANIA
EL SALVADOR	MOZAMBIQUE	UNITED STATES OF AMERICA
ERITREA	MYANMAR	URUGUAY
ESTONIA	NAMIBIA	UZBEKISTAN
ETHIOPIA	NEPAL	VENEZUELA
FINLAND	NETHERLANDS	VIETNAM
FRANCE	NEW ZEALAND	YEMEN
GABON	NICARAGUA	ZAMBIA
GEORGIA	NIGER	ZIMBABWE
GERMANY	NIGERIA	
GHANA	NORWAY	

THERAPEUTIC RADIONUCLIDE GENERATORS: ^{90}Sr/^{90}Y AND ^{188}W/^{188}Re GENERATORS

COPYRIGHT NOTICE

FOREWORD

Rapid progress in preclinical and clinical research realized over the past two decades has stimulated broad interest in the use of radionuclides for targeted therapy of cancer and for other therapeutic applications using unsealed sources. The use of radiopharmaceuticals labelled with short lived radioisotopes for these applications has advantages such as higher rates of dose delivery and shorter hospital stays. Wider use of targeted therapy using radiopharmaceuticals requires the reliable availability of cost effective products of short lived radionuclides from dependable sources and suppliers. The use of short lived radionuclides is thus often restricted to places with local production of these radionuclides or places that are well connected to production facilities. An important additional strategy is the use of radionuclide generator systems that utilize parent radionuclides with long physical half-lives of months or years. The daughter can be extracted from these radionuclide generators at periodic intervals to obtain short lived radionuclides for formulation of therapeutic radiopharmaceuticals. Hence, there is great interest in developing technologies for therapeutic radionuclide generators.

To address this need, the IAEA implemented a coordinated research project (CRP) on the development of generator technologies for therapeutic radionuclides. This publication is based on the work carried out at participating institutions in several Member States aimed at developing generator prototypes using various separation techniques. The two radionuclide generators described in this publication are based on ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generator systems. Strontium-90 has a physical half-life of over 28 years, and ^{188}W has a physical half-life of 69 days. Radionuclide generators prepared from these long lived parents can serve as convenient production systems to provide the therapeutic radioisotopes ^{90}Y and ^{188}Re on a routine basis. By adapting the technologies described in this publication, ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators can be fabricated for cost effective production of ^{90}Y and ^{188}Re for radiopharmaceutical preparation.

The IAEA thanks all the participants in the CRP for their contributions to this publication and F.F. Knapp, Jr., for his valuable help in editing this report. The IAEA officer responsible for this publication was M.R.A Pillai of the Division of Physical and Chemical Sciences.

EDITORIAL NOTE

CONTENTS

Chapter 1

INTRODUCTION

1.1. BACKGROUND

Radionuclide therapy using radiopharmaceuticals has been in existence for over 60 years and offers substantial benefits to cancer patients, in particular, patients suffering from thyroid cancer. Numerous clinical trials for treating other types of cancer using therapeutic radiopharmaceuticals are in progress, and their success will increase the demand for therapeutic radionuclides in the coming years. Those radioisotopes having short physical half-lives ranging from a few hours to a few days are useful for radionuclide therapy. The use of short lived radioisotopes for radionuclide therapy involves important challenges including the transport of the radionuclides and the need for frequent shipments. Radionuclide generators represent an efficient means for making short lived therapeutic radionuclides more widely available throughout the world.

To meet the requirements for sustained growth and future expansion of the application of therapeutic radiopharmaceuticals in nuclear medicine, particularly in oncology, it is important to develop and maintain a constant and reliable supply of therapeutic radionuclides of the required quality in the desired quantities. The IAEA has several activities to support programmes that foster the enhanced availability of therapeutic radionuclides and radiopharmaceuticals in Member States. One such activity was the coordinated research project (CRP) on the development of generator technologies for therapeutic radionuclides, which ran from 2004 to 2007, in which participants from 13 countries worked to develop generator technologies for the preparation of ^{90}Y and ^{188}Re usable for radionuclide therapy.

1.2. OBJECTIVE

The objectives of the CRP were:

(a) To develop reproducible methodologies for the preparation of ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators;
(b) To standardize quality control techniques for generator eluted therapeutic radionuclides;

(c) To optimize technologies for post-elution concentration of ^{188}Re;

(d) To prepare chromatography adsorbents having higher binding capacities and demonstrate their utility in the preparation of column generators.

The objective of this publication is to summarize the work done and the results achieved by the participating countries in the above areas.

1.3. SCOPE

This publication covers the results of the research undertaken in the development of ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators, studies on post-elution concentration of ^{188}Re, the use of higher capacity adsorbents based on zirconium and titanium composites, and analytical techniques developed for the quality control of generator produced radionuclides.

1.4. STRUCTURE

Chapter 2 of the report provides an overview of the CRP, the work accomplished in different laboratories and the project's achievements with respect to realizing the objectives set out at the beginning of the CRP.

Several protocols were developed by the participants, and some of these are sufficiently mature to be adapted by interested researchers. Chapter 3 details five such technologies developed during the course of the CRP. The details provided are sufficient for adaptation of the technologies in interested laboratories.

The main area of work under the CRP was the development of ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators. Chapters 4–10 summarize the results of the work on ^{90}Sr/^{90}Y generators undertaken by the different participants. Chapters 11–20 summarize the results of the work done on ^{188}W/^{188}Re generators, post-elution concentration of ^{188}Re and development of higher capacity adsorbents for ^{188}W, and provide details of the production of ^{188}W in a high flux research reactor.

Participants in the CRP published several papers in international journals and presented these data at national and international conferences. A list of journal publications by the participants is given in the end of the report as material for further reading.

Chapter 2

OVERVIEW OF THE CRP

2.1. INTRODUCTION

Radionuclide therapy using unsealed radioactive sources requires the reliable, cost effective availability of a variety of therapeutic radioisotopes. Therapeutic applications include the treatment of cancer, bone pain (palliation) and rheumatoid arthritis; bone marrow ablation; and inhibition of coronary restenosis. Radioisotopes of current interest for these applications include ^{131}I, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{166}Ho, ^{188}Re and ^{90}Y. Targeted therapy of cancer using radiopharmaceuticals generally requires the availability of high specific activity radioisotopes.

Radioisotopes having short physical half-lives ranging from a few hours to a few days are useful for radionuclide therapy. However, the use of short lived radioisotopes for radionuclide therapy has severe constraints, such as the need to supply a much larger amount in order to offset decay loss, difficulties associated with transport and the need for frequent shipments. All of these factors result in higher costs, especially for importation and distribution of therapeutic radionuclides. In many countries, radiopharmaceuticals using these short lived radionuclides often are not available owing to logistical considerations.

The use of radionuclide generators with long lived parent radionuclides offers an efficient means for making short lived therapeutic radionuclides readily available on an 'as needed' basis. A major advantage of generator produced radionuclides is that they have very high specific activity and can be used for the preparation of radiopharmaceuticals that target low density sites. Radionuclide generators are also a cost effective way to ensure a continuous and reliable supply of short lived radioisotopes.

The CRP on the development of generator technologies for therapeutic radionuclides organized by the IAEA focused on optimizing ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators that provide carrier free ^{90}Y and ^{188}Re therapeutic radioisotopes, respectively.

2.1.1. ^{90}Sr/^{90}Y generators

Yttrium-90 is a therapeutic radioisotope of enormous interest, and several established radiopharmaceuticals with this isotope are currently in use.

Yttrium-90 ($T_{1/2}$: 64.1 h; $E_{\beta max}$: 2.28 MeV) is a pure β^- particle emitter that can be prepared by the irradiation of ^{89}Y in a nuclear reactor or by the decay of ^{90}Sr. Yttrium-90 produced from a reactor is of very low specific activity owing to the small neutron capture cross-section (0.001 b) of ^{89}Y. As yttrium is mononuclidic, there is no need for enriched isotopes for irradiation. The radionuclidic purity of this directly (n,γ) activated product is generally very high. However, depending on the epithermal flux in the reactor, detectable levels of ^{89}Sr could be present owing to the (n,p) reaction. Because ^{89}Sr is a pure beta emitter, its presence may not be detected by the conventional methods of estimation of radionuclidic purity using gamma ray spectrometry.

There is unlimited potential availability of ^{90}Y, since it exists in a secular radioactive equilibrium with ^{90}Sr ($T_{1/2}$: 28.8 a). Strontium-90 is a major fission product, and the annual world production of ^{90}Sr in nuclear reactors amounts to several hundred megacuries. Currently, spent reactor fuel is reprocessed in a small number of countries, and these countries have the capability to develop the process chemistry required for large scale isolation of ^{90}Sr from fission product waste. There is a high level facility for recovery of ^{90}Sr (and other fission products) at Mayak, Russian Federation. A facility for the recovery of 55 500 GBq (1500 Ci) of pure strontium was set up at the Pacific Northwest National Laboratory, United States of America (USA), and the process chemistry used in this facility is documented [2.1].

Owing to the long physical half-life of ^{90}Sr, a single batch can be used indefinitely, which is an important advantage. However, because of the long half-life, the technology required for fabrication of ^{90}Sr/^{90}Y generators is considerably different from that used for other generators such as the ^{99}Mo/^{99m}Tc and ^{188}W/^{188}Re generator systems. The ^{90}Sr cannot be left in the column matrix any longer than necessary, because of denaturation resulting from energy deposition of the high energy β^- particles from decay of the ^{90}Sr and ^{90}Y, which often results in ^{90}Sr breakthrough in the eluate. Yttrium-90 used for therapy should be of very high radionuclidic purity (>99.998%), as the most probable contaminant, ^{90}Sr, is a bone seeker with a maximum permissible body burden (MPBB) of only 74 kBq (2 µCi). Currently, ^{90}Y is separated by using a combination of several separation techniques such as precipitation, solvent extraction and ion exchange chromatography, or by using ion selective resins. These operations are carried out at radiopharmaceutical manufacturing centres, and the ^{90}Y is shipped to hospitals. Consequently, ^{90}Y is an expensive radioisotope that is available only in places that are well connected to the suppliers, since its short half-life limits the distances it can be shipped.

The development of a ^{90}Sr/^{90}Y generator that can be operated in a central pharmacy could increase the availability of ^{90}Y. In smaller countries, such

generators could also be located in national radiopharmaceutical production centres.

The methods currently available for radionuclidic purity estimation that can reliably measure ^{90}Sr radionuclidic impurities at the desired low levels ($<2 \times 10^{-3}$%) cannot be adapted for use in a hospital pharmacy. Hence, there is also an important need for the development of a 'real time' quality control method for estimating the radionuclidic purity of ^{90}Y prior to patient administration.

2.1.2. ^{188}W/^{188}Re generators

Rhenium-188 ($T_{1/2}$: 16.9 h; $E_{\beta max}$: 2.12 MeV; E_{γ}: 155 keV (15%)) has a chemistry similar to that of ^{99m}Tc and thus can be converted into the chemical forms required for the preparation of various therapeutic radiopharmaceuticals. It can be prepared either by irradiation of enriched ^{187}Re in a nuclear reactor or as the daughter product of the ^{188}W/^{188}Re generator. The specific activity of the reactor produced ^{188}Re is generally low and will depend on the irradiation conditions, such as the neutron flux, time of irradiation and post-irradiation cooling time. There could also be radionuclidic impurities present from ^{186}Re depending on the enrichment of the target; morever, highly enriched ^{187}Re targets are expensive. On the other hand, the ^{188}Re obtained from the ^{188}W/^{188}Re generator is of high specific activity (near theoretical) and, potentially, high radionuclidic purity. The most likely radionuclidic impurity in a generator produced isotope is the parent radionuclide; such impurities can be minimized by using an efficient separation technique. However, the main problem in adapting this technology is the need for high specific activity ^{188}W ($T_{1/2}$: 69 d), which is produced by double neutron capture of ^{186}W in high flux research reactors. Even at high thermal neutron flux, which is only available at the SM reactor in Dimitrovgrad, Russian Federation, and at the High Flux Isotope Reactor (HFIR) at the Oak Ridge National Laboratory (ORNL), USA, only relatively low specific activity (148–185 GBq/g (4–5 Ci/g)) is available because of the low production cross-sections.

Member States having nuclear reactors with thermal neutron flux values of less than 5×10^{14} n·cm^{-2}·s^{-1} could still produce ^{188}W, but only with low specific activity (11–15 GBq/g). Generators using ^{188}W produced from such reactors will give ^{188}Re in a very large elution volume, which is not directly usable for preparation of radiopharmaceuticals. Hence, it is essential to develop post-elution concentration steps to increase the specific volume of ^{188}Re. Such techniques can also be used for increasing the length of time that adsorption column based generators can be used.

Alumina is the most commonly used adsorbent material for the preparation of ^{188}W/^{188}Re generators. Use of adsorbents with a higher capacity for ^{188}W could improve generator performance by producing higher capacity generators and high specific volumes of ^{188}Re, as well as allowing the use of relatively low specific activity ^{188}W.

2.2. OBJECTIVES OF THE CRP

The overall objectives of the CRP were (i) to develop technologies for the preparation of ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators in order to optimize generator fabrication and establish their use, and (ii) to standardize reliable quality control techniques for the eluted radionuclides to ensure their acceptability for clinical use. The following points were the specific objectives of the CRP:

(a) Development of reproducible methodologies for the preparation of ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators;
(b) Development and evaluation of chromatography adsorbents (zirconium/ titanium composites) having higher ^{188}W binding capacities, and demonstration of their utility in the preparation of column generators for ^{188}Re (and ^{99m}Tc);
(c) Comparison and optimization of technologies for post-elution concentration of ^{188}Re (and ^{99m}Tc);
(d) Development of quality control techniques for generator eluted therapeutic radionuclides.

2.3. KEY ISSUES ADDRESSED DURING THE CRP

The technologies for the development of the ^{90}Sr/^{90}Y generators are different from those for the ^{188}W/^{188}Re generators, and consequently the key issues to be addressed in the development of these generators varied. These are discussed below.

2.3.1. ^{90}Sr/^{90}Y generators

The key issues to be addressed in the development of ^{90}Sr/^{90}Y generators included the following:

(a) Use of the long lived parent radionuclide poses a big challenge with respect to the purity of the ^{90}Y, as the breakthrough of ^{90}Sr could increase as the generator shelf life increases.

(b) The ^{90}Sr parent radionuclide is very long lived ($T_{1/2}$: 28.8 a); hence the generators theoretically have a very long lifetime. However, leaving such long lived parent radionuclides in a column matrix can lead to substantial radiation degradation of the column matrix. Thus the generator developed should allow elution of the ^{90}Sr parent and its storage after every separation of the daughter product.

(c) Strontium-90 is a bone seeker, and its MPBB of 2 µCi (74 MBq) should not be exceeded [2.2]. The United States Pharmacopeia (USP) limit for the content of ^{90}Sr is 740 KBq per 37 GBq (or 20 µCi per Ci) of ^{90}Y at the expiration date, as given in the monograph for ^{90}Y-ibritumomab tiuxetan injection (Zevalin) [2.3]. Hence the radionuclidic purity should be greater than 99.998%, or ^{90}Sr contamination should be less than 2×10^{-3}% or 20 ppm. There is a need to modify the above limit, as patients are likely to receive several hundred millicuries of ^{90}Y labelled peptides or antibodies during the course of therapy.

(d) Quality control of the eluted ^{90}Y is an important issue. There is a need to develop an analytical technique that can measure ppm levels of ^{90}Sr in ^{90}Y. Both ^{90}Sr and ^{90}Y are beta emitters with overlapping β^- spectra, and hence conventional techniques for estimating radionuclidic purity may be of limited use. For these reasons, there is a need to develop 'real time' quality control procedures to estimate the purity of the ^{90}Y daughter product prior to clinical use.

2.3.2. ^{188}W/^{188}Re generators

The key issues to be addressed in the development of ^{188}W/^{188}Re generators included the following:

(a) Development of alumina based column generators using high specific activity ^{188}W obtained from one of the two high flux research reactors.

(b) Development of post-elution concentration techniques to allow the relatively low specific activity ^{188}W produced in reactors to be used in as many Member States as possible. A limiting factor in this case is the high generator elution volumes, which need to be effectively concentrated in order to increase the specific volume of ^{188}Re.

(c) Development of high capacity adsorbents as an alternative to alumina based chromatographic adsorbents for generator production.

2.4. WORK PLAN OF THE CRP

The scientists who participated in the CRP were actively involved in developing separation techniques for use in generator technologies. At the first research coordination meeting (RCM), held in Vienna in October 2004, the most critical production technology issues concerning the therapeutic radioisotope generators were reviewed. The participants agreed to focus efforts to develop $^{90}Sr/^{90}Y$ generators on the use of ion exchange resins, extraction chromatography or chelate loaded supported liquid membranes (SLMs). In the case of $^{188}W/^{188}Re$ generators, the work plan included the evaluation of various generator adsorbents in order to achieve a high load of ^{188}W on the generator column, in addition to the development of concentration methods for ^{188}Re eluates. A major obstacle was found to be the limited availability of high specific activity and high purity parent radionuclides. The need for high specific activity ^{188}W and ^{90}Sr was met by organizing the supply of these radionuclides through the IAEA. High specific activity ^{188}W was sourced from the Russian Federation, and ^{90}Sr was obtained from various commercial sources.

At the second RCM, held in April 2006 in Milan, the participants discussed the progress of the investigations carried out according to the initial work plan. Attempts to develop $^{90}Sr/^{90}Y$ generators had been undertaken in several laboratories, with varying results. The issue of possible ^{90}Sr contamination of the eluate coming from $^{90}Sr/^{90}Y$ generators was discussed. Efforts were aimed at developing technologies for the production of ^{90}Y suitable for therapeutic applications. Development of a suitable analytical technique for 'real time' quality control of eluted ^{90}Y was given high priority by the participants.

Adsorbents based on alumina, hydroxyapatite and various composite materials, as well as poly zirconium compound (PZC), had been studied by several of the participants for development of a $^{188}W/^{188}Re$ generator. The work plan for the second part of the CRP for the $^{188}W/^{188}Re$ generator included further evaluation of adsorbents such as alumina, hydroxyapatite particles, and PZC and poly titanium compound (PTC), with the goal of using these for generator fabrication. Further work on developing post-elution concentration methods was also planned.

At the final RCM, the participants reported substantial progress in achieving the objectives of the CRP. A summary of the work done in each participating laboratory is given in Section 2.5. Overall achievements of the CRP are listed in Section 2.6. Several specific protocols for the preparation of $^{90}Sr/^{90}Y$ and $^{188}W/^{188}Re$ generators were developed by the participants. In addition, an analytical technique based on extraction paper chromatography

(EPC) was developed for quality control of ^{90}Y for therapeutic applications. Those protocols that are readily adaptable by interested users are given in Section 3 of this publication.

2.5. SUMMARY OF THE WORK
REPORTED FROM DIFFERENT PARTICIPATING GROUPS

2.5.1. Brazil

The Nuclear and Energy Research Institute (IPEN) of Brazil imports ^{90}Y and produces ^{90}Y-citrate and ^{90}Y-hydroxyapatite particles as two different radiopharmaceuticals for radiosynovectomy. Because the price of ^{90}Y is very high and its distribution is extremely erratic, a decision was made to produce ^{90}Sr/^{90}Y generators in-house. A chromatographic generator was developed using cation exchange resins with activities of up to 5 mCi of ^{90}Sr. The generator is to be scaled up.

Technologies were developed for the preparation of a ^{188}W/^{188}Re generator with an alumina column as well as a WZr gel. Alumina based generators with activities of up to 1.85 GBq (50 mCi) of ^{188}W were successfully prepared. A quality control procedure was developed to evaluate the purity of ^{188}Re eluted from the generators. HEDP was labelled with ^{188}Re, and the results were compared with data obtained from commercial generators. IPEN can now prepare alumina based ^{188}W/^{188}Re generators for clinical applications by using imported high specific activity ^{188}W.

2.5.2. Cuba

In Cuba, ^{90}Sr/^{90}Y chromatographic generators based on ion exchange chromatography at activity levels of 300 MBq (8 mCi) and 3.5 GBq (100 µCi) were evaluated. The elution efficiency and radionuclidic purity of the eluted ^{90}Y were followed for several months to two years. It was observed that the generator shelf life decreased as the generator was scaled up to higher activity levels. The primary problem was a reduction of elution yields. Implementation of a weekly elution scheme together with the use of nitrate ions improved the performance of the higher activity generator.

A purification procedure to decrease the trace metal content in the ^{90}Y solution was adapted, which removed trace levels of ^{90}Sr as well. The same purification procedure was used to estimate the radionuclidic purity of the ^{90}Y in the eluants. A complete scheme for the separation, purification and quality control of the ^{90}Y was proposed for large scale production. The quality control

procedure, which combines two separation steps, allows the determination of 1 µCi (37 kBq) of ^{90}Sr in 1 Ci (37 GBq) of ^{90}Y solution. Labelling DOTA conjugated monoclonal antibodies gave radiochemical yields of over 95%, which confirmed the good quality of the ^{90}Y prepared from the generator.

Three batches of ^{188}W/^{188}Re generators were prepared and evaluated. Results of the quality control evaluation of the eluate were satisfactory. High radiolabelling yields were achieved with bisphosphonate ligands and monoclonal antibodies. The ^{188}Re labelled monoclonal antibodies that were prepared were used in a clinical trial.

2.5.3. Germany

Germany contributed its expertise in automation to this CRP. A procedure for the production of sterile chromatographic generators for therapeutic radionuclides like ^{188}Re was developed by modifying the known procedures for the production of sterile ^{99}Mo/^{99m}Tc generators. Generally, the requirements for radiation protection of personnel and for use of good manufacturing practice (GMP) must be taken into consideration. Automation of these processes contributes to meeting these requirements.

2.5.4. India

Prior to the CRP, a ^{90}Sr/^{90}Y generator based on an SLM was developed. During the CRP, this generator was modified to create a two stage generator in which a third compartment, containing a membrane loaded with octyl(phenyl)-N,N-diisobutylcarbamoylmethylphosphine oxide (CMPO), was added, which acted as a purification step. Using this generator, it was possible to separate high purity ^{90}Y [2.4].

A novel ^{90}Sr/^{90}Y generator based on an electrochemical procedure was developed in which ^{90}Y is preferentially electrodeposited on the cathode, leaving the ^{90}Sr^{+2} in the electrolyte. A second electrolysis yielded high purity ^{90}Y in the cathode, which could be dissolved in a very small volume of acetate solution. Separation yields of over 97% were achieved [2.5].

A sensitive and accurate analytical technique for estimation of the radionuclidic purity of ^{90}Y was developed at the Bhabha Atomic Research Centre (BARC) [2.6]. The so-called BARC method is based on extraction paper chromatography (EPC). The EPC approach is a combination of solvent extraction and paper chromatography techniques that enables detection of 1 Bq of ^{90}Sr in 1 MBq of ^{90}Y, which translates into a detection limit of approximately 10^{-4}% of ^{90}Sr in ^{90}Y.

Moderate capacity (2.4 GBq (65 mCi) and 0.6 GBq (16 mCi)) ^{188}W/^{188}Re generators were prepared by adsorbing high specific activity ^{188}W of 217 GBq (5.86 Ci) per gram of tungsten on alumina. The elution yield of perrhenate was approximately 80–85%, and the quality of the perrhenate was satisfactory, with a radiochemical purity of greater than 95% and ^{188}W breakthrough of less than 10^{-4}%.

Post-elution concentration of ^{188}Re was attempted using three different approaches. The first method involved elution of perrhenate in acetate buffer followed by trapping in diethylaminoethyl (DEAE) cellulose and elution in a small volume of saline, with an efficiency of 73 ± 2%. In the second procedure, elution of perrhenate was carried out with saline, followed by trapping in a Dowex anion exchanger and elution in a small volume of 0.2M NaI, and finally removal of I$^-$ with an AgCl column, with an efficiency of 72 ± 12%. The third procedure involved elution of perrhenate in saline and the removal of Cl$^-$ ions as AgCl precipitation by passing the eluent first through an Alltech IC-Ag$^+$ cation exchanger cartridge and then through a small Sep-Pak Accell Plus QMA (quaternary methyl amine) anion exchanger cartridge (130 mg) to retain the perrhenate. The ^{188}ReO$_4^-$ was finally eluted with a very small volume (1 mL) of normal saline, with an efficiency of 79 ± 3%.

2.5.5.   Italy

A ^{90}Sr/^{90}Y generator system was developed that overcame the problem of excessive manipulation of the eluate and that was also safe for administration, with low ^{90}Sr breakthrough. The new design consisted of two cation exchange columns connected in series. The first column contained the adsorbed ^{90}Sr, while the second served as a safety column to trap any possible leakage of ^{90}Sr from the first column. The ^{90}Sr was adsorbed on a high cross-linked cation exchange resin, and the ^{90}Y was eluted with acetate buffer solution. The pH and molarity of the acetate solution were optimized in order to efficiently elute the ^{90}Y in low volumes and to avoid the breakthrough of ^{90}Sr. The ^{90}Y acetate was used for radiolabelling studies.

A new simple and efficient method to detect ^{90}Sr breakthrough was developed based on a strontium resin minicolumn that is commercially available from Eichrom® Technologies. At low pH levels, this resin possesses a high affinity for strontium and a very low affinity for yttrium. A satisfactory quality control technique was developed that enabled the determination of ^{90}Sr at the permissible levels.

2.5.6. Republic of Korea

New ionic liquid type crown ethers (ILCEs) were synthesized and characterized as a novel medium for liquid–liquid extraction of the radioactive metal ion $^{90}Sr^{2+}$. A very efficient method based on modification of the polyethylene glycol chain length and anions was developed for synthesizing ILCEs with various physical and chemical characteristics. Novel ILCEs that are non-toxic, recyclable and economical were synthesized and employed for efficient extraction of ^{85}Sr. ILCEs have been found to behave like a multifunctional compound that discriminates metal cations according to ring size. They are also expected to be used for extraction of other radionuclides or heavy metals. The ILCEs obtain their selectivity through the ability to fine-tune and reorganize their crown ether structure and the resulting properties of the crown by changing their ring size and rigidity, changing their number and type of donor atoms, appending ionizable groups, and modifying their lipophilicity.

2.5.7. Mexico

Hydroxyapatite, an insoluble solid with anion exchange properties, was evaluated as an adsorbent for the preparation of $^{188}W/^{188}Re$ generators. Sorption studies were performed by batch experiments using the ^{188}W and ^{188}Re radiotracers. The variabilities of separation between tungsten and rhenium were calculated by the separation factor α, which showed that separation is possible using 0.9% NaCl solutions with pH values below 7. Hydroxyapatite based $^{188}W/^{188}Re$ generators were constructed. The ^{188}Re eluates obtained had phosphate concentrations that exceeded 1000 ppm, and the radiochemical purities were over 90%. The highest average elution efficiency was obtained in the generator eluted with 0.9% NaCl solutions at pH6 (80–70% yield), while the lowest efficiency and highest ^{188}W breakthrough occurred with 0.9% NaCl solutions at pH6.5 (<0.02% yield).

To optimize the preparation conditions of the alumina based $^{188}W/^{188}Re$ generators, the sorption behaviour of tungsten and rhenium on alumina was studied. The results showed that the alumina generators can be prepared and eluted with HCl (<0.1 mol/L) and 0.9% NaCl solutions (pH<5.5) using alumina with a particle size of between 200 and 300 mesh. The adsorption capacity calculated is 0.34 meq per gram of alumina, that is, 10.5 mg of tungsten per gram of aluminium. At this ratio, the tungsten sorption is about 99.9% and the rhenium sorption is about 3%. One alumina based $^{188}W/^{188}Re$ generator was prepared, and the radiochemical purity of the ^{188}Re eluants was greater than 95%.

Other alternative adsorbents such as titanium and zirconium [188]W-tungstate were also studied. The tungstates were synthesized by the sol-gel method. Titanium [188]W-tungstate generators prepared from [188]W-tungstate solution at pH4.5 presented the best [188]Re elution efficiency (73%) and the lowest [188]W breakthrough (0.3%). The generators gave a [188]Re radiochemical purity of nearly 100%. The high [188]W breakthrough in [188]Re eluates of these generators required an additional step to reduce the [188]W contamination to within permissible limits.

2.5.8. Poland

An in-house technology for the manufacture of ^{90}Y was developed at POLATOM prior to the CRP. Since there was a need for a reliable method for determining trace contamination of ^{90}Sr in ^{90}Y eluates, a quality control technique based on extraction chromatography using commercially available strontium specific resins was developed.

A portable [188]Re generator was developed using the alumina column and other elements of the 'dry bed' hardware of the [99]Mo/^{99m}Tc generator. High specific activity [188]W (Research Institute of Atomic Reactors (RIAR), Russian Federation) in the form of tungstic acid was first acidified and then adsorbed on alumina, and [188]Re was eluted as perrhenate with 0.9% NaCl with a radiochemical purity of over 98.0%, a radionuclidic purity of over 99.9% with respect to γ impurities, and [188]W breakthrough of less than 0.5×10^{-3}%. The radioactive concentration of [188]Re was greater than 100 mCi/mL, and no post-elution concentration was needed. These generators were mechanically and radiochemically stable for over six months. Dosimetric measurements were performed to ensure that the radiation dose on the outer surface of the generator remained within acceptable limits. The additional advantage of the generators is that they can be connected in series and eluted in one run without a significant increase of elution volume. This method extends the shelf life of the generator significantly and makes its use more economical. It is also possible to concentrate the [188]Re eluate, and the appropriate method involving $AgNO_3$-Dowex and ion exchange QMA minicolumns has been verified to provide over 90% of available radioactivity in a volume of less than 1 mL. The quality of the [188]Re eluates was tested using labelling of a phosphonate based (HEDP) radiopharmaceutical for palliative therapy of painful cancer metastasis to bone and labelling of a bombesin derivative, a potential agent for prostate cancer treatment.

2.5.9. Russian Federation

In the Russian Federation, a process has been developed to isolate ^{90}Sr from the high level waste of recently irradiated and reprocessed experimental samples of nuclear fuel, and an experimental batch of 12 Ci of ^{90}Sr has been successfully isolated from such waste. Mass spectrometric analyses demonstrated that the specific activity of the product was approximately 74 Ci/g, which is higher than that of commercially available ^{90}Sr and can be used for ^{90}Sr/^{90}Y generator development and/or production.

Tungsten-188 production by neutron irradiation in the SM research reactor was studied both theoretically and experimentally. A set of nuclear constants for accurate prediction of ^{188}W yield in the SM high flux reactor was refined. Effects of neutron flux depression and shielding on ^{188}W specific activity were studied. An optimized approach to ^{188}W irradiation based on experimental data was developed. A procedure for measuring the specific activity of ^{188}W was developed based on gamma spectrometry measurement of the activity and photocolorimetric measurement of the tungsten concentration in the sample solution. The radiochemical procedure that was developed for processing irradiated targets is reliable, reproducible and environmentally safe, and provides efficient purification from both radioactive and non-radioactive impurities. The facility for routine production of ^{188}W (more than 100 Ci/a) was put into operation in 2007. Fifteen batches of ^{188}W preparation were shipped to the participating countries to enable their work on ^{188}W/^{188}Re generator development.

A ^{188}Re concentrating procedure was developed based on preliminary removal of salt components (NaCl) by passage of the eluate through the Dowex 50 resin in Ag$^+$ form followed by sorption of rhenium on the small column of alumina. Distribution of ^{188}Re between alumina and NaCl solutions was studied at various salt concentrations and pH levels. It was demonstrated that the only chemical form of alumina applicable for efficient concentration of ^{188}Re is an acidic one. The dynamic capacity of Dowex 50 in Ag$^+$ form with regard to sodium chloride was evaluated, and the yield and purity of the ^{188}Re were determined. It was demonstrated that conductivity of eluate from the desalination column changes dramatically when the column capacity is exhausted. This effect can be used in the automation of the desalination process, ensuring efficient sorption of rhenium by the concentrating column.

2.5.10. United States of America

Participation in this project by ORNL included the provision of technical advice and guidance on the fabrication and set-up of the alumina

based ^{188}W/^{188}Re generator system and on the use of an effective post-elution tandem column system for concentration of the ^{188}Re bolus. Because of the importance of this CRP in providing technical capabilities in developing countries for the fabrication and use of the alumina based ^{188}W/^{188}Re generator, ORNL's association with this project led to the completion and introduction of a new fluid transfer system for the routine processing of reactor produced ^{188}W at ORNL as well as for fabrication of the ^{188}W/^{188}Re generators. In association with these efforts, a current good manufacturing practice (cGMP) quality programme was developed for distribution of these generators from ORNL as a bulk pharmaceutical ingredient.

2.5.11. Vietnam

Adsorbents based on PZC and PTC for the preparation of chromatographic ^{99m}Tc and ^{188}Re generators were synthesized. The chemical composition, molecular structure and physicochemical characteristics of these adsorbents were investigated. The adsorption properties of PZC and PTC sorbents in the different molybdate and tungstate solutions and the daughter nuclide elution performance were investigated. Molybdenum adsorption capacities of about 275 mg of molybdenum per gram of PZC and 270 mg of molydenum per gram of PTC, and a ^{99m}Tc elution yield of over 90% were achieved with both sorbents. Tungsten adsorption capacities of about 520 mg of tungsten per gram of PZC and 515 mg of tungsten per gram of PTC, and a ^{188}Re elution yield of over 80% were also achieved with the PZC and PTC sorbents. The ^{188}Re eluate concentration process was developed by eluting ^{188}Re from the tandem system of ^{188}W-PTC alumina columns with saline solutions of different concentrations. A concentration factor of greater than 6 was achieved by this technique, which has potential for ^{188}W/^{188}Re generator production using low specific radioactivity ^{188}W produced in medium flux research reactors.

2.6. SCIENTIFIC ACHIEVEMENTS OF THE CRP

This section details the important achievements of the CRP.

2.6.1. $^{90}Sr/^{90}Y$ generators

2.6.1.1. Electrochemical generator (the Kamadhenu generator)

A $^{90}Sr/^{90}Y$ generator system based on an electrochemical separation technique was developed in India. The process involves electrolysis of a mixture of ^{90}Sr and ^{90}Y in nitrate form at pH3 at a potential of –2.5V, using a 100–200 mA current and platinum electrodes. The ^{90}Y is deposited on the cathode, which is removed and subjected to a second electrolysis in an electrolysis bath containing 3mM HNO_3 and another platinum electrode. In this step, the cathode from the first electrolysis containing ^{90}Y is used as the anode. Upon electrolysis, ^{90}Y is leached and deposited on the fresh cathode, which is removed and dipped in acetate buffer to obtain ^{90}Y acetate, a form suitable for radiolabelling. Recovery of over 95% of the ^{90}Y was achieved in each cycle, with an overall decay corrected yield of over 90%. The recovered ^{90}Y had a high radionuclidic purity, with only 30.2 ± 15.2 kBq (817 ± 411 nCi) of ^{90}Sr per 37 GBq (1 Ci) of ^{90}Y (0.817 ± 0.411 ppm). Consistent and repeated separation was demonstrated using up to 1.85 GBq (50 mCi) of ^{90}Sr.

The electrochemical generator offers several advantages including the use of feed solution for electrolysis without further modification beyond pH adjustment. There is an insignificant loss of ^{90}Sr activity during the electrochemical processing. Minimal amounts of chemicals are used during the whole process, and hence there is very little possibility of the introduction of metal contamination. Because the generator can be 'milked' virtually indefinitely, it was named 'Kamadhenu'.

2.6.1.2. Two stage SLM based ^{90}Y generator

The SLM approach utilizes a polytetrafluoroethylene (PTFE) membrane impregnated with a suitable extractant and can be employed for separation of a desired chemical species from a mixture. This approach has been successfully demonstrated in the preparation of a $^{90}Sr/^{90}Y$ generator. Expanding on this work, a two stage SLM based $^{90}Sr/^{90}Y$ generator system was developed, using two different organophosphorous extractants, namely, 2-ethylhexyl 2-ethylhexyl phosphonic acid (KSM-17) and octyl(phenyl)-N,N-diisobutylcarbamoylmethylphosphine oxide (CMPO). The separation is achieved through the pH dependent preferential transport of the $^{90}Y^{+3}$ in the $^{90}Sr/^{90}Y$ mixture from one chamber to another.

The two stage SLM based generator consists of three compartments, which are separated by PTFE membranes (160 µm thick, 0.45 µm pores) incorporated with KSM-17 in the first membrane and CMPO in the second

membrane. The ^{90}Sr/^{90}Y mixture in HNO$_3$ at pH1–2 is placed in the first chamber, the second chamber contains 4M HNO$_3$ and the third chamber contains 1M acetic acid. The ^{90}Y is transported to the third chamber, leaving ^{90}Sr in the first chamber.

The major attributes of this generator are:

(a) The high purity of ^{90}Y^{+3} (<3.7 kBq of ^{90}Sr in 3.7 GBq of ^{90}Y) that results at the end of the separation, with yields of over 80%;

(b) The availability of ^{90}Y in the form of yttrium acetate, which is amenable to radiolabelling of biomolecules;

(c) The possibility of automation of the system, which could result in wider deployment and large scale operations.

2.6.1.3. Ion exchange based generator

A ^{90}Sr/^{90}Y generator system based on an ion chromatography separation technique was evaluated over several years in Cuba. This system uses Dowex 50WX8 (50–100 mesh) resin in Na$^+$ form as the matrix and a diluted solution of ethylenediaminetetraacetic acid (EDTA) disodium salt at pH4.7 to elute ^{90}Y. In this method, the ^{90}Sr is kept in EDTA solution in a vial for ^{90}Y in-growth. Before separation, the EDTA concentration is adjusted to 3–6 mmol/L by addition of fresh EDTA and the pH is adjusted to 4.5–6. The solution is passed through a column containing the cationic ion exchange resin in sodium form. Under these conditions, ^{90}Sr is retained on the column with a decontamination factor of 10^4 while ^{90}Y passes through the column. The ^{90}Sr is easily removed from the column in a small volume of diluted EDTA solution at pH11–13. Depending on the amount of ^{90}Sr/^{90}Y required, one or more columns can be connected in series. EDTA is removed from the ^{90}Y solution by wet ashing, and ^{90}Y is then recovered in a small volume of 0.02–0.05 mol/L HCl. The method was tested for 100 mCi of ^{90}Sr solution at ^{90}Y in-growth times of 1 day, 1 week and 1 month. Results showed that consistent and repeated separation can be achieved, and that the columns can be used at least three times because the radiation damage is negligible. Recovery of ^{90}Y from each column was greater than 98% and the loss of ^{90}Sr in the first column was less than 0.05%. The recovered ^{90}Sr solution did not require treatment before its use in the next separation.

2.6.1.4. Quality control of ^{90}Y

Yttrium-90 used for therapy should be of very high radionuclidic purity (>99.998%), as the most probable contaminant, ^{90}Sr, is a bone seeker with a

MPBB of only 74 kBq (2 µCi). None of the current methods for estimating radionuclidic purity is adequate to reliably measure ^{90}Sr radionuclidic impurities at such low levels. One of the major aims of the CRP was to develop a reliable technique to accurately determine the amount of ^{90}Sr in ^{90}Y used for therapy. Participants in the CRP were successful in developing techniques for estimating the radionuclidic purity of ^{90}Y. These are discussed in the following.

2.6.1.5. *Estimation of the radionuclidic purity of ^{90}Y using extraction chromatography*

The method for estimating the radionuclidic purity of ^{90}Y using extraction chromatography is based on a minicolumn containing Sr Resin (Eichrom® Technologies), a commercially available strontium specific resin that possesses high affinity for strontium and very low affinity for yttrium at low pH levels. In the present method, a home-made column (1 cm × 5 cm) loaded with 4 mL of Sr Resin was used. This allowed pure ^{90}Y to be obtained in the first fractions eluted with 8M HNO$_3$ and pure ^{90}Sr to be obtained in the last fractions eluted with 0.01M HNO$_3$. The modified procedure allows the estimation of ^{90}Sr in ^{90}Y at permissible levels.

2.6.1.6. *BARC method for estimation of the radionuclidic purity of ^{90}Y*

The BARC method for estimating the radionuclidic purity of ^{90}Y combines chelate based extraction with paper chromatography using paper impregnated with KSM-17, which is a ^{90}Y specific chelator. A paper chromatography strip impregnated with KSM-17 at the point of spotting is used for chromatography. Upon development with normal saline, ^{90}Sr moves to the solvent front, leaving ^{90}Y completely chelated and retained at the point of spotting. The activity at the solvent front (^{90}Sr) is quantified by liquid scintillation counting, and the data are compared with the total applied activity to provide the radionuclidic purity of the test solution. The method has a sensitivity of at least 74 kBq (2 µCi) of ^{90}Sr per 37 GBq (1 Ci) of ^{90}Y.

2.6.2. ^{188}W/^{188}Re generators

2.6.2.1. *Production and radiochemical processing of ^{188}W*

The ^{188}W needed by CRP participants was produced in the SM reactor in Dimitrovgrad, Russian Federation. Tungsten-188 is produced by double neutron capture of ^{186}W. The natural abundance of ^{186}W is 28.6%. A minimum thermal neutron flux greater than 5×10^{14} n·cm^{-2}·s^{-1} is essential to produce ^{188}W

in adequate quantities and of reasonable specific activity. By using isotopically enriched ^{186}W as the target, the specific activity of ^{188}W is augmented. The use of an enriched target is also important for avoiding the high radiation field contributed by other radioactive isotopes of tungsten (primarily ^{185,187}W). Otherwise, a thicker shielding will be needed for the transport of ^{188}W to the generator loading facilities and/or for the generator itself. A specific activity of 4–5 Ci/g (at delivery) is obtained by using an enriched target and following an irradiation cycle of about 20–24 d. With a shutdown between cycles, the specific activity decreases, since the intermediate ^{187}W radionuclide has a short half-life of only 23.8 h, and hence is not available for further reaction. Irradiation cycles of 28–30 d provided an increase of specific activity of up to 8–8.5 Ci/g (at delivery), but increased the burnup of target material to 40–45%. Longer irradiation led to higher burnup and to a specific activity of only 5–6 Ci/g (at delivery).

Tungsten oxide or metal tungsten (granular/powder, or pressed/sintered) enriched with ^{186}W is commonly used as a target material. The final product is typically supplied for generator loading as sodium tungstate solution. Sodium tungstate is produced by dissolving tungsten oxide in sodium hydroxide solution with moderate heating. This procedure is not difficult if WO_3 is irradiated in neutron fluxes of low or moderate intensity (10^{13}–10^{14} cm^{-2}·s^{-1}). When irradiated in a high flux reactor, part of the tungsten oxide turns into a barely soluble, black fraction. The quantity of this phase correlates with the integral neutron flux and can reach 30–50% of the target weight. The processing procedure used in this case was developed at RIAR and is based on dissolution of the irradiated target in sodium hydroxide in the presence of sodium hypochlorite with heating. The ^{191}Os impurity formed is removed at this stage by distillation. To ensure that the process is safe for the environment, ^{191}Os can be trapped by scrubbers filled with a solution of thiourea in concentrated hydrochloric acid and sodium hydroxide solution in ethanol.

Owing to the high burnup of ^{186}W to rhenium, the purification procedure is supplemented by removal of rhenium using anion exchange with the Dowex 1 resin in NO_3^- form. During dissolution of the irradiated material, it is contaminated with a silica impurity. To purify the solution, anion exchange chromatography with Dowex 1 resin in Cl$^-$ form is used to remove the silica. Additionally, some anionic impurities — products of the destruction of the oxidizing agent (chloride, chlorate and perchlorate ions, etc.) — as well as a number of other impurities of a cationic nature that commonly contaminate the product are also removed from the solution.

At the final stage of purification, the solution is desalinated, that is, excess sodium is removed by passing the solution through the Dowex 50 cation exchanger. To avoid tungsten precipitation at this stage, it is converted to

pertungstic acid by adding hydrogen peroxide. Following purification, the resulting solution of pertungstic acid is evaporated to dryness. The residue of tungstic acid is dissolved in the required quantity (close to the stoichiometric ratio) of sodium hydroxide.

If metallic granular/powder or pressed/sintered enriched ^{188}W targets are used, as at ORNL, the irradiated target material is first heated to 750–800°C in a quartz furnace while an air stream is passed over the target material for conversion to tungsten oxide for subsequent solution in base. In this case, a substantial amount of the Os^{191} radionuclidic impurity is also swept away from the target for subsequent trapping in the base. At ORNL, the resulting sodium tungstate stock solution is not purified further, since the possible presence of low amounts of ^{191}Os or ^{192}Ir in the ^{188}Re solution used for radiopharmaceutical preparation is inconsequential.

2.6.2.2.   *Preparation of alumina based ^{188}W/^{188}Re generators*

Participants in the CRP worked on an alumina based generator similar to the ^{99}Mo/^{99m}Tc generators. Alumina should be carefully meshed; the preferred particle size is 150–200 mesh. Heating of alumina at temperatures between 80 and 100°C for at least 4 h is also recommended. Before it is poured onto the column, the alumina should be thoroughly washed to remove all fines with diluted acid solution to activate the adsorption sites as much as possible prior to loading the ^{188}W.

The experimentally determined capacity of alumina for tungsten is in the range of 150–200 mg of tungsten per gram of Al_2O_3 in the batch method. However, when working in dynamic conditions, as during loading, this figure can be as low as 80–100 mg of tungsten per gram of Al_2O_3. These data are important for calculating the minimum amount of alumina needed to prepare the generator for a given specific activity of ^{188}W. Elution yields of ^{188}ReO$_4^-$ varied between 70 and 95%. The radiochemical purity of ^{188}Re (as perrhenate) was greater than 98%, the ^{188}W breakthrough was less than 0.5×10^{-3}%, and the levels of contamination with tungsten and aluminium were below 10 ppm as verified by inductively coupled plasma optical emission spectometry (ICP-OES). Labelling of molecules such as HEDP and bombesin with ^{188}Re was also performed, which confirmed the utility of the final ^{188}Re-perrhenate solution obtained from the alumina type generators.

The results of these studies showed that, using high specific activity ^{188}W and the standard alumina column, it is possible to produce a stable ^{188}W/^{188}Re generator providing ^{188}Re eluate suitable for medical purposes.

2.6.2.3. *Higher capacity adsorbents*

Inorganic polymer sorbents: The PZC and PTC based sorbents for the preparation of chromatographic ^{188}W/^{188}Re generators were synthesized by some of the participants. The chemical composition, molecular structure and physicochemical characteristics of these sorbents were studied.

The optimal conditions for ^{188}W-tungstate adsorption and for the elution of ^{188}Re were investigated. Adsorption capacities of up to 520 mg of tungsten per gram of PZC and 515 mg of tungsten per gram of PTC were reported. Elution yields greater than 80% were achieved with both the PZC and the PTC sorbents. Tungsten-188 breakthrough of 0.015% and elemental tungsten breakthrough of less than 5 µg/mL were found in the ^{188}Re eluate. The performance of the PTC sorbent closely resembled that of the PZC sorbent, except that the breakthrough of ^{188}W parent radionuclides was higher. The PTC column required a smaller volume of saline to elute ^{188}Re.

2.6.2.4. *Gel type generators*

Sol-gel method: Titanium and zirconium ^{188}W-tungstate gel generators were developed. The gels were prepared using the sol-gel method, which took about 3 h. The titanium and zirconium tungstate gels were synthesized from tetrabutyl orthotitanate and zirconium ethoxide solutions and sodium ^{188}W-tungstate solutions, respectively. The effect of the pH value of the ^{188}W-tungstate solution on generator performance was evaluated, as tungstate forms different chemical species depending on the acidity of the solution, and thus the gels formed from tungstate solution at different pH levels will constitute distinct structures with specific physicochemical properties. The use of acid or basic ^{188}W-tungstate solutions in the preparation of the gel generators reduces the ^{188}Re elution efficiency and increases ^{188}W breakthrough. The best ^{188}Re elution efficiency values (73%) were obtained with titanium ^{188}W-tungstate generators prepared from ^{188}W-tungstate solution at pH4.5. The lowest ^{188}W breakthrough percentages (0.3%) were obtained with the zirconium ^{188}W-tungstate generators prepared from ^{188}W-tungstate solution at pH4.5. The ^{188}Re radiochemical purity obtained in both types of generator approaches 100%, the pH level of eluates is about 4–7 and the elution volume is around 2–3 mL. The generator with the best performance was prepared from zirconium ^{188}W-tungstate; however, the ^{188}W breakthrough was always greater than 0.015%. There is a need to improve the performance of these generators.

Precipitation method: Tungsten trioxide was dissolved with 2M NaOH and tracer ^{188}W was added. The pH was adjusted to 4 with 2M HNO$_3$. A

solution of $ZrOCl_2.8H_2O$ (pH1.5) was added with heating at 50°C and stirring. The pH was adjusted to 4.5 with 2M NaOH solution. After the reaction, the gel was filtered, dried, cracked with saline solution and dried again. The dry gel was loaded onto a column previously loaded with 1 g of Al_2O_3. The generator was then eluted with known volumes of saline solution.

The WZr gel was characterized for structure by X ray diffraction with CuK alpha radiation; the particle size was determined by using a sieve distribution apparatus; and the tungsten and zirconium contents were estimated by neutron activation analysis and by UV visible spectrometry. X ray diffraction studies showed that the WZr gel is in an amorphous form. The particle size distribution was appropriate to give good performance of the gel type generators, with most of the particles in the range of 150–300 μm. The amount of tungsten and zirconium in the gel was 37% and 43%, respectively.

The performance of the WZr gel generators was good, with elution efficiency greater than 65% and elution yield greater than 80% in 6 mL. The results of the quality control studies showed that the [188]Re eluted is of good quality.

2.6.2.5. *Post-elution concentration of [188]Re*

The availability of methods for post-elution concentration of [188]Re to high specific volume solutions of [188]Re is important for the effective and routine use of [188]W/[188]Re generators. Freshly fabricated generators give adequate radioactive concentration and can be directly used for the preparation of radiopharmaceuticals. Several participants worked on [188]Re concentration systems, which are discussed below.

ORNL method for [188]Re concentration: The ORNL [188]Re concentration system is based on the sequential trapping of the macroscopic levels of the chloride anion on a silver impregnated cation column. Since chloride has been effectively removed from the solution exiting the cation column, the microscopic levels of the perrhenate can then be specifically trapped on the QMA anion column and, after washing with water, be removed in a small volume of saline. The volume of saline required, and thus the final volume that determines the [188]Re solution specific volume, is a function of the QMA column void volume. Although the silver cation and QMA anion columns are commercially available, the limitations of the milliequivalents of silver on the cation column (1.5–4.5 meq) may limit the chloride trapping capacity (i.e. 10 mL of 0.15M NaCl per 1.5 meq of Ag^+). Simple in-house preparation of the silver cation columns (see Section 3.5) provides more flexibility and reduces costs.

Other concentration systems: In addition to the ORNL procedure discussed above, several other [188]Re concentration systems were developed and tested by the CRP participants. Results are presented in more detail in the individual country reports included in this publication.

One of the systems developed for an alumina based generator using saline as an eluent is based on a two stage purification process involving the removal of chloride ions by adsorption on a cation exchange resin in a silver form, followed by adsorption of [188]Re on an alumina column or an anion exchange resin. The first stage uses AG-50W-X1 or Chelex-100 cation exchange resins. Rhenium, forming anionic species in the solution, passes through the column, while cationic species of alkali metals (Na^+) are retained by the resin. The rhenium elution profile for the cation exchange column is nearly identical to that for the alumina column. A feature of the process is a change in the pH of the final eluent. At the second stage, the chloride free eluate is passed through the small anion exchange column, providing isolation of [188]Re from the solution. Washing the column with normal saline provides sodium perrhenate solution with high activity, which can be used for radiolabelling procedures.

In an alternative approach developed in the Russian Federation, the chloride free eluate from the first column is passed through a small alumina column. Under salt free conditions, alumina adsorbs rhenium efficiently. The [188]Re is then eluted from the second column with a small volume of saline.

Similarly, the [188]Re eluate of a gel type generator (e.g. zirconium-tungstate gel), which is an aqueous solution, can be adsorbed on a small alumina column and eluted with saline. In the procedure developed in India, [188]Re is eluted from the generator with a solution of ammonium acetate, which is then trapped in a small anion exchange column of DEAE cellulose.

Columns used in the concentration systems are available from commercial sources (e.g. Analtech Ag Plus silver containing cation exchange cartridges, Alltech IC-Ag$^+$ anion exchange cartridges, Waters Sep-Pak Accell Plus QMA anion exchange cartridges, Millipore Sep-Pak QMA cartridges, or Waters Sep-Pak AccellW Light QMA cartridges). After each application, these columns should be disposed of and replaced with new ones, which is a drawback. The column required for the two column system based on silver cation exchange resin and alumina can be prepared in-house.

2.7. COOPERATION AMONG PARTICIPANTS

During the course of the CRP, there was fruitful collaboration and cooperation among the participating laboratories. Examples include the following:

(a) The chief scientific investigator from Brazil participated in a six month scientific visit to ORNL (USA) for the development of a ^{188}Re generator technology and other projects.

(b) Cooperation was established between the Russian Federation and Brazil through an intergovernmental programme in the field of radionuclide production and application, allowing for sharing of experience among corresponding participants in generator technology development.

(c) Poland and Germany began sharing experience concerning practical aspects of ^{188}W/^{188}Re generator handling. The two countries also share an approach to the automation of generator production.

(d) The chief scientific investigator from Mexico worked at ORNL as a guest researcher, investigating the adsorption capacity of hydroxyapatite for ^{188}Re under bilateral collaboration between Mexico and the USA (FUMEC-AMC).

(e) Italy provided technical assistance to Cuba for the development of a ^{90}Sr/^{90}Y generator.

(f) One of the staff members from Vietnam was trained in Italy in the preparation of ^{90}Sr/^{90}Y generators.

(g) Techne Generator Inc. of Japan provided PZC to Brazil, India and Mexico for use in the preparation of high capacity generators.

(h) The Russian Federation supplied 14 batches of ^{188}W (3.2 Ci) to Brazil, Cuba, India, Indonesia, Republic of Korea, Mexico and Poland through the IAEA.

(i) Poland supplied ^{85}Sr to Brazil, Cuba and Italy, supported by the IAEA, to help continue this research within the CRP.

2.8. CONCLUSION

The objectives of the CRP were to evaluate various generator and concentration technologies for ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators, to optimize generator fabrication and use, to standardize quality control techniques for the eluted radionuclides and to provide standardized procedures to participating laboratories.

Extraction chromatography using ion exchange resins, lanthanide selective resins (Eichrom), the SLM separation technique and electrochemical separation were successfully evaluated for separation of ^{90}Y from ^{90}Sr. Several technologies developed within the CRP can be used for the preparation of ^{90}Y suitable for radionuclide therapy. The need for a 'real time' quality control assay to estimate the radionuclidic purity of ^{90}Y was met by developing reliable analytical techniques. The BARC method for estimating the radionuclidic purity of ^{90}Y based on EPC is a significant achievement of the CRP owing to its novelty, simplicity and suitability for routine application in nuclear medicine departments [2.6].

The CRP succeeded in developing a protocol for the preparation of a ^{188}W/^{188}Re generator with high specific activity ^{188}W (>3 Ci/g) using the existing hardware of the ^{99}Mo/^{99m}Tc generator. The procedure can be adapted by Member States for generator production.

Adsorbents such as hydroxyapatite, PZC and PTC were studied for adsorption of ^{188}W in order to increase the radioactive concentration of eluted ^{188}Re. Post-elution concentration techniques were also developed by the participants to increase the specific volume of ^{188}Re. These technologies can be adapted for the preparation of ^{188}Re for radiopharmaceutical production. In conclusion, the CRP succeeded in achieving all the objectives set out at the onset of the project.

REFERENCES TO CHAPTER 2

[2.1] WESTER, D.W., et al., Large-scale purification of ^{90}Sr from nuclear waste materials for production of ^{90}Y, a therapeutic medical radioisotope, Appl. Radiat. Isot. **59** (2003) 35–41.

[2.2] NATIONAL BUREAU OF STANDARDS, "Maximum permissible body burden and maximum permissible concentrations of radionuclides in air and water for occupational exposure", National Bureau of Standards Handbook, Vol. 69, NBS, Gaithersburg, MD (1959) 38.

[2.3] UNITED STATES PHARMACOPEIAL CONVENTION, Yttrium (Y-90) ibritumomab tiuxetan injection, United States Pharmacopeia 30 NF 25, USP Convention, Rockville, MD (2007) 3487.

[2.4] DHAMI, P.S., et al., Studies on the development of a two stage supported liquid membrane system for the separation of carrier-free ^{90}Y using KSM-17 and CMPO as carriers, Sep. Sci. Technol. **42** (2007) 1107.

[2.5] CHAKRAVARTY, R., et al., Development of an electrochemical ^{90}Sr-^{90}Y generator for separation of ^{90}Y suitable for targeted therapy, Nucl. Med. Biol. **35** (2008) 245–253.

[2.6] PANDEY, U., DHAMI, P.S., JAGESIA, P., VENKATESH, M., PILLAI, M.R.A., A novel extraction paper chromatography (EPC) technique for the radionuclidic purity evaluation of ^{90}Y for clinical use, Anal. Chem. **80** (2008) 801–807.

Chapter 3

PROTOCOLS DEVELOPED UNDER THE CRP

3.1. SUPPORTED LIQUID MEMBRANE BASED ^{90}Sr/^{90}Y GENERATOR[1]

3.1.1. Introduction

Supported liquid membrane separation is based on selective extraction of a species from a mixture using a specific ligand held as a solution in an organic solvent within the pores of a semipermeable membrane. The membrane separates a cell into two chambers, one for holding the mixture of species and the other for collecting the pure species of interest. Supported liquid membrane based generators were conceptualized for separation of ^{90}Y from a mixture of ^{90}Sr and ^{90}Y [3.1–3.3]. Two ligands, namely KSM-17 and CMPO, are used in the construction of the generators. KSM-17 is used to preferentially extract ^{90}Y from a solution at pH1–2 to a solution of higher acidity; CMPO is used for extracting ^{90}Y from a highly acidic solution (3–4M HNO$_3$) to a solution of much lower acidity (1M CH$_3$COOH).

3.1.2. Materials

A high quality quartz glass device with two or three 5 mL chambers (for a single stage and a two stage generator, respectively), and with the provision for insertion of a PTFE membrane between the chambers, was fabricated locally. The PTFE membrane (thickness: 160 μm; porosity: ~84%; average pore diameter: 0.45 μm) was procured from Sartorius AG, Germany. The effective area of the membrane was approximately 1.13 cm^2. KSM-17 and CMPO were synthesized as per a previously reported procedure [3.4, 3.5]. The KSM-17 reagent is equivalent to the commercially available reagent PC88A from Daihachi Chemicals Industry Co. Ltd., Japan.

Strontium-90 (in equilibrium with ^{90}Y) as strontium nitrate adjusted to pH1–2 was used as the stock solution.

---

[1] Contribution from the Bhabha Atomic Research Centre, India.

3.1.3. Methods

3.1.3.1. Single stage SLM generator

In this system, the generator consists of two chambers (a feed and a receiver chamber), each with a capacity of 5 mL. The schematic diagram of the single stage SLM generator employing KSM-17 is shown in Fig. 3.1.

The PTFE membrane is impregnated with KSM-17 by immersion in undiluted KSM-17 for about 12 h prior to use. The membrane is removed from the KSM-17 solution, washed with deionized water and then inserted between the feed and receiver chambers. The feed chamber contains an equilibrium mixture of ^{90}Sr and ^{90}Y adjusted to pH1–2, and 5 mL of 1M HCl is taken in the receiver chamber. The solution in both chambers is stirred with the help of small PTFE coated magnetic stirrers. The system is operated for about 4 h, and the ^{90}Y solution transported into the receiver chamber is withdrawn with a syringe for use.

Typically, 40–50% of the ^{90}Y present in the mixture is transported to the receiver chamber within 4 h. If the system is operated for longer, the yields are better, but the chances of ^{90}Sr contamination of the product also become higher.

3.1.3.2. Two stage SLM generator

Although the single stage SLM generator could provide ^{90}Y of the required purity, the yield of ^{90}Y is low at 40–50% in 4 h. The yield increases (>80%) when the acidity of the feed is decreased (≥pH3) and that of the receiver phase is increased (≥3M). But these acidity conditions also result in ^{90}Sr contamination of the eluted ^{90}Y product. To overcome these limitations, a two stage SLM generator was conceived [3.3].
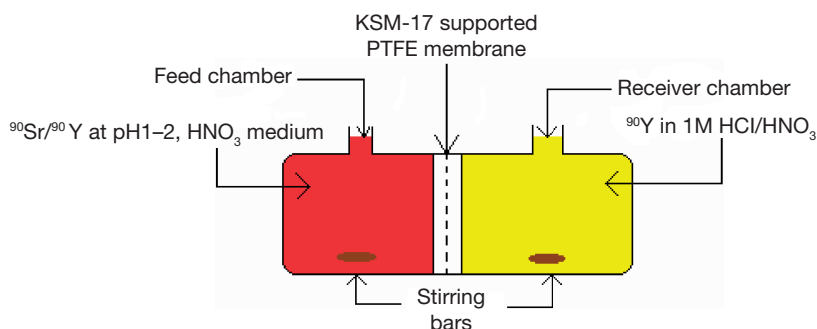
FIG. 3.1. Single stage SLM generator system.

The two stage SLM generator system was designed based on the solvent extraction properties of KSM-17 and CMPO under different acidity conditions. In this system, the generator consists of three 5 mL chambers (feed, inter-mediate and receiver chambers). A PTFE membrane impregnated with KSM-17 is prepared as described previously. Another PTFE membrane with CMPO is prepared by immersing it in 0.8M CMPO in n-dodecane for about 12 h prior to use. The schematic diagram of the cell is shown in Fig. 3.2.

The PTFE membrane containing KSM-17 is inserted between the feed and intermediate chambers, and the PTFE membrane with CMPO is inserted between the intermediate and receiver chambers. Five millilitres of the mixture of ^{90}Sr (in equilibrium with ^{90}Y) as nitrate adjusted to pH1–2 is placed in the feed chamber; 5 mL of 4M HNO_3 is placed in the intermediate chamber; and 5 mL of 1M CH_3COOH is placed in the receiver chamber. The system is operated for about 10 h with continuous stirring, and the ^{90}Y solution transported into the receiver chamber is available as ^{90}Y acetate for use.

Figure 3.3 depicts the transport of activity in the two stage SLM generator system. The activity in the feed, intermediate and receiver chambers, as a percentage of the total activity, is plotted versus time. Typically, about 85% of the ^{90}Y is transported to the final receiver chamber in 10 h.

3.1.4. Quality control of ^{90}Y

The purity of ^{90}Y was assayed by the radiometric method. The β^- activity of the product was estimated as a function of time. The initial β^- activity on the planchette, about 10^5 counts/min, was found to decay to the background
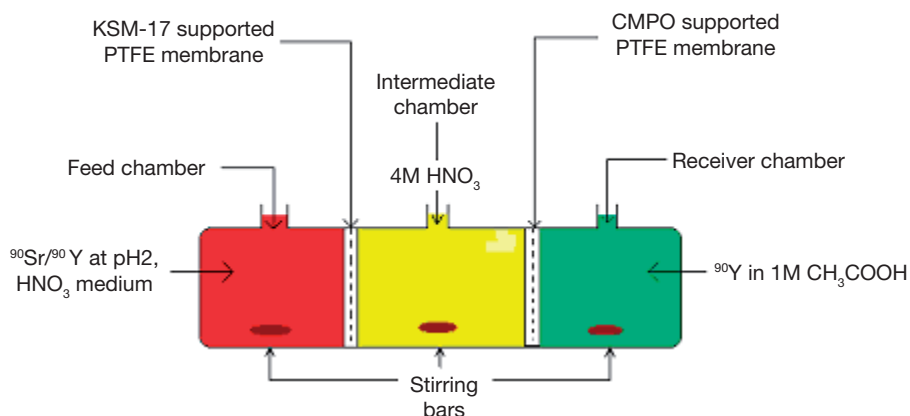
FIG. 3.2. Schematic diagram of a two stage SLM generator.
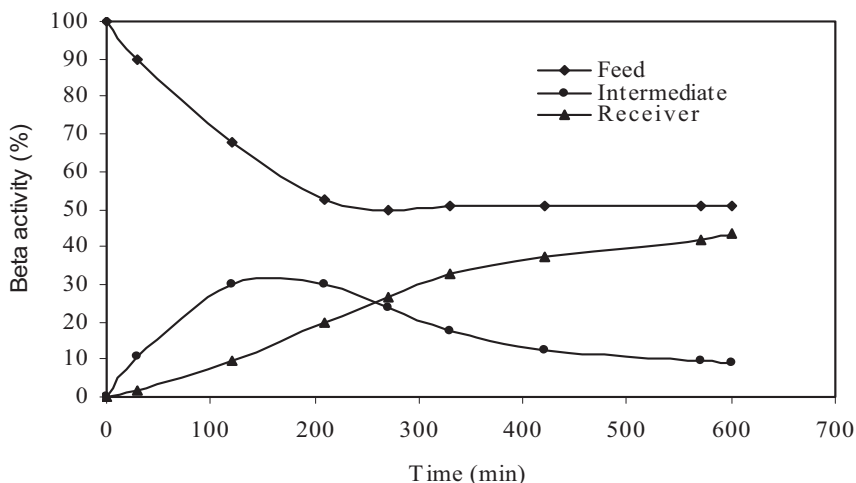
FIG. 3.3. Separation of ^{90}Y using the two stage SLM based $^{90}Sr/^{90}Y$ generator.

activity after about 26 d. The half-life of the product was estimated to be approximately 64 h, confirming the absence of ^{90}Sr in the product.

An EPC method was used to estimate the ^{90}Sr content in the eluted ^{90}Y [3.6]. The ^{90}Sr detected in the product of the SLM based generator was found to be within permissible limits.

3.2. ELECTROCHEMICAL $^{90}Sr/^{90}Y$ GENERATOR[1]

3.2.1. Introduction

For use in targeted therapy, the ^{90}Y should be of high specific activity and very high radionuclidic purity (>99.998%). An electrochemical $^{90}Sr/^{90}Y$ generator system was developed for the preparation of high specific activity ^{90}Y [3.7]. The system is based on the reports by Reischl et al. [3.8] and Yoo et al. [3.9] on the isolation of pure ^{86}Y in usable quantities greater than 3.7 GBq (>100 mCi) from milligram quantities (50–150 mg) of enriched ^{86}Sr using an electrochemical method. Details of the generator set-up are given below.

---

[1] Contribution from the Bhabha Atomic Research Centre, India.

3.2.2. Materials

Strontium-90 in equilibrium with ^{90}Y in 2M HNO_3 was used for the electrochemical studies. The high purity platinum metal plates used were procured from Hindustan Platinum Ltd, Mumbai. A potentiostat unit with 100 V compliance, a maximum current of 2 A, 1.2 nA current resolution and over 10^{13} Ω input impedance, less than 5 pF capacitance, and a 10 µHz–1 MHz built-in analyser for impedance was also used.

3.2.3. Methods

3.2.3.1. Electrochemical set-up

An open end quartz cylinder (50 mL capacity) fitted with an acrylic cap is used as the electrochemical cell. The electrodes are fabricated by spot welding platinum plates (75 mm × 10 mm × 0.5 mm) to a platinum rod. The electrodes are then fitted 5 mm apart on the acrylic cap, which, along with the electrodes, is fitted on the mouth of the quartz cylinder. The acrylic cap is used to raise and lower the electrodes. Provision for passing gas through an acrylic tube is made. An outlet (~2.5 mm) is provided in the acrylic cap for venting the gases. Figure 3.4 shows the electrochemical set-up.
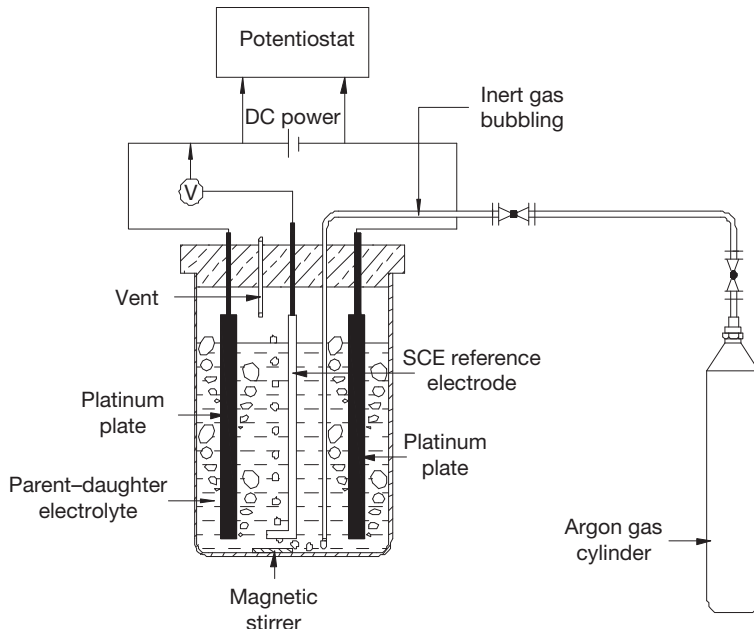
FIG. 3.4. Schematic diagram of the electrolysis cell used for the $^{90}Sr/^{90}Y$ generator.

3.2.3.2. First electrolysis

Strontium-90 as $^{90}Sr(NO_3)_2$ in 2M HNO_3 is used. The solution (1.85 GBq (50 mCi)) is placed in a 50 mL beaker and evaporated to dryness; it is then dissolved in 30 mL of 0.001M HNO_3 and transferred to the quartz electrochemical cell. The pH is adjusted to 2.5–3.0 using 3% ammonium hydroxide. The electrolysis cell is then covered with the acrylic cap together with the two platinum electrodes. Argon gas is gently bubbled through the solution for 10–15 min prior to applying current, and the electrolysis is performed potentiostatically at –2.5 V with respect to a saturated calomel electrode (SCE) for 90 min. At the end of the initial electrolysis, the acrylic cap and the electrodes are removed from the cell while the current is maintained. After the current is switched off, the cathode plate is removed from the acrylic cell and washed with 10 mL of acetone. After washing, the electrode is fitted to another acrylic cap, to which a cylindrical platinum electrode (2.5 mm (diameter) × 75 mm × 0.5 mm) is attached.

3.2.3.3. Second electrolysis (purification step)

A fresh quartz cell is filled with 30 mL of 0.003M nitric acid (pH2.5–3). The acrylic cap containing the electrodes is fitted to the quartz cell, and argon gas is bubbled through the solution for 10–15 min. The cylindrical electrode is connected as the cathode, and the original platinum plate containing ^{90}Y is connected as the anode. Electrolysis is performed for 45 min with a constant potential of –2.5 V and a 100 mA current, with argon gas continuously bubbled through the solution. At the end of electrolysis, the acrylic cap is removed from the solution while the voltage is maintained. The cylindrical platinum electrode with the deposited ^{90}Y is washed with 10 mL of acetone, followed by leaching of ^{90}Y with 500 μL of acetate buffer at pH4.75.

After use, the electrodes are washed with 3M HNO_3 and made ready for subsequent experiments. The feed solution in the first electrolytic cell is also preserved, since it retains most of the ^{90}Sr activity. The ^{90}Sr solution is allowed to stand for growth of ^{90}Y and is then used for further electrolysis at pH2.5–3.0. The activities of the electrolyte in the second cell as well as the acetone wash solution are then transferred into a waste container.

Yields of 97–98% of ^{90}Y deposition have been observed after the initial electrolysis step, as well as after the second electrolysis step.

3.2.4. Quality control of ^{90}Y

The BARC method for estimating the radionuclidic purity of ^{90}Y is used to estimate the ^{90}Sr in the eluted ^{90}Y [3.6]. Estimation of the amount of ^{90}Sr by this method gave values of approximately 30.2 ± 15.2 kBq (817 ± 411 nCi) of ^{90}Sr per 37 TBq (1 Ci) of ^{90}Y (0.817 ± 0.411 ppm) for different batches. The ^{90}Sr levels observed are very low and within acceptable limits.

3.2.5. Conclusion

The electrochemical separation procedure described above has been successfully demonstrated for separation of ^{90}Y from ^{90}Sr with high radio-chemical yield and purity. An electrochemical ^{90}Sr/^{30}Y generator such as this has very low operational costs and can provide a continuous supply of ^{90}Y suitable for therapeutic applications.

3.3. BARC METHOD FOR ESTIMATING THE RADIONUCLIDIC PURITY OF ^{90}Y BY EXTRACTION PAPER CHROMATOGRAPHY[1]

3.3.1. Introduction

Yttrium-90 based therapeutic radiopharmaceuticals are widely used for cancer treatment and for therapy of other diseases such as rheumatoid arthritis. An important condition for the use of ^{90}Y eluate obtained from ^{90}Sr/^{90}Y generators is that it should be devoid of any ^{90}Sr, since this long lived radioisotope (~28.8 a) accumulates in bone. The MPBB of ^{90}Sr is only 74 kBq (2 µCi) [3.10]. The ^{90}Sr impurity level in ^{90}Y is quoted by the manufacturers as being 740 or fewer kBq (20.0 µCi) of ^{90}Sr per 37 GBq (1 Ci) of ^{90}Y [3.11, 3.12]. To measure this level of purity, the ability to detect 20 or fewer disintegrations per minute (dpm) of ^{90}Sr in one million dpm of ^{90}Y is required.

The BARC method for estimating the radionuclidic purity of ^{90}Y is based on the EPC technique [3.7]. EPC is a combination of solvent extraction and paper chromatography techniques. A chromatography paper impregnated with a ^{90}Y specific chelate, KSM-17, at the point of application is used as the support for chromatography. Owing to its selective retention by KSM-17, Y^{+3} remains at the point of spotting while Sr^{+2} moves with the solvent front. The activity at

---

[1] Contribution from the Bhabha Atomic Research Centre, India.

the solvent front is estimated in a liquid scintillation counter and compared with the total spotted activity.

3.3.2. Materials

The KSM-17 used in these studies was synthesized at BARC [3.4]. The commercially available reagent equivalent to KSM-17 is PC88A (Daihachi Chemical Industry Co. Ltd., Japan). The scintillation cocktail was prepared from 900 mL of dioxane, 100 g of naphthalene and 1.2 g of PPO (2,5-diphenyl oxazole). Paper chromatography strips from Whatman (UK) were used for the assay.

3.3.3. Methods

The EPC technique is performed as described in the following.

Step 1. Preparation of test solution: A 'test solution' of 100 µL of ^{90}Y acetate with a radioactive concentration of 37 MBq/mL (1.0 mCi/mL) is prepared by dilution of the bulk solution with 0.5M ammonium acetate.

Step 2. Preparation of EPC paper: Whatman 1 chromatography paper (12 cm × 1 cm) marked in 1 cm segments is used, with 10 µL of KSM-17 applied between the second and third segments, after which the paper is allowed to air dry.

Step 3. Extraction paper chromatography: A 5 µL sample of the test solution prepared in step 1 is applied to the KSM-17 spot on the EPC paper and allowed to air dry. The EPC is then developed in an ascending manner using 0.9% saline as the developing solvent. After the solvent has moved to the top, the paper is removed and cut into 1 cm segments, and three segments of the solvent front are inserted in a liquid scintillation vial containing 10 mL of the scintillation cocktail. The paper should be segmented beginning at the solvent front and moving backwards. As the activity at the point of spotting is very high, contamination of the scissors due to contact with this activity may increase the activity of the subsequent strips. The samples are counted for 60 min. The counting must be done immediately (within a couple of hours after completion of the experiment), since the counts in the ^{90}Sr fraction will continue to increase during storage owing to growth of ^{90}Y. For example, ^{90}Y grows to 2% of its maximum value in 2 h, to approximately 23% in 1 d and to approximately 40% in 2 d. Therefore, the amount of ^{90}Sr will be overestimated if there is a time lag between the development of the paper strip and the sample counting.

Step 4. Calculation of results: In this case, the test solution contained 37 MBq/mL (1.0 mCi/mL), and thus the original activity used in the EPC was 1.85×10^5 Bq (5 µCi). Using the efficiency of the counter, the activity at the

solvent front of the paper strip is calculated. The percentage of radionuclidic impurity is then calculated from the above results. For example, 6000 counts obtained in the solvent front for a 60 min counting corresponds to 100 counts/min; if the efficiency of the counter is 90%, the activity is 111 dpm or 1.85 Bq. The radionuclidic impurity in this case is 0.001%, and the radionuclidic purity of the product is 99.999%. The solution thus contains 370 kBq (10 µCi) of ^{90}Sr in 37 GBq (1 Ci) of ^{90}Y.

Step 5. Setting the ^{90}Sr impurity limit for the ^{90}Y eluate: The ^{90}Sr impurity limit quoted by most commercial manufacturers is 740 kBq (20 µCi) of ^{90}Sr per 37 GBq (1 Ci) of ^{90}Y, which corresponds to 3.7 Bq or 222 dpm of ^{90}Sr per 185 kBq (5 µCi) of the spotted solution. Hence, ≤222 dpm in the solvent front corresponds to a ^{90}Sr contamination of ≤740 kBq (20 µCi) per 37 GBq (1 Ci) of ^{90}Y. The product is then consistent with the manufacturer specifications. If necessary, lower cut-off limits can also be set, based on the above method.

Step 6. Validation of the technique: This is an optional step to be followed for validation of the EPC technique. A 5 µL aliquot of the test solution is dispensed into a liquid scintillation vial. The vial is marked with the batch number and stored for about 60 d, by which time it is expected that 99.99999% of the ^{90}Y decays and only any ^{90}Sr contamination is present. At this point, any ^{90}Sr present will be in secular equilibrium with ^{90}Y. The vial is then counted in the liquid scintillation counter for 60 min. The counts correspond to any ^{90}Sr contamination and an equal amount of ^{90}Y. If gross counting is performed to include both ^{90}Y and ^{90}Sr windows, the activity measured can be halved to obtain the ^{90}Sr activity (assuming that there is not much difference in the efficiency for ^{90}Sr and ^{90}Y). The activity thus calculated for ^{90}Sr should be equal to the activity in the solvent front obtained during the EPC (step 4 above).

3.4. ^{188}W/^{188}Re ALUMINA BASED GENERATOR[2]

3.4.1.   Introduction

Alumina is well known and widely used as a support for ^{99}Mo/^{99m}Tc generators. Owing to the chemical similarity of the ^{188}W/^{188}Re pair and the ^{99}Mo/^{99m}Tc pair, it has also been introduced as a support for ^{188}W/^{188}Re generators [3.13, 3.14].

---

[2] Contribution from the Radioisotope Center POLATOM, Poland.

A portable [188]Re generator was developed using the alumina column and other elements of the 'dry bed' system of the [99]Mo/^{99m}Tc generator [3.15]. High specific activity [188]W in the form of tungstic acid was adsorbed on alumina, and [188]Re was eluted as perrhenate with 0.9% NaCl, with a radiochemical purity greater than 98.0% and a radionuclidic purity greater than 99.9% with respect to γ-impurities, and [188]W breakthrough of less than 0.5×10^{-3}%. The nominal activities of the [188]Re obtained were up to 500 mCi, with elution yields greater than 80%. The radioactive concentration of [188]Re was greater than 100 mCi/mL, and no post-elution concentration was initially required. The generators were mechanically and radiochemically stable for over 6 months. Details of the generator set-up are given below.

3.4.2.   Materials

Tungsten-188 (RIAR, Russian Federation) with a specific activity between 27 and 133 GBq per gram of tungsten was used for generator column loading. Aluminium oxide (Alumina A, ICN, MP Biomedicals, USA) and the standard glass columns, needles and shielding of [99]Mo/^{99m}Tc generators produced at the IAE Radioisotope Centre POLATOM were used for generator assembly.

3.4.3.   Methods

3.4.3.1.   Preparation of generator column

Aluminium oxide was stirred in deionized water and decanted several times until the supernatant was clear. The decanted alumina was then dried for 4 h at 80°C. About 2 g of dry alumina was loaded onto a column, fixed on the top with a bed of glass wool and closed by rubber seals and aluminium caps. The column was autoclaved for 0.5 h at 121°C to ensure its sterility. Before loading the [188]W, the column was activated by subsequent washing with the following solutions: 5 mL of 0.9% NaCl solution acidified to pH3 (flow rate: 10 mL/min), 5 mL of 32% HCl (flow rate: 5 mL/min) and 20 mL of 0.9% NaCl solution at pH3 (flow rate: 10 mL/min) to obtain effluent at pH3.

3.4.3.2.   [188]W loading on column

Before it was loaded onto the column, [188]W (27–133 GBq per gram of tungsten) was dissolved in 0.5M NaOCl (0.5 mL of NaOCl per gram of tungsten), 80% CH_3COOH (1 mL of CH_3COOH per gram of tungsten) and 32% HCl in order to lower the pH of the solution to 2.5 to obtain tungstic acid.

The ^{188}W solution (as Na^{188}WO$_4$) was then slowly loaded onto the column using a peristaltic pump (flow rate: 0.1 mL/min). The column was washed with NaCl solution (0.9% at pH5.0–5.5) in order to remove the unbound ^{188}W. Finally, the generator column was fixed into the generator shielding and placed in the plastic box, followed by the installation of the eluting needles. Figure 3.5 shows the layout of the ^{188}W/^{188}Re generator.

3.4.3.3. Testing of generator performance

The elution profile of the generator was investigated using four fractions, each containing 4 mL of 0.9% NaCl at pH5.0–5.5 (Fig. 3.6). Routine elutions were performed three times a week using 8 mL of eluent in two fractions of 4 mL each. The following tests were performed:

(a) Elution yield (total radioactivity of four 4 mL fractions);
(b) Measurement of pH (of the first fraction of each elution);
(c) Radiochemical purity (of the first fraction, once a week);
(d) Radionuclidic purity (of the second fraction, once every 2 weeks);
(e) Sterility and bacterial endotoxins (of the third fraction, once every 2 months);
(f) Chemical purity (ICP-OES) (of the second fraction, once every 2 months).
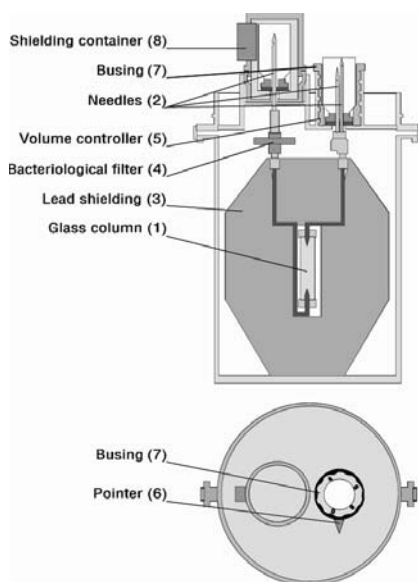
FIG. 3.5. Schematic view of the generator set-up.
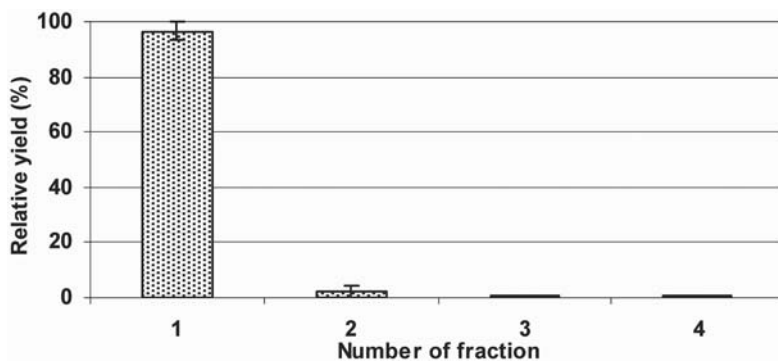
FIG. 3.6. Yields of ^{188}Re elution in collected fractions over ten consecutive elutions.

3.4.4. Methods used for quality control

The radioactivity of eluted fractions was measured with an accuracy of ±5% using an ionization chamber calibrated for ^{188}Re against a secondary standard solution. The ^{188}W (breakthrough) activity and radioactive impurities were measured with the use of a gamma spectrometer with a high purity germanium (HPGe) detector (DSA-2000, GX-2018, Canberra Inc.). The radio-chemical purity of ^{188}Re perrhenate was checked by paper chromatography (Whatman 1) using acetone as the developing solution. The chemical purity of the eluate was determined using an ICP optical emission spectrometer (Optima 3300XL, Perkin Elmer), with special consideration given to the presence of tungsten, aluminium and zirconium.

3.4.5. Conclusion

The procedure described above was tested in the fabrication of generators with the nominal activity of ^{188}Re in the range of 4–15 GBq at the calibration date. The chemical quantity of tungsten loaded onto the column was between 40 and 80 mg per gram of alumina. The elution profile of the generator is presented in Fig. 3.6, which shows the average values of generator yields collected in each fraction obtained in ten consecutive elutions (over a period of 4 weeks). More than 95% of the ^{188}Re activity was accumulated in first and second fractions.

The ^{188}W/^{188}Re equilibrium is reached in about 72 h; however, ^{188}Re can be obtained from the generator more often with a satisfactory yield. The activities of the ^{188}Re obtained from the generator ranged up to 500 mCi at the calibration date, and over 90% of activity was eluted in the first 4 mL

of effluent. The radioactive concentration of ^{188}Re was between 15 and 120 mCi/mL, and hence no post-elution concentration was initially required. The eluates were sterile and free of bacterial endotoxins. The radiochemical purity was greater than 98.0% and the radionuclidic purity was greater than 99.9% with respect to gamma impurities. Leakage of ^{188}W was less than 0.5×10^{-3}%, and chemical purity testing showed less than 10 ppm of aluminium.

3.5. IN-HOUSE PREPARATION OF SILVER CATION COLUMN FOR TRAPPING CHLORIDE ANION FROM SALINE ELUANT FOR CONCENTRATION OF ^{188}Re SOLUTION[3]

3.5.1. Introduction

Saline elution of the alumina based ^{188}W/^{188}Re generator system provides no carrier added solutions of ^{188}Re perrhenate [3.13–3.16]. Because of variations in the specific activity of the ^{188}W parent, the period of time the generator has been used since fabrication, and the ^{188}Re activity levels and specific volume (mCi per mL of saline) required, the availability of simple, effective methods for post-elution concentration and for increasing the specific volume of ^{188}Re eluate solutions is important. Post-elution concentration of ^{188}Re perrhenate by subsequent passage through a tandem silver cation–anion column system is one simple and cost effective method for obtaining very high concentrations of ^{188}Re. Although silver cation columns are commercially available, their cost and limited chloride trapping capability and shelf life are factors that suggest that in-house preparation of these columns is an important cost effective alternative. The method described here is a simple, economical and flexible way to prepare silver impregnated cation exchange columns with the chloride trapping capability required for concentration of saline generator eluants containing ^{188}Re.

3.5.2. Materials

An appropriate glass or plastic column with fittings should be assembled and leak tested with deionized water prior to use. Convenient disposable column systems fitted with Luer lock fittings are commercially available from BioRad. The BioRad #737-15-12 Econo-Column (1.5 cm outside diameter × 10 cm length) was used in the present procedure (Fig. 3.7). Columns are

---

[3] Contribution from ORNL, Oak Ridge, TN, USA.

available in a variety of sizes, and larger volume columns can be used if increased chloride trapping capacity is required. These glass columns have a glass frit at the bottom, and the top is a plastic pressure fit Luer assembly. AG 50X4 sulphonic acid resin (200–400) mesh, can be used as the cation material. The column described above holds a maximum of about 8 g of the resin (dry weight). A three way Luer valve should be connected between the bottom of the column Luer lock and a QMA anion trapping column, prewetted with DI water. Also required are 1N silver nitrate solution and saline solution.

3.5.3. Methods

3.5.3.1. Preparation of silver impregnated AG 50 column

One resin that can be used for the silver cation column is AG 50X4 sulphonic acid resin (200–400 mesh). A typical column system is shown in Fig. 3.7. A column of this size holds about 8 g of the AG resin (approximately 1.1 meq per mL of dry resin). About 2 g of the resin (~2 meq) for every 10 mL of 0.9% (0.15N) saline (1.5 meq) should be sufficient to ensure optimal trapping of the chloride anion. The column should be eluted from top to bottom in a vertical position so as not to disturb the column packing, and care should be taken to ensure that there are no air bubbles in the column packing. The top of the column can be packed with a fine glass wool plug to minimize disturbance and stabilize the column bed. The system is then wetted thoroughly by passing through 20–30 mL of DI water by gravity flow. A volume of 15–20 mL of 1N silver nitrate solution (1 meq/mL), for instance, is then passed through the loaded column. The silver nitrate solution used should contain a slight excess of the level of silver ion required to saturate the anion binding sites. The column is then washed with DI water (25–50 mL). Although gravity flow is probably adequate, it is recommended that, for washing and elution, a syringe or peristaltic pump be used at a slow flow rate (<1 mL/min) to ensure reproducibility and reliability.

FIG. 3.7. BioRad column: components and assembled column.

3.5.3.2. Quantification of silver loading

If quantification of the silver trapping capacity of the column is desired, a sample of the total eluant/wash can be titrated with a known concentration of sodium chloride solution to determine and quantitate the levels of silver ion present, and thus how much is bound to the resin. About 50–55 mL of saline can be passed through such a column prepared in this manner before the chloride anion is detected by elution into a silver nitrate solution. As the sodium chloride solution — which corresponds to 0.15 meq per millilitre of physiological (0.15M) saline — passes through the silver cation column, the appearance of the column material changes from an opaque white colour to an orange-brown colour in the areas where the insoluble AgCl is deposited within the column.

3.5.3.3. Testing and use of the silver cation column

Before use, a three way valve and a QMA anion trapping column are attached to the bottom of the silver cation column as shown in Fig. 3.8, and 25–50 mL of DI water is passed through to completely wet the system. It is suggested that, before use with the generator, a tracer level of [188]Re perrhenate solution (e.g. 5–10 µCi) be added to a saline solution for a few test elutions through the silver cation column prototype connected in tandem to a QMA anion trapping column, for instance, until the conditions are optimized. Under these conditions and with a column of this size, the [188]Re saline solution added to the silver cation column eluant will initially be detected after about 5 mL of saline has passed through the column (approximately the void volume). If the silver cation column has sufficient chloride trapping capacity for the volumes of saline that are expected to be used for the generator elution, all the [188]Re activity should be subsequently trapped in the QMA anion column. If significant levels of [188]Re are detected in the eluant from the QMA column, then all the chloride has not been trapped by the cation column, and chloride anion has been eluted and has competed with the perrhenate for QMA trapping. The use of this system is described in more detail in Ref. [3.17].

3.5.4. Summary and conclusions

In the procedure described here, a single silver cation column can be prepared that can potentially trap the chloride anion from any volume of saline. Since the cation resin is not tightly packed, as in the commercial columns, the generator/tandem trapping system should be eluted at a relatively low flow rate (0.25–0.30 mL/min). Lower flow rates will also minimize any
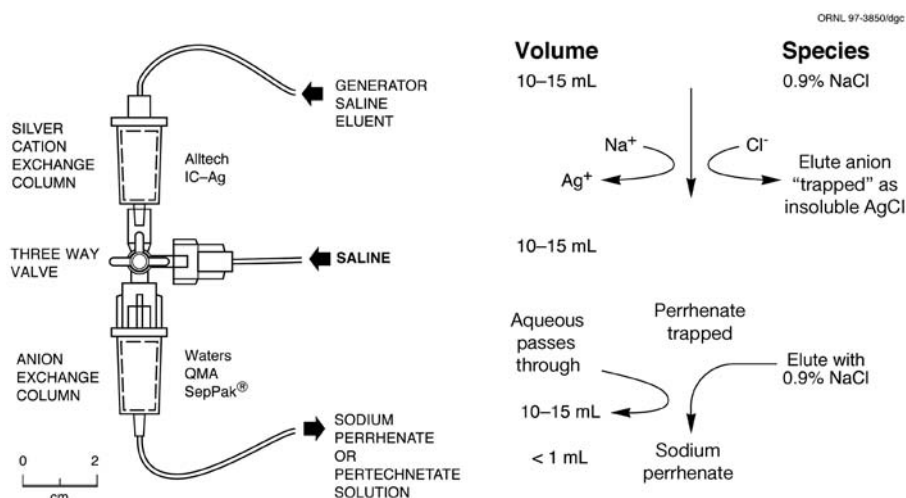
FIG. 3.8. Use of the tandem silver cation–QMA anion ^{188}Re perrhenate concentration system illustrated with the commercially available IC-Ag and QMA columns with 15 mL of saline eluant.

potential back pressure from the complete tandem trapping system, if the anion trapping is also used in series. Presumably, if the silver cation columns are thoroughly washed after use, following decay of any residual ^{188}Re, the packing can be carefully removed and discarded, and the column can be packed again for reuse. Although commercially available silver impregnated cation columns are widely used for concentration of ^{188}Re perrhenate solutions, they are expensive and have a limited chloride trapping capability (from 1.5–3 meq to 10–20 mL per column). The in-house preparation of these columns is an attractive alternative, and is a significantly more cost effective and versatile method for the preparation of columns capable of trapping the chloride anion from essentially any volume of saline.

REFERENCES TO CHAPTER 3

[3.1] ACHUTHAN, P.V., DHAMI, P.S., KANNAN, R., GOPALAKRISHNAN, V., RAMANUJAM, A., Separation of carrier-free ^{90}Y from high level waste by extraction chromatographic technique using 2-ethyl hexyl 2-ethyl hexyl phosphonic acid (KSM-17), Sep. Sci. Technol. **35** (2000) 261–270.

[3.2] VENKATESH, M., et al., Complexation studies with ^{90}Y from a novel ^{90}Sr-^{90}Y generator, Radiochim. Acta **89** (2001) 413–417.

[3.3] DHAMI, P.S., et al., Studies on the development of a two stage supported liquid membrane system for the separation of carrier-free ^{90}Y using KSM-17 and CMPO as carriers, Sep. Sci. Technol. **42** (2007) 1107–1121.

[3.4] MARWAH, U.R., "Synthesis of organophosphorous extractants for solvent extraction of metals", Proc. Natl Symp. on Organic Reagents–Synthesis and Use in Extraction Metallurgy (ORSEUM-94), BARC, Mumbai (1994).

[3.5] GATRONE, R.C., KAPLAN, L., HORWITZ, E.P., The synthesis and purification of carbamoyl methyl phosphine oxides, Solvent Extr. Ion Exch. **5** (1987) 1075–1116.

[3.6] PANDEY, U., DHAMI, P.S., JAGESIA, P., VENKATESH, M., PILLAI, M.R.A., A novel extraction paper chromatography (EPC) technique for the radionuclidic purity evaluation of ^{90}Y for clinical use, Anal. Chem. **80** (2008) 801–807.

[3.7] CHAKRAVARTY, R., et al., Development of an electrochemical ^{90}Sr-^{90}Y generator for separation of ^{90}Y suitable for targeted therapy, Nucl. Med. Biol. **35** (2008) 245–253.

[3.8] REISCHL, G., ROSCH, F., MACHULLA, H.J., Electrochemical separation and purification of yttrium-86, Radiochim. Acta **90** (2002) 225–228.

[3.9] YOO, J., et al., Preparation of high specific activity ^{86}Y using a small medical cyclotron, Nucl. Med. Biol. **32** (2005) 891–897.

[3.10] NATIONAL BUREAU OF STANDARDS, "Maximum permissible body burden and maximum permissible concentrations of radionuclides in air and water for occupational exposure", National Bureau of Standards Handbook, Vol. 69, NBS, Gaithersburg, MD (1959) 38.

[3.11] MDS-NORDION, Yttrium-90, radiochemical yttrium chloride solution, Y-90 fact sheet, available at:
http://www.mds.nordion.com/documents/products/Y-90_Can.pdf

[3.12] UNITED STATES PHARMACOPEIAL CONVENTION, Yttrium (Y-90) ibritumomab tiuxetan injection, United States Pharmacopeia 30 NF 25, USP Convention, Rockville, MD (2007) 3487.

[3.13] KNAPP, F.F., Jr., et al., Development of the alumina-based tungsten-188/rhenium-188 generator and use of rhenium-188-labelled radiopharmaceuticals for cancer treatment, Anticancer Res. **17** (1997) 1783–1796.

[3.14] KNAPP, F.F., Jr., Rhenium-188: A generator-derived radioisotope for cancer therapy, Cancer Biother. Radiopharm. **13** (1998) 337–349.

[3.15] KNAPP, F.F., Jr., et al., Availability of rhenium-188 from the alumina-based tungsten-188/rhenium-188 for preparation of rhenium-188-labelled radiopharmaceuticals for cancer treatment, Anticancer Res. **17** (1997) 1803–1808.

[3.16] MIKOLAJCZÁK, R., ZUCHLINSKA, M., PAWLAK, D., "Optimized alumina column for preparation of ^{188}W/^{188}Re generator", in Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine (Proc. 6th Int. Symp. on Technetium in Chemistry and Nuclear Medicine), Vol. 7, Forum-Brixen-Bressanoner, Italy (2006) 601–604.

[3.17] GUHLKE, S., et al., Tandem cation/anion column treatment of ammonium acetate eluants of the alumina-based tungsten-188/rhenium-188 generator: A new simple method for effective concentration of rhenium-188 perrhenate solutions, J. Nucl. Med. **41** (2000) 1271–1278.

Chapter 4

PRELIMINARY STUDIES OF THE DEVELOPMENT OF ^{90}Sr/^{90}Y GENERATORS AT IPEN, BRAZIL

J.A. OSSO, Jr., G. BARRIO, A. OLIVEIRA, B.S. MARCZEWSKI,
V. MORAES, F. CAMARGO, R.C. NIETO, K.N. SUZUKI,
C.R.B.R. DIAS, P.R.C. LOPES, N.C. SILVA, A.L.C.P. LIMA,
B.L. FAINTUCH, J. MENGATTI, E. BORTOLETI, N.P. SOSA,
C.P.G. DA SILVA
Radiopharmacy Centre,
Nuclear and Energy Research Institute (IPEN-CNEN/SP),
São Paulo, Brazil

Abstract

An objective of the coordinated research project was the development of techniques for the preparation of ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators. The Radiopharmacy Centre at IPEN-CNEN/SP has an established radioisotope production programme that supplies radiopharmaceuticals to the nuclear medicine community in Brazil. In the light of the demand for ^{90}Y based radiopharmaceuticals in Brazil, IPEN initiated a programme on the development of a ^{90}Sr/^{90}Y generator. The work done at IPEN in this connection is reported in the paper.

4.1. INTRODUCTION

Radiotherapy delivered via internal administration of radionuclides targeted via a tumour seeking carrier molecule is increasingly used in the treatment of cancer. Radionuclides emitting beta and alpha particles, and Auger electrons are of primary interest. From the point of view of ease of production, labelling stability and dose delivered, the beta emitting radionuclides are the primary choice. In particular, current interest is focused on the use of ^{32}P, ^{90}Y, ^{131}I, ^{153}Sm, ^{166}Ho, ^{177}Lu, ^{186}Re and ^{188}Re. The concept of radionuclide generators, so widely applied for the production of ^{99m}Tc (distributed in the form of ^{99}Mo/^{99m}Tc generators), is also an important strategy for delivering short lived radionuclides for use in therapy. Two generators that are of growing interest in the therapy field are ^{90}Sr/^{90}Y and ^{188}W/^{188}Re.

Yttrium-90 is of great interest for therapeutic applications owing to its pure high energy beta particles (E_{max}: 2.288 MeV, 100%) and appropriate half-life (64 h). Though ^{90}Y can be produced at low specific activity by direct activation in a reactor by the ^{89}Y$(n,\gamma)^{90}$Y reaction, the production method of choice is by the decay of the long lived fission product parent ^{90}Sr ($T_{1/2}$: 28.8 a). The daughter ^{90}Y can be separated by several techniques including solvent extraction and ion exchange.

4.2. MATERIALS

During this project, samples of ^{85}Sr and ^{90}Sr were received by IPEN, Brazil, with the following characteristics:

(a) ^{85}Sr: 10 mCi, 3.86 mL, calibrated on 29.11.2006;
(b) ^{90}Sr: 50 mCi, 5 mL, calibrated on 05.08.2005;
(c) ^{90}Sr: 50 mCi, 0.18 mL, calibrated on 29.11.2006.

4.3. EXPERIMENTAL PROCEDURES

4.3.1. ^{90}Sr/^{90}Y generators

The generators were prepared using cation exchange resins in order to separate ^{90}Y from ^{90}Sr. The solution containing the ^{90}Sr/^{90}Y pair was prepared in 1M HNO$_3$, and EDTA was used as the eluant.

Standardization of the samples of ^{90}Sr/^{90}Y and ^{90}Y: A liquid scintillation analyser (Tri-Carb 1900 TR, Packard Canberra Company) and a liquid scintillation cocktail (Ultima Gold XR) were used for determination of the ^{90}Sr/^{90}Y and ^{90}Y samples and standards. A pure sample of ^{90}Y that had been imported by IPEN was analysed for 60 min, and the spectrum was recorded. Calibration factors were then calculated from the count data.

^{90}Sr/^{90}Y generator #1: The first generator consisted of a glass chromato-graphic column (1 cm in diameter, 2 cm in height), fitted with a glass frit at the bottom and with both ends fitted with plugs. The column was assembled vertically. Before being loaded onto the column, the AG 50WX4 (100–200 mesh, H$^+$ form) cation exchange resin was activated with distilled water, 0.1M HCl and 0.1M NaOH, and finally washed with distilled water. The whole process was repeated three times. After activation, the resin was loaded onto the column and then conditioned with 50 mL of eluent (EDTA) by gravity flow. The EDTA solution was prepared by dissolving 0.279 g of sodium

ethylenediaminetetraacetic acid in 250 mL of water at buffer pH4.8 (0.003M EDTA). The loading solution was prepared by diluting 0.1 mL (5 mCi) of ^{90}Sr in 100 mL of 1M HNO$_3$. From this solution, 2 mL (100 µCi) was percolated onto the column, followed by 5 mL of EDTA solution. After allowing 24 h for adsorption, the column was washed with EDTA twice, and the generator was eluted with 15 mL of EDTA solution three days later and then every week thereafter. The activity of ^{90}Y in the samples was determined by liquid scintillation counting (LSC) for 30 min.

^{90}Sr/^{90}Y generator #2: The second generator consisted of a glass chromatographic column (1 cm in diameter, 8 cm in height) and was assembled vertically. In this generator, the ^{85}Sr was used as a tracer to investigate the separation efficiency. Before being loaded onto the column, the AG 50WX8 (200–400 mesh) resin was converted to the Na$^+$ form with 1M NaOH and then washed with distilled water. The whole process was repeated three times. After the conversion, the resin was loaded onto the column and conditioned with 100 mL of 0.003M EDTA solution at pH4.8.

The loading solution was prepared with 20 µL of ^{90}Sr (1.5 mCi) in 1M HNO$_3$ solution and 300 µL of ^{85}Sr (777 µCi). This solution was percolated onto the column, followed by 4 mL of EDTA solution. Immediately after this process, the column was washed five times with the same volume of EDTA solution. A 15 mL elution was performed after two days and weekly thereafter. In this condition the flow rate was 6 drops/min. The activity of ^{90}Y in the samples was determined by LSC for 30 min, and the activity of ^{85}Sr was determined by gamma ray spectroscopy using an HPGe detector. A paper chromatographic method was also performed for quality control of this generator system.

^{90}Sr/^{90}Y generator #3: A third generator was assembled as described for the second generator, but with the ^{90}Sr activity increased to 5 mCi.

4.4. RESULTS AND DISCUSSION

4.4.1. ^{90}Sr/^{90}Y

Standardization of the samples of ^{90}Sr/^{90}Y and ^{90}Y: Figure 4.1 shows the beta spectrum of the ^{90}Sr/^{90}Y pair and of ^{90}Y. The beta spectrum of ^{90}Y was recorded and used as a reference in order to check the elution efficiency of the generators. The energy channel used was between 50 and 800 keV.

^{90}Sr/^{90}Y generator #1: Figure 4.2 shows the beta spectrum of the eluent from the first generator.
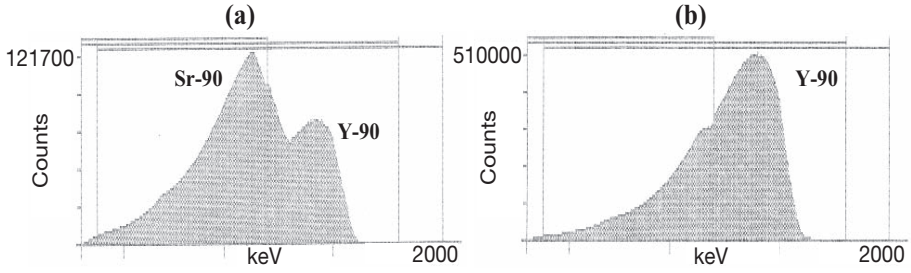
FIG. 4.1. Beta spectrum of ^{90}Sr/^{90}Y (a) and of ^{90}Y (b).
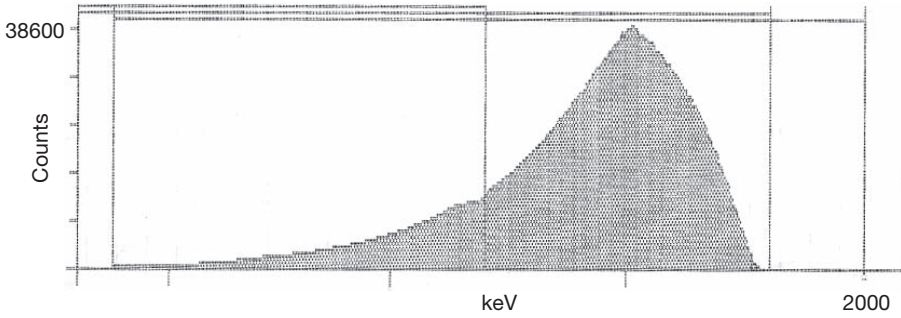
FIG. 4.2. Beta spectrum of the eluent from the first ^{90}Sr/^{90}Y generator.
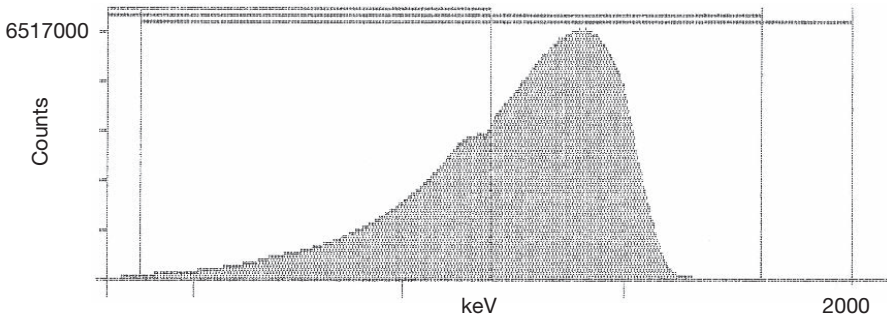
FIG. 4.3. Beta spectrum of the eluent from the second ^{90}Sr/^{90}Y generator.

The elution yields for this generator were very low — less than 7% after the third elution.

^{90}Sr/^{90}Y generator #2: Figure 4.3 shows the beta spectrum of the eluent from the second generator.

The elution yields for this generator are given in Table 4.1.

TABLE 4.1. ELUTION YIELDS FOR
THE SECOND ^{90}Sr/^{90}Y GENERATOR

Elution number	Elution yield (%)
1	7
2	5
3	7
4	7
5	48
6	50
7	46
8	95

The performance of this generator was good and showed that a period of contact between the ^{90}Y and EDTA is necessary to elute most of the activity. The quality control showed that the ^{90}Y contained no ^{90}Sr or ^{85}Sr impurities.

^{90}Sr/^{90}Y generator #3: The initial performance of the third generator is very similar to that of the second generator, but measurable amounts of ^{90}Sr and ^{85}Sr were detected.

4.5. CONCLUSION

During the past few years, the demand for ^{90}Y has grown considerably in Brazil. Currently, IPEN imports ^{90}Y for the production of two different radio-pharmaceuticals: ^{90}Y-citrate and ^{90}Y-hydroxyapatite. The price of ^{90}Y is very high and its distribution is very erratic, hence it is essential to produce in-house ^{90}Sr/^{90}Y generators. The work developed under this CRP is the beginning of this project and will be continued.

Chapter 5

DEVELOPMENT OF ^{90}Sr/^{90}Y GENERATOR TECHNOLOGY

JIN XIAO-HAI, GAO HUI-BO, BAI HONG-SHENG, YIN WEI,
HAN LIAN-GE
Beijing Atom High-tech. Co. Ltd,
China Institute of Atomic Energy,
Beijing, China

Abstract

A process was developed and evaluated for the separation and purification of multicurie quantities of ^{90}Y with sufficient chemical and radiochemical purity for use in medical applications, for example, treating rheumatoid arthritis and other inflammatory diseases, and cancer therapy.

5.1. INTRODUCTION

In recent years, ^{90}Y has become attractive for targeted radionuclide therapy. The ^{90}Y can be obtained from the decay of ^{90}Sr, and is separated from several types of ^{90}Sr/^{90}Y generator. A new process of separating and purifying multicurie quantities of ^{90}Y with sufficient chemical and radiochemical purity for use in medical applications was studied and is described here. This process involves the separation of ^{90}Y from ^{90}Sr by a highly selective and efficient strontium (added as a carrier) precipitation procedure. After this procedure, yttrium selective Eichrom resins are used to separate the ^{90}Sr and retain the ^{90}Y. The ^{90}Y is eluted from the resin column with 0.1 mol/L HCl. The eluted ^{90}Y can be converted to an acetate form suitable for radiolabelling studies.

5.2. PRECIPITATION PROCEDURE FOR ^{90}Sr/^{90}Y

The ^{90}Sr/^{90}Y stock solution must first be purified with a nitrate precipitation procedure (with $Sr(NO_3)_2$ as a carrier) in 80% nitric acid. Strontium (0.79 g) as a nitrate carrier was added to 10 Ci of ^{90}Sr/^{90}Y stock solution. The solution was evaporated at 120°C to a volume of 1–2 mL.

5.3. SEPARATION OF Sr(NO$_3$)$_2$ PRECIPITATE

Centrifugation and filtration were carried out to separate the precipitated Sr(NO$_3$)$_2$ from the concentrated solution, with the ^{90}Y remaining in the strong acid supernatant. The strontium present in the supernatant was analysed as described in the following.

The recovery of strontium for these experiments is summarized in Table 5.1.

5.4. SUPERNATANT PROCESSING

The supernatant containing ^{90}Y and part of the strontium was evaporated to dryness to remove the HNO$_3$, and the residue was dissolved in 0.1M HCl.

5.5. YTTRIUM SELECTIVE EICHROM RESIN CHROMATOGRAPHIC COLUMN

The Eichrom resin was treated with diluted YCl$_3$ solution for 24 h and then heated at 60–80°C for 24 h. The Eichrom resin was packed onto a column with a volume of 1.2 mL.

5.6. CHROMATOGRAPHIC SEPARATION

The solution containing ^{90}Y and ^{90}Sr was loaded onto the Eichrom treated column, which was then washed with 0.1M HCl to recover the ^{90}Sr. The ^{90}Y was eluted with 0.1–1.0M HCl, and the pure ^{90}Y in HCl solution was converted with 0.05M HCl or 0.1M acetic acid for subsequent radiolabelling studies. The ^{90}Sr recovered from the chemical processing procedures was stored for ^{90}Y growth and subsequent use.

TABLE 5.1. RECOVERY OF STRONTIUM

No.	Sr (mg)	Recovery efficiency of Sr (%)
1	0.33	99.6
2	0.29	99.7
3	0.34	99.5

Note: Experiments were carried out using 200 mCi per batch.

5.7.   PRODUCT QUALITY CONTROL

A major problem often encountered with $^{90}Sr/^{90}Y$ generator systems is ^{90}Sr breakthrough. Because ^{90}Sr is a bone seeker, the upper limit of ^{90}Sr in ^{90}Y eluate for human use is 74 kBq (2 µCi). In order to provide data concerning ^{90}Sr contamination, the radiochemical purity of the eluate was analysed by paper chromatography.

5.7.1.   Paper chromatography

Chromatography paper (30 ± 2.5 cm) eluted with 0.9% saline solution was used for the analyses. During the chromatography, ^{90}Sr moved with the solvent front, while ^{90}Y stayed at the origin. A typical chromatographic pattern of ^{90}Y-acetate is shown in Fig. 5.1.

5.7.1.1. Elution profile of yttrium selective Eichrom chromatographic column

A typical elution profile of ^{90}Y on an Eichrom column is shown in Fig. 5.2. As can be seen in the figure, the ^{90}Y elution efficiencies were very high. The elutions were carried out over short time periods of 5–10 min, and the recovery of ^{90}Y was greater than 99%.
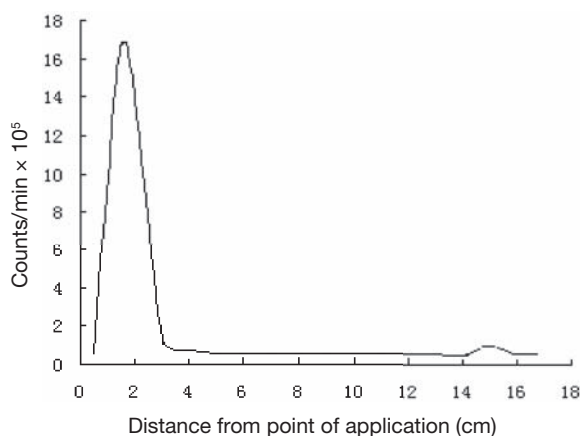
FIG. 5.1. *Typical chromatographic pattern of ^{90}Y-acetate.*
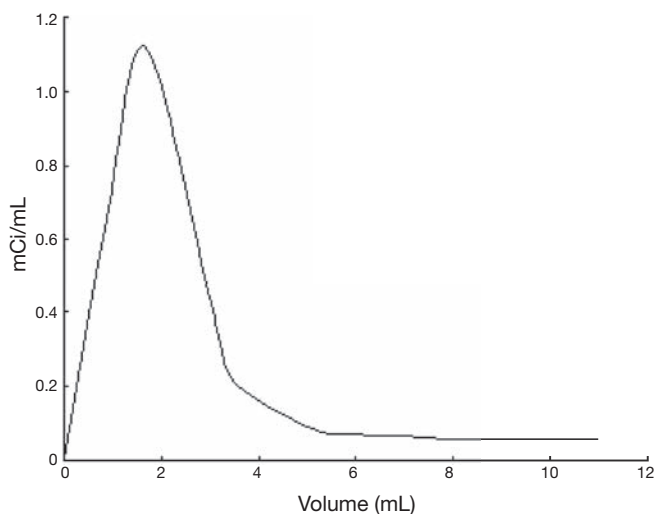
FIG. 5.2. Typical elution profile of ^{90}Y on an Eichrom column.

5.7.2.   Test for chemical purity

The chemical purity of the ^{90}Y eluate was determined by ICP-OES, the results of which are shown in Table 5.2.

TABLE 5.2. LEVELS OF IMPURITIES IN PURIFIED ^{90}Y

Element	µg/mL
Fe	0.20
Al	0.31
Pb	0.26
Ca	0.45
Ba	0.03
Si	0.50
Sr	0.40
Ni	0.38

5.8. RADIONUCLIDIC IMPURITY ANALYSIS

Gamma impurities: Gamma impurities were determined by gamma spectrometry using a GC 1520 detector with standard sources [57]Co and [60]Co (which emit 122 and 1332 keV radiation, respectively), and based on a resolution of 0.8 and 1.8 keV, respectively. The spectrum is recorded with an Accuspec multichannel analyser and Genie 2000 software (Canberra). The lower limit of total gamma impurities did not exceed 0.002%. Figure 5.3 illustrates that no gamma emitting impurities were detected, except for bremsstrahlung radiation.

Beta radiation impurities: Beta radiation was measured with a liquid scintillation spectrometer. The data were compared with a theoretical spectrum of ^{90}Y available in the spectrometer software.

5.8.1. Analysis of radioactive concentration

The ^{90}Y activity was measured using liquid scintillation after suitable dilution. The method uncertainty of ^{90}Y was about ±3%.

5.8.2. Final product specification

— Property: clear, colourless liquid;
— pH: 1.0–4.0;
— Radionuclidic purity: >99.9%;
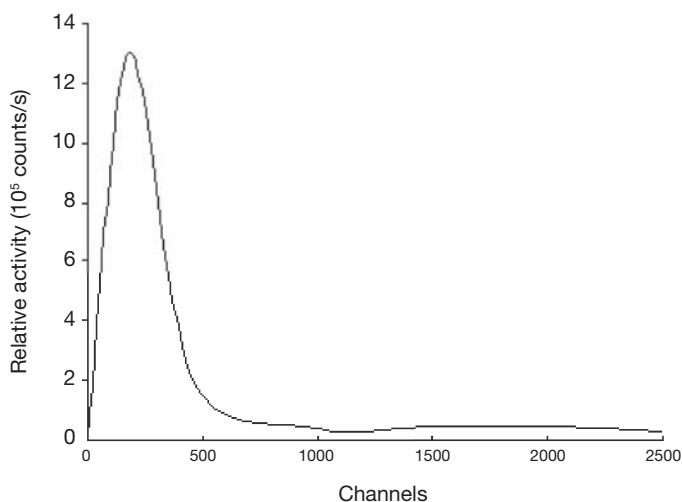
FIG. 5.3. Gamma spectrum of ^{90}Y sample on GC 1520 detector.

— Radiochemical purity: >99.0%;
— Radiochemical concentration: >100 mCi/mL;
— Specific activity: carrier free;
— Chemical purity: >99.9%;
— Fe: <0.2 ppm;
— Al: <0.3 ppm;
— Sr: <0.5 ppm;
— Pb: <0.26 ppm;
— Sterility: pyrogen free.

Chapter 6

DEVELOPMENT OF A REPRODUCIBLE METHODOLOGY FOR THE PRODUCTION OF ^{90}Y FROM A ^{90}Sr/^{90}Y CHROMATOGRAPHIC GENERATOR

A. XIQUES CASTILLO, M. TORRES BERDEGUEZ,
D. BECKFORD, R. LEYVA MONTAÑA,
E. CASANOVA GONZÁLEZ, Y. MORENO
Isotope Centre (CENTIS),
Havana, Cuba

Abstract

Yttrium-90 is considered to be one of the most important radionuclides for therapy owing to its nuclear properties and its ready availability from the long lived ^{90}Sr. In the framework of the coordinated research project, efforts were directed at developing a reproducible methodology for the production of ^{90}Y from a ^{90}Sr/^{90}Y chromatographic generator. A detailed study was conducted to deal with problems related to the scale-up of ^{90}Sr activities in chromatographic ^{90}Sr/^{90}Y generators. The stability and performance of the generator components, such as the resin and eluting agent, were evaluated. The elution efficiency for ^{90}Y is one of the parameters affected by the increase of loaded ^{90}Sr activity. Therefore, the use of a scavenging agent was assessed as a way to overcome the elution yield problems. Quality control procedures were reviewed, especially those regarding ^{90}Sr breakthrough and the chemical purity of the eluate through labelling of peptides. Finally, a production scheme based on ion chromatography was outlined for the production of large amounts of ^{90}Y.

6.1. INTRODUCTION

Yttrium-90 based radiopharmaceuticals for therapy are powerful tools for cancer treatment. The ^{90}Y for this purpose is usually obtained in a carrier free form from ^{90}Sr, which is a high yield fission product of ^{235}U with a half-life of 28 a. Unlike ^{99}Mo/^{99m}Tc and ^{188}W/^{188}Re generators, which produce 'ready to use' eluates, currently there is no ^{90}Sr/^{90}Y generator that can give a 'ready to use' ^{90}Y eluate. Yttrium-90 production is mainly based on two methods, extraction and ion chromatography, or on a combination of these methods. In the production of ^{90}Y, besides the radionuclidic purity requirement (^{90}Sr/^{90}Y ratio), there are further complications, including the low trace metal content

and the high radioactive concentration of the yttrium solution required to obtain good labelling yields.

This study deals with problems related to the scale-up of ^{90}Sr activities in ^{90}Sr/^{90}Y generators. Results are presented on the stability and performance of two different activity chromatographic generators.

6.2. MATERIALS AND METHODS

6.2.1. Radiochemicals

A 3 mCi amount (4 mCi/mL) of ^{85}Sr in chloride form was purchased from POLATOM, Poland. Strontium-90 (400 mCi, 50 Ci/g in 1M HNO$_3$) was purchased from IDB Holland B.V., Netherlands.

6.2.2. Preparation of ^{90}Sr/^{90}Y generators

A Dowex 50WX8 resin (50–100 mesh) in Na$^+$ form was stirred for several hours in a ^{90}Sr/^{90}Y EDTA solution (pH4–5), and then poured onto a glass column and thoroughly washed with 100 mL of 6 mmol/L EDTA solution. In this study, two different activity generators (8 and 100 mCi) were prepared. Generator elution was carried out with 5–7 mL of EDTA solution of variable concentrations (1–12 mmol/L). Carrier free ^{90}Y was obtained in the form of an EDTA complex. When necessary, EDTA was destroyed with concentrated HNO$_3$ and HClO$_4$.

6.2.3. Activity measurement

Yttrium-90 samples were measured in an ionization chamber (Capintec CRC 15R, USA) when used at the megabecquerel level and with a liquid scintillation counter (Wallac RackBeta 1209, Finland) when used at lower levels. LSC was achieved by both Cherenkov radiation and using Hisafe 3 and Ultima Gold scintillation cocktails. The ^{90}Sr was measured by LSC with a scintillation cocktail. The ^{85}Sr was measured by gamma spectrometry on an HPGe solid detector. Both ^{188}Re and ^{188}W were measured in the ionization chamber and the HPGe solid detector. The HPGe spectrometric system was calibrated according to calibration procedures established by the quality assurance system of the Radionuclide Metrology Department of the Isotope Centre of Cuba, which complies with the ISO 17 025 standards. The efficiencies for the measurement of ^{90}Sr and ^{90}Y by LSC were determined using a reference ^{90}Sr/^{90}Y solution standardized by the CIEMAT-NIST method.

6.2.4.   Evaluation of chelating agents

Different chelating agents were selected for elution and evaluation of an 8 mCi ^{90}Sr activity generator. Elution yield, ^{90}Sr breakthrough and elution volume were studied. Elution profiles were acquired for each, using two different flow rates (0.4 and 3 mL/min). The type and concentration of chelators were selected from those reported in several publications, although some modifications were made because of the differences in the ionic form of the resins used (Table 6.1). The column was initially washed with a column volume of the chelating agent solution and allowed to stand for at least 24 h before the next elution was performed with the desired chelate.

6.2.5.   Resin capacity determination

A 1M HCl solution was used to ensure that all functional groups were in the H^+ form. The conversion of strong functional groups from the H^+ into the Na^+ form was then achieved with a 1M NaCl solution, while 1M NaOH was used to convert both strong and weak functional groups. The concentration of H^+ was determined by potentiometric titration. Resin capacity was also determined by a strontium breakthrough curve with a [^{90}Sr]-Sr solution having a concentration of 20 mg/mL. Part of this solution was passed through the column, and 2 mL fractions were collected and measured.

6.2.6.   Irradiation of EDTA solutions

A 100 mmol/L EDTA solution was irradiated with a ^{60}Co gamma irradiator, with a dose rate of 2 kGy/h, at 15 kGy and 1024 kGy to determine the effect of radiolysis on EDTA. EDTA decomposition was determined by high performance liquid chromatography (HPLC) [6.1].

TABLE 6.1. CHELATING AGENTS IN SELECTED STUDIES

Chelating agent	Reference
EDTA disodium salt 0.6 mmol/L, pH4.5	[6.1]
Sodium acetate 0.6 mol/L, pH5.57	[6.2]
Sodium acetate 0.6 mol/L pH5.57: methanol (70:30)	[6.3]
Sodium citrate 0.5%, pH5.5	[6.4]
Sodium oxalate 1%, pH6.5	[6.5]

6.2.7.   Dynamic studies of ^{90}Sr and ^{90}Y retention on the column

6.2.7.1.   Flow rate

The ^{90}Sr/^{90}Y EDTA solutions (pH4.5) were passed through a column containing Dowex 50WX8 (50–100 mesh) in sodium form at different flow rates (0.1–3 mL/min). The ^{90}Y recovery and the decontamination factor for ^{90}Sr were determined.

6.2.7.2.   Column size

The ^{90}Sr/^{90}Y EDTA solutions (pH4.5) were passed through columns of three different sizes (diameter: 0.8 cm; height: 6, 14 and 17 cm). The ^{90}Y recovery and the decontamination factor for ^{90}Sr were determined.

6.2.7.3.   Effect of pH of EDTA solution on ^{90}Y recovery

The ^{90}Sr/^{90}Y EDTA solutions (pH4.5–6.5, in 0.5 increments) were passed through a column containing Dowex 50WX8 (50–100 mesh) in sodium form, and the ^{90}Y recovery and the decontamination factor for ^{90}Sr were determined.

6.2.7.4.   EDTA radiolysis products

Samples for analysis (two of 10 mL each) were prepared by mixing 0.6 mL of a 100 mmol/L irradiated (15 kGy) EDTA solution and 0.6 mL of a freshly prepared 100 mmol/L EDTA solution; enough water was then added to dilute the samples up to 10 mL. The pH of one solution was adjusted to 4.5, and that of the other to 6. In the same manner, two 10 mL samples were prepared using the 100 mmol/L irradiated (1024 kGy) EDTA solution. The resulting solutions were spiked with a small aliquot of both ^{90}Sr/^{90}Y equilibrium solution and ^{85}Sr solution, and passed through a 17 cm (0.8 cm diameter) column (Dowex 50WX8, 50–100 mesh, in sodium form). The ^{90}Y recovery and the decontamination factor for ^{90}Sr were then determined.

6.2.8.   Purification method

A washing step with a 2M HNO$_3$ solution was introduced in order to separate the ^{90}Sr and trace metals from the ^{90}Y. In this procedure, more than 99% of the ^{90}Sr (decontamination factor: 2×10^2) in the ^{90}Y solution is separated in 20 mL of the acid. The decontamination factor for ^{90}Y prepared in this manner is 10^4.

6.2.9.   Separation method for ^{90}Sr quality control

Five millilitres of solution containing the ^{90}Sr separated from the ^{90}Y using the purification procedure described in Section 6.2.8 was evaporated to near dryness. In this solution, the ^{90}Y has already been removed with a decontamination factor of 10^4. After the addition of 1 mL of 0.5% sodium citrate (25 mg of citrate ion), 2 mg of strontium carrier and 0.36 mg of yttrium carrier were added. The pH was adjusted to 3–5, and the solution was passed through a 32 cm × 0.4 cm anion exchange column (AG 1X4, 100–200 mesh, in hydroxide form), followed by the addition of enough water to collect 10 mL. To this solution was added 200 µL of 10M HCl; 4 mL of the resulting solution was then added to 16 mL of Ultima Gold scintillation cocktail and measured on a liquid scintillation counter for ^{90}Sr determination. This procedure gives a decontamination factor for ^{90}Y of 10^5, which means that a ^{90}Sr/^{90}Y ratio of 10^{-5} can be determined. However, as the aliquot of ^{90}Y is taken from the washing solution of the purification procedure, a total decontamination factor of 10^9 is achieved for ^{90}Y.

6.2.10.   Chemical purity of ^{90}Y

A 5.1×10^{-4}M diethylenetriaminepentaacetic acid (DTPA) solution (solution A) at pH6 was prepared by dissolving 0.1 g of the reagent in 500 mL of milliQ water. A 1M NaOH solution was used to facilitate the dissolution of DTPA and to adjust the pH to the desired value. Solutions at concentrations of 5.1×10^{-5}, 3.4×10^{-5}, 2.0×10^{-5}, 1.7×10^{-5} and 5.1×10^{-6}M were prepared by proper dilution of solution A. From the ^{90}Y solution to be tested, three different radioactive concentrations — 7.4, 74 and 740 kBq/mL (as checked by LSC) — were prepared by dilution with 0.01M HCl.

A series of seven test tubes was prepared with the above DTPA and ^{90}Y solutions corresponding to DTPA–^{90}Y molar ratios of 40 000, 4000, 400, 200, 150, 20 and 10. The pH was adjusted to 6–7 with a 0.075M NaOH solution, and the samples were left to stand for 30 min. A 0.5 µL aliquot was then spotted on an instant thin layer chromatography (ITLC) strip, and the chromatogram was run with saline. The strip was cut into two halves and counted in a liquid scintillation counter without scintillation cocktail. The ^{90}Y-DTPA complex was found in the upper half of the strip while the unchelated ^{90}Y remained in the lower half.

6.2.11. Radiolabelling of hR3 monoclonal antibody with ^{90}Y

The ^{90}Y aliquots (110–520 MBq, 3–12 µL) in 0.05N HCl were added to a solution containing 100–150 µL of ammonium acetate buffer (0.5 mol/L, pH7) and 100 µL (0.4 mg) of DOTA-hR3 monoclonal antibody. The reaction mixture was left at 42°C for 1 h; one-ninth of the reaction volume of a 10 mmol/L DTPA solution at pH6 was then added to complex the unreacted ^{90}Y and the mixture was allowed to stand for another 15 min at room temperature. Radiolabelling yield was determined by ITLC–silica gel (SG) with a mixture of ammonium acetate (10%) and methanol (1:1). It was also determined by HPLC with a TSK-Gel SW 3000 column (7.5 mm × 300 mm, 10 µm, TosoHass) using 1 mL/min of a solution containing 0.9% NaCl and 0.05% NaN$_3$.

6.3. RESULTS AND DISCUSSION

The possibility of using a weaker complexing agent was evaluated, since EDTA has to be completely removed from the ^{90}Y solution after its elution from the generator. The presence of any EDTA may affect the radiolabelling yield and/or alter the biodistribution of the ^{90}Y radiopharmaceutical.

As can be seen from the data summarized in Fig. 6.1 and Table 6.2, all eluting agents gave similar elution profiles, with the exception of sodium acetate, which seems to give the smallest elution volume. Elution with EDTA and citrate provided the highest elution yields. The lowest elution yield corresponded to the sodium acetate (0.6 mol/L at pH5.57):methanol (70:30) mixture. It was also found that significant air bubbles formed in the column when left to stand in this solution.
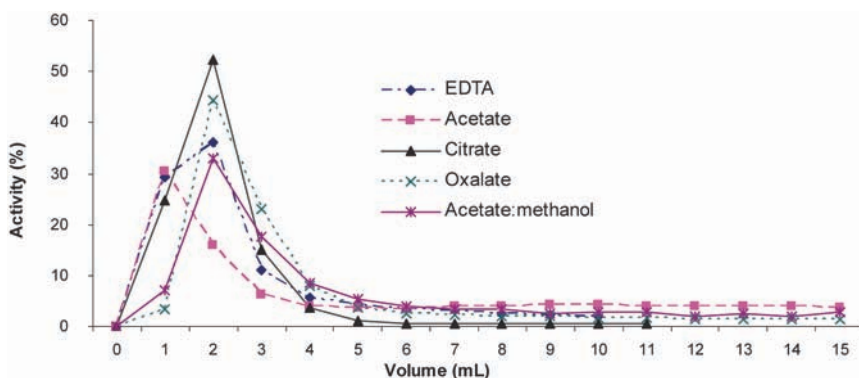
FIG. 6.1. Elution profiles of a 0.3 GBq ^{90}Sr/^{90}Y chromatographic generator using different eluting agents at a flow rate of 0.4 mL/min.

TABLE 6.2. YTTRIUM-90 ELUTION YIELDS FOR A 0.3 GBq ^{90}Sr/^{90}Y CHROMATOGRAPHIC GENERATOR USING DIFFERENT ELUTING AGENTS

Eluting agent	Elution yield (%)
EDTA	~100
Sodium acetate	45.0
Sodium acetate:methanol	8.9
Sodium citrate	99.7
Sodium oxalate	41.0

TABLE 6.3. STRONTIUM-90 CONTENT OF ELUATES FROM A 0.3 GBq ^{90}Sr/^{90}Y CHROMATOGRAPHIC GENERATOR USING DIFFERENT ELUTING AGENTS

Elution order	Eluting agent	Sr-90 breakthrough (mCi)
1	EDTA	8.4×10^{-6}
2	Sodium acetate	1.8×10^{-3}
3	Sodium acetate:methanol	1.1×10^{-2}
4	Sodium citrate	5.4×10^{-3}
5	Sodium oxalate	—[a]
6	Sodium oxalate	3.8×10^{-3}
7	EDTA	1.7×10^{-2}
8	Sodium citrate	9.1×10^{-2}
9	Sodium acetate	1.7×10^{-1}
10	EDTA	1.2×10^{-1}

[a] —: not available.

Table 6.3 shows the results obtained for ^{90}Sr breakthrough studies when the generator was subjected to a series of repeated elutions. The exact measure of the influence of each eluant on the ^{90}Sr content cannot be determined from these few trials. However, it can be seen that, after the generator was milked with sodium 0.6M sodium acetate (elutions 2 and 9), the amount of ^{90}Sr contamination increased significantly; in other words, the ^{90}Sr was being washed out from the column. This result is in contradiction with published results [6.1].

EDTA and sodium citrate gave the best results regarding ^{90}Y elution yield, although the effects on ^{90}Sr breakthrough were not conclusive. As a similar study comparing these two eluting agents showed that EDTA had much lower ^{90}Sr breakthrough, it was decided to continue working with EDTA.

Figures 6.2 and 6.3 show respectively the elution efficiencies of the 8 mCi (0.3 GBq) and of the 100 mCi (3.7 GBq) ^{90}Sr/^{90}Y generators subjected to almost identical conditions (eluent concentration, time elapsed between two consecutive elutions, etc.) and evaluated for a long time period.
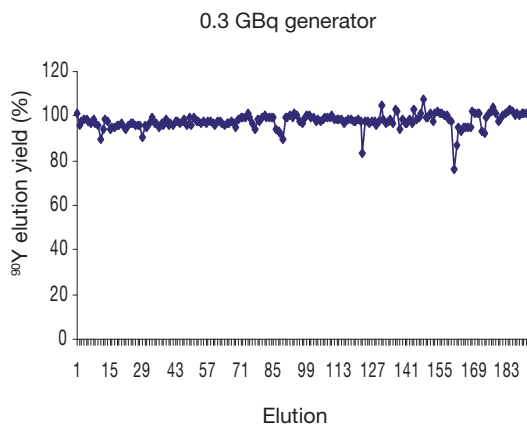
FIG. 6.2.   Yttrium-90 elution profile of a 0.3 GBq ^{90}Sr/^{90}Y generator; eluting agent: 6 mmol, pH4.5 EDTA solution.
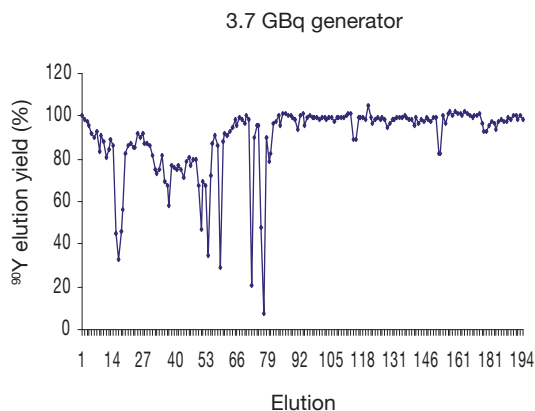
FIG. 6.3.   Yttrium-90 elution profile of a 3.7 GBq ^{90}Sr/^{90}Y generator; eluting agent: 6 mmol, pH4.5 EDTA solution.

As can be seen from the figures, the higher activity generator presented variable and unpredictable elution yields. Reproducible high yields were obtained after the addition of $NaNO_3$ to the eluting solution. The role of NO_3^- ions could not be elucidated in these studies, but the results suggest that the performance of higher activity generators could be improved with this known electron scavenger.

The two generators were dismantled after six years of evaluation, and the resins were analysed for changes in capacity and functional group composition. Figure 6.4 shows the breakthrough curves for strontium indicating that there is a loss of capacity of the resins and that this loss depends on the loaded activity of ^{90}Sr. The 3.7 GBq generator exhibits an almost 60% reduction of this parameter (Table 6.4). The analysis of functional groups shows an important and equal (within experimental error) loss of capacity for the higher activity generator. It can be seen that the formation of weak functional groups also increases with loaded activity (Table 6.5).

TABLE 6.4. EXCHANGE CAPACITY FOR STRONTIUM OF DOWEX 50WX8 RESINS

Resin	Mg of Sr/g of resin	Mmol of Sr/g of resin	Exchange capacity loss (%)
Not irradiated	203.5	2.3	—
0.3 GBq	134.2	1.5	34.0
3.7 GBq	85.7	0.98	57.9

TABLE 6.5. COMPOSITION OF DOWEX 50WX8 RESIN AFTER EXPOSURE TO DIFFERENT LEVELS OF ^{90}Sr ACTIVITY

Resin	Strong groups, total m.e.[a] (4 g)	Weak groups, total m.e.[a] (4 g)	Strong groups, m.e.[a] /g	Weak groups, m.e.[a] /g	Total m.e. left (%)	Weak groups/total groups (%)
Not irradiated	16.80	—	4.20	—	100	—
0.3 GBq	10.53	0.13	2.63	0.03	63.4	1.2
3.7 GBq	6.18	0.79	1.54	0.20	41.5	11.3

[a] m.e. = millequivalent.
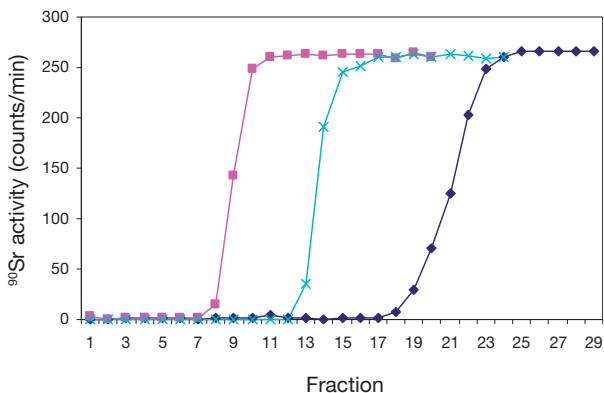
FIG. 6.4. Breakthrough curves for strontium for 4 g of Dowex 50WX8 (50–100 mesh) resin: ■ 3.7 GBq generator; + 0.3 GBq generator; ♦ not irradiated.
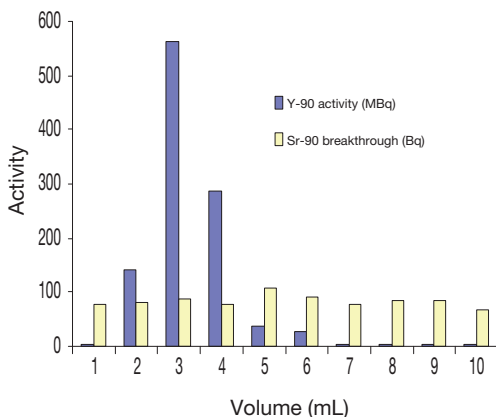
FIG. 6.5. Yttrium-90 and ^{90}Sr elution profiles in an eluate from the 3.7 GBq (100 mCi) generator; in-growth time: 1.2 d.

The amount of ^{90}Sr contamination in the ^{90}Y solution is the most important parameter to evaluate and confirm. It is known that, as the damage to the resin increases, ^{90}Sr levels in the eluent rise.

Figures 6.5 and 6.6 show the elution profiles for ^{90}Sr and ^{90}Y in two eluates from the 3.7 GBq activity generator. It can be seen that the presence of ^{90}Sr in the eluate is a consequence of two processes: ion exchange and radiolysis.

The data in Figs 6.5 and 6.6 suggest that shorter elapsed times between elutions and smaller optimized elution volumes reduce ^{90}Sr contamination in ^{90}Y.
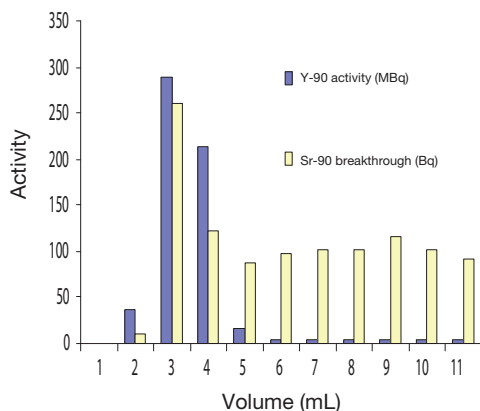
FIG. 6.6. Yttrium-90 and ^{90}Sr elution profiles in an eluate from the 3.7 GBq (100 mCi) generator; in-growth time: 27.2 d.

The ^{90}Sr content of each eluent from both generators was determined for every eluate. As can be seen in Figs 6.7 and 6.8, after a certain period the ^{90}Sr/^{90}Y ratio rises steadily and surpasses the limit of 2×10^{-5}, indicating the end of generator shelf life. It is assumed that at this time the resin loses its integrity and is unable to hold ^{90}Sr.

From the above observations it can be concluded that relatively high activity generators show poor elution yields upon prolonged use. Use of nitrate ions in the eluting solution improves the performance as ^{90}Y recovery improves. The shelf life of the generators is dependent on the loaded activity of ^{90}Sr. Higher activity generators will have a shorter shelf life owing to radiolysis.
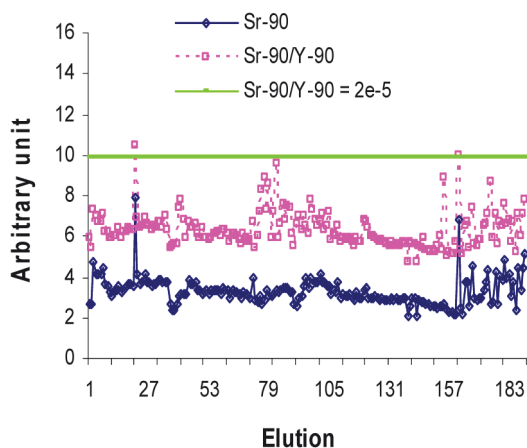
FIG. 6.7. Strontium-90 breakthrough behaviour of a 0.3 GBq ^{90}Sr/^{90}Y generator; eluting agent: 6 mmol, pH4.5 EDTA solution.
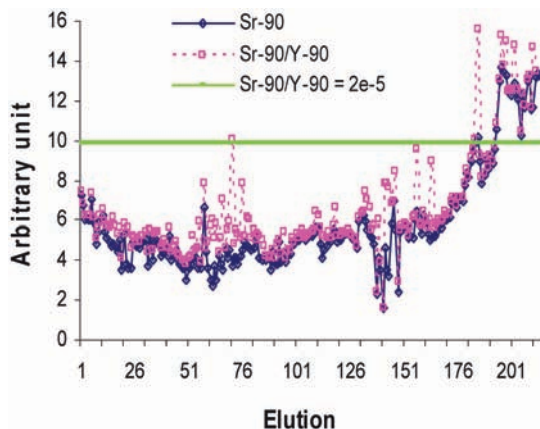
FIG. 6.8. Strontium-90 breakthrough behaviour of a 3.7 GBq ^{90}Sr/^{90}Y generator; eluting agent: 6 mmol, pH4.5 EDTA solution.

The dynamics of the EDTA Dowex 50WX8 resin system were investigated to evaluate the retention/elution of ^{90}Sr and ^{90}Y. Variables like flow rate, pH, column size and presence of radiolysis products of the eluting agent (EDTA) were evaluated [6.6]. The data listed in Table 6.6 indicate that, in the wide flow rate range of 0.1–3.0 mL/min, the decontamination factor for ^{90}Sr remains essentially the same. It was observed that an increase of column height (Table 6.7) improves the decontamination factor for ^{90}Sr. High decontamination values can be obtained for heights as low as 6 cm. The evaluation of the effect of the pH of the eluent showed that a high decontamination factor can be achieved for ^{90}Sr up to pH6 (Table 6.8). A further increase of pH results in significant elution of ^{90}Sr from the column. The above results suggest that a relatively rapid procedure can be implemented for the separation of the two radioisotopes at a pH range of 4–6. With a column of the proper size, a high decontamination factor for ^{90}Sr can be achieved with no ^{90}Y retention. After the separation, ^{90}Sr can be easily and quantitatively recovered in a small volume by changing the pH of the EDTA solution (Fig. 6.9). By minimizing the contact time between the radioisotopes and the resin (as is done in extraction methods), ^{90}Sr activities used for separation can be increased.

The ^{90}Y solution was found to be free of EDTA when analysed by HPLC. Since the trace metal content should be as low as possible in order to obtain good radiolabelling efficiencies, a purification procedure was used to purify every eluate before its use. A DTPA binding test was done prior to radiolabelling studies. More than 90% binding of ^{90}Y to DTPA at a DTPA:Y molar

ratio of 20 was taken as the criterion for low metal content. Normally, high radiolabelling efficiencies (>90%) were obtained when ^{90}Y was used for radiolabelling a monoclonal antibody.

TABLE 6.6. DECONTAMINATION FACTOR FOR ^{90}Sr-EDTA (pH4.5) IN DOWEX 50WX8 RESIN AT DIFFERENT FLOW RATES

Flow rate (mL/min)	Decomtanimation factor
0.1	$(2.1 \pm 0.1) \times 10^3$
0.5	$(2.5 \pm 0.3) \times 10^3$
1.0	$(2.4 \pm 0.2) \times 10^3$
3.0	$(1.6 \pm 0.8) \times 10^3$

TABLE 6.7. DECONTAMINATION FACTOR FOR ^{90}Sr-EDTA (pH4.5) IN DOWEX 50WX8 RESIN FOR DIFFERENT COLUMN HEIGHTS

Column height (cm)[a]	Decontamination factor
6	1.7×10^3
14	4.7×10^3
17	8.2×10^3

[a] All columns had a diameter of 0.8 cm.

TABLE 6.8. DECONTAMINATION FACTOR FOR ^{90}Sr-EDTA IN DOWEX 50WX8 RESIN AT DIFFERENT pH LEVELS

pH	Decontamination factor
4.5	$(2.2 \pm 0.1) \times 10^3$
5.0	$(2.7 \pm 0.3) \times 10^3$
5.5	$(2.8 \pm 0.1) \times 10^3$
6.0	$(2.3 \pm 0.3) \times 10^3$
6.5	$(1.7 \pm 0.1) \times 10^2$
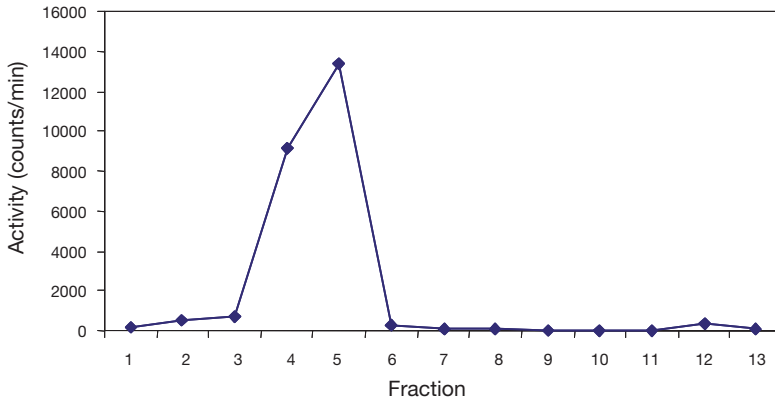
FIG. 6.9. Elution of ^{90}Sr from column with 6 mmol/L EDTA solution at pH9.
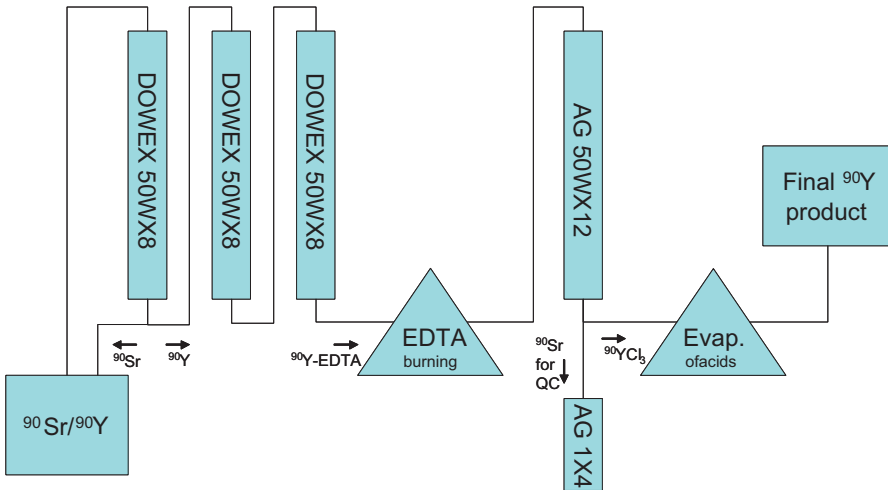
FIG. 6.10. Proposed scheme for ^{90}Y separation from ^{90}Sr/^{90}Y mixture.

Figure 6.10 shows a complete scheme for the separation of ^{90}Y from the ^{90}Sr/^{90}Y mixture proposed as result of this study. Radiation protection require-ments are fulfilled by partial automation of the process and shielding of columns with Pyrex glass, which reduces exposure and at the same time allows for visual control.

Three separations were run with 3.7 GBq (100 mCi) of ^{90}Sr. Results were as expected, and scaling to 400 mCi will be undertaken shortly.

6.4. CONCLUSIONS

Stability studies were carried out with two generators having different activity levels. Based on the results of the studies, a separation scheme was proposed to overcome problems associated with radiolysis when scaling-up the generator capacity. Separation at 400 mCi is planned for the immediate future to evaluate the proposed scheme. Radiological safety was improved with partial automation and shielding of columns. A quality control procedure involving two ion chromatographic separation procedures and LSC for ^{90}Sr determination was established.

ACKNOWLEDGEMENT

REFERENCES TO CHAPTER 6

[6.1] CHINOL, M., HNATOWICH, D.J., Generator produced yttrium-90 for radio-immunotherapy, J. Nucl. Med. **28** (1987) 1465–1470.

[6.2] CHINOL, M., FRANCESCHINI, R., PAGANELLI, G., PECORALE, A., PAIANO, A., "Simple production of yttrium-90 in a chemical form suitable to clinical grade radioconjugates", Radioactive Isotopes in Clinical Medicine and Research XXII (BERGMANN, H., KROISS, A., SINZINGER, H., Eds), Birkhauser, Basel (1997) 327–332.

[6.3] KAWASHIMA, T., Separation of carrier-free Y-90 from Sr-90 by cation exchange in a methanol-ammonium acetate medium, Int. J. Appl. Rad. Isot. **20** (1969) 806–808.

[6.4] DOERING, R.F., TUCKER, W.D., A simple device of milking high purity yttrium-90 from strontium-90, J. Nucl. Med. **4** (1963) 54–59.

[6.5] SUZUKI, Y., Preparation of carrier-free Y-90 from Sr-90 with ion exchange, IJARI **15** (1964) 559–602.

[6.6] NOWACK, B., KARI, F.G., HILGER, S.U., SIGG, L., Determination of Dissolved and Adsorbed EDTA Species in Water and Sediments by HPLC, Anal. Chem. **68** (1996) 561–566.

Chapter 7

DEVELOPMENT OF ^{90}Sr/^{90}Y GENERATOR TECHNOLOGIES AND THEIR EVALUATION FOR USE IN THE PREPARATION OF RADIOPHARMACEUTICALS

M. VENKATESH, A. DASH, U. PANDEY, P.S. DHAMI,
R. CHAKRAVARTY
Bhabha Atomic Research Centre,
Mumbai, India

Abstract

Under the coordinated research project (CRP), concerted efforts were made to develop ^{90}Sr/^{90}Y generator systems to obtain ^{90}Y in high yields and of high purity. A two stage ^{90}Sr/^{90}Y generator based on the supported liquid membrane (SLM) concept was developed in order to obtain ^{90}Y in acetate form as well as to minimize ^{90}Sr contamination of the ^{90}Y product to well below acceptable limits. In 10 h of operation, the generator yielded approximately 85% of highly pure ^{90}Y for therapeutic purposes. During the period of the CRP, approximately 1.85 GBq (500 mCi) of ^{90}Sr was recovered from high level liquid waste using multistep processes involving, for example, precipitation and ion exchange. A 740 MBq (20 mCi) capacity ^{90}Sr/^{90}Y generator based on a novel electrochemical procedure was also developed. Since the parent ^{90}Sr is a highly radiotoxic isotope, efforts were made to develop quality control procedures to detect ^{90}Sr contamination in the ^{90}Y eluted from the generator. A novel extraction paper chromatography technique was developed based on the high affinity of the reagent 2-ethylhexyl 2-ethylhexyl phosphonic acid (KSM-17) for ^{90}Y. This technique is capable of detecting levels of ^{90}Sr as low as 74 kBq (2 µCi) of ^{90}Sr in 37 GBq (1 Ci) of ^{90}Y. Quality control of the ^{90}Y eluted from the SLM based and electrochemical generators showed the ^{90}Sr levels to be much less than the allowed limits.

7.1. INTRODUCTION

There is considerable interest in the use of therapeutic radiopharmaceuticals in India, and the development of such radiopharmaceuticals is being actively pursued. In this context, ^{90}Y and ^{188}Re are very attractive because of their ready, cost effective availability from generator systems. The objectives of this CRP were in line with the activities pursued and gave the necessary support to develop procedures and devices related to therapeutic radionuclide

generators. During the period of the CRP, research efforts were focused on the development of generators for ^{90}Y and ^{188}Re, separation of ^{90}Sr from the high level liquid waste generated from spent nuclear fuel reprocessing (by the Purex process), post-elution concentration of ^{188}Re to produce a high concentration product amenable for labelling, and preparation of novel materials for use as a column matrix in generators and quality control of ^{90}Y.

7.2. ^{90}Sr/^{90}Y GENERATOR SYSTEMS

7.2.1. Separation of ^{90}Sr from high level liquid waste

Small aliquots of samples previously obtained from high level liquid waste for quality control analysis, accrued over time, were used to demonstrate the feasibility of separation of ^{90}Sr from such spent nuclear fuel processing solution waste. The ^{90}Sr used in these studies was separated from these high level liquid waste samples, which contained about 1–2 GBq (200–300 mCi) of ^{90}Sr/L. This waste also contained several other high activity components such as the actinides americium, plutonium and uranium; high yield fission products such as ^{137}Cs, ^{144}Ce and ^{106}Ru; and several elements such as aluminium, chromium, iron, manganese and nickel. These radioactive impurities were sequentially removed by solvent extraction of the actinides into tributyl phosphine, followed by adsorption of ^{137}Cs onto a column containing ammonium molybdophosphate resin, followed by repeated precipitation as hydroxide by addition of NaOH, at approximately pH9.0, in the presence of carrier strontium and iron to remove major impurities, and finally precipitation of strontium as carbonate. Using this procedure, nearly 17 GBq (500 mCi) of ^{90}Sr was separated, resulting in 7.4 GBq of high purity ^{90}Sr.

7.2.2. Development of a supported liquid membrane based ^{90}Sr/^{90}Y generator system

The SLM concept involves the use of a semipermeable membrane with pores where a liquid can be held. Such SLMs can be used for preferential extraction of a species of interest, by saturating the membrane with a solvent with a ligand specific for the species of interest [7.1]. Such membranes can be used to separate two chambers, one containing the mixture of species and the other for collecting the pure species of interest. SLM based generators were conceptualized for separation of ^{90}Y from a mixture of ^{90}Sr and ^{90}Y [7.2, 7.3]. The two ligands KSM-17 and CMPO were used in the construction of such an SLM based generator system. KSM-17 was used to preferentially extract ^{90}Y

from a solution at pH1–2 to a solution of higher acidity, and CMPO was used to extract ^{90}Y from a highly acidic solution (3–4M HNO_3) to a solution of much lower acidity (1M acetic acid). The ^{90}Sr isolated from high level waste arising from nuclear fuel reprocessing by the Fuel Reprocessing Division of BARC was used for the development of these generators at the Radiopharmaceuticals Division of BARC.

7.2.2.1. Single stage supported liquid membrane generators

A single stage SLM based system employing KSM-17 as a carrier supported on a PTFE membrane to obtain carrier free ^{90}Y was developed and is described separately in this document (see Section 3.1 on SLM based ^{90}Sr/^{90}Y generators). In brief, the various parameters influencing the transport of ^{90}Y across the membrane, such as transport time, acidity in the feed compartment, acidity in the product compartment, nature of the feed/receiver phase and concentration of the radionuclide, were optimized to obtain ^{90}Y of high purity. Normally, when operated for around 3–4 h, the generator yields high purity ^{90}Y. However, under these conditions only about 40% of the ^{90}Y is transported to the receiver.

This generator was used regularly to obtain approximately 370–740 MBq (~10–20 mCi) of ^{90}Y every week from purified ^{90}Sr separated from high level liquid waste. The ^{90}Y obtained from this generator system was free of ^{90}Sr, as verified by following the activity decay (almost complete decay of β^- activity after about 26 d) and by analysis by the EPC technique developed during the course of the CRP.

7.2.2.2. Two stage supported liquid membrane generators

Changing the acidity of the feed and the receiver chambers enabled the single stage SLM generator to give higher yields (>90%) of ^{90}Y. But such changes were always associated with ^{90}Sr contamination beyond acceptable limits in the eluted ^{90}Y product.

Hence, a two stage generator was conceived in order to overcome the above limitations using the properties of two different ligands, namely KSM-17 and CMPO [7.4]. Initially, a generator with three chambers separated by two SLMs was developed. Later, the same principle was used for a two stage sequential generator with two cells of two chambers each, separated by an SLM in each case.

Details of the methodologies used in the construction and usage of these generators are given elsewhere in this document (see Section 3.1 on SLM based

^{90}Sr/^{90}Y generators); a brief description of the features of these generators is given below.

Operation in simultaneous mode: In this system, the generator consists of three chambers (feed, intermediate and receiver chambers) with capacities of 5 mL each. A PTFE membrane impregnated with KSM-17 is inserted between the feed and intermediate chambers, and another PTFE membrane impregnated with 0.8M CMPO in n-dodecane is inserted between the intermediate and receiver chambers. In the feed chamber is placed 5 mL of the mixture of ^{90}Sr and ^{90}Y adjusted to pH1–2; 5 mL of 4M HNO$_3$ is taken in the second chamber, which acts as the intermediate chamber to receive ^{90}Y from the first chamber and transport it to the third chamber; and 5 mL of 1M CH$_3$COOH is placed in the receiver chamber. Optimally, when operated for about 10 h, the generator results in transportation of approximately 85% of the ^{90}Y to the receiver compartment.

This generator was used regularly to obtain around 370–740 MBq (~10–20 mCi) of high purity ^{90}Y every week, which was used for radiolabelling studies.

Operation in sequential mode: In this system, two cells of two compartments each were employed. The first cell was similar to the one stage generator. The first feed chamber contained 5 mL of the ^{90}Sr and ^{90}Y mixture adjusted to pH1–2, and the receiver chamber contained 5 mL of 3–4M HNO$_3$. The chambers were separated by an SLM saturated with KSM-17.

The second cell was operated after completion of the first cell operation, which generally lasted for around 4 h. The product in the receiver chamber of the first cell was removed at the end of the operation and placed in the feed chamber of the second cell. An SLM saturated with CMPO was used between the two chambers of this cell. The final product was obtained in the receiver chamber containing 5 mL of 1M acetic acid. Generally, this cell was operated for about 6 h, and high purity ^{90}Y could be obtained in an acetate form amenable for easy labelling with greater than 90% yield.

Thus, a range of SLM based ^{90}Sr/^{90}Y generators was developed, and their use for obtaining ^{90}Y of high purity with ^{90}Sr contamination low enough for use in the preparation of ^{90}Y labelled radiopharmaceuticals was successfully demonstrated.

7.2.3. Development of an electrochemical ^{90}Sr/^{90}Y generator

Based on the reports by Reischl et al. [7.5] and Yoo et al. [7.6], who used an electrochemical method to separate pure ^{86}Y into usable quantities greater than 3.7 GBq (>100 mCi) from milligram quantities (50–150 mg) of enriched ^{86}Sr for PET applications, a similar generator for separation of ^{90}Y from ^{90}Sr

was developed. The details of this generator and mode of operation are given elsewhere in this publication (see Section 3.2 on electrochemical ^{90}Sr/^{90}Y generators), while the salient features are mentioned below.

In this generator, the separation of ^{90}Y from ^{90}Sr is achieved due to the difference between the electrochemical potentials of Y^{+3} and Sr^{+2}. On applying a suitable electric potential, ^{90}Y was selectively deposited at the cathode from a mixture of ^{90}Sr and ^{90}Y. The effects on ^{90}Y deposition of applied potential and of the pH of the electrolyte solution were studied. The optimal pH was observed to be 2.5–3.0, as was reported by Reischl et al. [7.5]. A potential of –2.5 to –3.0 V was required for deposition of more than 90% of the ^{90}Y on the cathode, as shown in Table 7.1. An important observation from the experiments was that the electrolysis should be carried out at constant potential rather than constant current. This can generally be achieved using suitable instruments available for such purposes. However, in the absence of such instruments, the experiments were carried out using a standard reference electrode such as a calomel electrode, which is generally used for maintaining a desired constant voltage against an electrode. Since the possibility of strontium deposition increases with an increase in the voltage applied, later experiments were carried out at a potential of –2.5 V.

The proposed generator involves two steps for electrolytic separation. In the first, approximately 30 mL of ^{90}Sr(NO$_3$)$_2$ in 0.001M HNO$_3$, adjusted to pH2.5–3.0 using 3% ammonium hydroxide, is placed in a quartz electrochemical cell fitted with an acrylic cap fixed with platinum electrodes and necessary arrangements for passing gas. Argon gas is gently bubbled through the solution 10–15 min prior to applying the current, and the electrolysis is performed potentiostatically at –2.5 V with respect to SCE for 90 min.

TABLE 7.1. EFFECT OF THE APPLIED POTENTIAL ON THE ELECTROCHEMICAL DEPOSITION OF ^{90}Y^{+3}

Potential applied[a]	Y-90 deposited (%)
–1.0	4 ± 2
–1.5	53 ± 3
–2.0	80 ± 3
–2.5	97 ± 2
–3.0	>99

[a] The potential applied is with respect to a reference calomel electrode; $n = 3$.

A current of 200 mA is applied at this stage, which is seen to decrease slowly to 100 mA by the end of the initial electrolysis. The acrylic cap and the electrodes are then removed from the cell while maintaining the current. After the current is switched off, the cathode plate is removed, washed with 10 mL of acetone to remove any free ^{90}Sr adhering to the electrode surface and then fitted to another similar acrylic cap into which a cylindrical platinum electrode is attached for the second stage deposition. This acrylic cap is fitted to a fresh quartz cell filled with 30 mL of 0.003M nitric acid (pH2.5–3), the cylindrical electrode is connected as the cathode and the original platinum plate containing ^{90}Y is connected as the anode. The second electrolysis is performed for 45 min with a constant potential of –2.5 V and a 100 mA current with continuous bubbling of argon gas through the solution, as was done previously. In this step, the current decreases to 20–30 mA by the end of the electrolysis. In the second electrolysis, ^{90}Y is leached from the platinum plate and is deposited onto the cylindrical platinum electrode. At the end of the electrolysis, the acrylic cap is removed from the solution while maintaining the voltage, and the cylindrical platinum electrode with the deposited ^{90}Y is washed with 10 mL of acetone, followed by leaching of ^{90}Y with 500 µL of acetate buffer at pH4.75 to obtain pure ^{90}Y. After use, the electrodes are washed with 3M HNO$_3$ and used in subsequent experiments. The feed solution in the first electrolytic cell is also preserved, since it retains most of the ^{90}Sr activity. The ^{90}Sr solution is left to stand to allow growth of ^{90}Y, and is used for further electrolysis at pH2.5–3.0. The activities of the electrolyte in the second cell as well as in the acetone wash solution are transferred to a waste container for disposal.

Generators with activity levels of 1.85 GBq (50 mCi) were tested repeatedly using this procedure. It was observed that this generator could yield ^{90}Y of high purity with ^{90}Sr contents well below 10^{-4}%. The purity of ^{90}Y was measured by half-life estimation, by estimation of $^{85+89}$Sr activity by HPGe based gamma ray spectroscopy, by paper electrophoresis and by estimation of residual ^{90}Sr after long decay. The decay of the ^{90}Y obtained from the generator when followed for nearly 700 h (~11.5 half-lives of ^{90}Y) using a liquid scintillation counter conformed with the 64.1 h half-life of ^{90}Y, with no deviation at the lower end of the straight line decay curve, confirming that the ^{90}Y fraction was pure and contained negligible quantities of ^{90}Sr.

In the experiments carried out with ^{90}Sr/^{90}Y spiked with $^{85+89}$Sr, the ^{90}Y that was isolated was checked in an HPGe detector coupled to a 4K analyser to evaluate the photon peaks due to the gamma rays corresponding to $^{85+89}$Sr gamma activity. The spectrum did not show the presence of such peaks, thereby indirectly confirming the absence of ^{90}Sr in the recovered ^{90}Y.

The EPC technique was also used for the estimation of ^{90}Sr in eluted ^{90}Y [7.7], which gave the value of approximately 30.2 ± 15.2 kBq (817 ± 411 nCi) of ^{90}Sr per 37 TBq (1 Ci) of ^{90}Y (0.817 ± 0.411 ppm) for different batches. The ^{90}Sr levels observed were very low and within acceptable limits.

Table 7.2 summarizes some of the typical results of the performance of the generator over a 6 month period. It can be seen that consistent levels of ^{90}Y (93–95%) could be repeatedly recovered from the single ^{90}Sr feed.

7.2.3.1. Simulation study of recovery of ^{90}Y from strontium carrier added solution

The effects of macroscopic amounts of strontium on the electrochemical separation of ^{90}Y were investigated by using a strontium–yttrium mixture containing inactive strontium and yttrium carrier (22.5 mg of anhydrous strontium carbonate in 2M HNO$_3$ and 2.32 µg of yttrium oxide dissolved in 2M HNO$_3$) equivalent to 37 GBq (1 Ci) of ^{90}Sr, along with an equilibrium mixture of ^{90}Sr/^{90}Y containing 3.7 MBq (100 µCi) of ^{90}Sr as well as 3.7 MBq (100 µCi) of $^{85+89}$Sr. The separation of ^{90}Y by electrolysis was carried out as outlined above, and the activity content of the recovered ^{90}Y was measured to evaluate the electrochemical deposition yield. It was found that, at these levels of strontium and yttrium, the generator performed equally efficiently, with greater than 90% yields of ^{90}Y of high purity.

With this generator, it is necessary to follow the procedure very carefully in order to achieve the desired separation. Bubbling of an inert gas through the solution before and during electrolysis is essential to vent the gases produced during electrolysis as well as to keep the solution in a dynamic form. The best

TABLE 7.2. TYPICAL PERFORMANCE OF THE ELECTROCHEMICAL ^{90}Sr/^{90}Y GENERATOR

Sr-90 in the electrolyte (GBq/mCi)	Y-90 growth period (d)	Expected Y-90 activity (GBq/mCi)	Y-90 recovered (GBq/mCi)	Y-90 recovered (%)
1.85/50	15	1.810/48.93	1.6835/45.5	92.9
1.848/49.95	9	1.668/45.09	1.5725/42.5	94.3
1.847/49.92	33	1.8426/49.80	1.6872/45.6	91.6
1.843/49.81	16	1.812/48.97	1.691/45.7	93.4
1.841/49.76	13	1.7764/48.01	1.6872/45.6	95.1
1.8396/49.72	20	1.8267/49.37	1.706/46.1	93.3

results were obtained with helium and argon gases. Removal of the electrodes from the electrolytic cell under voltage was necessary to prevent the dissolution of a thin layer of deposition of ^{90}Y-hydroxide at ng–µg levels back into the electrolyte solution. Rinsing of the electrodes each time after electrolysis was necessary to remove the adherent ^{90}Sr, although this resulted in a decrease in the recovery of ^{90}Y of approximately 2% each time. Thus, although the electrolytic deposition yields were in the range of 97–98%, the final usable yields were around 95%. The time required for a complete run was about 3–4 h, and most of the ^{90}Y activity could be leached with 500 µL of 0.2M acetate buffer at pH4.75. Yttrium-90 can also be reconstituted in chloride or nitrate form, if desired. By appropriately adjusting the volume of the solution used for final dissolution, ^{90}Y could be obtained at high radioactivity concentrations. The recovery of ^{90}Y when the feed was simulated to represent 37 GBq (1 Ci) of ^{90}Sr was found to be equally good.

An electrochemical separation procedure was successfully demonstrated for separation of ^{90}Y from ^{90}Sr having high radiochemical yield and purity. Such a generator has very low operational costs and could provide a continuous supply of ^{90}Y suitable for therapeutic application.

7.2.4. Development of a quality control procedure based on extraction paper chromatography for estimation of ^{90}Sr in ^{90}Y

The quality control procedure based on EPC is essentially a combination solvent extraction of a species with a specific ligand and paper chromatography. The KSM-17 chelating agent has very high affinity for ^{90}Y and is the basis of the ^{90}Sr/^{90}Y generator system developed at BARC (see Section 7.2.2). The selectivity of KSM-17 for ^{90}Y was utilized to develop this novel EPC technique for determination of ^{90}Sr contamination in the eluted ^{90}Y [7.7], details of which are provided elsewhere in this report (see Section 3.1 on SLM based ^{90}Sr/^{90}Y generators).

To summarize, using regular chromatography grade paper (e.g. Whatman 1), the area at the point of application is saturated with KSM-17 by applying an adequate quantity (here, 10 µL of KSM-17 was used, which would be sufficient to chelate and keep bound micromolar quantities of Y^{+3}), well in advance of the actual quality control procedure. The ^{90}Y acetate test solution, with known radioactive concentration, is diluted appropriately with high accuracy to a concentration of 37 MBq/mL (1.0 mCi/mL). A known small aliquot (5 µL) of this test solution is then applied to the paper, and the paper is developed in saline. The KSM-17 retains Y^{+3} tightly at the point of application ($R_f = 0$) and Sr^{+2} migrates with the solvent front, resulting in sharp separation. After drying,

cutting and counting the paper in a liquid scintillation counter, the data for estimation of amounts of radioactivity in Sr and Y regions are provided.

Here, taking advantage of the high precision and accuracy with which the activity can be diluted and spotted on the paper using high precision pipettes, the activity was counted in a liquid scintillation counter for a long time (up to 1 h) to achieve the sensitivity necessary for measuring becquerel levels of ^{90}Sr in a sample of ^{90}Y in megabecquerel quantities. A detailed report has been published [7.7]. If the initial concentration of ^{90}Y is not accurately known, the sample may be accurately diluted and the activity measured in a liquid scintillation counter to derive the radioactive concentration value, provided the efficiency of the counter is known. Even if the efficiency of the counter is not known, as long as the efficiency is the same for both ^{90}Y and ^{90}Sr measurements, this method can still be used to derive the values for ^{90}Sr levels in ^{90}Y. A typical set of data from a sample is shown graphically in Fig. 7.1. By plotting the counts obtained on a logarithmic scale (Y axis), even the very low count rate of ^{90}Sr can be depicted along with the high count rate that is usually associated with ^{90}Y.

Validation of the method included:

(a)   EPC of known samples of ^{85}Sr to prove that all Sr^{+2} moves with the solvent front and that there is no misclassification error at $R_f = 0$ (Y^{+3} region).
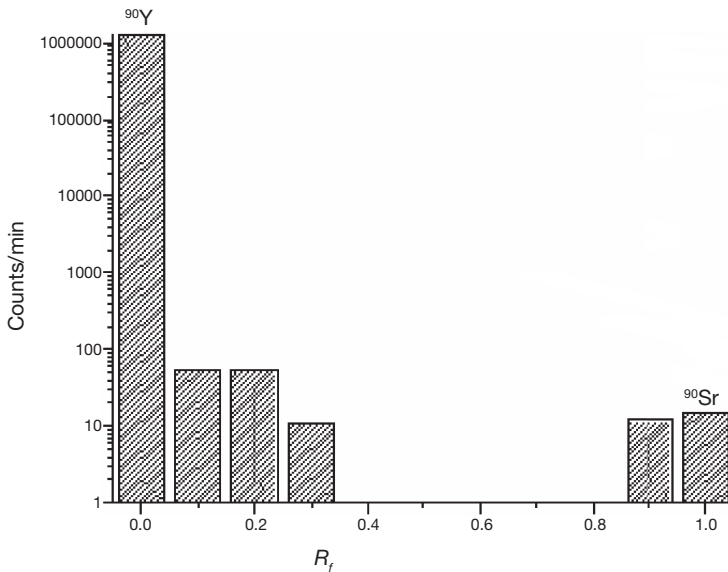
FIG. 7.1. *Typical EPC of a sample of ^{90}Y from the electrochemical generator.*

(b) EPC of an equilibrium mixture of ^{90}Sr/^{90}Y to show that the counts at the Y^{+3} and Sr^{+2} regions are the same (within counting errors, when counted immediately after EPC). This proves the complete separation as well as equal efficiency for counting both regions.

(c) EPC of an aliquot of ^{90}Y and counting of the ^{90}Y region after EPC, as well as counting of the same aliquot separately without EPC, by directly placing it in the scintillation vial and showing that the counts are not significantly different. This proves that all the ^{90}Y stays at $R_f = 0$, and that the paper does not quench the counts of ^{90}Y.

7.3. CONCLUSION

Two types of ^{90}Sr/^{90}Y generator were successfully developed based on SLMs in two stages and electrochemical deposition in two stages to obtain highly pure ^{90}Y that can be used for preparation of radiopharmaceuticals.

Also, a simple and reliable quality control procedure based on EPC for estimation of ppm levels of ^{90}Sr in ^{90}Y was developed, demonstrated and validated.

REFERENCES TO CHAPTER 7

[7.1] BARTSCH, R.A., WAY, J.D., Chemical separations with liquid membranes, ACS Symp. Series **642** (1996).

[7.2] ACHUTHAN, P.V., DHAMI, P.S., KANNAN, R., GOPALAKRISHNAN, V., RAMANUJAM, A., Separation of carrier-free ^{90}Y from high level waste by extraction chromatographic technique using 2-ethyl hexyl 2-ethyl hexyl phosphonic acid (KSM-17), Sep. Sci. Technol. **35** (2000) 261.

[7.3] VENKATESH, M., et al., Complexation studies with ^{90}Y from a novel [90]Sr-^{90}Y generator, Radiochim. Acta **89** (2001) 413.

[7.4] DHAMI, P.S., et al., Studies on the development of a two stage supported liquid membrane system for the separation of carrier-free ^{90}Y using KSM-17 and CMPO as carriers, Sep. Sci. Technol. **42** (2007) 1107.

[7.5] REISCHL, G., ROSCH, F., MACHULLA, H.J., Electrochemical separation and purification of yttrium-86, Radiochim. Acta **90** (2002) 225–228.

[7.6] YOO, J., et al., Preparation of high specific activity [86]Y using a small medical cyclotron, Nucl. Med. Biol. **32 (**2005) 891–897.

[7.7] PANDEY, U., DHAMI, P.S., JAGESIA, P., VENKATESH, M., PILLAI, M.R.A., A novel extraction paper chromatography (EPC) technique for the radionuclidic purity evaluation of ^{90}Y for clinical use, Anal. Chem. **80** (2008) 801–807.

Chapter 8

EVALUATION OF A METHOD TO DETERMINE ^{90}Sr CONTAMINATION OF ^{90}Y BY EXTRACTION CHROMATOGRAPHY

M. CHINOL*, C. ZONA**

 * European Institute of Oncology,
   Milan

** University of Milan and INFN, LASA,
   Segrate

   Italy

Abstract

Yttrium-90 is one of the most useful radionuclides for radioimmunotherapeutic applications. It has a half-life ($T_{1/2}$: 64.14 h) that is consistent with the rate of antibody accumulation in tumours, and it emits beta particles of high energy and decays to a stable daughter. It is significant that ^{90}Y is available conveniently and inexpensively from a radionuclide generator by decay of its parent, ^{90}Sr. Nevertheless, current and planned clinical applications of ^{90}Y labelled compounds employ activity levels that can only be readily obtained from commercial sources, not from in-house generators. The use of Eichrom's Sr Resin was evaluated both as an in-house generator and as a fast quality control tool for ^{90}Y solutions. In particular, for development as a generator, the percentage of the ^{90}Sr in the first 8M HNO$_3$ eluate was evaluated, as in this fraction the concentration of ^{90}Sr must be less than 10^{-5}%. For use as a tool for rapid quality control, the concentration of ^{90}Sr in the entire fraction eluted after separation of ^{90}Y was analysed. After the collection and analysis of β^- and γ spectra, it was concluded that use of the commercial Sr Resin minicolumn cannot give the results expected. This problem was solved by preparing radiochromatographic systems in house that gave very promising results, both as an in-house generator and as a quality control tool.

8.1. INTRODUCTION

Yttrium-90 has become a widely used radionuclide for cancer therapy owing to its physical properties, which include a high energy beta emission ($E_{\beta^-_{max}}$ = 2.280 MeV) [8.1, 8.2] with a range in tissue longer than that of

other β^- particles, no accompanying gamma ray emission in its decay, and a half-life ($T_{1/2}$: 64.14 h) [8.1, 8.2] that is comparable with the pharmacokinetics of many tumour targeting molecules.

Another advantage is its convenient availability by decay of its fission product parent ^{90}Sr ($T_{1/2}$: 28.78 a, E_{β^-} = 546 keV, $<E_{\beta^-}>$ = 182 keV) [8.1, 8.2] through the scheme shown in Fig. 8.1.

Usually, a radionuclide generator consists of a chromatographic column into which the parent radionuclide is loaded, with the daughter radionuclide being eluted using either aqueous or organic eluents [8.3, 8.4]. Many generator systems have been reported in the literature, but clinical applications of ^{90}Sr/^{90}Y have been carried out using commercial sources and not generator eluted ^{90}Y. The main reason for this choice lies in the chemical and radionuclidic purity of the ^{90}Y. The latter, in particular, is crucial for the safe use of ^{90}Y in humans [8.5]. Hence, accurate determination of ^{90}Sr contamination in ^{90}Y solutions needs to be further optimized for this radionuclide to be utilized in patient trials.

In this CRP, different generator systems have been proposed [8.6] and have shown good elution yields and the possibility to obtain ^{90}Y solutions in concentrations and chemical forms suitable for labelling biomolecules [8.7, 8.8]. However, a sensitive method to detect ^{90}Sr breakthrough is still lacking. Therefore, efforts here were focused on the development of a simple and efficient method to enable the assessment of whether a ^{90}Y solution meets the clinical requirements immediately after elution from the generator and prior to radiolabelling.
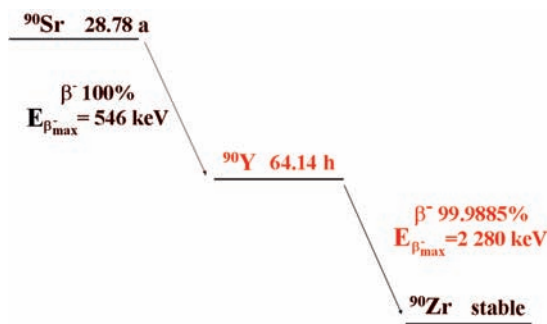
FIG. 8.1. Decay scheme of the ^{90}Sr/^{90}Y system.

8.2. MATERIALS

The materials provided by the IAEA included ^{90}Sr/^{90}Y (in 1.0M HNO$_3$ solution; activity: 120 µCi (4.44 MBq), certificate No. 1594, RITVERC, Russian Federation) and ^{85}Sr (certificate No. DP2–1–032/47/06/2, POLATOM, containing [^{85}Sr]SrCl$_2$ in 1.0M HCl with a radionuclidic purity of >99.5%; other radioisotopic impurities: ^{84}Rb: 3.5×10^{-2}%, ^{59}Fe: 59×10^{-2}%; activity: 100 µCi with specific activity >37 MBq/mg).

Purchased items included: ^{90}Y (PerkinElmer$^®$, Catalogue No. NEZ–306A, containing [^{90}Y]YCl$_3$ in 0.05M HCl with a ^{90}Sr/^{90}Y activity ratio at production of less than 1.0×10^{-7} Ci/Ci); Eichrom Sr Resin (mesh: 50–100 µm), 50×2 mL cartridges; and Eichrom Sr Resin (mesh: 50–100 µm), 25 g of resin.

All chemicals used in the experiments were of analytical or electronic grade to minimize the contamination of the final solutions.

8.3. METHODS

The method that was investigated is based on the Sr Resin commercialized by Eichrom$^®$ Technologies. This resin has a crown ether extracting system and consists of 1.0M 4,4´(5´)–di–butylcycloexane 18-crown-6 in 1–octanol. This extracting system has a different affinity and pH dependence for different elements owing to steric interactions between the cavity of the ether 18-crown-6 and electrostatic forces between the oxygens of the ether and the cations present in the mobile phase. In particular, this resin possesses a high affinity for strontium at low pH levels (high concentration of acid), whereas under the same conditions the affinity for yttrium is very low. In theory, this resin is a good support for a ^{90}Sr/^{90}Y generator, since using concentrated acids (i.e. 8M HNO$_3$) as an eluant would make it possible to quantitatively elute the yttrium, followed by elution of strontium using very diluted acids (i.e. 0.01M HNO$_3$). Based on this principle, the same method was applied for the quality control of the ^{90}Y solutions. To achieve this, it is necessary to have complete decontamination of yttrium and complete recovery of strontium. The activity present in strontium fractions would allow determination of the percentage of ^{90}Sr impurity present in the ^{90}Y solution, and therefore the radionuclidic purity.

The proposed method consists of the following steps:

(1)   Load the column with a solution containing ^{90}Sr and ^{90}Y.
(2)   Elute two fractions with 5 mL of 8M HNO_3 each to collect the ^{90}Y and achieve its decontamination and the removal of ^{90}Sr.
(3)   Elute two fractions with 5 mL of 0.01M HNO_3 each to recover the ^{90}Sr from the column.

According to the commercial specifications, this procedure should permit recovery of pure solutions of each radionuclide. However, liquid scintillation analysis of the eluted fractions did not allow the complete validation of the system and suggested ways to improve the system in order to achieve the goal of determining the radionuclidic purity of ^{90}Y solutions within permissible limits.

Other experiments based on this method were executed with ^{85}Sr, a pure γ emitter with a single γ emission at 514 keV, to evaluate the behaviour of the resin with strontium. This radionuclide allows rapid detection and measurement of radioactivity in the eluted fractions and on the column bed owing to its decay mode (γ emissions were measured with an HPGe detector (see Fig. 8.2) or with a NaI(Tl) scintillator).

In these experiments, it was initially decided to evaluate the Eichrom Sr Resin minicolumn and, subsequently, a chromatographic system prepared in house in order to improve the radiochemical separation.
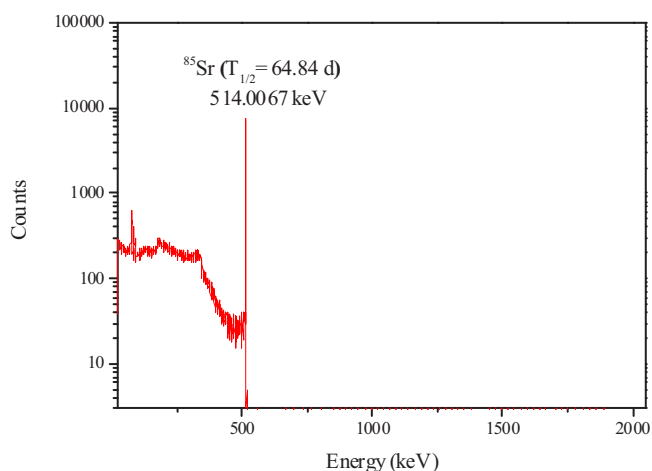
FIG. 8.2. Typical γ spectrum of ^{85}Sr obtained with an HPGe detector for 1000 s.

8.4.   RESULTS

8.4.1.   Evaluation of the column performance to produce pure fractions of ^{90}Y and ^{90}Sr

In the first experiment, one Sr Resin cartridge was loaded with 83 µL ($\sim$3.7 × 10^5 Bq) of ^{90}Sr/^{90}Y solution at secular equilibrium. Two fractions with 5 mL of 8M HNO$_3$ each were eluted, followed by two fractions with 5 mL of 0.01M HNO$_3$. From the eluted fractions, four samples were prepared for LSC by taking 50 µL of each radioactive solution and adding 20 mL of scintillation cocktail (Hionic Fluor, Packard). The spectra of the first fraction (supposed to contain pure ^{90}Y) and of the third fraction (supposed to contain pure ^{90}Sr) are shown in Fig. 8.3.

The separation of the two radionuclides appeared to be successful, but in order to verify whether the two fractions were really pure, the decay of the activity in the first fraction was followed up to 50 d to allow complete decay of ^{90}Y.

The decay curve plotted in a semi-log Cartesian 2D plane showed a tail (Fig. 8.4) due to an impurity with a longer half-life, which was identified as ^{90}Sr.

It is possible to determine the radionuclidic purity by acquiring the spectrum of the first fraction after the complete decay of ^{90}Y. The spectrum of the first fraction is shown in Fig. 8.5 (dashed line) along with that of pure ^{90}Y (red) and that of ^{90}Sr obtained after analytical deconvolution (green).
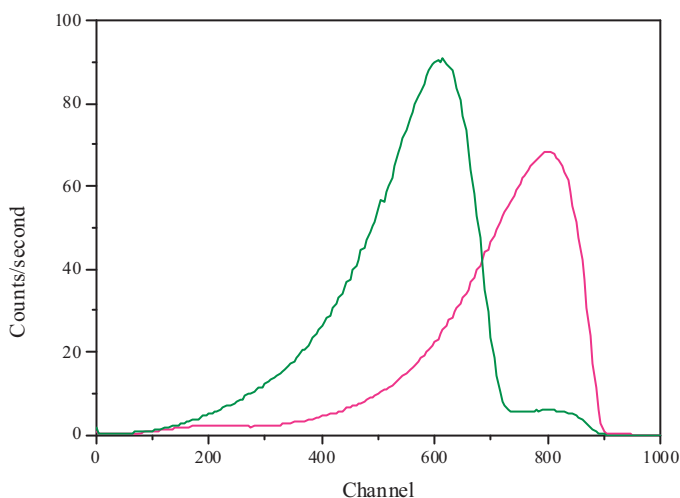
FIG. 8.3. Spectra of first fraction (red) and third fraction (green).
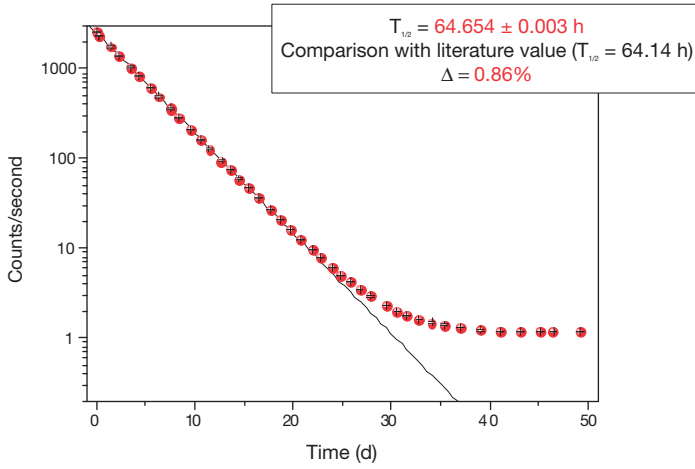
FIG. 8.4. Decay curve of the first fraction.
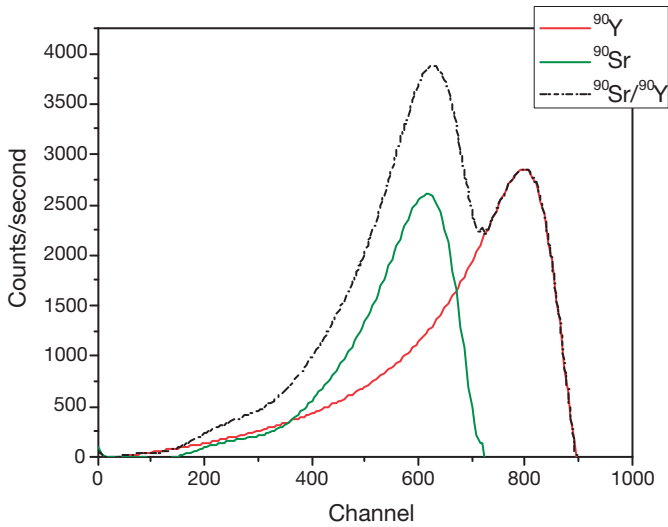
FIG. 8.5. Spectra after complete decay of ^{90}Y (dashed line).

From the deconvoluted spectra of ^{90}Sr, the radionuclidic impurity was calculated to be:

$$\frac{A_{^{90}\text{Sr}}}{A_{(^{90}\text{Y}+^{90}\text{Sr})}} = \left(8.81 \times 10^{-3} \pm 6.13 \times 10^{-4}\right)$$

8.4.2.   Detection of the ICRP level of ^{90}Sr in a commercial sample of ^{90}Y

In the second experiment, a Sr Resin cartridge was loaded with 10 μL of ^{90}Y (~3.97 × 10^7 Bq) to verify whether the system would allow detection of an amount of ^{90}Sr equal to that certified by the supplier, which meets the International Commission on Radiological Protection (ICRP) requirements of 10^{-5}%. The elution scheme was similar to that reported in the previous experiment.

Table 8.1 summarizes the results of the LSC of the eluted fractions. The counts reported in the first two columns depend on the dilution of the sample collected from the column. It is important to point out that the percentage of ^{90}Y recovered in the third fraction (1.23 × 10^{-2}%) corresponds to about 4883 ± 52 Bq, which is three orders of magnitude higher than the amount of ^{90}Sr that is supposed to be found in this fraction (<3.9 Bq) according to the PerkinElmer® certificate.

From the above experiments, it was concluded that it is impossible to detect the ^{90}Sr present in this commercial sample, because the ^{90}Y leaking out in the third fraction covers the counts due to the ^{90}Sr.

8.4.3.   Evaluation of column performance using ^{85}Sr

In the third experiment, a Sr Resin cartridge was loaded with a standard solution of ^{85}Sr from POLATOM, previously brought to dryness and recovered with 5 mL of 8.0M HNO$_3$. The results of the separation are shown in Table 8.2.

It can be seen that the yield (%) of ^{85}Sr in the first fraction is comparable with that obtained in the first experiment, in which a solution at the secular equilibrium of ^{90}Sr/^{90}Y was passed through the column. The experience accrued so far has shown that using a single cartridge under the conditions recommended by Eichrom® Technologies does not make it possible to achieve the needed radiochemical separation.

TABLE 8.1. EXPERIMENT TWO:
RADIOCHEMICAL YIELDS

Fraction	Yield (%)		SD
I – 8M	98.85	±	0.85
II – 8M	1.40	±	0.020
III – 0.01M	1.23×10^{-2}	±	1.30×10^{-4}
IV – 0.01M	4.53×10^{-4}	±	4.28×10^{-5}
Washing – 0.01M	1.63×10^{-4}	±	4.81×10^{-5}

TABLE 8.2. EXPERIMENT THREE:
RADIOCHEMICAL YIELDS

Fraction	Yield (%)		SD	
I	7.5×10^{-3}	$\pm$	3.2×10^{-4}	
II – 8M	1.7×10^{-3}	$\pm$	5.5×10^{-4}	
III – 8M	3.9×10^{-3}	$\pm$	7.1×10^{-4}	
IV – 0.01M	91.88	$\pm$	0.59	
V – 0.01M	1.26	$\pm$	0.025	93.15 ± 1.93
Column	4.9	$\pm$	0.19	

TABLE 8.3. EXPERIMENT FOUR:
RADIOCHEMICAL YIELDS

Fraction	Yield (%)		SD	
I	3.18×10^{-4}	$\pm$	1.92×10^{-5}	
II – 8M	7.92×10^{-7}	$\pm$	6.02×10^{-8}	
III – 8M	9.88×10^{-6}	$\pm$	8.16×10^{-7}	
IV – 0.01M	1.4×10^{-5}	$\pm$	1.12×10^{-6}	
V – 0.01M	87.21	$\pm$	2.74	90.8 ± 8.28
VI – 0.01M	3.6	$\pm$	0.11	
Column	4.83	$\pm$	0.15	

8.4.4. Evaluation of different chromatographic conditions using [85]Sr

In the fourth experiment, an attempt was made to improve the efficiency of separation by using two Sr Resin cartridges in tandem. An aliquot (2.75 mL) of the [85]Sr solution in 8M HNO_3 was passed through the columns. The results are shown in Table 8.3. Some of the parameters, such as the activity retained on the column, are similar to those of previous experiments; however, the percentage of [85]Sr recovered in the first fraction is one order of magnitude lower. The separation has been improved by the use of the two columns. In further investigations, the goal of complete decontamination of the ^{90}Y fractions was reached.

8.4.5. Evaluation of a column prepared in house using [85]Sr

In the fifth experiment, efforts were made to further improve the efficiency of separation using a 1 cm × 5 cm column loaded with 4 mL of Sr Resin that was prepared in house. An aliquot (2.8 mL) of the [85]Sr solution in 8M HNO_3 was passed through the columns. The results are shown in Table 8.4. By using the column prepared in house, it was possible to further reduce the percentage of [85]Sr eluted in the first fraction to a level below detection; that is, to the level of about 10^{-5}%.

8.4.6. Evaluation of column prepared in house using [90]Y

In this experiment, the separation efficiency of the column prepared in house (1 cm × 5 cm) was tested by loading an aliquot of pure [90]Y (2.7 mL) in 8M HNO_3. The recovery of ^{90}Y in the first fractions eluted with 8M HNO_3 was more than 99%; most important, in the fourth and fifth fractions the ^{90}Y was under the detectable limit, which means that it would not interfere with the counting of potential contamination of ^{90}Sr present in the sample under evaluation.

8.5. CONCLUSION

Using the chromatographic system prepared in house and loaded with the Eichrom Sr Resin, it is possible to achieve the instant determination of ^{90}Sr at the permissible limit by measuring the fractions eluted with dilute acid.

TABLE 8.4. EXPERIMENT FIVE: RADIOCHEMICAL YIELDS

Fraction	Yield (%)		SD	
I		$<7 \times 10^{-5}$		
II – 8M		$<7 \times 10^{-5}$		
III – 8M		$<7 \times 10^{-5}$		
IV – 0.01M		$<7 \times 10^{-5}$		
V – 0.01M	96.7	±	0.57	97.58 ± 1.57
VI – 0.01M	0.88	±	0.013	
Column	4.08	±	0.035	

REFERENCES TO CHAPTER 8

[8.1]   FIRESTONE, R.B., BAGLIN, C.M., CHU, F.S.Y., Table of Isotopes, 8th Ed., 1998 Update on CD-ROM, John Wiley and Sons, New York (1998).

[8.2]   PFENNING, G., KLEWE-NEBENIUS, H., SEELMANN-EGGEBERT, W., Karlsruher Nuklidkarte, 6. Auflage 1995, korrigierter Nachdruck 1998, KFK, Karlsruhe, Cruckhaus Haberbeck GmbH, Lippe, Germany (1998).

[8.3]   LIESER, K.H., Nuclear and Radiochemistry: Fundamentals and Applications, 2nd revised ed., Wiley and Verlag VHC, Berlin (2001).

[8.4]   CHINOL, M., HNATOWICH, D.J., Generator-produced yttrium-90 for radio-immunotherapy, J. Nucl. Med. **28** (1987) 1465–1470.

[8.5]   INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION, Limits for Intakes of Radionuclides by Workers, ICRP Publication 30, Part 1, **2** (1979) 77–78.

[8.6]   DU, J., CHINOL, M., SAVONEN, A., HILTUNEN, J., Simple and safe production of yttrium-90 from a new type of $^{90}Sr/^{90}Y$ generator, Radiochim. Acta **93** (2005) 111–113.

[8.7]   KWEKKEBOOM, D.J., et al., Overview of results of peptide receptor radio-nuclide therapy with 3 radiolabeled somatostatin analogs, J. Nucl. Med. **46** (2005) 62S–66S.

[8.8]   URBANO, N., et al., Evaluation of a new biotin-DOTA conjugate for pretargeted antibody guided radioimmunotherapy (PAGRIT®), Eur. J. Nucl. Med. Mol. Imaging **34** (2007) 68–77.

Chapter 9

IONIC LIQUID TYPE CROWN ETHER AS A NOVEL MEDIUM FOR LIQUID–LIQUID EXTRACTION OF THE RADIOACTIVE METAL ION $^{85}Sr^{2+}$

SANG HYUN PARK

Radiation Research Division for Biotechnology,
Korea Atomic Energy Research Institute,
Daejeon, Republic of Korea

Abstract

1,13-dichloro-4,7,10-trioxatridecane (2-[2-(1-chloro-2-ethoxy)ethoxy]ethyl chloride) was synthesized by chlorination of 1,13-dihydroxy-4,7,10-trioxatridecane (triethylene glycol). Treatment with imidazole and sodium ethoxide provided $1N,1N'$-tris(oxoethylene)-diimidazole, which was then converted to an ionic liquid type crown ether (ILCE) with reaction with 1,9-dichloro-3,6-trioxaoctane. The anion of the ILCE was then exchanged by an anion exchange method. Ultimately, a very efficient synthetic pathway was developed for the preparation of ILCEs having various physical and chemical characteristics by a modification of the polyethylene glycol chain length and anions. The $^{85}Sr^{2+}$ was successfully extracted into the $[(3,2)O_{Et}Im][Cl]$ phase, but was not extracted into the $[(2,2)O_{Et}Im][Cl]$, $[(3,3)O_{Et}Im][Cl]$ and $[(4,3)O_{Et}Im][Cl]$ phases.

9.1. INTRODUCTION

Interest in radiopharmaceuticals for the treatment of serious illnesses such as cancer and rheumatoid arthritis has increased during the past decade, and ^{89}Sr, ^{186}Re, ^{153}Sm, ^{90}Y and ^{166}Ho are currently used in routine clinical practice. Strontium-89 is a radionuclide used for palliative treatment of bone cancers and for treatment of prostate cancer [9.1]. Strontium-90 is the parent radionuclide of the ^{90}Y generator used as a radiotherapeutic nuclide [9.2]. Accordingly, many methods have been evaluated for the separation of ^{90}Y for use in nuclear medicine. Strontium radioisotopes can be extracted by using crown ethers, and 18-crown-6 (18C6), dicyclohexano-18-crown-6 (DCH18C6) and 4,4′(5′)-di-(*tert*-butylcyclo-hexano)-18-crown-6 (Dtb18C6) have been studied for extraction of the Sr^{2+} ion from aqueous solutions [9.3]. In the absence of an extractant, the distribution ratio for the metal ion indicates a strong preference for the aqueous phase. In a typical liquid–liquid extraction experiment, the crown ether resides in the hydrophobic extraction phase, and

serves to dehydrate and complex the metal ions for removal from the aqueous phase [9.4, 9.5]. To enhance the efficiency of such a process, an organic solvent is selected to sustain the biphasic system while maximizing the hydrophobic and complexing properties of the extracting phase. However, the volatile organic compounds (VOCs) commonly employed in traditional liquid–liquid separations can have high hazard ratings and low flash points, indicating associated health and safety concerns. While liquid–liquid separations utilizing VOC diluents have extensive applications in industry, from chemical synthesis to hydrometallurgy, such practices often generate large volumes of contaminated solvents. Ending such reliance on separations that consume large quantities of VOCs has become a target area for the development of 'green' industrial processes that are inherently safer and less polluting [9.6–9.10].

In recent years, ionic liquids have attracted much attention as recyclable media for organic synthesis [9.3, 9.11–9.13]. The materials are considered 'green' solvents since they are non-volatile, non-flammable, non-toxic, thermally stable and recyclable. Limited solubility of ionic species in non-ionic organic solvents is the main problem associated with conventional solvent extractions. For these reasons, we have evaluated the synthesis of new ILCEs for a liquid–liquid extraction of metal ions. The new crown ethers contain a large polyoxyethylene (POE) ring, which is capable of interacting with metal ions to produce a complex of associates. Certain modifications can be made to produce a molecule designed for optimal results for specific applications. The goal is to develop novel sequestering agents to achieve the extreme selectivity required to extract specific radionuclides.

9.2. EXPERIMENTAL PROCEDURES

Polyethylene glycol in benzene was treated with pyridine and thionyl chloride to give compounds 1a–4a. A solution of imidazole (0.20 mol) in 100 mL of absolute ethanol was treated with compounds 1a–4a (0.10 mol) in the presence of sodium ethoxide. The mixture was stirred and refluxed for 6 h to give compounds 1b–4b. Treatment of compounds 1b–4b (0.20 mol) in 250 mL of anhydrous acetonitrile with 0.20 mol of compounds 1a–4a provided compounds 1–4 in good yields (Fig. 9.1).

Instrumental analyses confirmed the chemical structures of the target compounds 1a and 3. The ring size of the ILCE can be regulated by an increase of the ether chain length. Physical characteristics of the ILCE can be regulated by the anion exchange reactions. Sodium trifluoroacetate was added to a solution of the $[(2,2)O_{Et}Im][Cl]$ **1** prepared in acetone as described above, and
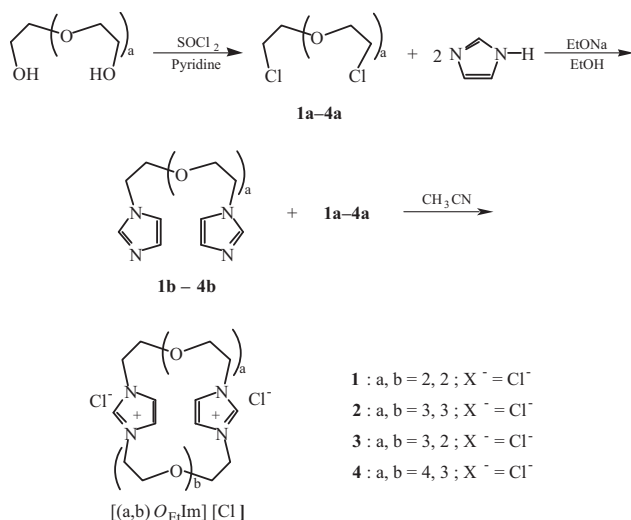
FIG. 9.1. Synthesis of $[(a,b)O_{Et}Im][Cl]$.
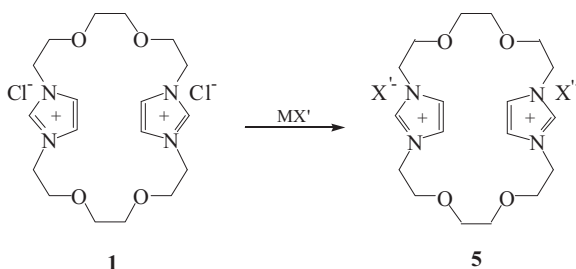
FIG. 9.2. Synthesis of ILCE by anion exchange reaction.

the mixture was stirred at room temperature for 24 h. Other anion substituted ILCEs can be prepared in the same way as **5** from $AlCl_4^-$, $Al_2Cl_7^-$, BF_4^-, SbF_6^-, NO_3^-, HSO_4^-, $CF_3SO_3^-$, $(CF_3SO_3)_2N^-$ (see Fig. 9.2).

Strontium-85 was produced at the HANARO research reactor (30 MW) at the Korea Atomic Energy Research Institute by neutron irradiation of an encapsulated $^{84}SrCO_3$ target for 24 min at a neutron flux of $(2.5 \times 10^{13}$ n·cm^{-2}·s^{-1}). The target was cooled for 24 h and then dissolved in deionized water and 1M nitric acid. The radionuclidic purity of the ^{85}Sr was estimated by gamma ray spectrometry (GEM-10175 HPGe detector coupled to a multichannel analyser, ORTEC, Oak Ridge, USA). A typical gamma ray spectrum obtained from the HPGe detector shows photopeaks due to the gamma rays of ^{85}Sr and ^{87m}Sr; the 514.0 and 388.4 keV photopeaks were used for the assay. The initial specific activity of ^{85}Sr was 189 Bq/mg. The radioactivity was measured using an

ionizing chamber (Capintec 15R, BIODEX Atomlab 200, USA) at the calibration value for ^{85}Sr set by the manufacturer.

Metal ion distribution ratios were determined by mixing 1 mL of ILCE and 1 mL of aqueous phase, followed by vortexing (2 min) and centrifuging (2000g, 2 min) to equilibrate the phases. Addition of the metal ion tracer (~407 Bq, 5 µL) was followed by two intervals of vortexing (2 min) and centrifuging (2000g, 2 min) to ensure that the phases were fully mixed and separated. The phases were separated and dispensed into vials, from which 100 µL of each phase was removed for a radiometric analysis. Because equal volumes of both phases were removed for analysis, the distribution ratio (D) for the metal ions was determined as follows:

$$D = \frac{\text{Activity in the ILCE lower phase}}{\text{Activity in the aqueous upper phase}}$$

Each experiment was performed in duplicate, and the results agreed to within 5%. The ^{85}Sr^{2+} ion was successfully extracted into the cyclo-{1N,1N'-[(3,6,9-trioxa)-1,11-undecyl]}-{3N,3N'-[(3,6-dioxa)-1,8-octyl]}-diimidazolium chloride {[(3,2)O_{Et}Im][Cl] **3**} phase, but it was not extracted into the [(2,2)O_{Et}Im][Cl] **1**, [(3,3)O_{Et}Im][Cl] **2** and [(4,3)O_{Et}Im][Cl] **4** phases (Table 9.1).

9.3. RESULTS AND DISCUSSION

Novel ILCEs that are non-toxic, recyclable and economical can be readily synthesized and employed for efficient extraction of strontium. The new imidazolium ionic liquid type reinforces the conventional reducing agents,

TABLE 9.1. DISTRIBUTION OF ^{85}Sr

ILCE	Distribution of Sr-85 (Bq)		Distribution ratio
	Aqueous phase	ILCE phase	
[(2,2)O_{Et}Im][Cl] **1**	390	Not detected	0
[(3,3)O_{Et}Im][Cl] **2**	323	Not detected	0
[(3,2)O_{Et}Im][Cl] **3**	17	356	21
[(4,3)O_{Et}Im][Cl] **4**	369	Not detected	0

which require very stringent conditions for preparation. The crown ethers described in this report possess POE substituent groups. Their increased density should allow the imidazolium cores to adhere more tightly to the strontium ions in order to maximize the interaction. ILCEs have been found to behave like multifunctional compounds that discriminate a metal cation according to their ring size. Also, the ILCEs are expected to be used for extraction of other radionuclides or heavy metals. The ILCEs obtain their selectivity through the ability to fine-tune and reorganize their crown ether structure and the resulting properties of the crown by changing their ring size and rigidity, changing their number and type of donor atoms, appending ionizable groups, and modifying their lipophilicity.

ACKNOWLEDGEMENT

REFERENCES TO CHAPTER 9

[9.1] CIPRIANI, C., et al., Gamma camera imaging of osseous metastatic lesions by strontium-89 bremsstrahlung, Eur. J. Nucl. Med. **24** (1997) 1356–1361.

[9.2] WOOD, D.J., ELSHANI, S., DU, H.S., NATALE, N.R., WAI, C.M., Separation of 90Y from 90Sr by solvent extraction with ionizable crown ethers, Anal. Chem. **65** (1993) 1350–1354.

[9.3] VISSER, A.E., SWATLOSKI, R.P., REICHERT, W.M., GRIFFIN, S.T., ROGERS, R.D., Traditional extractants in nontraditional solvents: Groups 1 and 2 extraction by crown ethers in room-temperature ionic liquids, Ind. Eng. Chem. Res. **39** (2000) 3596–3604.

[9.4] BRADSHAW, J.S., IZATT, R.M., BORDUNOV, A.V., ZHU, C.Y., HATHAWAY, J.K., Comprehensive Supramolecular Chemistry, Vol. 1: Molecular Recognition, Pergamon Press, Oxford (1996) 39.

[9.5] MOYER, B.A., Comprehensive Supramolecular Chemistry, Vol. 1: Molecular Recognition, Pergamon Press, Oxford (1996) 377.

[9.6] ADLER, S., BEAVER, E., BRYAN, P., ROBINSON, S., WATSON, J., Vision 2020: 2000 Separations Roadmap, American Institute of Chemical Engineers, New York (2000).

[9.7] ANASTAS, P.T., WARNER, J.C. (Eds), Green Chemistry: Theory and Practice, Oxford University Press, Oxford (1998).

[9.8] Synthesis and Processing with Alternative Resources, Roadmapping Workshop Report, Department of Energy, Office of Industrial Technologies, Washington, DC (2000).

[9.9] LONG, T.E., HUNT, M.O., Solvent-Free Polymerizations and Processes: Minimization of Conventional Organic Solvents, ACS Symposium Series 713, American Chemical Society, Washington, DC (1998).

[9.10] SHERMAN, J., CHIN, B., HUIBERS, P.D., GARCIA-VALLS, R., HATTON, T.A., Solvent replacement for green processing, Environ. Health Perspect. **106** (1998) 253–271.

[9.11] SHENG, D., JU, Y.H., BARNES, C.E., Solvent extraction of strontium nitrate by a crown ether using room-temperature ionic liquids, J. Chem. Soc. Dalton Trans. (1999) 1201–1202.

[9.12] OLIVIER-BOURBIGOU, H., MAGNA, L., Ionic liquids: perspectives for organic and catalytic reactions, J. Mol. Catal. A: Chem. **182** (2002) 419–437.

[9.13] VISSER, A.E., et al., Task-specific ionic liquids incorporating novel cations for the coordination and extraction of Hg2+ and Cd2+: synthesis, characterization, and extraction studies, Environ. Sci. Technol. **36** (2002) 2523–2529.

Chapter 10

DETERMINATION OF ^{90}Sr IN THE ^{90}Y ELUATES OF THE ^{90}Sr/^{90}Y GENERATOR

R. MIKOLAJCZAK, M. ZUCHLINSKA, A. KORSAK, E. ILLER,
D. PAWLAK, Z. ZELEK, M. KONIOR, J.L. PARUS
IAE Radioisotope Centre POLATOM,
Otwock-Świerk, Poland

Abstract

A set of two extraction chromatography columns connected in series was used for the determination of trace levels of ^{90}Sr in ^{90}Y eluates. The first column is filled with Sr Resin and the second with DGA Resin. Strontium-90 is retained on the first column and ^{90}Y on the second column. Strontium-90 is eluted with water from the first column and measured using liquid scintillation counting. The remaining ^{90}Sr eventually appears in the liquid leaving the DGA column. The use of the DGA column itself seems to be sufficient for ^{90}Sr determination at the detection limit of 10^{-5}%.

10.1. INTRODUCTION

Progress in the development of ^{90}Sr/^{90}Y generators is limited by the fact that most of the laboratories participating in this CRP are not equipped to measure low levels of ^{90}Sr breakthrough in the ^{90}Y eluates, and hence the radionuclidic purity of the generators is difficult to assess. In this report, preliminary data are presented on a method for determination of a trace level of ^{90}Sr contamination in the ^{90}Y eluates involving chemical separation using solid phase extraction chromatography. The method will be further improved in ongoing studies.

Determination of low level radionuclidic impurities in the presence of high quantities of long lived ^{90}Sr is generally difficult because of the high energy beta radiation of the constantly accumulating ^{90}Y. Thus, in the case of gamma spectrometry, the continuous bremsstrahlung spectrum stemming from ^{90}Y beta radiation prevents the determination and quantification of underlying weak gamma peaks of impurities. The continuous high energy beta spectrum of ^{90}Y makes it equally impossible to determine beta emitting impurities by liquid scintillation beta spectrometry and complicates the alpha/beta discriminative liquid scintillation measurements. It is therefore desirable in a number of cases

to selectively separate ^{90}Sr from all possible impurities and also from the short lived ^{90}Y daughter. The rapid radioactive decay of the latter in the mixture obtained would permit subsequent precise determination of the impurities. The separation method that is applied (in this case, extraction chromatography) must be validated with respect to selectivity of ^{90}Sr separation (no impurities should be 'lost' or eliminated along with the ^{90}Sr).

The extractant system of Eichrom Sr Resin is 1.0M 4,4′(5′)-di-t-butyl-cyclohexano 18-crown-6 (crown ether) in 1-octanol, which is loaded onto an inert chromatographic support. The bed density of Sr Resin is approximately 0.35 g/mL. The uptake of strontium by the Sr Resin increases with increasing nitric acid concentration.

The Eichrom DGA Resins are extraction chromatographic materials in which the extractant system is either N,N,N′,N′-tetra-n-octyldiglycolamide (DGA Resin, Normal) or N,N,N′,N′-tetrakis-2-ethylhexyldiglycolamide (DGA Resin, Branched). The bed density of both DGA Resins is approximately 0.38 g/mL, with a working capacity of 7.23 mg of ^{90}Sr per mL of resin and 11 mg of yttrium per mL of resin.

The four alkaline earth cations on DGA Resin normally do not show any significant uptake from HCl, and only strontium and calcium show moderate uptake from nitric acid concentrations of about 0.5 to about 5M. Yttrium(III) is much more strongly retained on the resin than Sr(II) from both nitric and hydrochloric acids across all concentrations. Coupling the Sr Resin with DGA Resin, Normal would allow for excellent separation of yttrium from strontium for radiopharmaceutical purification or a single step $^{89/90}$Sr measurement procedure.

10.2. SEPARATION OF ^{90}Sr AND ^{90}Y BY EXTRACTION CHROMATOGRAPHY

Extraction chromatography is used for selective separation of the long lived ^{90}Sr from ^{90}Y, and from all radionuclidic impurities potentially present in the initial ^{90}Sr solution in equilibrium, hereinafter referred to as ^{90}Sr solution. This separation permits, after the disintegration of the short lived ^{90}Y, the quantification of impurities with sufficiently low detection limits. For selective retention of ^{90}Sr, Sr Resin (Eichrom Technologies) is used [10.1, 10.2].

The procedure is as follows:

(1) Sr Resin (0.5 g) is soaked in 3M HNO$_3$ over a period of 18–20 h in a laboratory glass beaker. A glass column is filled with the resin and washed with 20 mL of 3M HNO$_3$.

(2)   A known aliquot (0.25 mL) of the ^{90}Sr solution to be analysed is taken by weight and diluted with 2.5 mL of 6M HNO$_3$.

(3)   The obtained solution in 6M HNO$_3$ is loaded on the column and washed with 5 mL of 3M HNO$_3$.

The ^{90}Sr free eluate obtained is used as stock solution for further radio-activity measurements. The ^{90}Sr is then stripped from the column with diluted HCl and taken for LSC.

10.3. EVALUATION OF RECOVERY OF BETA EMITTERS FROM Sr RESIN

The Sr Resin is characterized by high selectivity for Sr^{2+} cations and by negligible retention of other cationic/anionic elements, save lead, in 3–6M nitric acid solutions [10.1]. This resin can therefore be used for separation of the long lived ^{90}Sr from ^{90}Y and from all radionuclidic impurities possibly present in the initial ^{90}Sr solution. This separation permits, after the decay of the short lived ^{90}Y, the quantification of impurities with sufficiently low detection limits. In addition, experiments were performed in order to validate the complete recovery of a number of potential radionuclidic beta impurities at the moment of separation of ^{90}Sr. Precise experimental conditions used for the determination of impurities were thus validated [10.3].

Standard solutions of the radionuclides ^{35}S (E_{max}: 167.5 keV, T$_{1/2}$: 87.44 d), ^{36}Cl (E_{max}: 709.5 keV, T$_{1/2}$: 3.01 × 10^5 a), ^{63}Ni (E_{max}: 65.9 keV, T$_{1/2}$: 100.1 a), ^{99}Tc (E_{max}: 293.6 keV, T$_{1/2}$: 2.14 × 10^5 a) and ^{45}Ca (E_{max}: 256.9 keV, T$_{1/2}$: 163 d) were used to determine the recovery of these beta emitting radionuclides from the Sr Resin.

The complete recovery of the radionuclides justifies the use of the Sr Resin for the collective separation of ^{90}Y and of the potential radionuclidic impurities from ^{90}Sr.

10.4. RESULTS

To determine the traces of ^{90}Sr in ^{90}Y, the following procedure was developed. Two extraction chromatography columns are connected in series. The first column is filled with 1 g of Sr Resin and the second column with 1 g of DGA Resin. The ^{90}Y solution in 3M HNO$_3$ (about 100 mCi) is fed onto the first column. Strontium-90 is retained on the first column and ^{90}Y on the second

TABLE 10.1. RECOVERY OF SELECTED BETA EMITTERS
FROM Sr RESIN (ELUTION WITH 5 mL OF 3M HNO_3)

Radionuclide	Radioactivity loaded on column (kBq)	Radioactivity collected from column		Recovery (%)	SD (%)
		(kBq)	(mean kBq)		
S-35	51	51.05 52.15 53.10	52.1	102.1	0.84
Cl-36	1.22	1.265 1.195 1.180	1.21	99.2	0.04
Ni-63	18.9	16.406 16.483 16.450	16.446	87	0.03
Tc-99	10.28	10.540 10.647 10.441	10.543	102.5	0.084
Ca-45	142.29	151.15 152.20 146.50	149.95	105.3	2.5

one. The columns are separated, and the ^{90}Sr is eluted with water from the first column and measured using a liquid scintillation counter.

The liquid emerging from the tandem columns should contain the rest of the ^{90}Sr. When necessary, the residual amount of ^{90}Y is removed on the additional DGA column.

10.5. CONCLUSION

The extraction chromatography method can be applied for determination of trace amounts of ^{90}Sr in ^{90}Y eluates obtained from $^{90}Sr/^{90}Y$ generators; however, this system requires further work and validation.

REFERENCES TO CHAPTER 10

[10.1] HORWITZ, E.P., DIETZ, M.L., Process for the separation and purification of yttrium-90 for medical applications, United States Patent No. 5368736, Nov. 29 (1994).

[10.2] HORWITZ E.P., MCALISTER, D.R., BOND, A.H., BARRANS, R.E., Novel extraction of chromatographic resins based on tetraalkyldiglycolamides: Characterization and potential applications, Solved Extraction Ion Exchange **23** (2005) 219.

[10.3] JUNTUNEN, P., NIKULA, T.K., Fast method for determination of minute ^{90}Sr impurities in ^{90}Y solution for quality control purposes, Eur. J. Nucl. Med. Mol. Imaging **34** (2007) 355.

Chapter 11

DEVELOPMENT OF A ^{188}W/^{188}Re GENERATOR, POST-ELUTION CONCENTRATION OF ^{99m}Tc AND EVALUATION OF HIGH CAPACITY ADSORBENTS

J.A. OSSO, Jr., G. BARRIO, A. OLIVEIRA, B.S. MARCZEWSKI,
V. MORAES, F. CAMARGO, R.C. NIETO, K.N. SUZUKI,
C.R.B.R. DIAS, P.R.C. LOPES, N.C. SILVA, A.L.C.P. LIMA,
B.L. FAINTUCH, J. MENGATTI, E. BORTOLETI, N.P. SOSA,
C.P.G. DA SILVA
Radiopharmacy Centre,
Nuclear and Energy Research Institute (IPEN-CNEN/SP),
São Paulo, Brazil

Abstract

The objective of the coordinated research project was the development of techniques for the preparation of ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators. The research at IPEN-CNEN/SP focused on developing a generator technology using high specific activity ^{188}W imported from the Russian Federation. The development of a ^{188}Re gel type generator, using the experience acquired by IPEN in recent years through the ^{99m}Tc gel generator project, is discussed. Quality control procedures were developed to ensure the purity of the eluted ^{188}Re, and special attention was given to post-elution concentration of ^{188}Re.

11.1. INTRODUCTION

Radiotherapy delivered via internal administration of radionuclides targeted via a tumour seeking carrier molecule is increasingly used for the treatment of cancer. Radionuclides emitting beta and alpha particles, and Auger electrons are of primary interest. From the point of view of the availability of production facilities, radiolabelling stability and dose delivered, the beta emitting radionuclides are the primary choice.

Rhenium-188 is a high energy beta emitter with a maximum beta energy of 2.12 MeV. Its 17 h half-life requires relatively rapid targeting and non-target clearance for useful therapeutic application. Gamma imaging is also possible owing to its 155 keV gamma emission (15%). The similarity of its chemistry to that of technetium makes ^{188}Re an attractive radionuclide for therapeutic use

including radioimmunotherapy, radionuclide synovectomy and bone pain palliation. Rhenium-188 can be attached to antibodies, peptides and other molecules such as lipiodol and DMSA. Rhenium-188 of modest specific activity can be produced by direct activation in a reactor. However, the production method of choice is by the decay of the longer lived parent ^{188}W (T$_{1/2}$: 69.4 d), which is produced through a double neutron capture reaction on ^{186}W. Depending on the specific activity of ^{188}W, chromatography based on alumina or a gel type generator can be performed. In both cases, no carrier added (NCA) ^{188}Re is eluted with saline solution in the form of sodium perrhenate. The chromatographic generator with alumina is suitable for high specific activity ^{188}W, and the technology is similar to that used for ^{99}Mo/^{99m}Tc generators assembled with fission produced ^{99}Mo. The gel generator is an option when using low specific activity ^{188}W. Gels and polymers containing zirconium or titanium can be used. A post-elution concentration step can be used to concentrate the perrhenate solution to higher specific volume.

Another important aspect of the research is the use of high capacity adsorbents for the preparation of ^{188}W/^{188}Re and ^{99}Mo/^{99m}Tc generators, such as PZC developed in Japan and made available through the IAEA.

The following issues were studied during the CRP: development of methodologies for the preparation and quality control of ^{188}W/^{188}Re generators, and development of technologies for post-elution concentration of ^{188}Re in order to improve the radioactive concentration.

11.2. MATERIALS

During the project, two batches of ^{188}W of about 200 mCi each were received from the SM reactor, Dimitrograd, Russian Federation.

11.3. EXPERIMENTAL PROCEDURES

11.3.1. Evaluation of adsorbents for ^{188}W/^{188}Re generators

Generators based on an alumina column: Generators were prepared with 2 g of alumina previously conditioned with 0.1M HCl and dried. A known volume of ^{188}W solution was taken, and the pH was adjusted to 2.0 with 8M HCl. This solution (1 mL) was loaded onto the column, and elutions were performed with a solution of 0.9% NaCl.

Preparation of a gel type ^{188}W/^{188}Re generator: The gel generator studied was a zirconium tungstate (WZr) generator based on a project developed at

IPEN for the production of a gel based ^{99}Mo/^{99m}Tc generator. Tungsten trioxide (1 g) was dissolved with 2M NaOH, 1.0 mL of the ^{188}W (15 mCi) supplied by the IAEA was added and the pH was adjusted to 4 with 2M HNO$_3$. A solution of ZrOCl$_2$.8H$_2$O (3 g in 42 mL of H$_2$O, at pH1.5) was added with heating at 50°C and stirring. The pH was adjusted to 4.5 with 2M NaOH. After the reaction, the gel was filtered, dried, cracked with saline solution and dried again. The dry gel was loaded onto a column previously loaded with 1 g of Al$_2$O$_3$, and the generator was eluted with known volumes of saline solution.

The WZr gel was characterized as follows. Structure identification of the gel was performed by X ray diffraction with alpha CuK radiation. Particle size was determined using a sieve distribution apparatus, weighing the sieves before and after the distribution. Determination of tungsten and zirconium was done by neutron activation analysis and by UV visible spectrometry.

Quality control of ^{188}Re: The quality control of ^{188}Re eluted in both types of generator included estimation of radiochemical purity, chemical purity and radionuclidic purity. Aluminium, tungsten and zirconium impurities were estimated by UV visible spectrometry and ICP-OES. Radionuclidic impurity was measured by estimating ^{188}W breakthrough by γ spectroscopy. Radio-labelling studies of HEDP were done with the eluted ^{188}Re in perrhenate form.

11.4. RESULTS AND DISCUSSION

Figures 11.1 and 11.2 show the elution behaviour of the ^{188}W/^{188}Re generator based on an alumina column. Elution yields were greater than 90% in a volume of 6 mL of the eluate. The results of the quality control tests indicated that the eluted ^{188}ReO$_4^-$ was of good quality.

A series of radiolabelling experiments was performed with ^{188}Re eluted from the generators prepared in house in order to prove its quality. In one experiment, HEDP was radiolabelled with ^{188}Re using a kit in solution form containing 30 mg of HEDP, 3 mg of ascorbic acid and a variable amount of the reducing agent (SnCl$_2$.2H$_2$O), and adjusting the final volume to 1.0 mL. The labelling was performed with 30 min of heating (100°C) followed by 60 min of cooling. The results were in agreement with the results obtained using ^{188}Re eluted from a commercial ^{188}W/^{188}Re generator supplied by ORNL.

The results of the characterization of the WZr gels showed that the gels were of good quality. X ray diffraction studies showed that the WZr had an amorphous form. The particle size distribution was appropriate to give a good performance of the gel type generators, with most of the particles ranging between 150 and 300 μm. The amounts of tungsten and zirconium in the gel were 37% and 43%, respectively. The performance of the WZr gel generators
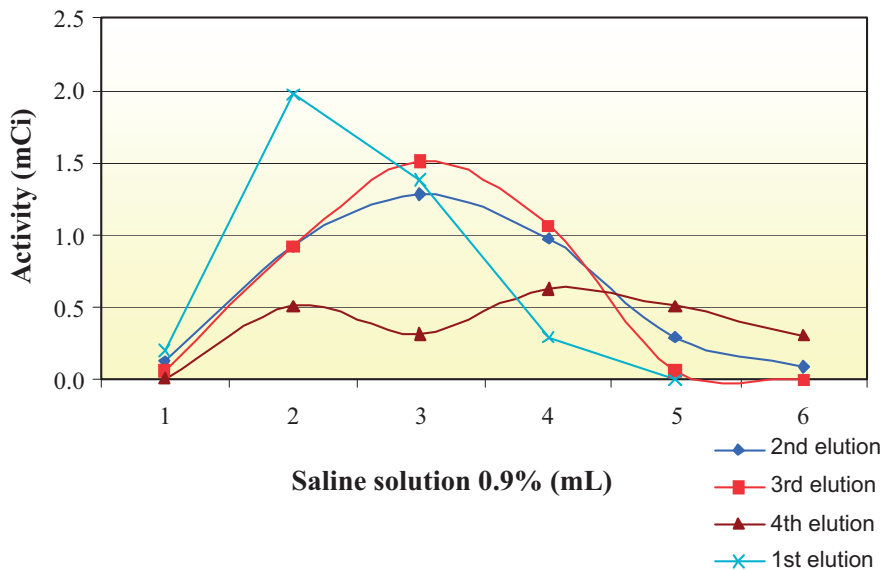
FIG. 11.1. Elution of $^{188}W/^{188}Re$ generator based on an alumina column.
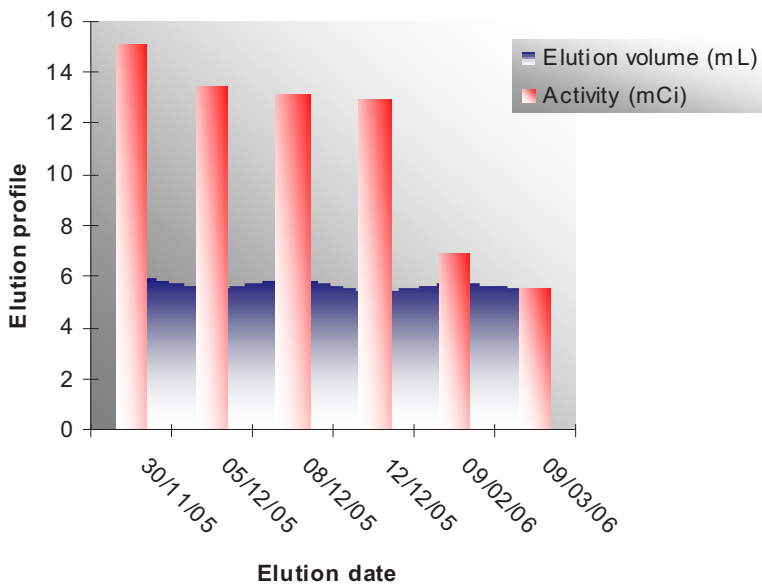
FIG. 11.2. Elution profile of $^{188}W/^{188}Re$ generator based on an alumina column.

was good, with an elution efficiency greater than 65% and an elution yield greater than 80% in a volume of 6 mL.

Radiolabelling of HEDP with $^{188}ReO_4^-$ was also performed. The results were promising and comparable with those obtained with $^{188}ReO_4^-$ eluted from a generator from ORNL as well as with those obtained with the alumina based generator produced in house. The results of the quality control studies were satisfactory for both generators. The level of ^{188}Re as perrhenate was greater than 99%, the breakthrough of ^{188}W was less than 10^{-5}%, and the levels of aluminium, tungsten and zirconium were below the recommended upper limits.

In conclusion, technologies were developed for the preparation of both alumina based and WZr gel type $^{188}W/^{188}Re$ generators. IPEN-Brazil plans to import ^{188}W and prepare in-house generators for clinical applications.

ACKNOWLEDGEMENT

BIBLIOGRAPHY

MARCZEWSKI, B., DIAS, C.R., MORAES, V., OSSO, J.A., Jr., Liquid kit for preparation of rhenium-188, Brazilian Arch. Biol. Tech. **48** (2005) 137–140.

MORAES, V., MARCZEWSKI, B., DIAS, C.R., MARTINS, P.A., OSSO, J.A., Jr., Study of preparation of generators of gels of ^{99}Mo-^{99m}Tc based to gels of molybdenum with zirconium, titanium, cerium and hafnium, Radiol. Bras. **39** Suppl. 2 (2006) 96–97.

MORAES, V., MARCZEWSKI, B., DIAS, C.R., OSSO, J.A., Jr., Study of gels of molybdenum with cerium in the preparation of generators of ^{99}Mo-^{99m}Tc, Brazilian Arch. Biol. Tech. **48** (2005) 51–56.

OSSO, J.A., Jr., OLIVEIRA, A., MARCZEWSKI, B.S., FAINTUCH, B.L., Viability studies for the preparation of ^{188}W-^{188}Re generators at IPEN/CNEN-SP, World J. Nucl. Med. **3** (2004) S37.

OSSO, J.A., Jr., SILVA, N.C., LIMA, A.L.V., LANDINI, L., NIETO, R.C., MORAES, V., Development of ^{99}Mo-^{99m}Tc gel type generators at IPEN-CNEN/SP, World J. Nucl. Med. **1** (2002) 819.

Chapter 12

EVALUATION OF ALUMINA BASED
^{188}W/^{188}Re CHROMATOGRAPHIC GENERATORS

A. XIQUES CASTILLO, M. TORRES BERDEGUEZ,
D. BECKFORD, R. LEYVA MONTAŇA,
E. CASANOVA GONZÁLEZ, Y. MORENO
Isotope Centre (CENTIS),
Havana, Cuba

Abstract

Within the framework of the coordinated research project, different alumina based ^{188}W/^{188}Re chromatographic generators were prepared and evaluated. The ^{188}W activities loaded into the generators ranged from 200 to 400 mCi, and two different amounts of alumina (2 and 8 g) were used. The lowest ^{188}W breakthrough levels were obtained for the generator containing 8 g of alumina, while the best elution profile corresponded to the 2 g alumina generators. Regarding elution efficiency, the performance of all generators was similar and ranged from 70 to 80% yields of ^{188}Re. The eluate quality was evaluated through the labelling of monoclonal antibodies and diphosphonates.

12.1. INTRODUCTION

Rhenium-186 was the first rhenium radioisotope applied in nuclear medicine, owing to its $E_{\beta\,max}$ of 1.07 MeV and $E_{\gamma\,max}$ of 137 keV (very close to the 140 keV of ^{99m}Tc). Nevertheless, ^{186}Re is produced by (n,γ) reaction from enriched ^{185}Re targets, which generally leads to low specific activities that prevent its use in radioimmunotherapy. As an added disadvantage, the 3.78 d half-life generally requires the shipment of activities higher than are intended for use in the clinic, and its cost is therefore increased. Such inconveniences are absent in the case of ^{188}Re obtained from ^{188}W/^{188}Re generators. Although the initial cost of the ^{188}W/^{188}Re isotopic generator is high, the long, useful shelf life (6–12 months) lowers the costs of ^{188}Re [12.1]. Generator produced ^{188}Re is carrier free and has high specific activity. In this study, three alumina based ^{188}W/^{188}Re chromatographic generators were prepared and evaluated.

12.2. MATERIALS AND METHODS

12.2.1. Radiochemicals

High specific activity ^{188}W (4–5 Ci/g) in NaOH solution was purchased from RIAR (Dimitrograd, Russian Federation), and supplied by the IAEA. Three shipments were received, containing 200, 400 and 500 mCi, respectively.

12.2.1.1. Preparation of ^{188}W/^{188}Re generators

Eight gram alumina generator: Acid alumina (Merck) was activated with 10 mL of 0.1M HNO$_3$ and then washed with 100 mL of HCl solution adjusted to pH2. The pH of the ^{188}W solution was adjusted to 1–2 with 2M HCl and loaded onto a column containing 8.3 g of alumina. After loading, the column was washed with 100 mL of 0.9% NaCl solution. The evaluation of the generator was started 24 h after preparation.

Two gram alumina generator: Prior to acid activation, the alumina was heated for 10 h at 400°C. It was then acid washed with 100 mL of HCl at pH2. After the addition of 20 μL of 30% H$_2$O$_2$, the ^{188}W solution was heated in a water bath at 80°C for 20 min. After cooling, 2M HCl was added in quantities sufficient to lower the solution pH to 1.5–2. The solution was loaded onto a 1.8 g alumina column at a flow rate of 0.3 mL/min and then washed with 100 mL of saline.

12.2.1.2. Elution of ^{188}W/^{188}Re generators

Generator elution was carried out with 0.9% NaCl solution. To obtain the elution profiles, several 5 mL fractions were eluted, and the elution volume was later adjusted to 10 mL for the 8 g alumina generator and to 5 mL for the 2 g alumina generator.

12.2.1.3. Radiolabelling of monoclonal antibody with ^{188}Re

One millilitre of h-R3 monoclonal antibody (MoAb) was added to a sterilized vial, followed by the addition of 4.8 μL of 2-mercaptoethanol. The vial was shaken vigorously and allowed to stand for 30 min, with occasional shaking every 10 min. Radiolabelling was accomplished by dissolving a pyrophosphate kit (CENTIS) in 5 mL of nitrogen bubbled saline solution, to which were added the previously reduced MoAb and 5–6 mCi of ^{188}Re. The mixture was allowed to stand for 3 h at room temperature. Quality control was performed by paper chromatography (Whatman 3MM) with acetone (free

^{188}Re) and saline ([^{188}Re]-pyrophosphate). The presence of colloids was evaluated by ITLC with EtOH:NH$_3$:H$_2$O (2:1:5 vol./vol./vol.).

12.2.1.4. Radiolabelling of HEDP with ^{188}Re

Rhenium-188 (3–5 mCi) was added to an HEDP kit containing 0.1 mg of NaReO$_4$, 2.6 mg of SnF$_2$, 7.5 mg of HEDP and 3.4 mg of gentisic acid, followed by incubation for 30 min at 80°C. Quality control was performed by paper chromatography (Whatman 1) with methylethylketone to determine free ^{188}Re. The presence of colloids was evaluated by ITLC with saline.

12.3. RESULTS AND DISCUSSION

A problem faced in preparing the generator was the need to adjust the ^{188}W solution. When reaching a pH level of around 4, the pH paper strips failed to show any colour changes. Adding H$_2$O$_2$ and heating the ^{188}W solution for the preparation of the two 400 mCi generators helped to avoid this situation.

Figure 12.1 shows the elution profile of the 200 mCi ^{188}W/^{188}R generator that was prepared using 8.3 g of alumina. The elution efficiencies ranged from 70 to 80%. As can be seen, the volume required to eluate 90% of the recoverable activity was as high as 20 mL, which is not optimal since higher activity per millilitre is desired for radiolabelling. The ^{188}W breakthrough values were very low, and in many cases no breakthrough was detected.
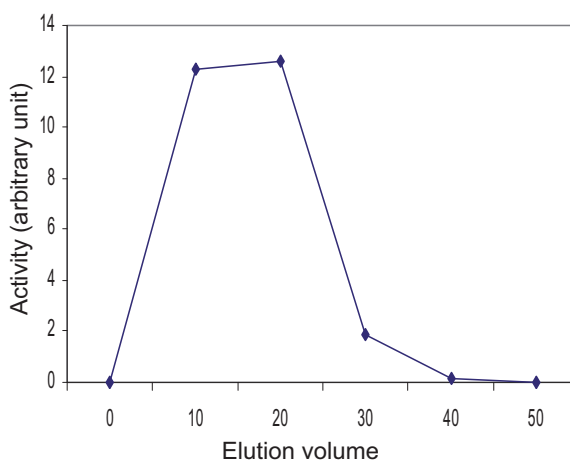
FIG. 12.1. Rhenium-188 elution profile with 0.9% NaCl solution of a 200 mCi generator prepared using 8.3 g of Al$_2$O$_3$.
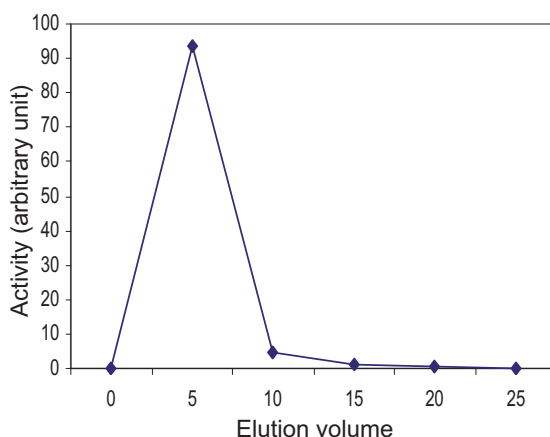
FIG. 12.2. Rhenium-188 elution profile with 0.9% NaCl solution of a 400 mCi generator prepared using 1.8 g of Al$_2$O$_3$.
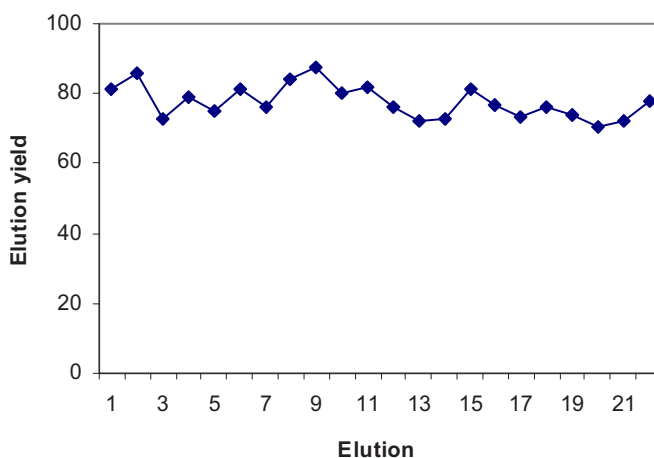
FIG. 12.3. Elution efficiency behaviour of a 400 mCi generator.

Reduction of the column size and consequently the amount of alumina to about 2 g resulted in better [188]Re elution profiles (Fig. 12.2). In these two generators, 5 mL of NaCl solution was enough to eluate 94–96% of the recoverable activity. Elution efficiencies were similar to those of the 8 g alumina generator. Figure 12.3 shows the [188]Re elution efficiency behaviour of a 400 mCi generator over a period of time. Elution yields varied between 70 and 87%, and the average value was 77.6%. The [188]W breakthrough was somewhat higher for this smaller column generator (10^{-3}–10^{-4}%) but agreed with values reported by other participants.

Radiolabelling of MoAb h-R3 and HEDP was greater than 95% with eluates from the three generators.

12.4. CONCLUSIONS

Three ^{188}W/^{188}Re generators were successfully prepared and evaluated regarding elution efficiency and ^{188}W breakthrough. Preparation of radiopharmaceuticals with the eluates from these generators was accomplished with radiolabelling yields greater than 95%.

ACKNOWLEDGEMENT

REFERENCE TO CHAPTER 12

[12.1] KNAPP, F.F., et al., Availability of rhenium-188 from the alumina-based tungsten-188/rhenium-188 generator for preparation of rhenium-188-labeled radiopharmaceuticals for cancer treatment, Anticancer Res. **17** (1997) 1783.

Chapter 13

AUTOMATION IN GENERATOR TECHNOLOGY: TECHNOLOGICAL RECOMMENDATIONS FOR THE DEVELOPMENT AND PRODUCTION OF STERILE GENERATORS AND FOR POST-ELUTION CONCENTRATION

D. NOVOTNY, G. WAGNER
Isotope Technologies Dresden GmbH,
Dresden, Germany

Abstract

Different methods are used for the loading of sterile radionuclide generators. The arrangement of the necessary boxes and laminar flow modules is discussed for the aseptic loading process of the inactive sterile generator and for loading processes that include steam sterilization of the loaded column or the loading solution in vials. The use of an aseptic loading process at a facility is illustrated with a detailed description of a new on-line aseptic loading process. Methods for the post-elution concentration of ^{188}Re generator eluates are described, and considerations for the automation of the concentration process are discussed.

13.1. INTRODUCTION

The development of a procedure for the production of sterile generator systems and post-elution concentration of generator eluates poses many problems regarding complete or partial automation of the production process. The technological solution for the automated processes should guarantee maximum radiation protection of production personnel, on the one hand, and the achievement of good manufacturing practice (GMP) requirements for radiopharmaceutical production, on the other hand. The production of the chromatographic generators as radiopharmaceuticals, especially a sterile ^{188}W/^{188}Re generator, and post-elution concentration of generator eluates are considered in this report. The facilities for the production of sterile chromatographic radionuclide generators have to meet the requirements for radiation protection of personnel and the GMP regulations for pharmaceutical production. The loading process of the generator is carried out in a lead shielded box unit in combination with a laminar flow unit. The shielding of the

production facilities and of the generator itself depends on the processed radio-isotopes and the activity levels. Different methods for the loading of the generator column can be applied: some aseptic loading methods are based on sterile filtration, while another loading method is based on steam sterilization of the loaded column. The advantages and disadvantages of the different methods are discussed relating to the necessary production time, the possibility of process automation, the costs of the installation and the availability of the required facilities. As an example, the experience with an on-line process for aseptic loading of the sterile ^{99}Mo/^{99m}Tc generator is discussed in detail. Post-elution concentration of ^{188}Re eluates is discussed, and the possibility of automating this process under GMP conditions is considered.

13.2. PRODUCTION OF STERILE CHROMATOGRAPHIC GENERATORS

The following considerations for the production of sterile chromato-graphic generators are based on past experience with the well known production technologies of the ^{99}Mo/^{99m}Tc sterile generators. Automated procedures for the production of sterile generators were developed for small charge sizes of 10–30 pieces, on the one hand, and for more than 100–200 pieces, on the other hand. Many different types of ^{99}Mo/^{99m}Tc sterile generator system meet the requirements for radiopharmaceutical production and guarantee a simple elution operation in nuclear medicine departments. It is preferable to choose a commercially available type of ^{99}Mo/^{99m}Tc sterile generator that is suitable for the development of the ^{188}W/^{188}Re sterile generator. This can be then adapted to the requirements of a larger column, a higher elution volume and a reduction of the possible additional brems-strahlung radiation. The inner hole in the lead container can be enlarged for the installation of a larger column. Furthermore, an aluminium tube with a wall thickness of 3–4 mm can be inserted in the inner hole of the lead container to reduce the formation of bremsstrahlung radiation. The selection of the generator components and the handling of the generator are done as per the selected generator type. In this case, many details of the known production procedure for this generator type can be adapted.

The loading of the generator column filled with alumina is the most essential step in the production of sterile generators. A column needle set is inactively assembled, and the column is then loaded using one of two general procedures:

(1)   Activity loading and washing of the column needle set in a non-sterile procedure, followed by steam sterilization and aseptic assembly of the generator system;

(2)   Steam sterilization of the inactive column needle set, complete aseptic assembly of the inactive and sterile generator system, and activity loading and washing under sterile conditions.

Figure 13.1a represents two typical column needle sets (variants A and B), which can be loaded and washed in a non-sterile procedure. The procedure for loading and washing can be automated completely or partially. The advantage of variant B lies in the separate septum connections for the loading and washing process. The loaded and washed column needle sets are sterilized in the steam sterilizer according to GMP regulations and are then placed in the generator lead shielding via remote control. The completion of the generator assembly must be carried out under aseptic conditions. Because

1-Connector for needle set   1-Connector for final assembly
2-Connector with septum for the
loading process
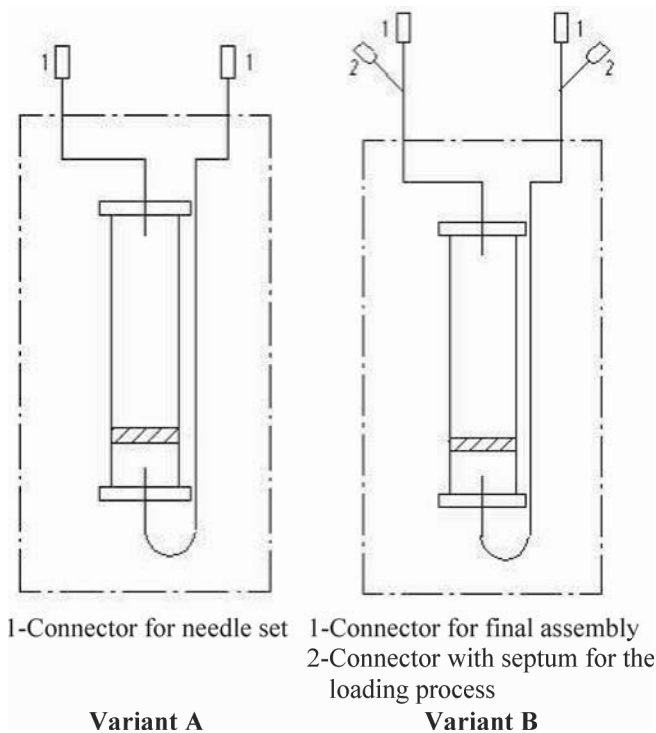
Variant A   **Variant B**

FIG. 13.1a. Two variants of the column needle set with activity loading and washing of the column needle set in a non-sterile procedure, followed by steam sterilization and aseptic assembly of the generator system.

3-Eluate sterile filter
4-Air sterile filter
Variant C

5-Special needle connection
for loading procedure
Variant D
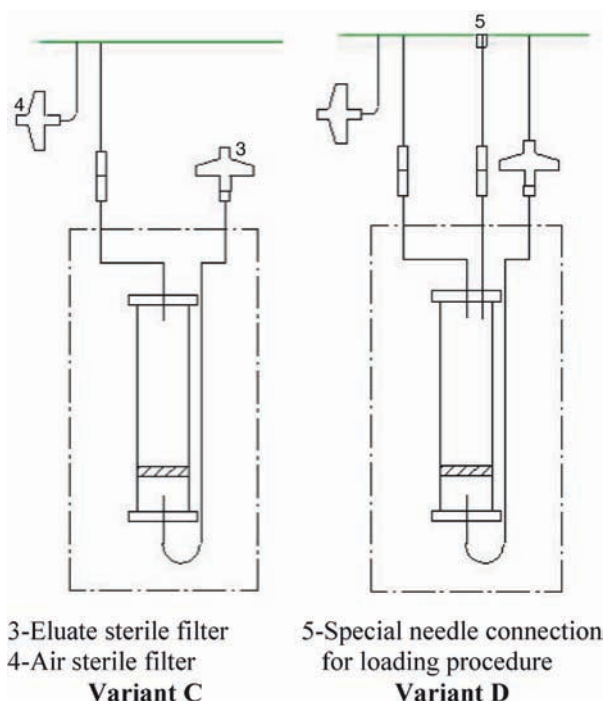
FIG. 13.1b. Two variants of the column needle set with steam sterilization of the inactive column needle set, complete aseptic assembly of the inactive and sterile generator system, and activity loading and washing under sterile conditions.

of the small charge size for the production of the $^{188}W/^{188}Re$ sterile generator, complete automation of the final assembly of the active generator would be too expensive; therefore, the final assembly must be carried out manually by production personnel under clean room class A laminar flow conditions. The advantage of this procedure is the direct steam sterilization of the loaded column (important for the registration of the generator as a radiopharmaceutical). The disadvantage is the manual final assembly of the radioactive generator, which could lead to radiation exposure of the production personnel involved.

Figure 13.1b shows two variants of the column needle set in which the column needle sets are inactively assembled and sterilized by steam sterilization. The sterilized column needle sets are aseptically assembled in a complete sterile generator system. It is possible to check the sterile inactive generator for proper function before initiation of the loading process. The complete sterile generator is then loaded with radioactivity and washed in an aseptic procedure.

There are two different procedures for this loading and washing process:

(1) Preparation of the loading and washing solution, dispensing in vials and steam sterilization of these vials. Sterile and evacuated vials are also prepared. The loading and washing process is carried out as in the usual elution procedure under the laminar flow module for clean room class A installed in the lead shielded box (vial method). The box itself should meet at least clean room class C conditions.

(2) On-line process for the loading and washing of the generators, which includes the sterile filtration as the sterilization procedure. Such on-line procedures are used by some large commercial producers of ^{99}Mo/^{99m}Tc sterile generators (see Fig. 13.7 for the scheme of a possible on-line process).

The aseptic loading and washing process with a complete preassembled sterile generator has the advantage that production personnel have to carry out fewer operations on the radioactive sterile generator, and hence there is a maximum reduction of the radiation exposure of the production personnel. The disadvantage of this procedure is the difficulty of satisfying the stringent GMP requirements for the production of a radiopharmaceutical. With variant C of the column needle set, there is a risk that the inlet needle unit may be radioactively contaminated and that the contamination may exceed the allowed level. Variant D of the column needle set has a separate inlet needle for the loading and washing process, but this set is much more complicated with respect to production and assembly.

The following procedures are preferred for the production of the ^{188}W/^{188}Re sterile generator under the condition of small charge sizes (2–10 pieces):

(a) Activity loading and washing process for a complete preassembled inactive sterile generator according to the vial method;

(b) Activity loading and washing process for variant A of the column needle set, and subsequent manual final assembly.

The production of the ^{188}W/^{188}Re sterile generator is to be carried out in a production unit consisting of the preparation box, the loading box and a laminar flow module installed close to the loading box. The boxes should be shielded with 100 mm thick lead walls, and at least the front side of the boxes should be made of 10 mm thick organic glass. The boxes should be connected with a double door lock. An access door should be installed in the rear wall of each box. The preparation box should be equipped with a double door lock for

inactive material transfer and a bottom lock for the transfer of radioactive materials and solid waste. The air filtering of the box should guarantee clean room class D conditions inside the box. The loading box should be equipped with a double door lock for the transfer of the generators. The air filtering of the box should guarantee clean room class C conditions inside the box, and a laminar flow module installed inside the box should ensure clean room class A conditions where the generator is loaded. The laminar flow module installed outside the loading box is used for the manual final assembly of the generators and the transfer of the generators to the loading box. The in-cell equipment depends on the chosen production procedure for the sterile generators. The necessary work inside the boxes can be divided into the following steps:

(1) Input of the radioactive bulk material;
(2) Preparation of the loading solution;
(3) Dispensing of the loading and washing solutions;
(4) Loading and washing of the generator column;
(5) Transfer of the generators and final assembly.

Highly automated on-line loading processes are possible (see Fig. 13.7 for an example). In such a scheme, the radioactive bulk material is transferred over a double door lock into the preparation box. The container of the bulk material is opened with a special opener, and the bulk solution is transferred by a peristaltic pump to a mixing vessel. The adjustment of the solution to the required pH value and to the required radioactive concentration is carried out in the mixing vessel. The dispensing of the prepared loading solution can be carried out with a simple syringe unit, a syringe pump dispenser or a peristaltic pump dispenser. For the loading procedure, a sterile filtration unit with adapter and a vacuum unit with adapter, collecting vessel and pump are necessary. The difficulty of this procedure consists in the choice of the suitable sterile filter membrane. For small production charge sizes, it is preferable to use the special Gemini filter membranes, which have hydrophilic and hydrophobic zones. In general, in the case of small production charge sizes, it is preferable to use the procedure with sterile filtration and loading of a completely preassembled, sterile generator system.

13.3. VARIANTS OF THE FACILITY LAYOUT FOR THE PRODUCTION OF CHROMATOGRAPHIC TYPE STERILE RADIONUCLIDE GENERATORS

The loading of a chromatographic generator can be carried out with an aseptic procedure or with procedures that include steam sterilization of the loaded column or of the loading solution filled in closed vials. The process steps are quite different and require different equipment inside the boxes. Automation of the loading process is much more difficult, especially for those procedures that include steam sterilization of the loaded chromatographic column. The requirements for the installation of the box and laminar flow units for all loading methods differ in general in the integration of a double door steam sterilizer in the entire arrangements.

13.3.1. Small scale production: Aseptic loading procedure on the basis of sterile filtration

Small scale production usually involves production campaigns involving up to 25 generators. The aseptic loading procedure is characterized by the following general production steps:

(1) Preparation of the inactive sterile generator;
(2) Transfer of the bulk radioactivity to the dispensing cell;
(3) Preparation of the loading solution (adjustment to the required pH value and radioactive concentration);
(4) Dispensing of the loading solution in the required portions;
(5) Sterile filtration of the loading solution and loading of the generator column;
(6) Washing of the generator column;
(7) Packaging of the generator.

In Fig. 13.2 a simple box arrangement for the necessary boxes and laminar flow module is shown. This box arrangement can be installed in a single room that ideally will meet clean room class C requirements. The preparation of the complete inactive sterile generator must be carried out in another room. The processing of the bulk radioactivity and the preparation and dispensing of the loading solution take place in the dispensing box. The sterile filtration of the loading solution and the loading and washing of the generator column are carried out in the loading box under a laminar flow module. The loading box is connected over a double door lock with the laminar flow module. The inactive sterile generator is transferred with a special carriage from another clean room

into the production room and placed on a special tray under the laminar flow module outside the box unit. The tray is then moved into the loading box through the double door lock. The lead of the shielding boxes is between 5 and 10 cm thick, and the boxes are equipped with ball tong manipulators. This is a relatively inexpensive and simple facility that can be installed within a small area. The intake and exhaust air ducts are equipped with high efficiency particulate air (HEPA) filters.

Among the advantages of this arrangement of the boxes and laminar flow module are that the costs for this facility are low and that installation is possible even where only small areas are available. Further advantages are that this process can be automated with low costs and that the radiation exposure to personnel is low because only minimal manual assembly of the loaded generator is required. However, the disadvantage is that the preparation of the inactive sterile generator and the packaging of the loaded generator are carried out in separate rooms, which means that the generators have to be manually transported from room to room. Furthermore, this process arrangement allows the loading of only 3–4 generators, which are placed on the tray, resulting in a discontinuous loading and packaging process and requiring more production time compared with a continuous process run.
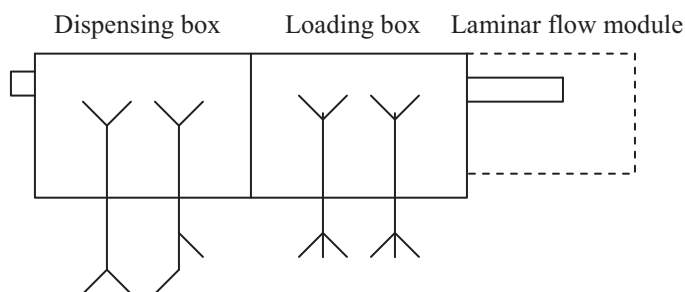
FIG. 13.2. Small scale production: Aseptic loading procedure on the basis of sterile filtration — installation in a single room.

13.3.2. Large and small scale production: Aseptic loading procedure on the basis of sterile filtration

Here, the small scale production involves production campaigns of up to 25 generators, and the large scale production involves production campaigns of up to 250 generators. The aseptic loading procedure is characterized by the following general production steps:

(1)   Preparation of the inactive sterile generator;
(2)   Transfer of the bulk radioactivity to the dispensing cell;
(3)   Preparation of the loading solution (adjustment to the required pH value and radioactive concentration);
(4)   Dispensing of the loading solution in the required portions;
(5)   Sterile filtration of the loading solution and loading of the generator column;
(6)   Washing of the generator column;
(7)   Packaging of the generator.

Figure 13.3 presents a box arrangement for the necessary boxes, roller conveyor and laminar flow modules for both small and large scale production. The differences between arrangements for large scale and small scale production lie in the different thicknesses of the lead shielding and the lead glass windows, and in the use of different types of manipulator. For large scale production, lead shielding with a thickness of 15–20 cm and master–slave manipulators are needed. In the case of large scale production, it is possible that two additional shielded boxes connected to each other will be needed.

The dispensing box and the line with the loading box should be installed in two separate but neighbouring rooms with different clean room classifications. Clean room class D conditions are sufficient for the room with the dispensing box, while the room with the loading box should meet at least clean room class C conditions. The equipment inside the boxes is similar for small and large scale production. The advantage of this arrangement of boxes and laminar flow modules is that it is possible to carry out a continuous production process. The loading box and the laminar flow modules are connected with a roller conveyor for the generator trays. The preparation of the inactive sterile generators is carried out in one of the laminar flow modules. These inactive generators are transferred on trays to the loading box over a double door lock. After loading and washing, the loaded generators are transferred again over a double door lock to the second laminar flow module for final assembly. The closed generators are then transported with the roller conveyor to the packaging room.

The advantage of this box and laminar flow module arrangement is that it allows for continuous preparation. The preparation of the inactive generator, the loading and washing process and the packaging process are carried out without the need for manual transport, which is very advantageous for meeting the GMP regulations. Heavy manual labour can be avoided and radiation exposure of personnel can be minimized through the automation of all possible

Room 1   Wall   Room 2

Roller conveyor

Laminar flow
module or box

Dispensing box   Loading box

Laminar flow
module or box
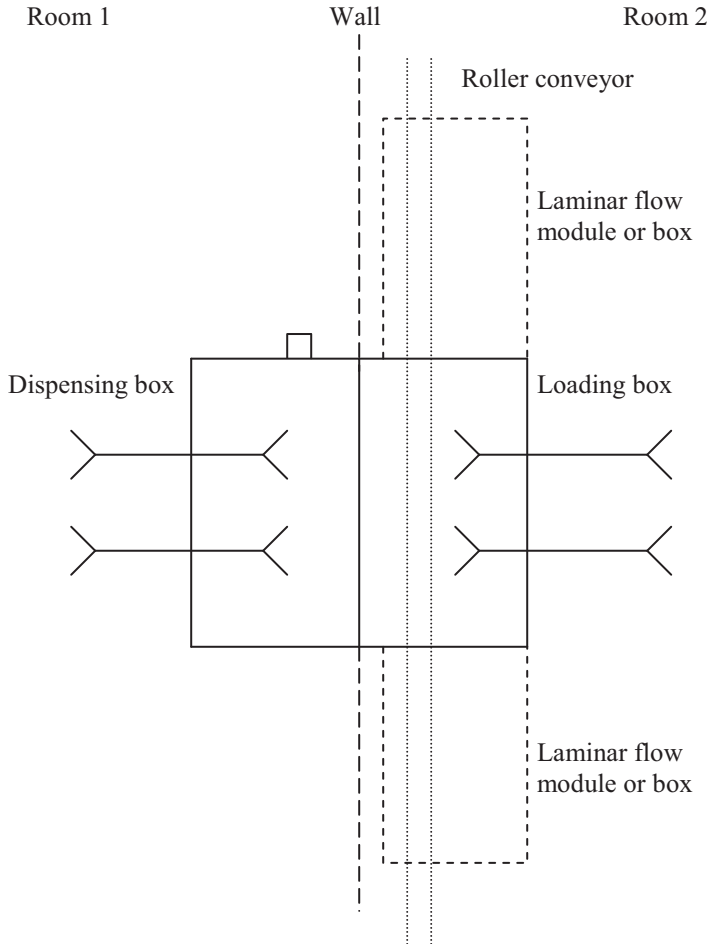
FIG. 13.3. Large and small scale production: Aseptic loading procedure on the basis of sterile filtration — installation in two rooms.

process steps. The disadvantages are that a large area of connected rooms is required and that the costs for the installation of such a facility are relatively high, especially if master–slave manipulators and thick lead glass windows are required.

13.3.3.   Large and small scale production: Steam sterilization of loaded column or the loading solution

Besides the aseptic loading process for the chromatographic generator, there are two other methods for generator production. In the first method, the loaded column is steam sterilized, followed by final assembly of the complete generator under aseptic conditions; in the second method, the loading solution is dispensed in closed vials, which are then steam sterilized, followed by loading of the generators corresponding to the elution process. The general box and laminar flow module arrangements for these processes are shown in Figs 13.4 and 13.5. The difference between the arrangements for the aseptic loading process and those for these processes is that in the latter the dispensing box is connected with the loading box through a double door steam sterilizer.

The important steps of the generator loading process including sterilization of the loaded column are:
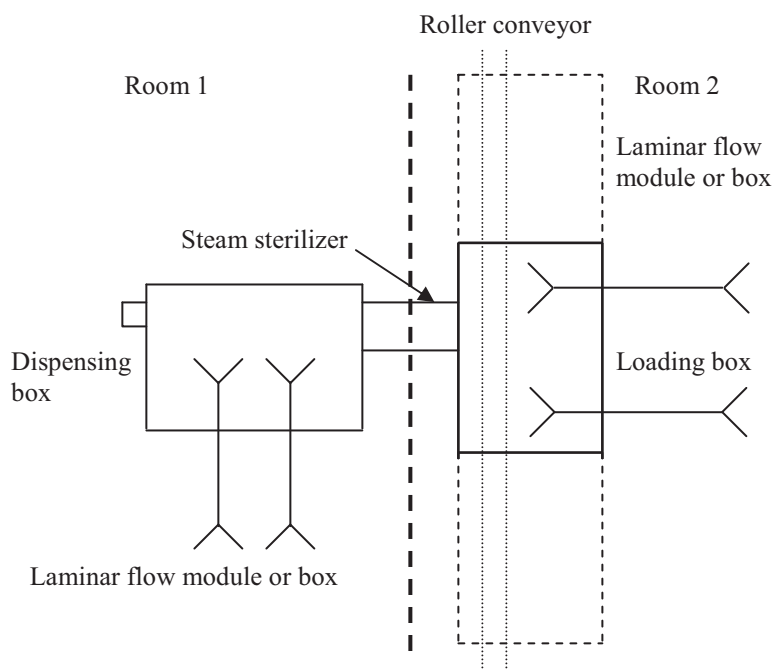
FIG. 13.4.   *Large and small scale production: Steam sterilization of the loaded column (variant I).*

Roller conveyor

Room 1

Room 2

Laminar flow
module or box

Steam sterilizer

Dispensing box

Loading box

Laminar flow
module or box
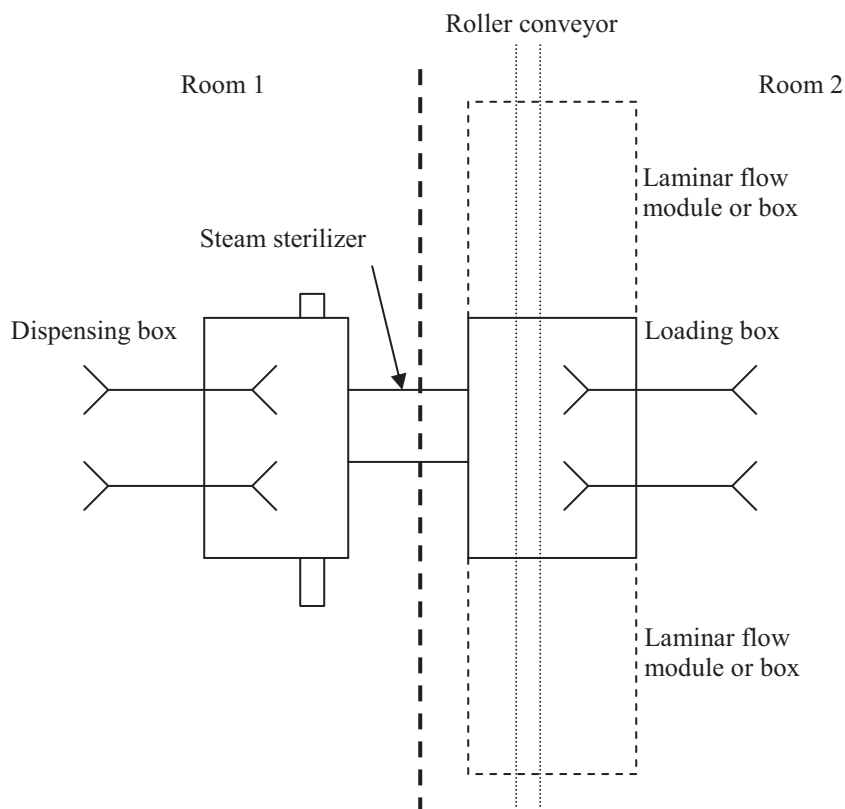
FIG. 13.5. Large and small scale production: Steam sterilization of the loading solution dispensed in vials (variant II).

(1) Transfer of the bulk radioactivity to the dispensing cell;
(2) Preparation of the loading solution (adjustment to the required pH value and radioactive concentration);
(3) Dispensing of the loading solution in the required portions;
(4) Loading and washing of the columns;
(5) Steam sterilization of the loaded columns;
(6) Assembly of the sterilized column in the generator shielding and assembly of the needle and filter system;
(7) Packaging of the generator.

Concerning the box shielding, the ventilation system and the use of different manipulator types, the parameters mentioned previously for the arrangements for the aseptic methods are also required here (see Sections 13.1

and 13.2). The disadvantage of this procedure is that extensive, manual assembly of the loaded generator is required. These assembly procedures must be performed under clean room class A conditions, and relatively high radiation exposure of personnel, especially of their hands, unfortunately cannot be avoided. The automation of these active assembly procedures is very expensive and is only acceptable for large production campaigns. A further disadvantage of this procedure is the time required for the steam sterilization process. The whole process time is longer than that for the aseptic loading procedure.

Another variant that includes steam sterilization in the loading procedure involves initial dispensing of the necessary portions of loading solution into vials, followed by steam sterilization of the vials. After steam sterilization, the loading and washing process corresponding to the elution process is continued. The separate steps of this procedure are:

(1) Preparation of the inactive sterile generator;
(2) Transfer of the bulk radioactivity to the dispensing cell;
(3) Preparation of the loading solution (adjustment to the required pH value and radioactive concentration);
(4) Dispensing of the loading solution in the required portions into vials;
(5) Steam sterilization of the vials containing the loading solution;
(6) Loading and washing of the generators according to the procedure for elution into the loading cell;
(7) Final assembly of the generator;
(8) Packaging of the generator.

This procedure can be very easily automated. Furthermore, it is advantageous that the radiation exposure of personnel is minimized. The disadvantages are that a significant amount of solid radioactive waste (vials) is generated, that there is a loss of loading solution remaining in the vial (~5–8%) and that a longer production time is necessary because of the steam sterilization process.

13.4. PRACTICAL EXPERIENCE WITH AN ON-LINE PROCEDURE FOR GENERATOR LOADING

A small scale facility for the production of sterile ^{99m}Tc generators was designed, manufactured and installed in the Radioisotope Production Department in Savar, Bangladesh. This facility has been in routine operation for nearly three years. On the basis of the experience gained at this facility, the aseptic loading procedure was improved in a step by step manner, and the

results of this process are reported here. Figure 13.6 shows the box and laminar flow module arrangement based on the scheme shown in Fig. 13.2. The facility consists of a dispensing box with two ball tong manipulators, a loading box with two ball tong manipulators and a laminar flow module in the front of the shielded box unit. The facility is installed in a small room. The box shielding consists of 10 cm thick lead brick walls, and the rear wall is moveable in the vertical plane. The boxes are equipped with HEPA filters for the intake and exhaust air ducts.

The in-cell procedure has been largely automated to a so-called on-line procedure. Figure 13.7 shows the touch screen of the computer controlled system. With the on-line procedure, the operator is not required to handle the radioactive material inside the box, except for the container with the bulk activity. The operator has to fix the container with the bulk activity in a special device. After opening the flask containing the bulk material, further transfer and handling of the radioactive material is controlled using the on-line procedure. The pumps, valves and mixing device are switched on by pressing the corresponding symbol on the touch screen. The dispensing of the loading solution is carried out with the syringe pump, which can also be operated via the touch screen. Calibration of the syringe pump using the touch screen is also

FIG. 13.6. Front view of an installed small scale production facility: Aseptic loading procedure on the basis of sterile filtration (dispensing box, loading box and laminar flow module).
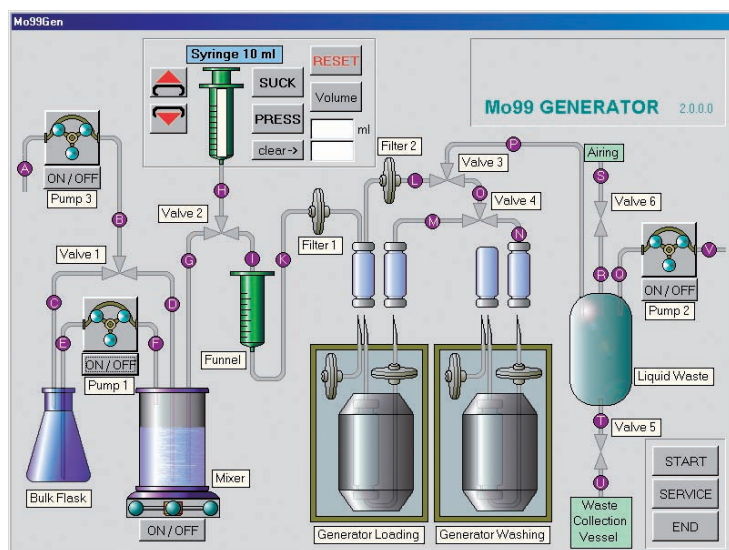
FIG. 13.7. Touch screen of the computer controlled loading system.

FIG. 13.8. Three way valve, small and large membrane pumps with Luer lock connectors.

possible with special software. The loading adapter and the vacuum adapter are moved pneumatically by pressing the bottom of the box control panel. The switching on of the adapters can be integrated into the computer controlled system, although a second touch screen monitor is then required.

Figure 13.8 shows the special three way valve as well as small and large membrane pumps. These devices are commercially available. The valves work in such a way that one can switch on only two different connections. The connection to the tubes is realized by Luer lock connectors, also shown in the

FIG. 13.9. *Mixing device (magnetic stirrer and heater) with beaker holder, beaker and beaker insert with Luer lock connectors.*

figure. The installed pumps are membrane pumps, equipped with Luer lock connectors.

The mixing device for the preparation of the loading solution is shown in Fig. 13.9. It is a commercially available unit that combines a magnetic stirrer and a heater. In a normal production run only the stirrer is needed. If the use of the heater is required, the heater can be switched on and off with help of the manipulator. The stirrer is equipped with a special holder for a glass or plastic beaker. An insert with the necessary connectors for the different tube connections is installed on the top of the beaker. A moveable dispenser, an Eppendorf pipette for taking measured samples and a pH electrode are installed over the mixing device.

The syringe dispenser (see Fig. 13.10) consists of a step motor and a commercially available 10 mL plastic syringe. The syringe can be changed very easily. The prepared loading solution is dispensed with the syringe dispenser into the funnel (see Fig. 13.7), which is connected to the sterile loading adapter via a special sterile filter (hydrophobic/hydrophilic). The loading adapter is connected to membrane pump 3 via a hydrophobic sterile filter (see Fig. 13.7). The loading solution is sucked from the funnel into the loading adapter, and then the loading adapter is pneumatically connected to the generator inlet needle and the vacuum adapter is pneumatically connected to the outlet needle of the generator. The loading solution is sucked through the sterile generator. The arrangement of the adapter system is shown in Fig. 13.11. The washing process is carried out in the next generator position with a 20 mL vial filled with sterile saline and a vacuum adapter. Only the loading and washing procedure is

FIG. 13.10. Syringe dispenser.

FIG. 13.11. Loading adapters with sterile filters and pneumatically moveable adapter holders.

carried out in the loading box under a laminar flow module. All other in-cell equipment is installed in the dispensing box.

Four generators placed on a moveable tray can be loaded and washed. When the loading procedure for these four generators is finished, the tray is transferred over a double door lock to the laminar flow module outside the shielded boxes. The assembly of the loaded generators is completed. After transfer of the ready generators to a transport carriage, four new inactive sterile generators are placed on the tray and the loading procedure for them can be started.

13.5. POST-ELUTION CONCENTRATION OF ^{188}Re

The ^{188}W/^{188}Re radionuclide generator has become one of the most attractive radioisotope generators for providing useful quantities of radionuclides in the field of therapeutic nuclear medicine [13.1, 13.2]. The commercially available ^{188}W/^{188}Re generators are based on an alumina filled column analogous to the ^{99}Mo/^{99m}Tc generators [13.3, 13.4]. The ^{188}W/^{188}Re generators are offered on the market as non-sterile generators (so-called radiochemical). The radiochemical and chemical preconditions for the production of ^{188}W/^{188}Re generators do not always allow elution of the ^{188}Re eluate with the radioactive concentration necessary for all relevant applications in nuclear medicine. The parent ^{188}W nuclide can be produced only with a relatively low specific radioactivity, which means that a large amount of alumina is needed as adsorption material on the generator column. The use of large amounts of alumina results in large volumes for the elution of the ^{188}Re daughter nuclide, resulting in a relatively low radioactive concentration of the ^{188}Re in the generator eluate.

Post-elution concentration of the eluate is therefore often necessary, because the ^{188}Re activity is needed in a volume of 1–2 mL for radiolabelling. Use of the simple evaporating process for the eluate solution is not possible because the salt concentration in the final solution becomes too high.

Guhlke et al. [13.5] developed two procedures for post-elution concentration of ^{188}Re eluates. Figure 13.12 shows the process scheme for post-elution concentration proposed by Knapp [13.4, 13.5] for when the ^{188}W/^{188}Re sterile generator is eluted with isotonic NaCl solution. This procedure is applied primarily in hospitals, because the commercially available ^{188}W/^{188}Re radionuclide generator is based on elution with saline. A number of other post-elution concentration systems have been described in the literature [13.6–13.8]. Post-elution concentration must be carried out in the hospital. Unfortunately, equipment for the post-elution concentration process is not commercially available. Rather, the user of such a concentration system must construct special equipment, with varying levels of automation. In the following,

Saline reservoir

Air

Peristaltic pump

Beta probe

^{188}W/^{188}Re generator

Syringe with water

Alumina columns
(^{188}W breakthrough)

Silver cation
exchange columns

Beta probe

Waters
QMA Sep Pak
Anion exchange column

Sterile filter

Container for liquid waste
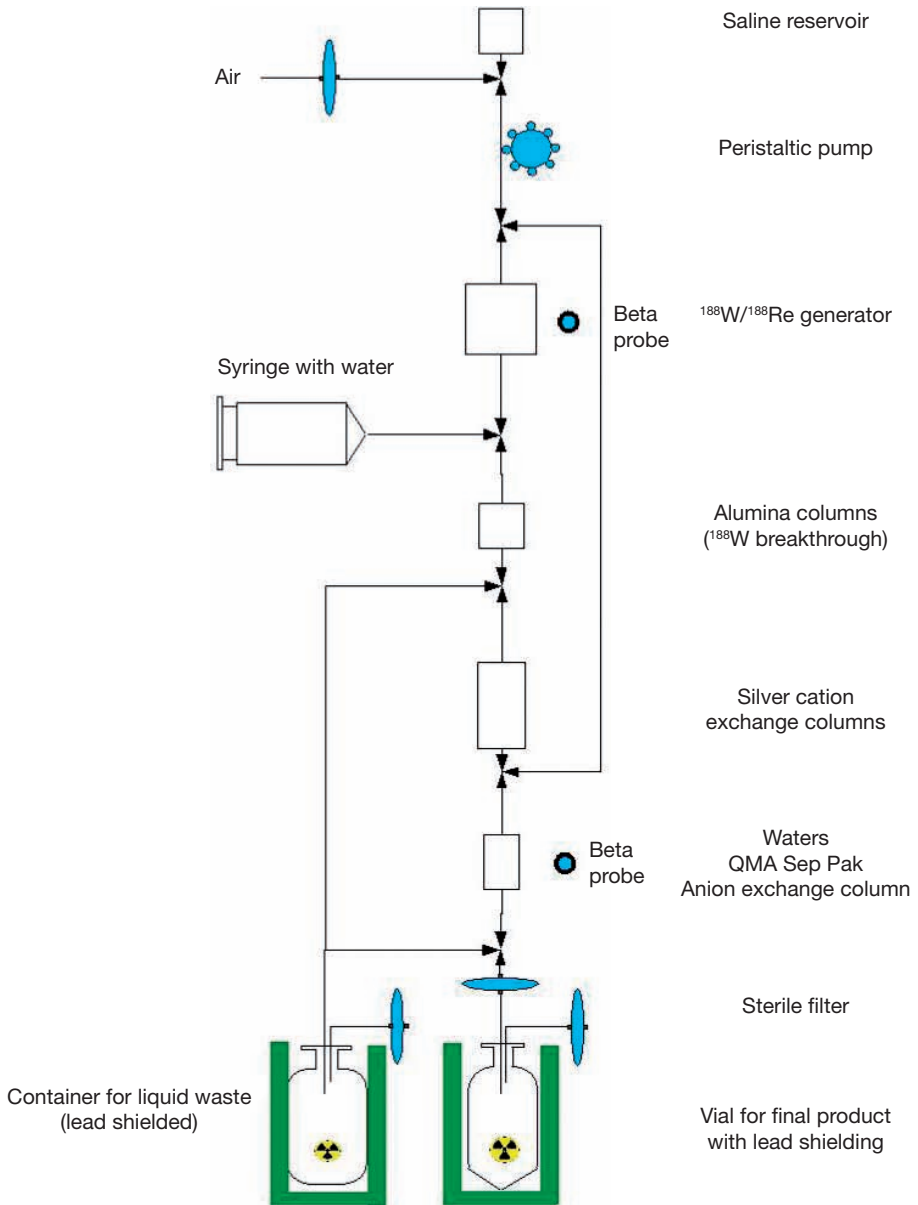(lead shielded)

Vial for final product
with lead shielding

FIG. 13.12. Schematics of a concentration unit for the ^{188}Re eluate.

information is provided on the construction and installation of a post-elution concentration unit that meets the GMP regulations and the requirements for radiation protection of personnel:

(a) The entire concentration unit should be installed in an acrylic glass box with laminar flow in a clean room with class A conditions. This box should have lead shielding with a lead glass window on at least the front side. The preparation box should be installed in a clean room with at least class C conditions.
(b) The QMA column, the vial for the final product and the collecting vessel for the liquid waste should be shielded with plastic material and lead.
(c) The process should be automated and controlled by a computer or by a manipulator if the concentration unit is installed in an isolator. This measure will reduce the extremity (hand) dose to the staff. It is very dangerous to handle the ^{188}Re activities manually because of the high β^- energy of ^{188}Re.

A semi-automated system for post-elution concentration of ^{188}Re eluates was developed and successfully installed in the Department of Nuclear Medicine at the University Hospital in Dresden, Germany. This system meets the conditions listed above and is presented briefly here as an example. The basis of this automated system is the ORNL procedure of Knapp et al. (see Fig. 13.12) [13.4, 13.5]. Commercially available components like ion exchange cartridges, valves, pumps, filters and tubes were used for the system. Software was developed for controlling this process by computer. Two collimated measuring probes were installed to follow the ^{188}Re activity during the concentration process. One of the measuring probes was installed at the alumina column and the other at the QMA column. The complete concentration system was shielded by installation in a closed acrylic box (1.5 cm thick) behind a lead wall (3 cm thick). The computer controlled system allows the following programmes:

(a) Concentration of the radioactivity from the generator to the exchange cartridge;
(b) Drying of the generator;
(c) Elution of the anion exchange column;
(d) Generator elution only.

Solutions of ^{188}Re perrhenate of up to 25 GBq/mL were obtained over a period of some years with this concentration unit without component failure. The cation and anion exchange cartridges were changed after each

concentration run, and the connecting tubes were changed once a year. The silver cation exchange and the QMA anion exchange cartridges are not commercially available as sterile components. Therefore, it is necessary to install a sterile filtration step as the final step of the concentration procedure. Concentration ratios of up to 20:1 were routinely reached. The flow rate during the process was constant at 1.5 mL/min. The whole concentration process (generator elution, concentration and generator drying) took about 30 min. With the introduction of the automated post-elution concentration unit, the finger exposure of the radiochemist could be reduced by a factor of 100.

Because of the lack of suppliers for such a complete concentration unit, it is necessary that the automated concentration system be developed by the user. In the development of this automated system, the following is to be considered:

(a) Places of accumulated [188]Re activity, like the anion exchange cartridge or the vial for the final solution, should be additionally shielded by a combination of organic glass and lead. Formation of bremsstrahlung radiation will be considerably reduced by the organic glass shielding; however, as bremsstrahlung radiation has relatively high energy, 3 cm thick lead shielding is recommended.

(b) The manual handling of process steps should be avoided or reduced as much as possible to prevent high radiation exposure of the hands of personnel.

(c) Commercially available material in sterilized form should be preferred as components for the automated system. The tube connections should be so-called Heidelberger connection tubes with Luer lock connectors at both ends.

The concentration process is an aseptic pharmaceutical process and must be carried out in a laminar flow box under clean room class A conditions. Such boxes are commercially available as so-called [99mTc] workbenches. Figure 13.13 shows a generator workbench (Hans Wälischmiller GmbH) designed for the preparation of radiopharmaceuticals, especially those based on [99mTc]; however, the workbench can be modified for the processing of [188]Re. The construction and function correspond to current mechanical standards and meet the requirements and rules established for radiopharmaceutical work under clean room conditions, for radiation hygiene and for radiation protection. The elution of the generators under laminar flow class A conditions guarantees cGMP conformity. The construction of an optimum lead shielding configuration allows the utilization of up to four generators of different manufactures and easy switching from one generator to another. The workbench is designed for use in nuclear medicine departments, hospitals and other medical

environments. An activimeter is included in this workbench unit with a touch screen monitor and a lead shielded ionization chamber. The computer of the activimeter can also be used for the computer controlled system of the concentration unit. As a precondition for installation of such a workbench, the installation room must meet clean room class C conditions. The second box, shown on the right hand side of Fig. 13.13, is a box for the preparation of radiopharmaceuticals. It has acryl glass shielding and partial lead shielding on the front side, and is equipped with ball tong manipulators. This box is also equipped with a clean room class A laminar flow module and can be used for the installation of such a concentration unit.

The effectiveness of a concentration unit depends on the elution volume of the ^{188}W/^{188}Re radionuclide generator. The necessary elution volume and the elution profile of a chromatographic generator depend on the volume of the column bed and the relation between the diameter and the length of a generator column. The elution profile of a column with a smaller diameter is much sharper than that of a column with larger diameter, which means a smaller elution volume is required with a column having a smaller diameter. On the other hand, a certain column bed volume is required to adsorb the large ^{188}W activity necessary. The shielding of the generator also depends on the adsorbed ^{188}W activity. The smallest shielding is possible if the ^{188}W activity is in a spherical form, but this compromises the requirement for a column with

FIG. 13.13. Workbench for the preparation of labelled compounds with generator eluates (left) and for radiopharmaceutical preparation (right)(source: Hans Wälischmiller GmbH).

a small diameter and low elution volume. The manufacturer of such $^{188}W/^{188}Re$ radionuclide generators must optimize the column geometry to meet the requirement of an elution volume that is as small as possible, and the weight of the necessary transport shielding for the generator.

The elution behaviour of the $^{188}W/^{188}Re$ radionuclide generators produced at ORNL and at POLATOM was evaluated in the Department of Nuclear Medicine of the University Hospital in Dresden. The elution profiles of both generator types are shown in Fig. 13.14. The figure shows that the ^{188}Re activity can be eluted with 7–8 mL of saline for the POLATOM generator, whereas more than 20 mL is needed for the ORNL generator. The reason for this difference is that the column diameter of the POLATOM generator is much smaller than that of the ORNL generator. The total activity of a POLATOM generator is only approximately 20 GBq, compared with 55 GBq for the ORNL generator.
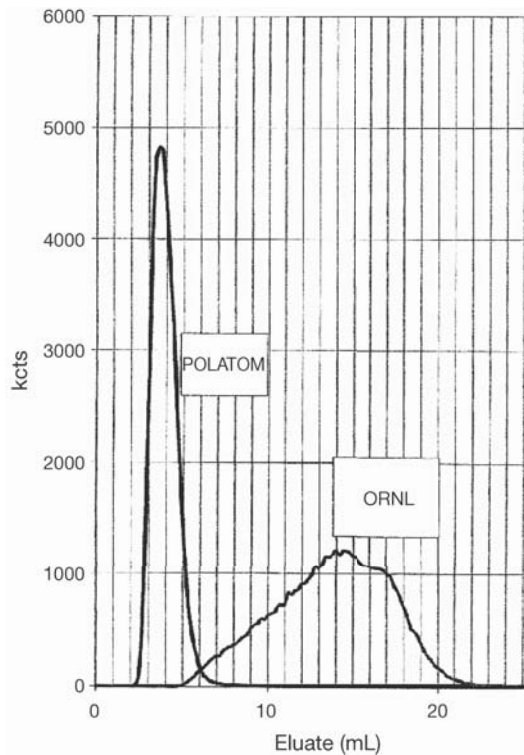

FIG. 13.14. Elution profiles of $^{188}W/^{188}Re$ generators supplied by POLATOM (Poland) and ORNL (USA).

In a cooperative effort between POLATOM and the Department of Nuclear Medicine in Dresden, the POLATOM generator design was modified in such a way that the generator could be connected very easily to the post-elution concentration unit. This modification included replacement of the elution needles with Luer lock connectors and closure by Luer lock stoppers, similar to the ORNL design. This modified generator is connected to the concentration unit using commercially available Heidelberger connection tubing. This connecting procedure permits the connection of two or three generators in series. The tests with the three POLATOM generators connected in series were very successful. Figure 13.15 shows the elution profile of one POLATOM generator, and Fig. 13.16 shows that of three POLATOM generators connected in series. In the case of three generators connected in series, the elution volume is only increased from 7 to 12 mL. In the case of three fresh POLATOM generators with approximately 20 GBq per generator, the total activity of 60 GBq can be eluted with 12–14 mL of saline. In the case of the elution of an ORNL generator with 55 GBq, more than 20 mL is required. The reason for the difference in the elution volume is the geometry of the column. The in-series connection of the generators with elution needles is also possible if the needles are connected with Heidelberger connection tubing and if they are closed on both sides with Luer lock stoppers with a small septum (commercially available).

This system for connecting generators in series is a possibility for prolonging the use of older generators, which is an important financial aspect in the management of a hospital.
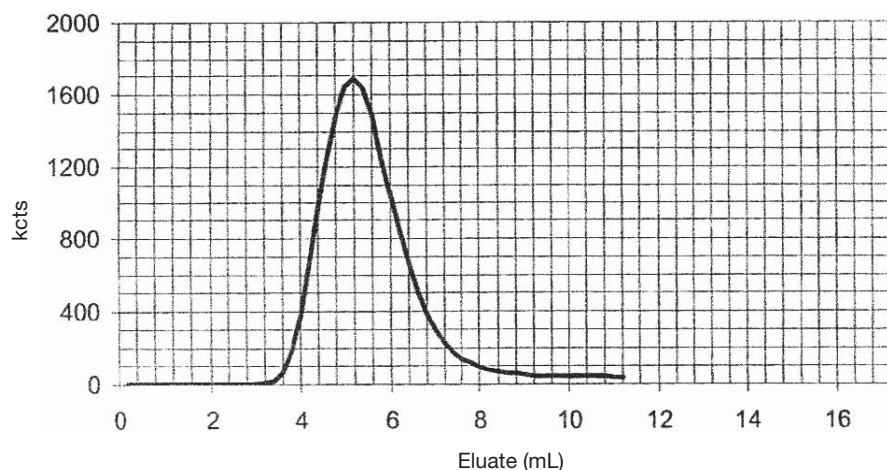
FIG. 13.15. Elution profile of one $^{188}W/^{188}Re$ generator (source: POLATOM, Poland).
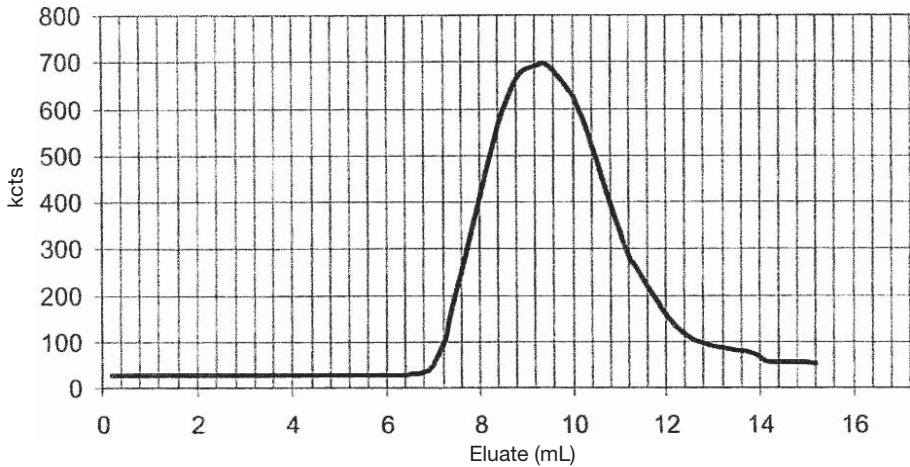
FIG. 13.16. *Elution profile of three $^{188}W/^{188}Re$ generators connected in series (source: POLATOM, Poland).*

13.6. SUMMARY AND CONCLUSIONS

A procedure for the production of sterile chromatographic generators for therapeutic radionuclides such as ^{188}Re can be developed by modifying existing procedures for $^{99}Mo/^{99m}Tc$ sterile generators. Automation of the production processes ensures that these processes meet the requirements for radiation protection of personnel and the GMP regulations. Because of the activity level, generator production normally will not exceed 10 generators, and thus a useful balance must be found between the demand for automation and the possible benefits. The loading of a complete preassembled sterile generator is recommended to avoid manual operations as much as possible. Modification of commercially available $^{99}Mo/^{99m}Tc$ sterile generators to create $^{188}W/^{188}Re$ sterile generators may decrease the costs of developing a $^{188}W/^{188}Re$ sterile generator for routine production. The procedure for post-elution concentration of the ^{188}Re eluate proved to be very worthwhile. Unfortunately, equipment for a concentration unit is not yet commercially available, and therefore only some helpful advice concerning the installation of such concentration equipment can be given in this report.

REFERENCES TO CHAPTER 13

[13.1] JEONG, J.M., CHUNG, J.K., Therapy with [188]Re-labeled radiopharmaceuticals: An overview of promising results from initial clinical trials, Cancer Biother. Radiopharm. **18** (2003) 707–717.

[13.2] LAMBERT, B., DE KLERK, J.M., Clinical applications of [188]Re-labelled radiopharmaceuticals for radionuclide therapy, Nucl. Med. Comm. **27** (2006) 223–229.

[13.3] KNAPP, F.F., CALLAHAN, A.P., BEETS, A.L., MIRZADEH, S., HSIEH, B.-T., Processing of reactor-produced [188]W for fabrication of clinical scale alumina-based [188]W/[188]Re generators, Appl. Radiat. Isot. **45** (1994) 1123–1128.

[13.4] KNAPP, F.F., Jr., Set-up, general use and quality control of the ORNL tungsten-188/rhenium-188 generator system and methods for concentration of rhenium-188 to high specific volume solutions, Oak Ridge National Laboratory (1999).

[13.5] GUHLKE, S., et al., Tandem Cation/Anion Column Treatment of Ammonium Acetate Eluants of the Alumina-Based Tungsten-188/Rhenium-188 Generator: A New Simple Method for Effective Concentration of Rhenium-188 Perrhenate Solutions, J. Nucl. Med. **41** (2000) 1271–1278.

[13.6] JACKEL, B., CRIPPS, R., GUNTAY, S., BRUCHERTSEIFER, H., Development of semi-automated system for preparation of [188]Re aqueous solutions of high and reproducible activity concentrations, Appl. Radiat. Isot. **63** (2005) 299–304.

[13.7] McKILLOP, J.H., MARTIN-COMIN, J., KNAPP, F.F., Jr., BRITTEN, A.J., Highlights of the European Association of Nuclear Medicine Congress 2006, Eur. J. Nucl. Med. Mol. Imaging **34** (2007) 274–293.

[13.8] MUSHTAQ, A., Preparation of high specific-volume solutions of technetium-99m and rhenium-188, Appl. Radiat. Isot. **58** (2003) 309–314.

Chapter 14

DEVELOPMENT OF ^{188}W/^{188}Re GENERATORS

M. VENKATESH*, S.K. SARKAR**, R. CHAKRAVARTY*,
G. ARJUN**, A. DASH*, P. SARASWATI**

 * Bhabha Atomic Research Centre

** Board of Radiation and Isotope Technology

Mumbai, India

Abstract

An alumina based column generator was made using ^{188}W as H$_2$WO$_4$. Rhenium-188 having very high radionuclidic and radiochemical purity (>99%) was eluted from the generator with high elution efficiency (>80%). Three different techniques for the concentration of ^{188}Re obtained from the generator using tandem ion exchange columns were developed. The ^{188}Re could be successfully concentrated more than 10-fold using a post-elution concentration technique. The usefulness of noble sorbents such as poly zirconium compound (PZC) and poly titanium compound (PTC) in the preparation of a ^{188}W/^{188}Re generator was explored. The adsorption of ^{188}W in PTC was optimum at ~pH5–6, and the breakthrough and adsorption capacities of tungsten at this pH level were found to be about 62 and 120 mg/g, respectively. The elution efficiency of this generator was about 60–70%, and the ^{188}Re eluted was of very high radionuclidic and radiochemical purity (>99%). The adsorption capacity of the PZC based generator was about 140–160 mg/g, and its elution efficiency was about 60–70%. These findings provide the basis for the preparation of a ^{188}W/^{188}Re generator and post-elution concentration of ^{188}Re obtained from a generator.

14.1. INTRODUCTION

The properties of ^{188}Re that make it attractive for therapy (T$_{1/2}$: 16.9 h, E$_{\beta^-\text{max}}$: 2.12 MeV, E$_\gamma$: 155 keV suitable for imaging (15%)), its availability from a ^{188}W/^{188}Re generator system with a long useful shelf life, and its chemical properties, similar to those of $^{99\text{m}}$Tc, prompted this study of ^{188}W/^{188}Re generators. Preparation of in-house generators and of novel materials for use in generator columns, and modes of post-elution concentration of the eluted ^{188}Re perrhenate were pursued and are detailed here.

14.2. ^{188}W/^{188}Re GENERATOR

14.2.1. Preparation and evaluation of alumina based ^{188}W/^{188}Re generators

Alumina based chromatographic generator systems, similar to those available for ^{99m}Tc, were prepared for obtaining ^{188}Re. Active acidic aluminium oxide (100–200 mesh, Brockman Grade 1 for chromatographic analysis) was used to prepare the 2 g columns. Tungsten-188 with a specific activity of 216.8 GBq (5.86 Ci) per gram of tungsten (on reference date) as sodium tungstate in 0.26M NaOH (35 mg of tungsten per millilitre), with a concentration of 7.6 GBq (0.205 Ci) per millilitre, was obtained from RIAR (Dimitrovgrad, Russian Federation) through the IAEA. The pH level of the $Na_2{}^{188}WO_4$ solution (0.26M NaOH) was adjusted to 2–3 with 0.1N HCl, and the required amount of activity was loaded onto the column under controlled vacuum pressure (flow rate: 1 mL/min.) after assessing the exact activity of the ^{188}W in a precalibrated dose calibrator. The column was placed in shielded housing and handled inside appropriate facilities. The column was washed with 100 mL of normal saline and, after allowing growth of the ^{188}Re, eluted with 10 mL of saline. A few elutions were carried out and, since tungsten breakthrough was significant, a purification column of 2 g of alumina was used after elution to 'mop up' the tungsten breaking through. Several generators having a capacity of between 0.6 and 2.4 GBq were prepared and tested. The radiochemical purity of the eluted ^{188}Re perrhenate in 0.9% NaCl tested by ITLC was greater than 99%, and the radionuclidic purity estimated by γ-spectroscopy using an HPGe-MCA was also greater than 99%. The generator performance in terms of ^{188}Re yield and ^{188}W breakthrough is presented in Table 14.1.

TABLE 14.1. PERFORMANCE OF THE ALUMINA BASED ^{188}W/^{188}Re GENERATORS PREPARED IN-HOUSE

Generator No.	W-188 (GBq (mCi))	No. of elutions	Re-188 yield (%)	W-188 breakthrough (%)
1	0.6 (16)	16	83.3 ± 3.23	10^{-5}–10^{-3}
2	2.4 (65)	10	82.5 ± 1.89	10^{-5}–10^{-4}
3	0.49 (13.3)	7	84.6 ± 1.9	10^{-5}–10^{-4}
4	2.37 (64)	8	87.4 ± 0.52	10^{-5}–10^{-4}

14.2.2.   Post-elution concentration of ^{188}Re perrhenate from the generator

The use of low specific activity ^{188}W and of old generators results in low radioactivity concentrations of the eluted ^{188}Re perrhenate, which is not suitable for radiolabelling of biomolecules. Post-elution concentration is essential in such cases. Reports in the literature [14.1–14.3] on effective post-elution concentration of ^{188}Re using tandem ion exchange columns prompted an exploration of possible means of post-elution concentration of the ^{188}Re perrhenate eluate. Post-elution concentration of no carrier added ^{188}Re perrhenate is based on its selective retention on a tiny anion exchange column and subsequent recovery in a small volume of suitable eluent. This concentration of perrhenate is possible only when the ^{188}Re eluate is free of any other macroscopic anionic species. Three methods of post-elution concentration were tried, as described below.

14.2.2.1. Use of IC-Ag and Sep-Pak Accell Plus QMA anion exchanger column

A Maxi-Clean IC-Ag, Ag$^+$ form cation exchanger cartridge (Alltech Associates, USA) and a Sep-Pak Accell Plus QMA anion exchange cartridge (Waters Corporation, Milford, USA) were used in the first method of post-elution concentration, as reported by Knapp et al. [14.1, 14.4]. The Maxi-Clean IC-Ag cartridge was conditioned with 5 mL of deionized water. Rhenium-188 eluate obtained from a ^{188}W/^{188}Re generator in 10 mL of normal saline solution was freed of macroscopic Cl$^-$ ions as AgCl precipitate by passage through an Alltech IC-Ag$^+$ cation exchange cartridge. This ^{188}Re perrhenate eluate free of chloride anion was then passed through the small Sep-Pak Accell Plus QMA anion exchange cartridge (130 mg) to retain the perrhenate, and was subsequently re-eluted with a very small volume (1 mL) of normal saline. The effluent from the IC-Ag cartridge and a few mL of deionized water used for washing were measured to assess any loss of ^{188}Re activity in the concentration process. Using this method, ^{188}Re yield of $79 \pm 3\%$ was obtained, with a concentration factor of about 10. The ^{188}W breakthrough was well below $10^{-4}\%$ and at times was undetectable.

14.2.2.2. Use of Dowex 1X8 and AgCl column

A Dowex 1X8 anion exchanger (Cl$^-$ form, 200–400 mesh) with a capacity of 3–5 meq/g (Sigma Chemicals) and extra pure AgCl were used in this method of post-elution concentration. Between 10 and 12 mg of Dowex 1X8 resin was taken in a 2 mL syringe and placed in a polypropylene tube (~8 mm × 1 mm) with a few millilitres of water. The other end of the tube was packed with glass

wool. Both ends of the tube were fitted with miniature barbed polypropylene fittings. Ten millilitres of normal saline solution was passed through the resin column and washed with 5 mL of water (~5 bed volumes of the resin column). Between 1 and 1.5 g of commercial AgCl salt was taken in a glass column (12 mm × 8 mm) with a sintered disc (G-2), closed with a silicon rubber septum, washed with a few millilitres of deionized water and used.

Between 20 and 40 mL of ^{188}Re eluate in normal saline obtained from the generator was passed through the Dowex 1X8 anion exchange column (placed in appropriate shielding) at a flow rate of 2–3 mL/min using controlled vacuum pressure. The activities in the effluent from the Dowex 1 column and in the subsequent washings with a few millilitres of deionized water were measured to assess the adsorption of the perrhenate. These were treated as radioactive waste and appropriately disposed of. The no carrier added ^{188}Re perrhenate adsorbed on the tiny anion exchange column was re-eluted with 5–6 mL of 0.2M NaI solution and passed through the AgCl column (1 g, 12 mm × 8 mm) placed in proper shielding (6–7 mm of lead). The effluent of ^{188}Re perrhenate obtained by washing the column with 1.5–1.8 mL of deionized water was collected in a 10 mL vial. This ^{188}Re perrhenate was free of iodide (removed as AgI precipitate) and isotonic with normal saline. In this system, there was a loss of ^{188}Re activity (6–12% in the case of 20 mL primary eluate volume and 17–25% in the case of 40 mL primary eluate volume) and the yield of ^{188}Re was about 72.4 ± 12%. However, the ^{188}W breakthrough was below 10^{-4}%.

14.2.2.3. Use of a single column of DEAE cellulose

The third method devised for post-elution concentration involved the construction of a generator bed free of chloride ions and elution of the ^{188}Re perrhenate in acetate buffer. This method was based on earlier work with ^{99m}Tc pertechnetate [14.5,14.6]. The ^{188}Re perrhenate eluted was then trapped on a DEAE cellulose column and eluted in a small volume of saline.

Briefly, the generator was washed initially with approximately 200 mL of 1:1 vol./vol. 0.025M NH_4OAc:0.7M AcOH at ~pH3, to remove the chloride (Cl$^-$) ions. The effluents were checked for the absence of chloride ions by AgNO$_3$ testing. The generator was then set aside to allow for the growth of ^{188}Re. The ^{188}W/^{188}Re generator was then eluted with 20–25 mL of acidic ammonium acetate [14.2] and passed through a small anion exchange column of DEAE cellulose (300 mg, 10 mm × 8 mm) to trap ^{188}Re perrhenate. Subsequently, ^{188}Re was recovered in 4 mL of normal saline. The mean practical yield of ^{188}Re in this method was 72.9 ± 2.3% (n = 11). The time required for the concentration process was 15–20 min. The DEAE cellulose column was flushed with 5–6 mL of deionized water to keep the system ready for the next elution. It

was possible to use the same DEAE cellulose column up to 11 times. In this system, the tungsten breakthrough was well below 10^{-4}% and at times was undetectable.

Thus it was shown that alumina based ^{188}W/^{188}Re generators of low strength could be prepared in-house, and successful post-elution concentration methods were demonstrated.

14.3. NOVEL MATERIALS FOR COLUMN MATRIX FOR USE IN RADIONUCLIDE GENERATORS

14.3.1. Development of a titanium polymer sorbent for ^{188}W/^{188}Re generators

Materials with a higher capacity for tungsten adsorption are of great interest owing to the low specific activities of ^{188}W, which necessitates the use of large alumina columns, which in turn leads to low radioactive concentration or to tungsten breakthrough.

Dadachova et al. [14.7] proposed a new concept in which ^{188}W obtained by (n,γ) reaction of natural tungsten can be incorporated into a titanium tungstate based gel. However, this is a complex procedure. Brodskaya et al. [14.8] have reported a method for chromatographic separation of tungsten and rhenium using organophosphorous resins. A major disadvantage of this process is the radiation degradation of the resin, which is sensitive to radiation damage. Another alternative approach is emerging from research being conducted in Japan [14.9, 14.10] in which reactor irradiated molybdenum (i.e. low specific activity) was adsorbed into a zirconium polymer, with higher uptake capacity for ^{99}Mo than for alumina. Expanding on the above work, an attempt was made to synthesize a new titanium polymer prepared by the polymerization reaction of TiCl$_4$ with isopropyl alcohol. Application of this polymer for the preparation of a ^{188}W/^{188}Re generator and the elution characteristics of ^{188}Re were studied.

14.3.1.1. Synthesis of the polymeric titanium adsorbent

Titanium tetrachloride was mixed with isopropyl alcohol in the ratio of 1:2 in a beaker with vigorous stirring. The material obtained was water soluble. To make this into an insoluble polymer, it was heated for 2 h at 150°C. This product was insoluble in water and in most of the mineral acids and alkalis. The dried cake was ground to a fine powder and sieved with a 25–50 mesh sieve.

14.3.1.2. Optimization of the adsorption parameters

The distribution ratio (K_d) of ^{188}W in 0.1M HNO$_3$ was determined at different time intervals and the results are shown in Fig. 14.1. It can be seen that about 45 min is required to reach the equilibration. In all subsequent experiments, the polymer was adsorbed with the ^{188}W activity for 45 min.

It was observed that the maximum adsorption of ^{188}W as tungstate on the titanium polymer occurred at pH5–6. While both ^{188}W-tungstate and ^{188}Re as perrhenate were adsorbed, when eluted with saline, perrhenate exhibited far less affinity (approximately 600-fold lower) for the matrix.

In order to estimate the saturation capacity of the titanium polymer and the concentration at which breakthrough begins, adsorption of ^{188}W on the titanium polymer was determined under dynamic conditions using an ion exchange chromatographic column in the presence of different carrier concentrations of tungsten in the feed. The breakthrough capacity and saturation capacity of tungsten were found to be 62 and 120 mg/g, respectively, indicating that approximately 62 mg of tungsten per gram of titanium polymer can be loaded without any breakthrough being observed.

A process demonstration run was carried out with this adsorbent using 1 mCi of ^{188}W, and the elution behaviour of the ^{188}Re was studied. It was observed that only about 60–70% of the ^{188}Re on the column could be eluted with saline, but that approximately 92% of this was eluted in the first 3–5 mL. Further study of this material is needed and will be done as the next step in generator development.
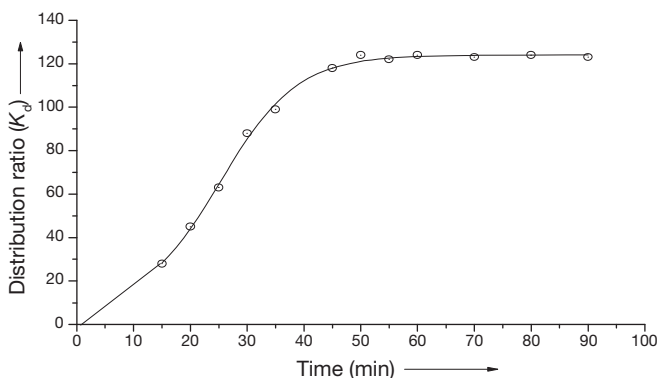

FIG. 14.1. Kinetics of the adsorption of ^{188}W on titanium polymer.

14.4. CONCLUSION

Alumina column based ^{188}W/^{188}Re generators for use in research studies were prepared, and three methods of post-elution concentration for obtaining ^{188}Re in a high radioactive concentration were evaluated. A novel titanium polymer was also prepared, and some preliminary studies on its use as a matrix column for ^{188}W/^{188}Re generators were initiated.

ACKNOWLEDGEMENTS

REFERENCES TO CHAPTER 14

[14.1] KNAPP, F.F., Jr., BEETS, A.L., MIRZADEH, S., GUHLKE, S., "Use of a new tandem cation/anion exchange system with clinical-scale generators provides high specific volume solutions of technetium-99m and rhenium-188", Modern Trends in Radiopharmaceuticals for Diagnosis and Therapy, IAEA-TECDOC-1029, IAEA, Vienna (1998) 419–425.

[14.2] GUHLKE, S., et al., Simple new method for effective concentration of ^{188}Re solutions from alumina-based ^{188}W/^{188}Re generator, J. Nucl. Med. **41** (2000) 1271–1278 .

[14.3] GUHLKE, S., et al., Convenient concentration of ^{188}Re perrhenate or ^{99m}Tc pertechnetate eluates from ^{188}W/^{188}Re or (n,γ) produced ^{99}Mo/^{99m}Tc generators to high specific volumes, J. Labelled Compd. Radiopharm. **40** (1998) 294.

[14.4] KNAPP, F.F., Jr., BEETS, A.L., MIRZADEH, S., GUHLKE, S., Concentration of perrhenate and pertechnetate solutions, US Patent No. 5729821 (1998).

[14.5] SARKAR, S.K., ARJUN, G., SARASWATHY, P., RAMAMOORTHY, N., Post-elution concentration of ^{99m}TcO$_4^-$ by a single anion exchanger column: I: Feasibility of extending the useful life of column chromatographic ^{99m}Tc generator, Appl. Radiat. Isot. **55** (2001) 561–567.

[14.6] SARKAR, S.K., ARJUN, G., SARASWATHY, P., RAMAMOORTHY, N., Post-elution concentration of $^{99m}TcO_4^-$ by a single anion exchanger column: II: Preparation and evaluation of jumbo alumina column chromatographic generator for ^{99m}Tc, Nucl. Med. Commun. **22** (2001) 389–397.

[14.7] DADACHOVA, M.S., LE, V.S. LAMBRECHT, R.M., DADACHOVA, E., Development of a titanium tungstate-based $^{188}W/^{188}Re$ gel generator using tungsten of natural isotopic abundance, Appl. Radiat. Isot. **57** (2002) 641–646.

[14.8] BRODSKAYA, G.A., GAPUROVA, O.U., GUREEV, E.S., Chromatographic separation of W and Re on organophosphorus resins, Radiokhimiya **32** (1990) 56.

[14.9] TANASE, M., et al., ^{99m}Tc generator using a new inorganic polymer adsorbent for (n,γ) ^{99}Mo, Appl. Radiat. Isot. **48** (1997) 607–611.

[14.10] MATSUOKA, H., et al., Application of PZC to $^{188}W/^{188}Re$ generators, J. Nucl. Radiochem. Sci. **6** (2005) 189–191.

Chapter 15

NOVEL AND EFFICIENT PREPARATION OF [188]Re(I) TRICARBONYL PRECURSOR [[188]Re(OH$_2$)$_3$(CO)$_3$]$^+$ FOR THE LABELLING OF BIOMOLECULES

SANG HYUN PARK
Radiation Research Division for Biotechnology,
Korea Atomic Energy Research Institute,
Daejeon, Republic of Korea

Abstract

A novel and efficient method for preparing the [188]Re(I) tricarbonyl precursor [[188]Re(OH$_2$)$_3$(CO)$_3$]$^+$ has been developed by reaction of [188]Re perrhenate with Schibli's reagent in the presence of borohydride exchange resin (BER) as a reducing agent and an anion scavenger. The precursor was produced in more than 97% yield by reacting a solution of BER (3 mg), borane ammonia (BH$_3$·NH$_3$, 3 mg) and potassium boranocarbonate (K$_2$[BH$_3$CO$_2$], 3 mg) in 0.9% saline with a solution of sodium perrhenate (Na[188]ReO$_4$) with up to 50 MBq of activity and concentrated phosphoric acid (85%, 7 µL) at 60°C for 15 min. HPLC and TLC revealed the complete consumption of unreacted [188]Re perrhenate ion and less than 3% colloidal [188]ReO$_2$. The precursor is produced with high radiochemical purity and labelling efficiency under milder conditions than those required for conventional reducing agents.

15.1. INTRODUCTION

The [99m]Tc(I) and [188]Re(I) tricarbonyl precursors [M(OH$_2$)$_3$(CO)$_3$]$^+$ are excellent starting materials for the synthesis of [99m]Tc(I) and [188]Re(I) tricarbonyl complexes, and for the radiolabelling of target specific biomolecules [15.1–15.7]. Recently, a user friendly kit formulation (IsoLink[TM]) has been developed using potassium boranocarbonate (K$_2$[BH$_3$CO$_2$]) for preparation of the ^{99m}Tc precursor complex. This solid reagent serves both as a source of carbon monoxide and as a reducing agent for technetium. It has also been used by Schibli and co-workers for the preparation of the corresponding [188]Re precursor complex ('Schibli's kit') [15.8]. This approach involved the reduction of [188]Re perrhenate eluate (1 mL) in neutral solution with 3 mg of K$_2$[BH$_3$CO$_2$] and 5 mg of BH$_3$·NH$_3$ by incubation at 60°C for 15 min. The

amounts of reducing agents and acid (concentrated phosphoric acid) were carefully balanced, not only to avoid fast hydrolysis of the boranes, but also to maintain a sufficiently low pH level to stabilize reduced rhenium intermediates. The preparations resulted in yields of the desired precursor complex of greater than 85%. Perrhenate (7±3%), colloidal $^{188}ReO_2$ (<5%) and a by-product of unknown composition were also detected.

To increase the yields further, we evaluated borohydride exchange resin (BER) as an additional reducing agent and an anion scavenger [15.9].

15.2. EXPERIMENTAL PROCEDURES

Unless otherwise stated, all chemicals were of reagent grade and were used without further purification. Sodium perrhenate ($Na^{188}ReO_4$) was eluted from a $^{188}W/^{188}Re$ generator (ORNL, Oak Ridge, TN, USA) using 0.9% saline. For the separation of $[^{188}Re(OH_2)_3(CO)_3]^+$, HPLC analyses were performed on a Waters system equipped with a radiometric detector using a reversed phase XTerra^{TM} RP$_{18}$ 5 μm column (4.6 mm × 250 mm, Waters, Ireland). HPLC solvents consisted of methanol (solvent A) and 0.05M TEAP (tetraethyl-ammonium phosphate) buffer, pH2.25 (solvent B). The HPLC gradient was as follows: 0–5 min: a linear gradient to 0% A/100% B from 100% A/0% B; 5–8 min: a linear gradient to 25% A/75% B from 0% A/100% B; 8–11 min: a linear gradient to 34% A/66% B from 25% A/75% B; 11–22 min: a linear gradient to 100% A/0% B from 34% A/66% B; 22–24 min: a linear gradient to 0% A/100% B from 100% A/0% B. The flow rate was 1 mL/min. For the separation of $^{188}Re(I)$ tricarbonyl histidine, HPLC analyses were performed on a Perkin Elmer system equipped with a radiometric detector (IsoScan LC gamma, Biostep, Germany) using a Hypersil ODS column (packing material 10 μm, 250 mm × 4 mm, Knauer, Berlin, Germany). HPLC solvents consisted of ethanol (solvent A) and 0.05M TEAP buffer at pH1.95 (solvent B). The HPLC gradient was as follows: 0–10 min: a linear gradient to 100% A/0% B from 0% A/100% B; 10–20 min: 100% A/096 B; 20–25 min; a linear gradient to 0% A/100% B from 100% A/0% B. The flow rate was 1 mL/min. All solvents for the mobile phase were of HPLC grade and prefiltered with a 0.2 μm pore size bottle filter. The ITLC analyses were performed on a TLC analysis system equipped with a gamma ray scanner (RITA TLC Analysis, Raytest, Germany). TLC was performed using either silica gel plates (60F$_{254}$, Merck, Darmstadt, Germany) and 99% methanol/1% concentrated HCl as an eluting solvent, or paper (Whatman No. 1) and 99.5% methanol/0.5% 6M HCl as an eluting solvent.

15.3. SYNTHESIS AND RADIOLABELLING

15.3.1. ^{188}Re(I) tricarbonyl precursor [^{188}Re(OH$_2$)$_3$(CO)$_3$]$^+$

A 10 mL vial containing tetrahydroborate exchange resin (BER, 3 mg), borane ammonia (BH$_3$·NH$_3$, 3 mg) and potassium boranocarbonate (K$_2$[BH$_3$CO$_2$], 3 mg) was capped with a rubber stopper. A solution of 1 mL of sodium perrhenate (Na^{188}ReO$_4$) with up to 50 MBq and 7 µL of concentrated phosphoric acid (85%) was added to the vial using a 20 mL syringe; the vial was then heated to 60°C in a boiling water bath for 15 min. Pressure from the evolving gas (about 10 mL) was balanced with the syringe. After cooling to room temperature, the neutral ^{188}Re(I) tricarbonyl precursor was obtained (Fig. 15.1). The yield was greater than 97%, as determined by HPLC and TLC.

15.3.2. ^{188}Re(I) tricarbonyl histidine

A 10 mL vial containing histidine (500 µL) was capped with a rubber stopper. A solution of 800 µL of [^{188}Re(OH$_2$)$_3$(CO)$_3$]$^+$ in saline with up to 50 MBq of activity was added to the vial using a 1 mL syringe. The reaction vial was sealed and heated to 75°C for 30 min. After 30 min, the reaction mixture was cooled to room temperature (Fig. 15.1). The yield was greater than 97%, as determined by HPLC and TLC.

15.3.3. Tetrahydroborate exchange resin (BER)

The tetrahydroborate exchange resin (BER) as a reducing agent was prepared by the method reported in Ref. [15.8]. Chloride form resin (Amberlite® ion exchange resin, 12.5 g) was slurry packed with water into a 30 mL fritted glass funnel mounted on a filter flask. An aqueous sodium tetrahydroborate solution (200 mL, 0.25M) was slowly passed through the resin
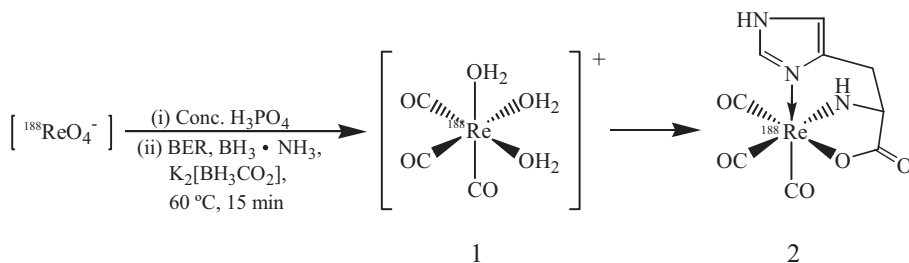
FIG. 15.1. Synthesis of ^{188}Re(I) tricarbonyl precursor (1) and ^{188}Re(I) tricarbonyl histidine (2).

over a period of 30 min. The resulting resins were washed thoroughly, first with distilled water until they were free of excess $NaBH_4$, and finally with ethanol. The tetrahydroborate form anion exchange resin was then partially air dried by removing ethanol on the surface of the BER. This resin was analysed for its tetrahydroborate content by hydrogen evolution upon acidification with 0.08M HCl, and the average capacity of the BER was found to be 2.5 meq of tetra-hydroborate ion per gram of resin.

15.4. RESULTS

The HPLC chromatograms of $^{188}Re(I)$ tricarbonyl precursor and $^{188}ReO_4^-$ showed the retention times of those species to be 4.7 and 9.8 min, respectively. The retention time of the $^{188}Re(I)$ tricarbonyl precursor was compared with that of the $^{99m}Tc(I)$ tricarbonyl precursor and was found to be identical. The radiolabelling yield of the $^{188}Re(I)$ tricarbonyl precursor in the reaction mixture was determined by HPLC analysis and found to be greater than 99%. The HPLC chromatogram of a typical $^{188}Re(I)$ tricarbonyl precursor in the reaction mixture is shown in Fig. 15.2. The complex was stable (>95%) for approximately 3 h. After this time, decomposition of the complex was observed. Paper electrophoresis investigations in aqueous solution confirmed the cationic charge of $^{188}Re(I)$ tricarbonyl precursor in a neutral solution. The assay for the formation of the $^{188}Re(I)$ tricarbonyl precursor, reduced
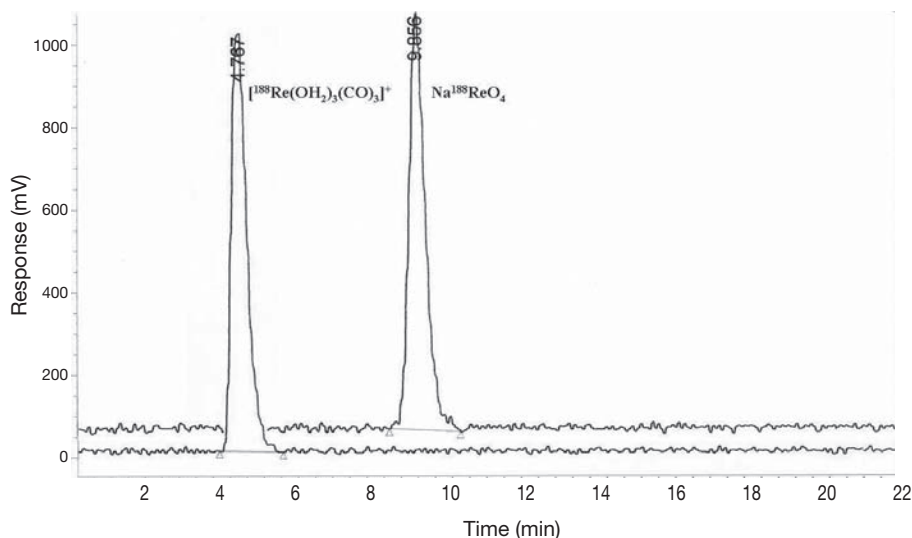
FIG. 15.2. HPLC chromatograms of $^{188}Re(I)$ tricarbonyl precursor and $Na^{188}ReO_4$.

hydrolyzed ^{188}Re and ^{188}Re perrhenate ion was achieved by investigating their positions using ITLC. Rhenium-188(I) tricarbonyl precursor: >95% (R_f = 0.4); reduced hydrolyzed ^{188}Re: less than 3% (origin); ^{188}Re perrhenate ion: 0% (R_f = 0.8).

The HPLC chromatogram of ^{188}Re(I) tricarbonyl histidine showed the retention time of the complex to be 11.4 min. The radiolabelling yield of ^{188}Re(I) tricarbonyl histidine in the reaction mixture was determined by HPLC analysis and found to be over 97%. The HPLC chromatogram of ^{188}Re(I) tricarbonyl histidine in the reaction mixture is shown in Fig. 15.3. The retention time of ^{188}Re(I) tricarbonyl histidine was compared with that of ^{99m}Tc(I) tricarbonyl histidine and was found to be identical.

15.5. DISCUSSION

BER contains tetrahydroborate ion (BH_4^-) bound to the cation which is supported on the polystyrene matrix. The cation has a quaternary alkyl ammonium functionality used for adhering the tetrahydroborate ion or negatively charged species. A schematic illustration of the use of BER is shown in Fig. 15.4.

The results of the present studies demonstrate the use of BER as a novel reducing agent and an anion scavenger. The ^{188}Re(I) tricarbonyl precursor having high radiochemical purity and labelling efficiency can be prepared without the need for nitrogen gas flushing and ice bath cooling, as is necessary in the conventional method [15.8]. BER has the added advantages of being
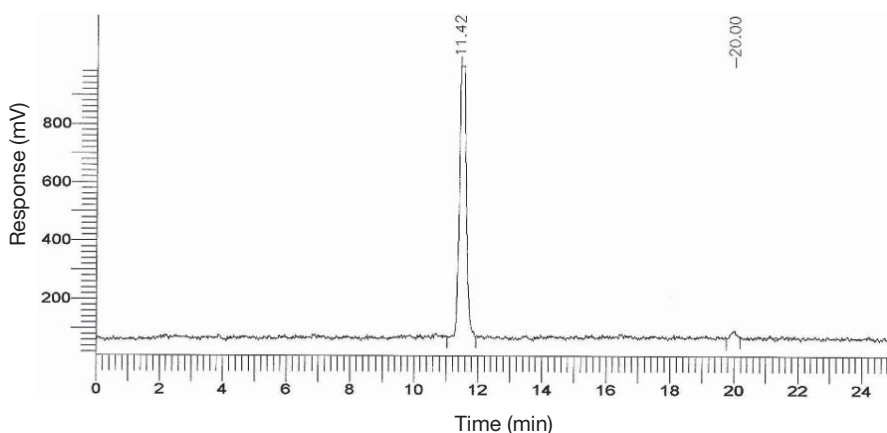
FIG. 15.3. HPLC chromatogram of ^{188}Re(I) tricarbonyl histidine.

X^- = BH_4^- ; BER

= $^{188}ReO_4^-$; Perrhenate bound to cation

= Anion ; Anion bound to cation
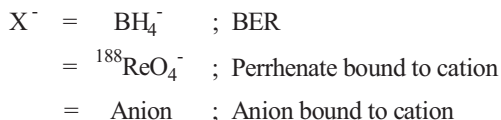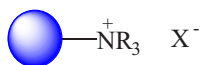
FIG. 15.4. BER as a solid phase reducing agent and an anion scavenger.

stable over a wide range of pH values (2–11) and of being biologically active molecules, as well as being easily removed through filtration when being administrated [15.9]. This approach thus provides the potential for the economical production of ^{188}Re(I) tricarbonyl precursor without the formation of unreacted $^{188}ReO_4^-$, colloidal $^{188}ReO_2$ or negatively charged impurities by reinforcing the conventional reducing agent requiring very stringent conditions for preparation.

ACKNOWLEDGEMENTS

REFERENCES TO CHAPTER 15

[15.1] MUNDWILER, S., KÜNDIG, M., ORTNER, K., ALBERTO, R., A new [2+1] mixed ligand concept based on [^{99m}Tc(OH$_2$)$_3$(CO)$_3$]$^+$: a basic study, Dalton Trans. (2004) 1320–1328.

[15.2] PIETZSCH, H.J., et al., Chemical and biological characterization of technetium(I) and rhenium(I) tricarbonyl complexes with dithioether ligands serving as linkers for coupling the Tc(CO)$_3$ and Re(CO)$_3$ moieties to biologically active molecules, Bioconjugate Chem. **11** (2000) 414–424.

[15.3] SCHIBLI, R., et al., Influence of the denticity of ligand systems on the in vitro and in vivo behavior of ^{99m}Tc(I)-tricarbonyl complexes: a hint for the future functionalization of biomolecules, Bioconjugate Chem. **11** (2000) 345–351.

[15.4] ARTERBURN, J., CORONA, C., VENKATESWARA, R., CARLSON, K.E., KATZENELLENBOGEN, J.A., Synthesis of 17-α-substituted estradiol-pyridin-2-yl hydrazine conjugates as effective ligands for labeling with Alberto's complex *fac*-[Re(OH$_2$)$_3$(CO)$_3$]$^+$ in water, J. Org. Chem. **68** (2003) 7063–7070.

[15.5] SEIFERT, S., et al., Reactivity of technetium(I) thioether carbonyl complexes towards histidine — an EXAFS study in solution, Inorg. Chim. Acta **322** (2001) 79–86.

[15.6] BAYLY, S.R., FISHER, C.L., STORR, T., ADAM, M.J., ORVIG, C., Carbohydrate conjugates for molecular imaging and radiotherapy: ^{99m}Tc(I) and ^{186}Re(I) tricarbonyl complexes of *N*-(2′-hydroxybenzyl)-2-amino-2-deoxy-D-glucose, Bioconjugate Chem. **15** (2004) 923.

[15.7] ALBERTO, R., et. al., A novel organometallic aqua complex of technetium for the labelling of biomolecules: synthesis of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ from $[^{99m}TcO_4]^-$ in aqueous solution and its reaction with a bifunctional ligand, J. Am. Chem. Soc. **120** (1998) 7987–7988.

[15.8] SCHIBLI, R., et al., Steps toward high specific activity labelling of biomolecules for therapeutic application: preparation of precursor $[^{188}Re(OH_2)_3(CO)_3]^+$ and synthesis of tailor-made bifunctional ligand systems, Bioconjugate Chem. **13** (2002) 750–756.

[15.9] PARK, S.H., GWON, H.J., PARK, K.B., Synthesis and characterization of ^{99m}Tc-labeled biologically active molecules using borohydride exchange resin as a reducing agent for the preparation of radiopharmaceuticals, J. Label. Compd. Radiopharm. **47** (2004) 683–697.

Chapter 16

DEVELOPMENT OF INORGANIC ADSORBENTS AS MATRICES OF GENERATORS FOR THERAPEUTIC RADIONUCLIDES

F. MONROY-GUZMAN*, V.E. BADILLO ALMARAZ*,
T. RIVERO GUTIERREZ*, L. GALICO COHEN*,
J. COSGROVE**, F.F. KNAPP, Jr.**, P. ROJAS NAVA*,
C.J. ROSALES*

* National Nuclear Research Institute (ININ),
  Mexico City, Mexico

** Oak Ridge National Laboratory (ORNL),
   Oak Ridge, United States of America

Abstract

The aims of the study were (i) to prepare ^{188}W/^{188}Re generators based on ^{188}W-tungstates and hydroxyapatite to evaluate their feasibility and (ii) to determine the sorption properties of alumina to ascertain the optimal conditions for fabrication of alumina based ^{188}W/^{188}Re generators. Titanium and zirconium ^{188}W-tungstate were synthesized using ^{188}W-tungstate solutions at four different pH values and were then used to prepare ^{188}W/^{188}Re generators. The sorption behaviour of tungsten and rhenium on hydroxyapatite and alumina in a NaCl medium was evaluated based on results of batch experiments. Three parameters were assessed: NaCl solution pH, alumina particle size and sorption capacity. The results demonstrate that ^{188}Re is not adsorbed, whereas ^{188}W is strongly adsorbed in NaCl on both adsorbents. Hydroxyapatite and alumina ^{188}W/^{188}Re generator systems were constructed and eluted in NaCl solutions. The performance of the titanium and zirconium ^{188}W-tungstate, hydroxyapatite and alumina based ^{188}W/^{188}Re generators was evaluated.

16.1. INTRODUCTION

Alternative methods of ^{188}Re generator preparation using low or medium specific activity ^{188}W have been developed from matrices of heteropolyanions formed from ^{188}W-isopolytungstates with atoms such as zirconium and titanium [16.1, 16.2] or with adsorbents having a high capacity such as anion exchangers, activated carbon or zirconium dioxide [16.3, 16.4]. To find new options for the

production of ^{188}Re generators that are efficient and easy to manufacture, titanium tungstate and zirconium tungstate were formulated and their effect on generator performance was evaluated; hydroxyapatite was also evaluated as a potential adsorbent material for ^{188}W/^{188}Re generator systems. The ^{188}W-heteropolytungstates were synthesized using the sol-gel method, and sorption studies were designed to examine the affinity of hydroxyapatite for the tungsten and rhenium to provide evidence of the feasibility of this system. The performance of the generator systems constructed using hydroxyapatite and ^{188}W-heteropolytungstates was evaluated. At present, carrier free ^{188}Re is obtained commercially as Na^{188}ReO$_4$ from alumina based ^{188}W/^{188}Re generators. The work presented here focused on tungsten and rhenium sorption on alumina as a function of the HCl concentration, the pH of the 0.9% NaCl solution, the alumina particle size and the weight of the alumina (capacity).

16.2. METHODS

16.2.1. Radionuclides

The ^{187}W was produced by irradiation of tungsten oxide (WO$_3$) in the TRIGA Mark III reactor of the National Nuclear Research Institute (ININ) in Mexico. The ^{188}Re was provided by ININ's Department of Nuclear and Radioactive Materials as solutions of sodium ^{188}Re perrhenate (Na^{188}ReO$_4$) obtained from elution of a ^{188}W/^{188}Re generator made at ORNL (USA). The sodium ^{188}W-tungstate solutions (Na$_2$^{188}WO$_4$) were provided by ORNL (37 kBq/µL), and by RIAR (Russian Federation) with IAEA support (7.6 and 19.4 GBq/mL). All radioactivity measurements were performed using a calibrated gamma spectrometer with coaxial HPGe detector (7229P, Canberra) connected to a PC multichannel analyser (ACUSSPECT-A, Canberra).

16.2.2. ^{188}W-tungstate gel based generators

16.2.2.1. Preparation of ^{188}W-tungstate gel based generators

The titanium tungstate gels were synthesized from tetrabutyl ortho-titanate and sodium ^{188}W-tungstate solutions. Gels were prepared using ^{188}W-tungstate solutions of four different pH values (see Table 16.1) at a Ti:W molar ratio of 1:1. The gels were stirred and dried for 2.5 h at 80°C and then

TABLE 16.1. PREPARATION CONDITIONS OF THE TITANIUM
AND ZIRCONIUM TUNGSTATES

Series	Cation	pH level of tungstate	X^{4+}	X:W molar ratio	Addition order
I	Ti	12, 7, 4.5, 1.95	$C_{16}H_{36}O_4Ti$	1:1	Ti to W
II	Zr	12, 7, 4.5, 1.95	$(C_2H_5O)_4Zr$	1:1	Zr to W

placed on 3.75 mL polyethylene columns. The zirconium tungstate gels were prepared from zirconium ethoxide solutions and sodium ^{188}W-tungstate solutions following the process previously described. Gels were prepared using ^{188}W-tungstate solutions of four different pH values at a Zr:W molar ratio of 1:1. The columns were washed with 50 mL of 0.9% NaCl and were eluted every three days for a period of three months.

16.2.3. Hydroxyapatite based ^{188}W/^{188}Re generators

16.2.3.1. Determination of distribution coefficients

Distribution coefficients (K_d) of rhenium and tungsten in hydroxyapatite were determined by a radiotracer technique in 0.9% NaCl as a function of pH. For this purpose, 25 mL of 0.9% NaCl solution was mixed with 250 mg of hydroxyapatite. The pH of the 0.9% NaCl solutions was adjusted to the selected values. Solid and aqueous solutions were mixed well, and 100 µL of the radioactive solution (3.7 kBq/µL), containing the ^{187}WO$_4^{2-}$ or ^{188}ReO$_4^-$, was then added and the solutions were shaken for 24 h. Finally, the hydroxyapatite and the liquid phase were separated by centrifugation, and the distribution coefficients were calculated using the 686 keV photopeak for ^{187}W and the 155 keV photopeak for ^{188}Re. The feasibility of separating the ^{187}WO$_4^{2-}$ or ^{188}ReO$_4^-$ ions was determined from the K_d values by calculating the separation factors ($\alpha_{A,B}$).

16.2.3.2. Preparation of ^{188}W/^{188}Re generators

From the adsorption data obtained for tungsten and rhenium, hydroxyapatite based ^{188}W/^{188}Re generators were constructed. The effects on ^{188}W/^{188}Re generator performance of the different pH levels of the 0.9% NaCl solutions (series A), the particle size of the hydroxyapatite (series B) and the eluant (series C) were evaluated. Chromatography columns (0.8 cm × 4 cm) were filled with hydroxyapatite (500 mg) previously mixed with the selected medium, where ^{188}WO$_4^{2-}$ is strongly retained while ^{188}ReO$_4^-$ is weakly adsorbed.

The medium under investigation was then percolated through the column. The generators were eluted every 3 d for a period of 1 month.

16.2.4. Analysis of generator eluants

The eluted ^{188}Re and ^{188}W activity was measured in an HPGe detector. The ^{188}W breakthrough (%) was determined by quantification of the 290 keV photopeak for ^{188}W and the 155 keV photopeak for ^{188}Re. The ^{188}Re elution profile was obtained by collecting 500 μL fractions. The radiochemical purity of the ^{188}Re eluate was determined by paper chromatography using 3 CHR (Whatman®) paper as the solid phase and acetone as the mobile phase. The R_f of ^{188}ReO$_4^-$ was 1. The titanium and zirconium concentrations in the ^{188}Re eluates were determined. The presence of phosphates was determined by photometry using AQUANAL® professional vario H powder packs (Riedel-deHaën).

16.2.5. Alumina based ^{188}W/^{188}Re generators

16.2.5.1. Determination of distribution coefficients and separation factors

Acidic aluminium oxide (Fluka, 0.05–0.15 mm, pH4.5) for chromatography was used in these experiments. The alumina was sieved and the particles were separated into the following four sizes: less than 200, 200–300, 300–400, greater than 400 mesh. Rhenium and tungsten distribution coefficients were determined by a radiotracer technique using ^{187}W and ^{188}Re under static conditions. The general procedure for obtaining the K_d values was as follows: Precisely weighed alumina was mixed with 30 mL of the medium (HCl or 0.9% NaCl, see Table 16.2). Sorbent and aqueous solutions were brought to equilibrium by shaking the mixture for 3 d, after which 100 μL of the solutions containing the tracer elements was added to the mixture, which was then shaken for 3 h. The alumina and liquid phase were then separated by centrifugation. Alumina adsorption characteristics were determined by comparing the ^{187}W (686 keV) or ^{188}Re (155 keV) activities of 4 mL aliquots with those of 4 mL aliquots of the reference solutions. The reference solutions were prepared with the same amount of the tracer solutions in 30 mL of the medium. Four parameters were evaluated: HCl concentration, pH of the 0.9% NaCl solutions, alumina particle size and capacity of the alumina (see Table 16.2). Using the K_d values, the feasibility of separating the ^{187}WO$_4^{2-}$ or ^{188}ReO$_4^-$ ions was determined by calculating the separation factors ($\alpha_{A,B}$), and an alumina based ^{188}W/^{188}Re generator was then prepared. The generator was eluted every 3 d and the ^{188}Re eluates were evaluated following the analysis described in Section 16.4.

TABLE 16.2. SORPTION CONDITIONS OF TUNGSTEN
AND RHENIUM ON ALUMINA

Series	Medium	pH of the medium	Concentration	Alumina (mg)	Alumina particle size (mesh)	W/Al$_2$O$_3$ (mg/g)
W-1	HCl	0–6	3–10^{-6} mol/L HCl	150	300–400	18
Re-1	HCl	0–6	3–10^{-6} mol/L HCl	150	300–400	0.06 mCi/mL
W-2	NaCl	1–12	0.9% NaCl	150	300–400	18
Re-2	NaCl	1–12	0.9% NaCl	150	300–400	0.06 mCi/mL
W-3	NaCl	5.6	0.9% NaCl	150	> 200 200–300 300–400 < 400	18
W-4	NaCl	5.6	0.9% NaCl		300–400	2–200

16.3. RESULTS

16.3.1. [188]W-tungstate gel based generators

The titanium and zirconium [188]W-tungstate gels were prepared using the sol-gel method, which allows the synthesis of the gels in about 3 h, compared with the 6–7 h required for the precipitation method. Figures 16.1 and 16.2 show the performance of the titanium and zirconium [188]W-tungstate based generators, respectively. The pH level of the [188]W-tungstate solution used for the preparation of the titanium and zirconium [188]W-tungstate based generators influenced the efficiency and the [188]W breakthrough of the generators. Both parameters decreased when the gels were synthesized with more acidic [188]W-tungstate solutions.

The best [188]Re elution efficiency (~73%) was obtained from the titanium [188]W-tungstate based generators; however, the lowest [188]W breakthrough (0.3%) was obtained from the zirconium [188]W-tungstate based generators. The [188]Re radiochemical purity obtained from both types of generator is less in the gels prepared with basic [188]W-tungstate solutions (83–87%) than in those prepared with acidic [188]W-tungstate solution, which had a [188]Re radiochemical purity of 100%. In the case of the titanium [188]W-tungstate based generators, the [188]Re eluate volumes were about 2.5 mL and showed traces of titanium. On the other hand, the generator prepared from a [188]W-tungstate solution at pH12 initially released about 99% of the [188]WO$_4^{2-}$ adsorbed during the washing.
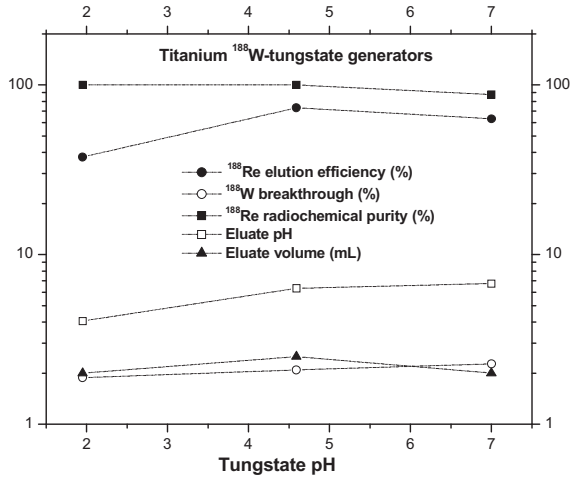
FIG. 16.1. Performance of the titanium ^{188}W-tungstate based generator.
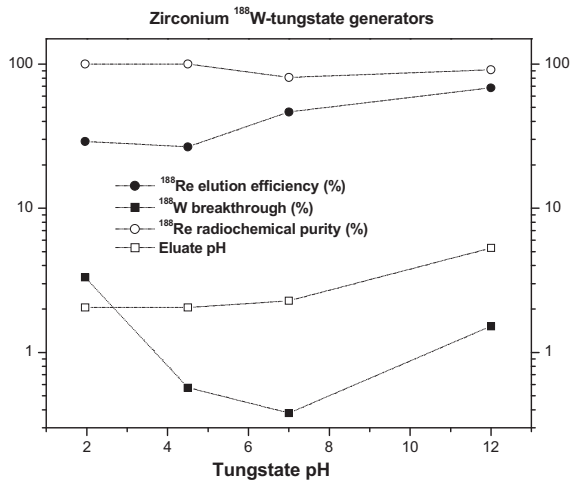
FIG. 16.2. Performance of the zirconium ^{188}W-tungstate based generator.

16.3.2. Hydroxyapatite based ^{188}W/^{188}Re generators

The $\alpha_{W/Re}$ separation factors shown in Fig. 16.3 indicate that tungsten and rhenium can be readily separated with 0.9% NaCl solutions at pH levels below 7.5. Based on these data, hydroxyapatite based generators were constructed using four 0.9% NaCl solutions at pH5.5, 6.0, 6.3 and 6.5 (series A), and using hydroxyapatite particles of three sizes (series B). The performance of these

generators was evaluated and the results are shown in Figs 16.4 and 16.5. For all the [188]Re eluates obtained in both series, the pH was 6.5, the phosphate concentration was greater than 1000 ppm and the radiochemical purity was greater than 90%. The lowest [188]W breakthrough and highest average elution volumes were obtained in the generators eluted with 0.9% NaCl solution at pH6.5 and with hydroxyapatite particles between 38 and 75 μm in size. The efficiency of the [188]W/[188]Re generators decreased with the pH value of the NaCl solution, but the particle size of the hydroxyapatite appeared to have no significant effect. The mean efficiencies obtained were about 65%, whereas the elution volumes and [188]W breakthrough values decreased with a decrease of the hydroxyapatite particle size and with an increase of the pH value of the NaCl solution. The generators in series A and B showed that phosphate ions are released during the elution of [188]Re, leading to the proposal to wash the generators after elution with 0.9% NaCl solutions, using 0.01 mol/L $CaCl_2$ or 0.004 mol/L NaH_2PO_4 solutions, in order to avoid the dissolution of hydroxyapatite.

A third series of generators (series C) was then fabricated and evaluated using the method previously described. The performance of these generators as a function of the eluant is shown in Fig. 16.6. Washing the generators with 0.01 mol/L $CaCl_2$ or 0.004 mol/L NaH_2PO_4 solutions after elution with 0.9% NaCl solutions caused an increase of the [188]W breakthrough in the [188]Re eluate. However, there was no apparent effect on the [188]Re elution efficiency, the eluate pH or the radiochemical purity. The presence of phosphate ions in the [188]Re eluates shows that the hydroxyapatite continues to dissolve.
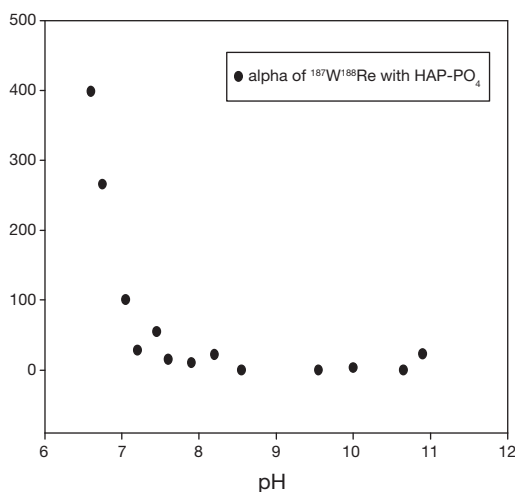
FIG. 16.3. Separation factors of tungsten and rhenium ($\alpha_{W/Re}$) on hydroxyapatite.
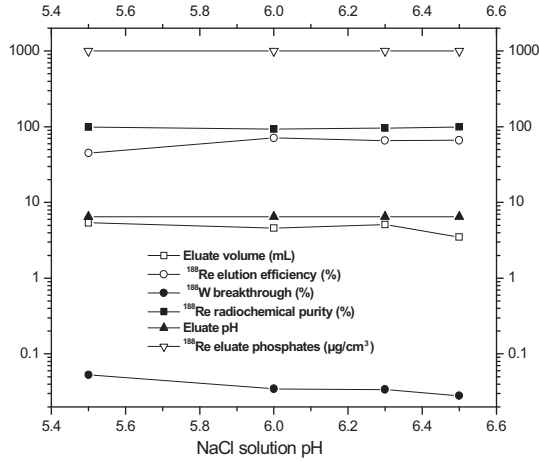
FIG. 16.4. *Performance of the hydroxyapatite based* $^{188}W/^{188}Re$ *generators as a function of the 0.9% NaCl solution pH (series A).*
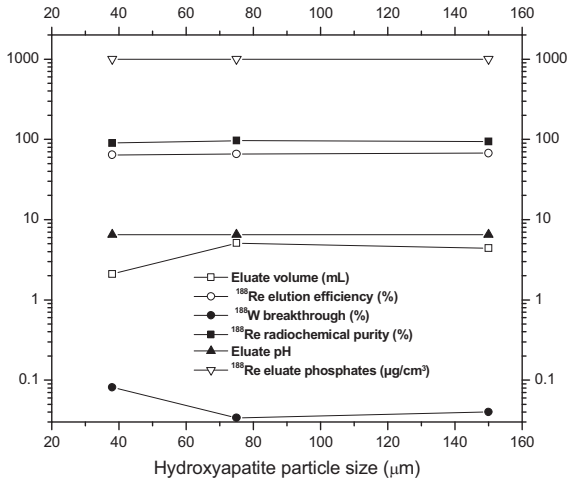
FIG. 16.5. *Performance of the hydroxyapatite based* $^{188}W/^{188}Re$ *generators as a function of the hydroxyapatite particle size (series B).*
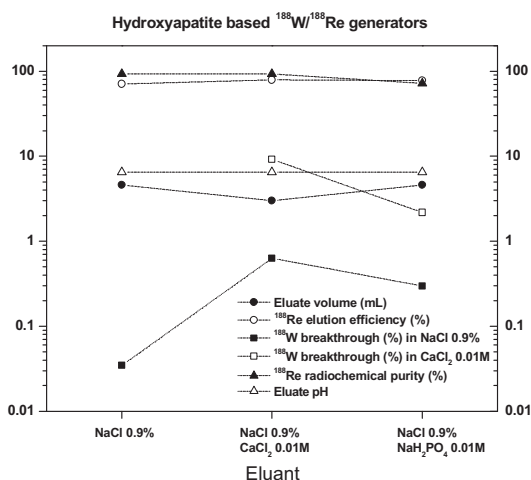
FIG. 16.6. *Performance of the hydroxyapatite based $^{188}W/^{188}Re$ generators as a function of the eluant (series C).*

16.3.3.   Sorption behaviour of tungsten and rhenium on alumina

16.3.3.1. In HCl medium

The tungsten sorption behaviour on alumina as a function of the HCl concentration can be expressed mathematically by Eq. (16.1). The K_d values decrease with an increase of the HCl concentration. The distribution coefficients are more than 1000 cm^3/g at HCl concentrations of less than 0.1 mol/L.

$$\log K_d = 2.64 - 0.45 \log [HCl] \tag{16.1}$$

Around 99% of the tungsten is sorbed on alumina at HCl concentrations of between 1×10^{-6} and 0.1 mol/L, and this percentage decreases radically at concentrations of more than 0.1 mol/L. Rhenium presents K_d values and percentage sorption unchanged at HCl concentrations of between 1×10^{-6} and 1×10^{-3} mol/L; at HCl concentrations of between 1×10^{-3} and 0.1 mol/L, both parameters show a drastic decrease. At concentrations greater than 0.1 mol/L, K_d values and percentage sorption are practically constant. It is important to note that the maximum K_d value and percentage of sorption for rhenium are 63 cm^3/g and 40%, respectively. For HCl concentrations greater than 0.1 mol/L, the rhenium practically is not sorbed on alumina.

16.3.3.2. In 0.9% NaCl medium

The K_d values and the percentage sorption of tungsten on alumina are about 7 cm^3/g and 1%, respectively, at pH levels greater than 7, which indicates that tungsten is not sorbed on alumina in basic 0.9% NaCl solutions. In an acidic medium (<pH5.5), K_d values and sorption percentages of over 700 cm^3/g and 90%, respectively, were observed. Tungsten is strongly sorbed on alumina in 0.9% NaCl solutions with pH values of less than 5.5. In the case of rhenium, results show the K_d values are very low, around 2 and 3, between pH1 and 12. Consequently, the sorption percentages are also low, about 2 and 4%, indicating that rhenium is not sorbed on alumina in saline medium between pH1 and 12.

Figure 16.7 shows the effect of the particle size of alumina on the adsorption of the tungsten in 0.9% NaCl solutions. The distribution coefficients and the percentage sorption present a Gaussian behaviour with maximum values at particle sizes of 200–300 mesh. The lowest K_d values and percentage sorption were obtained using alumina particle sizes of between 200 and 400 mesh.

The sorption capacity of alumina in 0.9% NaCl solutions was determined by means of the weight variation of alumina and tungsten in the tungsten sorption experiments. The K_d values and the percentage sorption of tungsten on alumina as a function of the weight of the alumina and the weight ratio of the tungsten to the alumina can be expressed mathematically by Eqs (16.2) and (16.3):
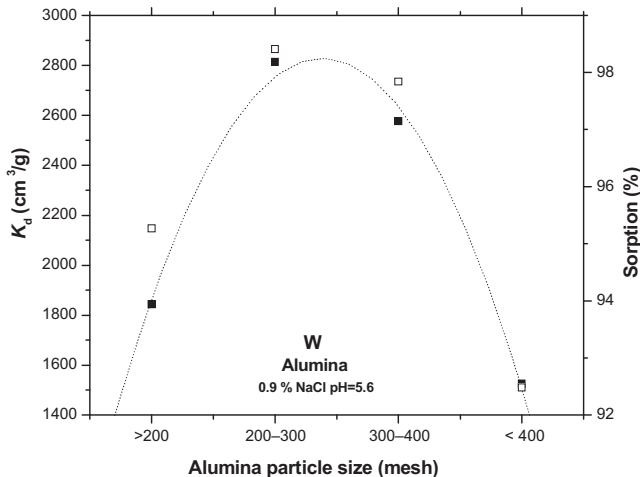

FIG. 16.7. Effect of the alumina particle size on the sorption behaviour of tungsten.

$$\log K_{\mathrm{d}} = 4.09 + 0.67 \log g + 0.25 \log g^2 \tag{16.2}$$

$$S\% = 100.18 - 0.199\,R \tag{16.3}$$

where g is the alumina weight and R is the weight ratio of tungsten (mg) to alumina (g). From the weight ratio values, the capacity of alumina was determined to be 0.34 meq per gram of alumina, which is equal to 10.5 mg of tungsten per gram of alumina. At this ratio, the tungsten sorption is about 99.9%, and at a ratio of 20 mg of tungsten per gram of alumina, the sorption is about 96%.

In summary, alumina is an excellent adsorbent for tungsten in solutions of diluted HCl (<0.1 mol/L) and at pH values below 5.5 in 0.9% NaCl solutions, while rhenium is not sorbed under these conditions. These results agree with the separation factors (α) for tungsten and rhenium, given by expressions (16.4) and (16.5) for HCl and saline media, respectively, which indicate the possibility of efficiently separating tungsten and rhenium in diluted HCl solutions (<0.1 mol/L HCl) and at pH levels below 5.5 in 0.9% NaCl solutions:

$$\log [\alpha] = -1.76 + 0.25 \log [\mathrm{HCl}] \tag{16.4}$$

$$\log [\alpha] = -5.40 + 0.809\,\mathrm{pH} - 0.025\,\mathrm{pH}^2 \tag{16.5}$$

In accordance with the previous results, it is possible to prepare alumina based ^{188}W/^{188}Re generators from HCl solutions (<0.1 mol/L) or 0.9% NaCl solutions (<pH5.5) that can be used to adsorb the ^{188}W and to elute the ^{188}Re. The preferred alumina particle size for preparing these generators is 200–300 mesh, and a ratio of 10.5 mg of tungsten per gram of alumina is recommended. An alumina based ^{188}W/^{188}Re generator was then prepared using an alumina particle size of 200–300 mesh in 0.01 mol/L HCl. The alumina (2.2 g) was added to a glass column (12 mm × 70 mm), which was washed with 50 mL of 0.01 mol/L HCl and to which was added the ^{188}W (49.1 g/L, 0.2 GBq). The pH of the sodium ^{188}W-tungstate was adjusted to 6 with 0.2 mol/L HCl. The column was again washed with 20 mL of 0.01 mol/L HCl and 20 mL of 0.9% NaCl. Preliminary results of the generator performance showed the efficiency and radiochemical purity to be greater than 95%.

The ratio of 10.5 mg of tungsten per gram of alumina chosen for preparing the ^{188}W/^{188}Re generator could be increased because 92% of the tungsten is still sorbed on alumina at a ratio of 45 mg of tungsten per gram of alumina; this is an increase of about 75% in the tungsten weight on alumina and consequently a decrease of the chromatographic column size and of the elution volumes of ^{188}Re.

16.4. PROSPECTS

Hydroxyapatite is an excellent anion exchanger that can adsorb about 0.9% of the weight of tungsten [16.6]. The adsorption studies of tungsten and rhenium on hydroxyapatite in 0.9% NaCl medium showed that it is feasible to construct hydroxyapatite based [188]W/[188]Re generators if 0.9% NaCl solutions at pH levels below 7 are employed as the eluant. The [188]Re elution efficiency and the [188]W breakthrough of these generators depend on the pH of the 0.9% NaCl solution. The release of phosphate ions during the elution of these generators shows that the hydroxyapatite is being dissolved by the eluant. Washing the generators with 0.01 mol/L $CaCl_2$ or 0.004 mol/L NaH_2PO_4 after elution with 0.9% NaCl solutions was proposed in order to stop the release of phosphate ions. However, washing did not improve the elution conditions, and in fact caused a decrease of the [188]Re elution efficiency and an increase of the [188]W breakthrough. It is therefore necessary to find a mechanism that allows the release of the phosphate ions to be avoided during the elution of the generators.

Regarding the titanium and zirconium [188]W-tungstate based generators, the gels were prepared by the sol-gel method, which reduced the process time to 3 h. Use of acidic or basic [188]W-tungstate solutions in the preparation of the gel generators reduces both the [188]Re elution efficiency and [188]W breakthrough. It is known that the tungstate forms different chemical species depending on the acidity of the solution, consequently the gels formed from the tungstate solution at different pH levels will constitute distinct structures with specific physicochemical properties. In accordance with our results, the generator with the best performance was that prepared from zirconium [188]W-tungstate; however, the [188]W breakthrough of the [188]Re eluates was always greater than 0.015%. Tungstates based on other metals have been synthesized, and their solubility in 0.9% NaCl medium has been determined. Calcium and manganese tungstates have a solubility of less than 10^{-4} g/mL and their use in generator preparation is being explored.

On the subject of alumina based [188]W/[188]Re generators, the analytical studies of tungsten and rhenium sorption on alumina have shown that these generators can be prepared and eluted with HCl (<0.1 mol/L) and 0.9% NaCl solutions (<pH5.5). It is advisable to use alumina with a particle size of 200–300 mesh, because the best sorption behaviour of tungsten (higher K_d values and percentage sorption) is obtained with these particle sizes. The alumina capacity is about 0.34 meq (or 10.5 mg of tungsten) per gram of alumina; at this ratio, about 99.9% of the tungsten is sorbed on alumina. The generator prepared with 0.01 mol/L HCl solutions to fix the [188]W and eluted with 0.9% NaCl solutions at pH5.5 is still being analysed. Preliminary results show the efficiency and radiochemical purity to be greater than 95%.

ACKNOWLEDGEMENTS

REFERENCES TO CHAPTER 16

[16.1] DADACHOV, M., LAMBRECHT, R.M., HETHERINGTION, E., An improved tungsten ^{188}W/^{188}Re gel generator based on zirconium tungstate, J. Radioanal. Nucl. Chem. Letters **188** (1994) 267–278.

[16.2] DADACHOV, M., LAMBRECHT, R.M., ^{188}W/^{188}Re gel generators based on metal tungstates, J. Radioanal. Nucl. Chem. Letters **200** (1995) 211–221.

[16.3] LEE, B., IM, H.-J., LUO, H., HAGAMAN, E.W., DAI, S., Synthesis and Characterization of Periodic Mesoporous Organosilicas as Anion Exchange Resins for Perrhenate Adsorption, Langmuir **21** (2005) 5372–5376.

[16.4] KHALID, M., MUSHTAQ, A., IQBAL, M.Z., Sorption of tungsten (VI) and rhenium (VII) on various ion-exchange materials, Sep. Sci. Technol. **36** (2001) 283–294.

[16.5] MONROY-GUZMÁN, F., CORTÉS ROMERO, O., LONGORIA, L., MARTÍNEZ CASTILLO, T., Titanium molybdate gel as ^{99}Mo/^{99m}Tc generator matrix, Synthesis and Applications of Isotopically Labelled Compounds. Vol 8. (DEAN, D.C., FILER, C.N., McCARTHY, K.E., Eds.), Wiley, England (2004) 321–324.

[16.6] BADILLO-ALMARAZ, V.E., Étude des mécanismes de rétention d'actinides et de produits de fission sur l'hydroxyapatite, Ph.D. Thesis, University of Paris XI, Paris (1999).

Chapter 17

DEVELOPMENT OF A ^{188}W/l^{188}Re GENERATOR

R. MIKOLAJCZAK, M. ZUCHLINSKA, A. KORSAK, E. ILLER,
D. PAWLAK, Z. ZELEK, M. KONIOR, J.L. PARUS
IAE Radioisotope Centre POLATOM,
Otwock-Świerk, Poland

Abstract

The fabrication of a ^{188}W/^{188}Re generator is described in detail, including the stability testing and quality control methods used. Studies of the elution profiles of four generators showed that about 90% of the available activity was contained in a 4 mL volume of saline solution with high radioactive concentration. The generators were usable for over 6 months, and the quality of the eluate was within the approved specifications. An illustration of a shielding container made of tungsten for a ^{188}Re eluate vial is also included.

17.1. INTRODUCTION

Rhenium-188 is a radioisotope of high therapeutic potential for nuclear medicine that belongs to the group of beta-gamma emitters (maximal energy of beta radiation: 2.11 MeV; energy of gamma rays: 155 keV) [17.1–17.7]. With beta particle penetration in soft tissues of about 8 mm, cancer tissues can be destroyed, while the gamma emissions permit imaging to locate accumulation. Rhenium-188-HEDP is used as an effective pain palliation agent in painful bone metastases, and ^{188}Re-DMSA is used for cancer treatment. Rhenium-188 complexes with peptides and monoclonal antibodies and their use in therapy against cancer are also in progress. Sterile and pyrogen free solutions of ^{188}Re agents loaded into a balloon have been used in brachytherapy of coronary vessels to prevent restenosis.

Owing to the short half-life of ^{188}Re, deliveries to remote customers can create logistical problems. These can be solved by delivering ^{188}W/^{188}Re generators as a source of ^{188}Re. The ^{188}Re solution is obtained by eluting the generator with 0.9% acidified saline. Here, the generator column and lead shielding used in a standard ^{99}Mo/^{99m}Tc generator (fission produced ^{99}Mo) have been used to fabricate ^{188}W/^{188}Re generators. Depending on the needs, the elution can be performed every second day, or even more often, with yields

resulting from the decay of ^{188}W and growth of ^{188}Re. The received eluate is sterile and can be used immediately after elution. The generators can be used for a long time, over 6 months, because the parent ^{188}W radionuclide has a half-life of 69 d. The fabricated generators were evaluated for a period of 8 months, and the quality of the eluate was within the approved specifications.

17.2. MATERIALS AND METHODS

17.2.1. Generator preparation

Aluminium oxide (Alumina A, ICN, MP Biomedicals) was stirred in deionized water and decanted several times until the supernatant was clear. The decanted alumina was then dried for 4 h at 80°C. Dry alumina (2 g) was loaded onto a column, which was fixed on the top with a bed of glass wool and closed with rubber seals and aluminium caps. The column was autoclaved for 0.5 h at 121°C. Before loading the ^{188}W, the column was activated by subsequent washing with the following solutions: 5 mL of 0.9% NaCl solution acidified to pH3 (flow rate: 10 mL/min), 5 mL of 32% HCl (flow rate: 5 mL/min) and 20 mL of 0.9% NaCl solution at pH3 (flow rate: 10 mL/min) to obtain effluent at pH3.

The ^{188}W (RIAR, Russian Federation) with a specific activity of between 27 and 133 GBq per gram of tungsten before loading onto the column was dissolved in 0.5M NaOCl (0.5 mL NaOCl per gram of tungsten), 80% CH_3COOH (1 mL CH_3COOH per gram of tungsten) and 32% HCl in order to lower the solution pH to 2.5 to obtain tungstic acid. The ^{188}W solution (as Na^{188}WO$_4$) was then slowly loaded onto the column using a peristaltic pump (flow rate: 0.1 mL/min). The column was washed with 20–50 mL of 0.9% NaCl solution (pH5.0–5.5) at a flow rate of 0.1 mL/min in order to remove the unbound ^{188}W. Finally, the generator column was fixed into the generator shielding and placed in the plastic box, followed by installation of the eluting needles.

17.2.2. Stability testing of the generator

The performance of generators was checked by elution three times a week (every second day, usually Monday, Wednesday and Friday) using 16 mL of 0.9% NaCl solution (the eluent for the ^{99}Mo/^{99m}Tc generator, pH5.0–5.5); four fractions of 4 mL each were collected. The following tests were carried out:

— Elution yield (total radioactivity eluted);
— Measurement of pH (in the first fraction of each elution);
— Radiochemical purity (once a week, in the first fraction);
— Radionuclidic purity (once every 2 weeks, in the second fraction);
— Sterility and bacterial endotoxins (once every 2 months, in the third fraction);
— Chemical purity by ICP-OES (once every 2 months, in the second fraction).

17.2.3.   Methods used in quality control

The radioactivity of ^{188}Re was measured using an ionization chamber (KG 4π-50 with a Keithley Electrometer type 485). A certified solution was used for calibration of the system; the estimated accuracy of measurements was ±5%. The ^{188}W breakthrough and radioactive impurities were measured using an efficiency calibrated gamma spectrometer with an HPGe detector. The radiochemical purity of ^{188}Re perrhenate was checked using paper chromatography (Whatman 1) with acetone as the developing solution. The chemical purity of the eluate was determined using an ICP-Optical Emission Spectrometer (Optima 3300XL, Perkin-Elmer), with special attention given to the presence of aluminium, tungsten and zirconium.

17.3. RESULTS

17.3.1. ^{188}W/^{188}Re generator elution profile

The elution profile of the first elution after generator preparation (8×4 mL) is presented in Fig. 17.1. More than 95% of the ^{188}Re radioactivity is accumulated in the first and second 4 mL fractions.

Standard elutions of the ^{188}W/^{188}Re generator were performed using 16 mL of acidified saline solution (4×4 mL). Figure 17.2 presents average values of generator yields in each collected fraction and their standard deviations, obtained in ten consecutive elutions (over a period of 4 weeks).

The generator was manufactured on 29.06.2005 with a column loaded with 19.81 GBq of ^{188}W. The elution yield on 18.07.2005 was 84–88% of the expected radioactivity. The generator was eluted with eight eluent portions of 0.5 mL each. The cumulative elution profile is presented in Fig. 17.3.
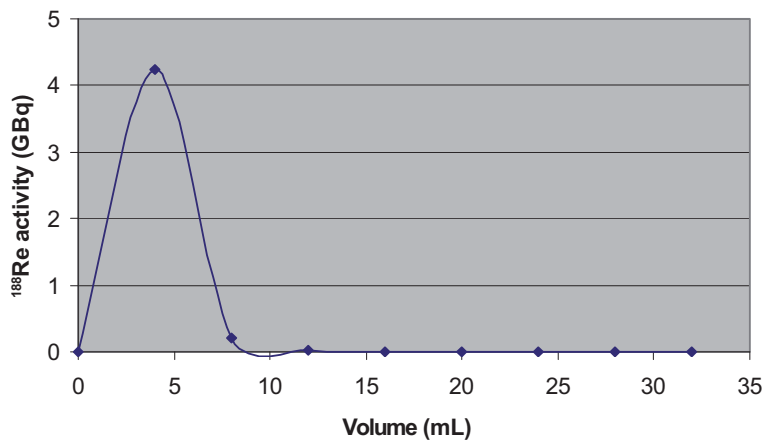
FIG. 17.1. Elution profile of the $^{188}W/^{188}Re$ generator.
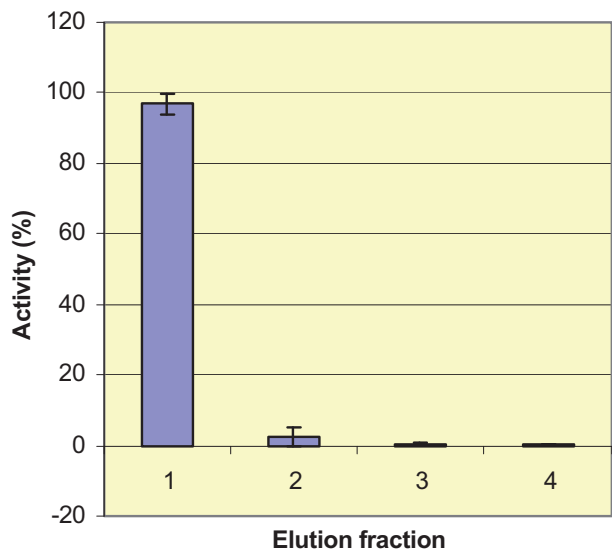
FIG. 17.2.   Relative yields of ^{188}Re elution in collected fractions over ten consecutive elutions.
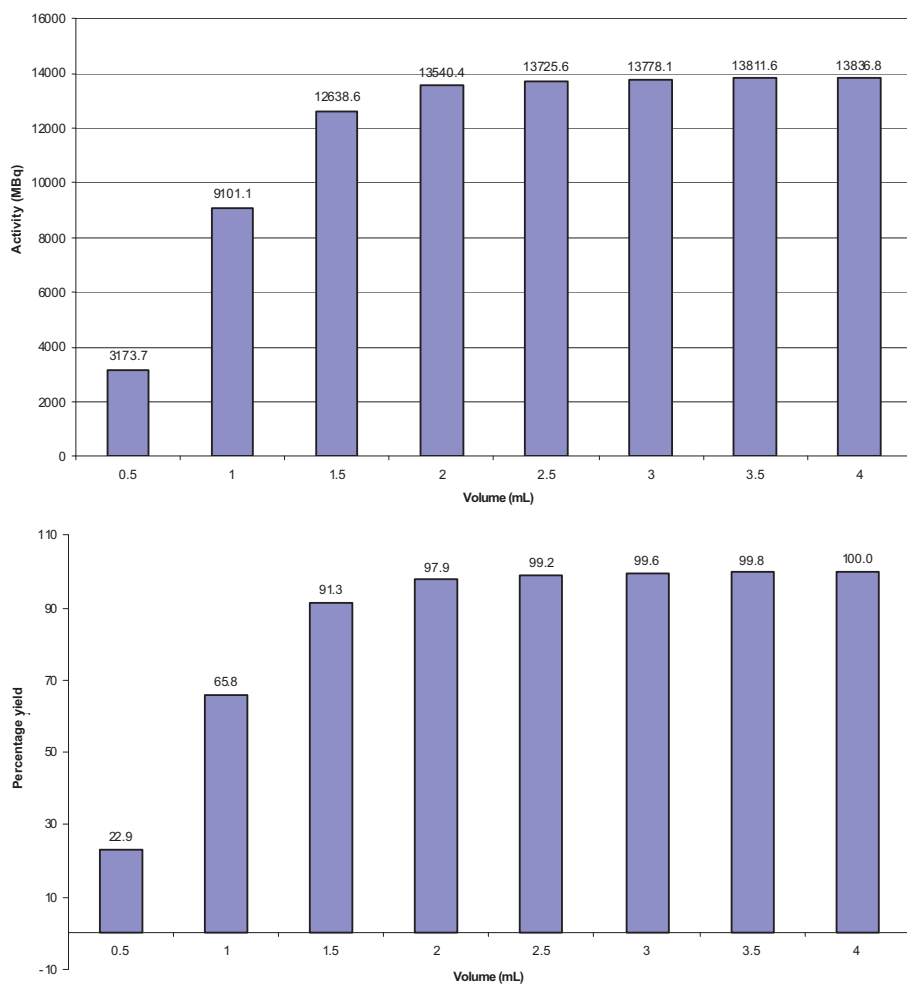
FIG. 17.3. Cumulative elution profile expressed as radioactivity (top) and percentage yield (bottom).

17.3.2. Long term stability of ^{188}W/^{188}Re generators

The stability of the generator was evaluated according to the schedule given above over a period of 4 months. The total yield of the ^{188}W/^{188}Re generator measured as the sum of the radioactivity collected in all four elution fractions is presented in Fig. 17.4.
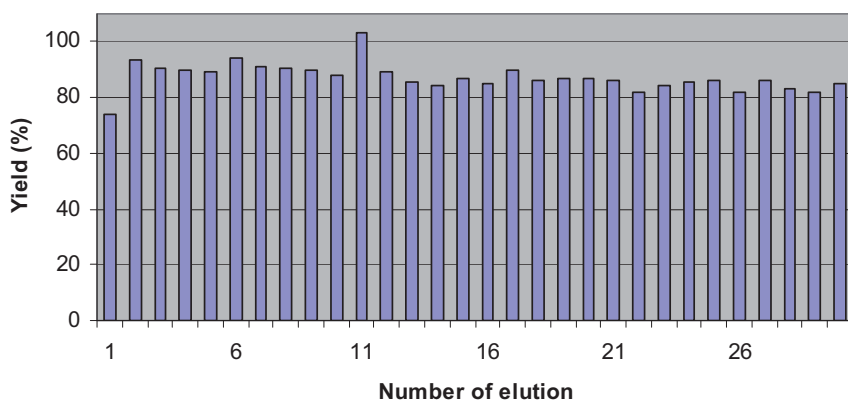
FIG. 17.4. Total yield of the $^{188}W/^{188}Re$ generator over the stability testing period.

The results of the quality control studies obtained during the generator evaluation period are summarized in Table 17.1. The first column indicates the elution number; the second column shows the time of generator evaluation in days from the first elution; the third column provides the total radioactivity of ^{188}Re obtained on the day of elution; the fourth column shows the elution yield of ^{188}Re expressed as the ratio of the measured radioactivity of ^{188}Re to the calculated radioactivity at elution date. The next columns contain data on eluate pH, radiochemical purity, chemical purity and radionuclidic purity. The sterility and bacterial endotoxin levels were determined in the eluates of the generators at 2 week intervals.

The experimentally obtained yields of ^{188}Re were compared with theoretical yields of ^{188}W and ^{188}Re, and the results are shown in Fig. 17.5.

To fully evaluate the generator's performance, four $^{188}W/^{188}Re$ generators were prepared as described previously. Detailed data on these generators are summarized in Table 17.2.

TABLE 17.1. DATA ON ^{188}W/^{188}Re GENERATOR PERFORMANCE
(Duration of observation: 18.08.2005 to 21.11.2005; radioactivity of ^{188}W loaded onto the column: ~7.48 GBq; specific activity of ^{188}W: 27.28 GBq per gram of tungsten)

Elution No.	Time of evaluation (d)	Total Re-188 radioactivity on day of elution (GBq ± 1.1%)	Yield (%)	Eluate pH	Radio-chemical purity (%)	Chemical purity (ppm)	Radio-nuclidic purity of W-188 (%)
1	4.10	5.61	82.11	4.5			
2	8.09	5.62	85.62	4.5	100		
3	12.11	5.06	80.35	5.0			Not detected
4	15.16	4.10	82.64	4.5–5.0			
5	18.13	4.77	84.14	5.0			
6	22.19	4.80	84.25	5.0			
7	26.13	4.61	81.60	5.0	100		
8	28.11	3.90	81.57	5.0			
9	33.15	4.18	78.49	5.0			
10	35.05	3.45	82.39	5.0			
11	40.04	3.94	78.12	5.0			
12	42.05	3.26	81.20	5.5	100		
13	47.06	3.62	78.44	5.5–6.0			
14	50.07	3.30	79.29	5.5–6.0			
15	54.09	3.29	79.46	5.0			
16	57.23	3.13	81.17	5.0			
17	61.08	3.13	80.85	5.0	100		
18	64.13	2.96	82.17	5.5		Al = 0.484, W<10	1.4×10^{-4}%
19	68.23	2.96	79.86	5.5			
20	70.25	2.52	80.01	5.5			
21	76.20	2.65	77.97	5.5–6.0			
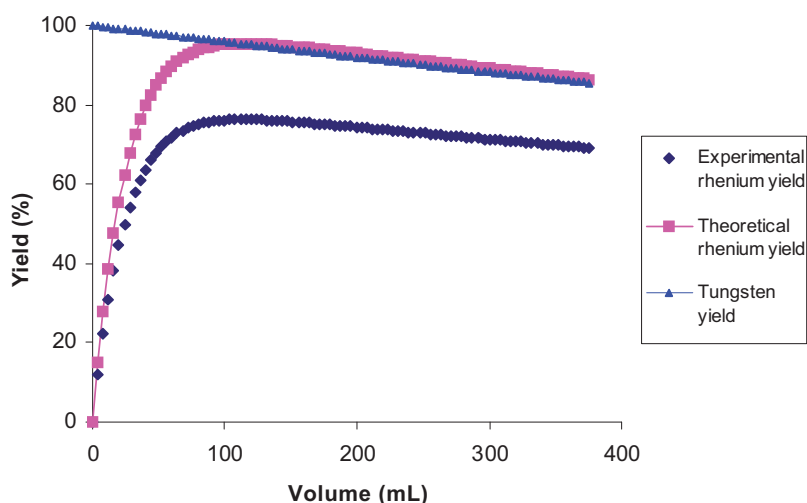
FIG. 17.5. *Experimental and theoretical yields of ^{188}Re and ^{188}W.*

TABLE 17.2. SUMMARY OF FABRICATED GENERATORS

Generator	Radioactivity of loaded W-188 (GBq)	Specific activity of loaded W-188 (GBq/g of W)	Date of fabrication	End of evaluation
GM 1	5.5	133.16	3.03.2005	07.10.2005
GM 2	11.01	97.42	10.06.2005	02.11.2005
GM 3	19.81	132.75	29.06.2005	20.07.2005
GM 4	7.48	27.28	18.08.2005	21.11.2005

Generator GM3 was observed for 3 weeks at the IAE Radioisotope Centre; after preliminary testing, it was sent for regular use to clinics in Dresden, Germany. Over a period of time ranging from 76 to 185 d, data on ^{188}Re radioactivity (per batch and cumulative), percentage yield, and radiochemical, chemical and radionuclidic purity were accumulated. About 200 elutions were carried out. Figure 17.6 shows the ^{188}Re yields of the four generators when eluted over a period of time.
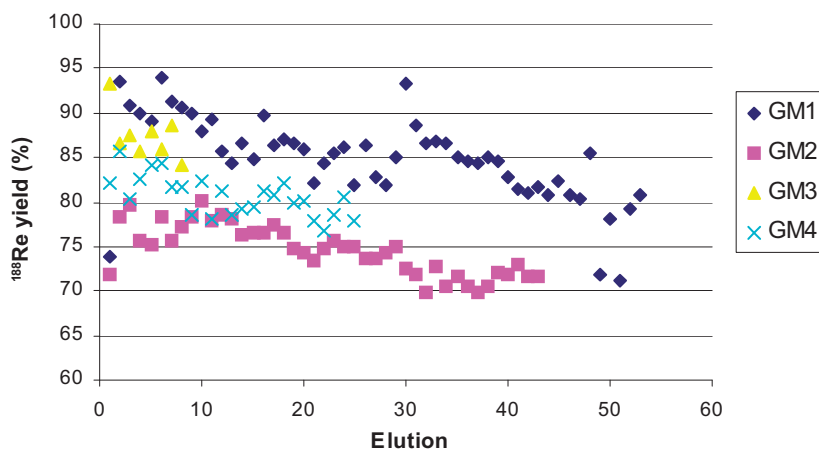
FIG. 17.6. Rhenium-188 elution yields of the four generators.

The variation of elution yield results may be due to measurement error in the determination of the ^{188}W radioactivity loaded onto the column. Therefore, for further definition of the generator specification, it was decided to use a nominal (calibrated) radioactivity of ^{188}Re eluted from the generator, and not the radioactivity of ^{188}W loaded onto the column, as the specified parameter. Because the sorption capacity of the alumina column is limited and the specific activity of available ^{188}W also varies within a rather limited range of values, it was assumed that it would not be possible to produce a generator with an expected ^{188}Re radioactivity greater than 480–500 mCi on the day of first elution.

It was noticed that the elution yield tended to decline over time. This decline may be due to reduced ^{188}Re recovery from the ^{188}W adsorbed on the column and not to the ^{188}W breakthrough, since the radionuclidic purity examinations did not show any increased levels of ^{188}W contamination in the eluates. The generators were sterile and the endotoxin levels were within the limits for use in humans.

On the basis of the series of experiments, it was confirmed that the ^{188}W/^{188}Re generator technology developed leads to ^{188}Re eluates with the following parameters:

(a) Elution yields: 70–90%;
(b) pH: 5.5–6.0;
(c) Chemical purity: Al: <10 ppm; W: <10 ppm;
(d) Radiochemical purity: >98%;
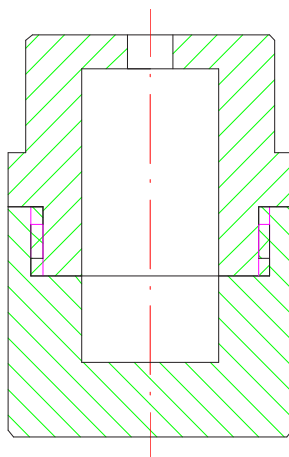
FIG. 17.7. Tungsten container for shielding the eluate vial.

(e)   Radionuclidic purity: ^{188}W: <0.5%; other gamma impurities: <0.1%;

(f)   Eluates are sterile and free of bacterial antitoxins.

The tests confirmed that the ^{188}W/^{188}Re generators can be systemically used over a period of at least 6 months. The quality of the eluates has been verified by HEDP and bombesin analog radiolabelling. The two generators have been evaluated in the Clinic for Nuclear Medicine in Dresden, Germany, with positive reports from the direct user.

17.3.3.   Shielding containers for ^{188}Re eluates

A container for the eluate vial made from tungsten was designed and then tested in working conditions in order to improve shielding of this container and to increase the safety of generator elution.

The ^{188}Re elutions were carried out using the standard lead container for shielding the eluate vial. At higher concentrations of ^{188}Re, this container did not provide sufficient protection. Therefore, a container made of tungsten was prepared in order to improve shielding during elution. A drawing of this container is given in Fig. 17.7.

17.4. CONCLUSIONS

According to the literature [17.7], ^{188}W/^{188}Re generators can be used for over 6 months, because the parent radionuclide, ^{188}W, has a long half-life

$(T_{1/2}: 69$ d); here, the generator was evaluated for that period of time. The generator presented here makes use of the generator column, shielding and elution set-up that proved useful and reliable when used for ^{99}Mo/^{99m}Tc generators. It offers a user friendly elution technique, low elution volume and high radioactive concentration of the eluate, and can be used for over 6 months. It can be used in clinics for routine applications as well as in research laboratories. The quality of the ^{188}Re solution from the generator has been tested in labelling of a ^{188}Re-HEDP phosphonate based radiopharmaceutical for palliative therapy of painful cancer metastasis to bone.

REFERENCES TO CHAPTER 17

[17.1] LIEPE, K., RUNGE, R., KOTZERKE, J., Systemic radionuclide therapy in pain palliation, Am. J. Hosp. Palliat. Med. **22** (2005) 457–464.

[17.2] LEE, S.W., et al., Incidence and predictors of late recurrence after β-radiation therapy with a ^{188}Re-MAG3-filled balloon for diffuse in-stent restenosis, Am. Heart J. **151** (2006)158–163.

[17.3] LAMBERT, B., et al., ^{188}Re-HDD/lipiodol therapy for hepatocellular carcinoma: an activity escalation study, Eur. J. Nucl. Med. Mol. Imaging **33** (2006) 344–352.

[17.4] LAMBERT, B., DE KLERK, J.M., Clinical applications of ^{188}Re-labelled radiopharmaceuticals for radionuclide therapy, Nucl. Med. Commun. **27** (2006) 223–229.

[17.5] WANG, S.J., et al., Histologic study of effects of radiation synovectomy with rhenium-188 microsphere, Nucl. Med. Biol. **28** (2001) 727–732.

[17.6] FERRO-FLORES, G., et al., Preparation, biodistribution, and dosimetry of ^{188}Re-labeled MoAb ior ceal and its f (ab')2 fragments by avidin-biotin strategy, Nucl. Med. Biol. **26** (1999) 57–62.

[17.7] KNAPP, F.F., Jr., et al., Availability or rhenium-188 from the alumina-based tungsten-188/rhenium-188 generator for preparation of rhenium-188-labeled radiopharmaceuticals for cancer treatment, Anticancer Res. **17** (1997) 1783–1795.

Chapter 18

DEVELOPMENT OF ^{188}W PRODUCTION TECHNOLOGY

R. KUZNETSOV, V. TARASOV, Y. ROMANOV, A. PAKHOMOV,
S. KLIMOV, V. LEBEDEV, A. BARANOV, V. GAVRILOV,
T. IVANOVA
Federal State Unitary Enterprise
'State Scientific Center of Russian Federation',
Research Institute of Atomic Reactors (RIAR),
Dimitrovgrad, Russian Federation

Abstract

Under the coordinated research project (CRP), the processing of high specific activity ^{188}W produced by neutron irradiation in the SM research reactor was studied theoretically and experimentally. The effects of neutron flux depression and shielding on ^{188}W specific activity were studied, and an optimized approach to ^{188}W production based on experimental data was developed. A procedure for ^{188}W specific activity estimation was developed based on gamma spectrometry measurement of ^{188}W activity and on photocolorimetric measurement of tungsten concentration in the sample solution. The procedure allowed experimental data to be obtained for use for the optimization of ^{188}W production. A radiochemical procedure for irradiated target processing providing efficient purification from both radioactive and non-radioactive impurities was developed. Under the CRP, 15 batches of ^{188}W were prepared and shipped to the participant countries to support their research on ^{188}W/^{188}Re generator development.

18.1. INTRODUCTION

The main goal of RIAR's participation in the CRP, under the research agreement, was to improve the technology of ^{188}W production and to supply CRP participants with ^{188}W for their experimental studies of ^{188}W/^{188}Re generators. The main features of ^{188}W production in the reactor were established, and optimized irradiation modes using the SM high flux reactor, as well as post-irradiation technology, were developed that considerably improved the quality of the final product. The principal results of the study are presented in this report.

18.2. FEATURES OF ^{188}W REACTOR PRODUCTION

The principal features of ^{188}W production in the nuclear reactor (Fig. 18.1) are as follows:

(a)   Relatively low isotopic abundance of ^{186}W in the natural mixture of tungsten isotopes (28.43%);
(b)   Production of ^{188}W by two sequential neutron captures, through the short lived ^{187}W ($T_{1/2}$: 23.8 h) predecessor.

These features determine that production of ^{188}W of high specific activity requires:

 (i)   Use of highly enriched (more than 90%) ^{186}W target material;
(ii)   Provision of the highest rates of neutron capture by ^{186}W and ^{187}W nuclei (i.e. irradiation should be performed at the highest available thermal neutron flux density).

18.2.1.   Nuclear constants describing accumulation of ^{188}W

Various aspects of ^{188}W reactor production are discussed in a number of papers [18.1–18.3]. Unfortunately, data referenced in these papers, both experimental and theoretical, concern specific reactors and irradiation modes. Thus, initially there were no reliable nuclear data available for ^{187}W and ^{188}W.

To develop technology for ^{188}W production, the system of nuclear constants applied for prediction of ^{188}W accumulation in the SM research
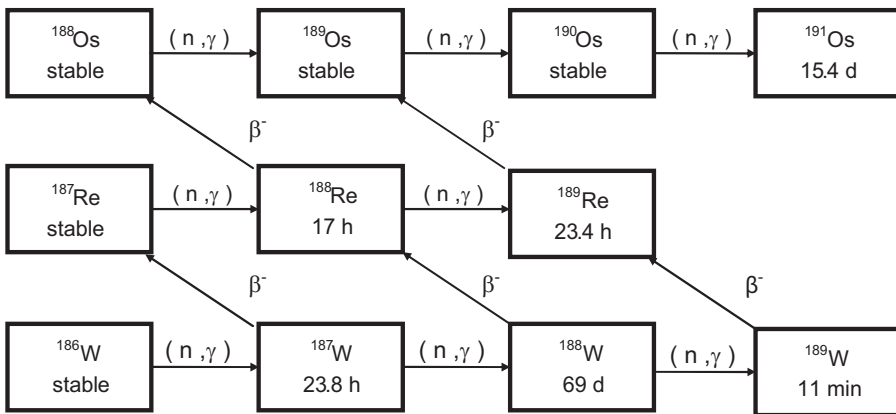

FIG. 18.1. Tungsten-188 production chain.

reactor was analysed and refined. A set of experimental targets was irradiated in various reactor positions, providing considerable variation of neutron flux density and spectra. Irradiated material was dissolved in basic solution, and activity was measured by gamma spectrometry, followed by calculation of parameters of ^{188}W accumulation. The specific activity of ^{188}W was determined using the procedure described below. Data produced were used to study the kinetics of ^{188}W accumulation and to develop a revised system of nuclear constants (Table 18.1). Based on these data, a more accurate prognostic system for ^{188}W production in the SM reactor was developed.

Analysis of experimental data describing ^{188}W production allowed us to draw a number of important conclusions:

(a) The thermal neutron flux density and duration of continuous irradiation are the most critical conditions for ^{188}W production. The concentration of ^{188}W nuclei is also dependent on the concentration of short lived ^{187}W, so after any intermediate reactor shutdown (as well as at operation power decrease), the ^{188}W specific activity decreases, increasing again only after irradiation is continued, giving a distinctive 'pit' in the 'specific activity–irradiation time' dependency (Fig. 18.2).

(b) The duration of irradiation is critical for ^{188}W production because of the kinetics of production and decay of short lived ^{187}W. In the case of the SM reactor, which uses campaigns consisting of two or three 'micro-campaigns' (8–11 d each), the duration of the last microcampaign is the most important.

(c) The ratio of the thermal cross-section and resonance integral values shows that irradiation in hard neutron spectra (i.e. in high flux of fast neutrons) does not lead to an increase of ^{188}W specific activity.

Research reactors traditionally used for radionuclide production can be classified on the basis of the neutron flux density in irradiation positions:

TABLE 18.1. NUCLEAR CONSTANTS FOR SELECTED NUCLIDES

Nuclide	Decay constant λ (s^{-1})	Thermal cross-section σ (b)	Resonance integral I_∞ (b)
W-186	—	37.9	485
W-187	8.09×10^{-6}	64.0	2 760
W-188	1.16×10^{-7}	1 000	50 000

(i)   High flux reactors with a neutron flux density greater than 1×10^{15} cm$^{-2}\cdot$s^{-1};

(ii)   Medium flux reactors providing a neutron flux density of around 5×10^{14} cm$^{-2}\cdot$s^{-1};

(iii) Low flux reactors having a neutron flux density of around 1×10^{13} cm$^{-2}\cdot$s^{-1}).

Low flux reactors are not considered to be suitable facilities for ^{188}W production, as they can only provide ^{188}W of very low specific activity. It should be noted that medium flux reactors can provide a longer duration of continuous operation (owing to the lower power rating in the active core), which is also important. Nevertheless, the highest possible specific activity of ^{188}W (produced from isotopically enriched ^{186}W) is 55.5–74 GBq/g (1.5–2 Ci/g) for medium flux reactors and 185–296 GBq/g (5–8 Ci/g) for high flux reactors. There are only two high flux reactors in the world (HFIR, Oak Ridge, USA, and SM, Dimitrovgrad, Russian Federation), whereas several medium flux reactors are in operation.

It is interesting to note that our calculations show that irradiation of natural tungsten (instead of isotopically enriched) in the high flux reactor provides a specific activity of ^{188}W comparable with that from medium flux reactor irradiation. Unfortunately, production of ^{188}W in that case is accompanied by production of ^{185}W, which generates ^{185}Re. The latter decreases the specific activity of ^{188}Re after its separation in the generator.
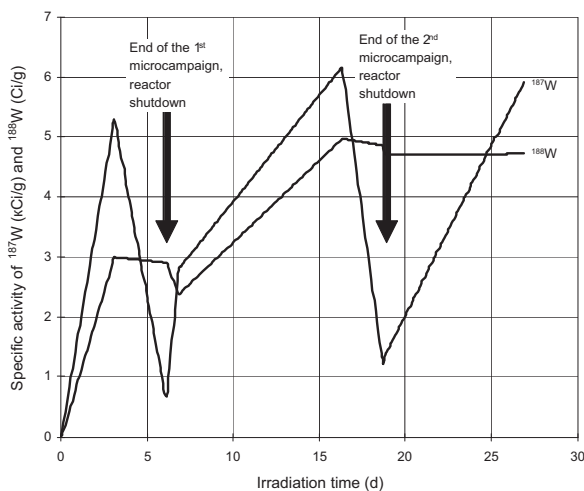

FIG. 18.2. *Specific activity of* ^{187}*W and* ^{188}*W calculated for the real operation mode of the SM reactor (irradiation in the neutron trap).*

18.2.2. Effects of [186]W self-shielding and neutron flux depression on [188]W production

A reliable calculation procedure predicting [188]W production requires consideration of the following features:

(a) The large cross-section of thermal neutron absorption by the [186]W nuclei requires that the value of neutron flux depression in the bulk of the irradiated target be determined.

(b) The resonance integral values of a number of nuclides of the considered transmutation chain require consideration of non-stationary effects of nuclei self-shielding.

The effects of resonance self-shielding by the [186]W nuclei and the scale of thermal neutron depression for tungsten oxide targets were evaluated.

18.2.2.1. Depression of thermal neutron flux

Depression is determined as a blocking (depression) coefficient; that is, the ratio of thermal neutron flux density in the bulk of the target (Φ_0) to that in the surrounding moderator (Φ_B).

The ABG method described in Ref. [18.4] was used to calculate the blocking coefficient. This method provides a means to obtain a result without solving the diffusion equation for the absorbing zone (in this case, the tungsten oxide target), thus avoiding large calculation errors. It should be noted that the blocking effect depends on two parameters only: target optical thickness and the ratio of macroscopic cross-sections of neutron scattering to absorption in the target. Macroscopic cross-sections were calculated taking into account the difference between the temperature of the neutron gas in the target and that in the moderator, and probabilities of neutron adsorption were calculated based on estimations of probability of first nuclei collision [18.5].

The calculated dependence of the thermal neutron depression on the tungsten oxide target (enriched with [186]W) diameter is presented in Fig. 18.3. For a target diameter of approximately 5 mm (the geometry of our targets), the neutron flux is around 0.85 rel. units.
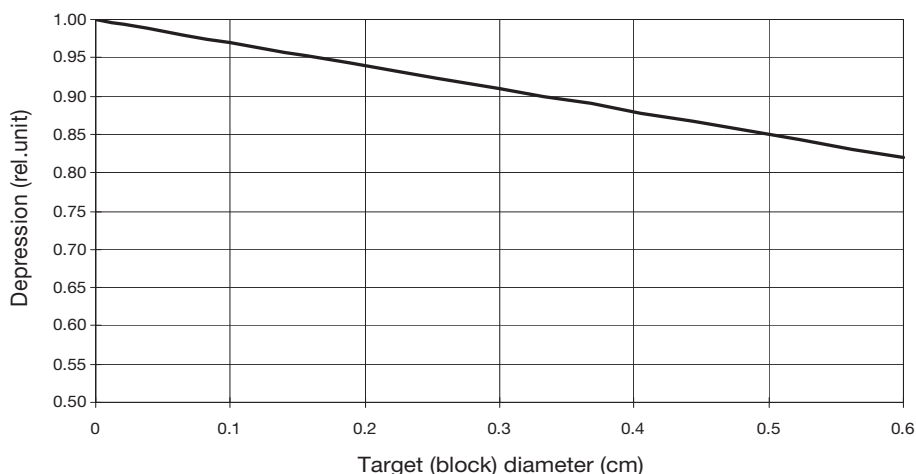
FIG. 18.3. *Thermal neutron depression versus $^{186}WO_3$ cylinder target diameter.*

18.2.2.2. Evaluation of ^{186}W resonance self-shielding

Calculation of the effective resonance integral of ^{186}W (equal to 485 b for 'infinite dilution') was based on evaluation of the self-shielding effect; that is, the decrease of the nuclear reaction rate referenced to one nucleus. The resonance self-shielding coefficient was calculated for the approximation of 'intermediate resonance' using the ChainSolver computer code [18.6], and the parameters of resonances were taken from the NKE code [18.6]. The dependence of the resonance self-shielding coefficient for the ^{186}W nuclei on optical thickness is shown in Fig. 18.4. For the actual target optical thickness (~3 $\times 10^{21}$ cm^{-2}), the self-shielding coefficient is large (~0.4). Under irradiation concentration of the ^{186}W nuclei, changes are considerable and thus the self-shielding effect is non-stationary and must be considered in prognosis of ^{188}W yield.

18.3. MEASUREMENT OF ^{188}W SPECIFIC ACTIVITY

The specific activity of ^{188}W routinely produced in high flux reactors is typically 148–222 GBq/g (4–6 Ci/g), and in the case of a 'thin' target it can reach 296–444 GBq/g (8–12 Ci/g). Unfortunately, no procedures for determinating the specific activity of ^{188}W are described in the literature, and the specific activity values referenced in various publications were determined
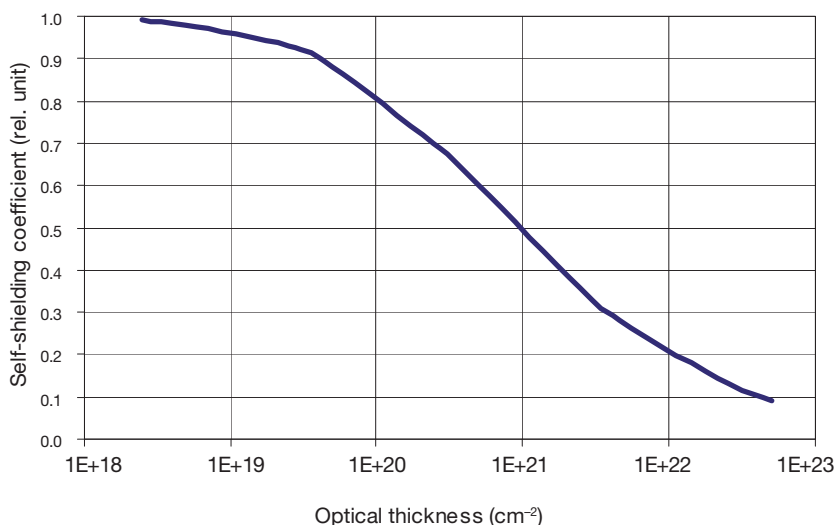
FIG. 18.4. Resonance self-shielding coefficient of ^{186}W versus optical thickness of cylinder target (5 mm diameter).

theoretically or experimentally as a ratio of the measured ^{188}W activity and the target weight, neither of which has high accuracy. The theoretical (calculation) approach requires correctly measured cross-sections of nuclide transmutation as well as actual parameters of neutron fields, and these data are not always available. Such an experimental approach does not consider burnup of target material, which cannot be neglected for long term irradiation in a high flux reactor.

A procedure was developed for measuring the specific activity of ^{188}W based on a combination of gamma spectrometry in the sample solution and determination of tungsten concentration in that solution by using photocolorimetry to determine the concentration of the tungsten-thiocyanate complex of W(V).

The procedure is based on the formation of a coloured complex compound of W(V) and thiocyanate ion. Tungsten is reduced to the five valence state using a freshly prepared solution of titanium (III) chloride. Optical density is measured at a wavelength of 398 nm. The tungsten concentration is determined by comparison of the optical density of the test solution with that of calibration solutions. An example of a calibration curve is presented in Fig. 18.5. The procedure allows determination of the tungsten concentration within a range of 0.002–0.01 mg/cm^3. It is simple and does not require rare reagents or analytical equipment. It was found that the error limits
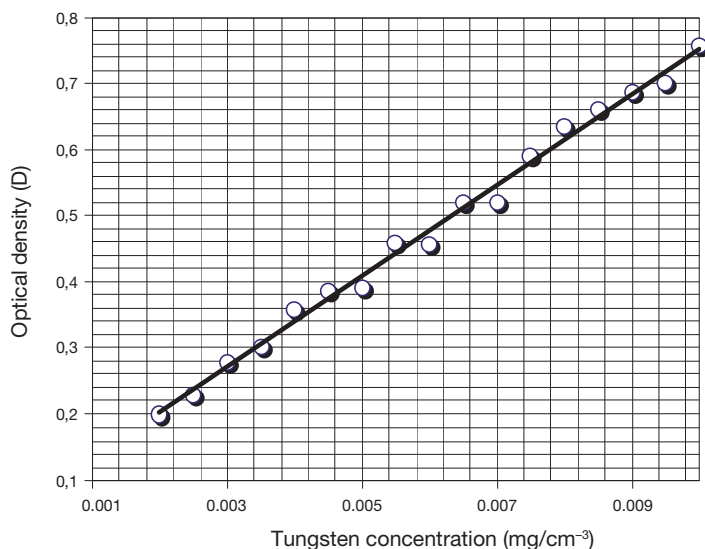
FIG. 18.5. Calibration curve used for measurement of tungsten concentration.

are below 13% considering an error of calibration curve below 7.5% and bulk activity measurement error is below 10%.

18.4. LARGE SCALE PRODUCTION OF [188]W

A typical cycle (campaign) of the SM high flux reactor consists of two microcampaigns of 10 effective days each, with a 2 d shutdown in between. Some campaigns consist of three microcampaigns, whose duration can vary by several days, depending on the radionuclide production plan or experimental programmes implemented at the reactor. It was demonstrated that the duration of the last microcampaign is the critical factor affecting [188]W specific activity.

Results of trial irradiations, presented in Table 18.2, demonstrate that the irradiation plan realized for target Nos 10.11 and 44.45 is close to optimal. This irradiation plan consists of three microcampaigns, with the last one being 9–10 effective days long. In this case, the [188]W specific activity was approximately 370 GBq/g (10 Ci/g), which is much higher than the specific activity reached by targets irradiated during two microcampaigns.

It should be noted that tungsten burnup for targets irradiated during three microcampaigns is higher than that of targets irradiated during two microcampaigns. Nevertheless, it can be stated that, owing to the considerable

TABLE 18.2. RESULTS OF TRIAL IRRADIATIONS

Target No. (irradiation schedule, effective days)	Irradiation time (effective days)	Tungsten target weight (mg)	W-188 activity at EOI (GBq (Ci))	W-188 specific activity at EOI (GBq/g (Ci/g) of W)	W weight at EOI (mg)	W burnup (%)
Target No. 88–93 (10-2-10)	17.29	2868.9	485.8 (13.13)	242 (6.5)	2007.64	30.0
Target No. 10.11 (10-2-10-2-10)	26	1277.92	307.1 (8.3)	375.6 (10.2)	817.7	36.0
Target No. 31 (10-2-10)	17.25	640.3	88.8 (2.4)	210.9 (5.7)	418.1	35.0
Target No. 44.45 (10-2-10-2-9)	24.46	1040.1	210.9 (5.7)	349.3 (9.4)	603.8	42.0

Note: EOI = end of irradiation.

increase in specific activity (approximately 1.7 times), the three campaign cycle is more effective for large scale production of [188]W.

These data also confirm the need to optimize the irradiation plan and production schedule, as the considerable increase in specific activity leads not only to increased yield of [188]W, but also to considerable burnup of the target material; that is, its less effective use.

18.5. PROCESSING OF IRRADIATED TARGETS

The processing of irradiated targets includes their conversion to a soluble state, removal of impurities (both radioactive and non-radioactive) and adjustment of the concentration of components.

Tungsten oxide enriched with [186]W isotope is commonly used as a target material. The most common approach to producing sodium tungstate is to dissolve the irradiated target in sodium hydroxide solution at moderate heating. This procedure is not difficult if WO_3 is irradiated in neutron fluxes of low or moderate intensity (10^{13}–10^{14} cm^{-2}·s^{-1}), that is, while producing low specific activity [188]W. Irradiation of tungsten in a high flux reactor dramatically changes its properties; in particular, the post-irradiation physical state is barely soluble in basic solutions [18.7, 18.8]. This phase is nearly black in colour. The quantity of this phase is correlated with the total fluence of neutrons and can reach 30–50% of the weight of the target material [18.7]; it can be dissolved in the presence of the oxidizing agent sodium hypochlorite [18.9]. This approach

is useful in the case of tungsten oxide, since the irradiated material is completely dissolved in diluted sodium hydroxide solution in the presence of approximately 5% NaOCl. This approach was used in the technology developed in this study.

In the early stages of development (1996–2000), the processing technology was limited by the dissolution of irradiated material and the adjusting of ^{188}W bulk activity, as the main idea was to collect experimental data and to study ^{188}W production in the reactor. It is appropriate to note that there were no special product quality requirements from the customers, but only requirements regarding the specific activity. In the second stage of the work, the research was focused on improving product quality by removing impurities.

Irradiation of ^{186}W in a high density neutron flux can lead to the production of a considerable quantity of ^{191}Os, depending on the irradiation conditions (Table 18.3). The yield of ^{191}Os correlates with the burnup of target ^{186}W and, less directly, with ^{188}W specific activity.

First, irradiation of ^{186}W in a neutron flux of high density produces a considerable quantity of volatile ^{191}Os; depending on the irradiation conditions, the yield is 2.59–11.1 GBq (70–300 mCi) per gram of tungsten (up to 2–3% by activity). The flow chart for ^{188}W processing and purification is shown in Fig. 18.6. Dissolution of tungsten oxide in the presence of an oxidizing agent allows nearly all the ^{191}Os to be distilled, decreasing its content in the final product to less than 0.1%. To ensure the ecological safety of the process, a special device was designed providing nearly complete osmium trapping (Fig. 18.7). This device includes scrubbers filled with a solution of thiourea in

TABLE 18.3. PARAMETERS OF IRRADIATED TARGETS DURING ROUTINE PRODUCTION OF ^{188}W

Initial target weight (mg)	Duration of irradiation (effective days)	W-188 activity at EOI (GBq (Ci))	W-188 specific activity at EOI (GBq/g (Ci/g))	W-186 burnup (%)	Yield of Os-191 at EOI (GBq (mCi) per g of target W-186)
758.8	19.66	111.0 (3.0)	196.1 (5.3)	24.4	5.9 (162)
1911.7	17.47	333.0 (9.0)	210.9 (5.7)	17.5	3.7 (99)
2970.0	19.9	514.3 (13.9)	225.7 (6.1)	22.9	2.8 (77)
3132.4	17.73	510.6 (13.8)	214.6 (5.8)	24.2	2.6 (71)
2061.9	23.56	373.7 (10.1)	233.1 (6.3)	22.2	7.3 (196)
3579.4	25.54	880.6 (23.8)	373.7 (10.1)	34.1	12.4 (334)

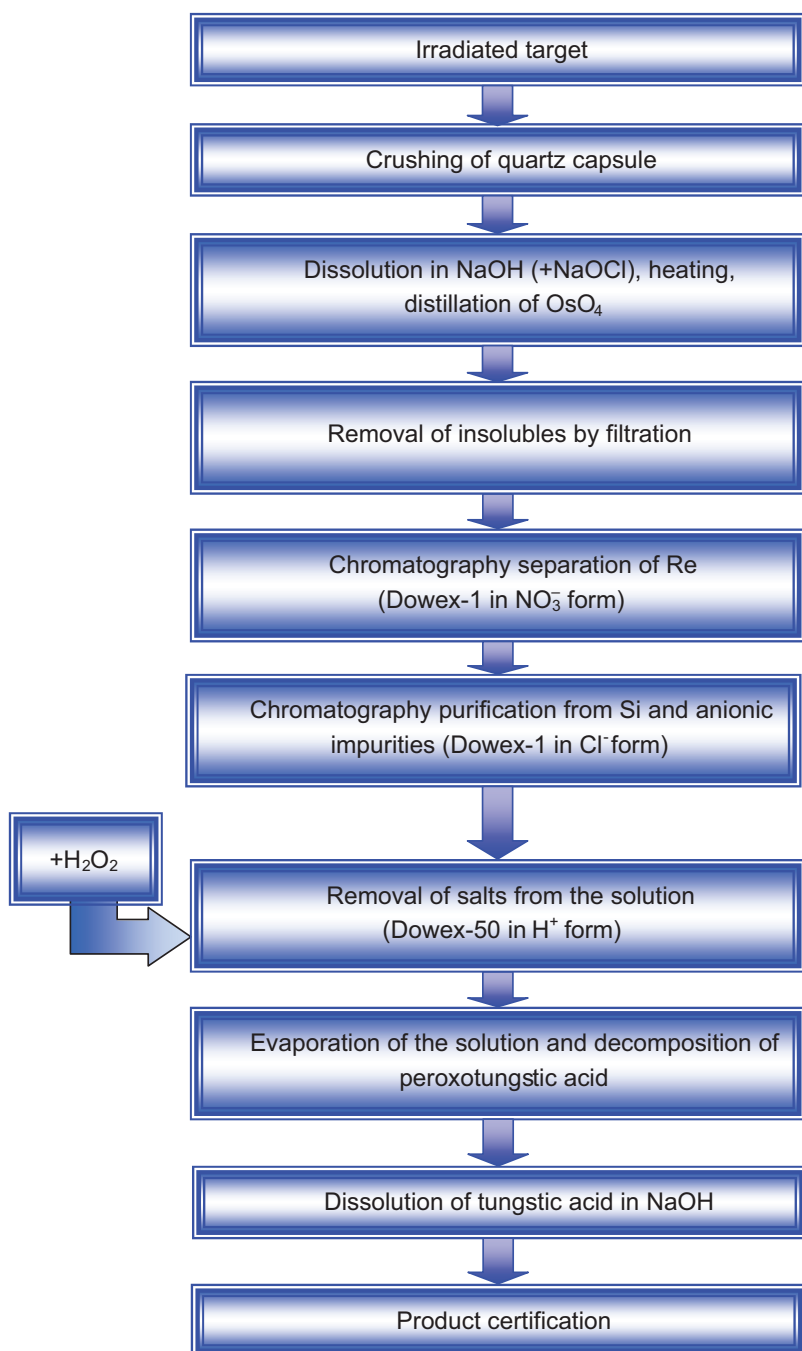**Note:** EOI = end of irradiation.

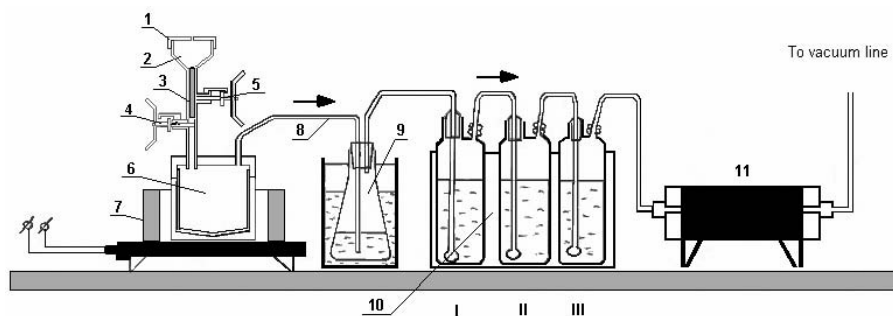*FIG. 18.6. Reprocessing procedure.*

FIG. 18.7. Apparatus used for quartz capsule crushing and tungsten oxide dissolution: 1: cap with ventilation hole; 2: funnel; 3: capsule with irradiated material; 4: fixing screw; 5: crushing screw; 6: dissolver body; 7: heater; 8: line for vapour removal; 9: condensate collector; 10: scrubbers; 11: coal trap.

concentrated hydrochloric acid and sodium hydroxide solution in ethanol. After irradiation in the SM high flux reactor during a campaign of 21 d (which is typical), up to 20% of target ^{186}W burns out to ^{187}Re. Therefore, the technology was supplemented with a procedure for purification from rhenium by anion exchange with the Dowex 1 resin in NO_3^- form.

Tungsten oxide is irradiated in quartz capsules that are destroyed mechanically within the device used for irradiated target dissolution (this provides direct access of basic solution to the tungsten oxide powder). As the target is dissolved in sodium hydroxide solution, quartz is also partially dissolved, contaminating the tungsten solution with silicates. Here, anion exchange chromatography with Dowex 1 resin was used to remove silica from the solution. This procedure is performed after purification from rhenium. In addition, some anionic impurities — products of oxidizing agent destruction (e.g. chloride, chlorate and perchlorate ions) — are also removed from the solution. The same is true for a number of other impurities of a cationic nature that commonly contaminate the product.

At the final stage of purification, the solution is desalinated; that is, excess sodium is removed by passage through the Dowex 50 cation exchanger. To avoid tungsten precipitation inside the column, hydrogen peroxide is added to the solution, forming pertungstic acid. The solution of pertungstic acid is evaporated to dryness. The residue of tungstic acid is dissolved in the required quantity (close to the stoichiometric ratio) of sodium hydroxide.

The total content of radioactive impurities in the final product is less than 0.2–0.5%. The ^{188}W specific activity depends on the irradiation time and is typically 148–166.5 GBq/g (4–4.5 Ci/g) at the delivery date for a 185–259 GBq

(5–7 Ci) batch. A facility that will have a production capacity of at least 100 Ci of [188]W per year is under development.

Under the CRP, a total of 15 batches of [188]W were produced and shipped to the participant countries during the 2005–2007 period.

REFERENCES TO CHAPTER 18

[18.1] KNAPP, F.F., et al., Report ORNL/TM-12222, Oak Ridge National Laboratory, Oak Ridge, TN (1992).

[18.2] SCHENTER, R.E., Comparison of Medical Isotope Production in Fast and Thermal Reactor Systems, WHC-SA-0956-FP, Westinghouse Hanford Company, Richland, WA (1990).

[18.3] KNAPP, F.F., et al., Processing of reactor produced [188]W for fabrication of clinical scale alumina-based [188]W/[188]Re generators, Appl. Radiat. Isot. **45** (1994) 1123–1128.

[18.4] BAT, G.A. (Ed.), Theory, Principles and Calculation Methods for Nuclear Power Reactors, Energoizdat, Moscow (1982) (in Russian).

[18.5] BEKURTZ, K., VIRTZ, K., Neutron Physics, Atomizdat, Moscow (1968) (in Russian).

[18.6] VAKHETOV, F.Z., ROMANOV, Y.G., TARASOV, V.A., A set of programs for nuclides transmutation calculation, SSC RIAR Proceedings, RIAR, Dimitrovgrad (2003) (in Russian).

[18.7] TOPOROV, YU.G., TARASOV, V.A., KUZNETSOV, R.A., GONCHAROVA, G.V., Production of tungsten-188, Proc. of the Second All-Russian Conf. on Radiochemistry, Dimitrovgrad, 27–31 October 1997, Dimitrovgrad, RIAR (1997) 265 (in Russian).

[18.8] KLEIN, J.A., et al., "Production of tungsten-188 at Oak-Ridge National Laboratory", Isotope Production and Applications in the 21st Century, Proc. of the 3rd International Conf. on Isotopes, Vancouver, Canada, 6–10 September 1999 (STEVENSON, N., Ed.), World Scientific (1999) 454–457.

[18.9] EHRHARDT, G.J., WOLFANGEL, R.G., DEUTSCH, E.A., Process for the Preparation of Rhenium-188 and Technetium-99m Generators, U.S. Patent 5,382,388, Jan.17 (1995).

Chapter 19

A ^{188}Re CONCENTRATING SYSTEM

R.A. KUZNETSOV, S.I. KLIMOV, N.V. TETUKOVA,
N.N. GUBANOVA
Federal State Unitary Enterprise
'State Scientific Center of the Russian Federation',
Research Institute of Atomic Reactors (RIAR),
Dimitrovgrad, Russian Federation

Abstract

A system for post-elution concentration of ^{188}Re was developed in which salt components (NaCl) were removed by passing the eluate through Dowex 50 cation exchange resin in Ag$^+$ form, followed by sorption of rhenium on a small column of alumina. Distribution of ^{188}Re between the alumina and the NaCl solution was studied varying the salt concentration and the pH level. It was found that only the acidic form of alumina is effective for concentration of ^{188}Re. It was also found that removal of salt components (NaCl) from the eluate is necessary for effective concentration of ^{188}Re, and that the sodium chloride concentration should be decreased to 0.001 mol/L. A dynamic capacity of Dowex 50 in Ag$^+$ form with regard to sodium chloride was found to be 0.8–1.1 mg equivalents per cm^3 of resin. Rhenium losses are negligible during desalination, and the final solution is not contaminated with silver ions. It was demonstrated that the conductivity of the eluate from the desalination column is only a few millisieverts at normal column operation. Exhausting the column capacity leads to a sharp (1000–10 000-fold) increase of the eluate conductivity. This phenomenon can be used to control the desalination process, ensuring both the effective sorption of rhenium by the concentrating column and the reliability and safety of the entire concentrating system.

19.1. INTRODUCTION

The aim of this study was to develop a ^{188}W/^{188}Re generator that can be optimized to provide routine samples of high activity concentrated ^{188}Re solutions (up to 18.5 GBq/cm^3) for the synthesis of radiopharmaceuticals (e.g. labelled monoclonal antibodies used in radioimmune therapy and applied in balloon angioplasty). Alumina based (sorption type) generators of 37 GBq activity provide ^{188}Re bulk activity at the level of 1.85–3.7 GBq/cm^3; however, post-elution concentration can be used to provide ^{188}Re concentration factors

greater than 10. It should be noted that production of these generators is possible if the specific activity of the ^{188}W is at least 148–166.5 GBq/g. At low specific activities, the weight of tungsten on the generator column is proportionally increased, necessitating an increased column size and decreasing the eluate specific volume. In such cases, a higher concentration factor is required.

The use of a concentration procedure follows from the need to ensure long term exploitation of the generator. The latter is caused by the high price of the generator (currently $7000–8000 for a 12.95–18.5 GBq generator produced by ORNL and up to $15 000 for a 37 GBq generator), which in turn affects the cost of ^{188}Re radiopharmaceuticals and the entire treatment procedure. The long half-life of the parent radioisotope (69 d) allows the generator to be used for 2–3 half-lives, that is, for at least 4–6 months. However, the bulk activity of the eluate decreases in proportion to the activity of the parent radionuclide; thus ^{188}Re concentration is needed to provide eluate having the required parameters. The concentration factor should be not less than 50 at the end of the generator operation period.

A number of ^{188}Re concentration procedures have been described in the literature (see review below). However, because previously described systems have a number of disadvantages that may limit their clinical application, research aimed at developing new concentration systems continues.

In the system for ^{99m}Tc concentration recommended for extending the working life of ^{99}Mo/^{99m}Tc generators that is described in Ref. [19.1], salts (Na$^+$ and Cl$^-$ ions) are removed by passing the eluate through a column containing Dowex 50 cation exchanger in Ag$^+$form, followed by sorption of ^{99m}Tc by an alumina column, with the technetium being washed out from the latter with the saline (0.15 mol/dm^3 NaCl). As technetium and rhenium have similar chemical properties, and as separation of ^{99m}Tc and ^{188}Re from parent radionuclides is implemented in similar sorption systems, it is reasonable to assume that this system is suitable for ^{188}Re concentration. The goal of this study was to evaluate this assumption experimentally and to produce data for prototype development.

19.2. ^{188}Re CONCENTRATING SYSTEMS

The use of evaporation as a concentrating procedure is not appropriate for ^{188}Re eluate containing 0.9% NaCl. The dry residue produced from 20 cm^3 of eluate will contain 90 mg of NaCl. To synthesize labelled compounds — for example, monoclonal antibodies — the ^{188}Re solution volume often needs to be less than 1 mL; in this case, the concentration of sodium chloride would be

more than 90 mg/cm^3, or 1.5 mol/dm^3, a level that is unacceptable for most biologically active compounds.

A number of approaches to solving the problem have been proposed by Knapp et al. [19.2–19.4] involving the use of tandem type generators consisting of an alumina based generator column with one or two columns attached for ^{188}Re concentration.

The first approach [19.2, 19.3] uses the AG 50W-X1 or Chelex-100 cation exchange resins (Bio Rad Laboratories). The ^{188}Re eluate is passed through the ion exchange column attached directly to the generator column, with the anionic ^{188}Re species in the solution passing through the column and the cationic species of alkali metals (Na$^+$) being retained by the resin substituting protons. In this way, perrhenic acid solution in HCl is produced. The rhenium elution profile for the cation exchange column is nearly identical to that for the alumina column. For example, while passing 12 cm^3 of eluate through a 3.6 g cation exchange AG 50W-X1 column, the maximum value of the activity was at 6 cm^3, more than 95% of the activity was found at 4–10 cm^3, and it was completely eluted with 12 cm^3 of solution. This profile fully corresponds to that of the generator column. A feature of the process is the changing of the pH of the solution eluent after passing through this cation column. The initial pH of the eluate (produced from the generator column) is almost 5.6; after passing through the cation exchanger, the pH decreases to less than 1. The efficiency of Na$^+$ cation removal can be controlled using this pH decrease phenomenon. The sodium chloride free solution can be concentrated by evaporation. In accordance with the terminology of analytical chemistry, the described procedure of chromatography removal of salt components provides so-called relative concentration of ^{188}Re. Absolute concentration is provided by evaporation.

The second procedure for ^{188}Re concentration is based on anion exchange with the AG-1 resin (BioRad Laboratories) [19.3, 19.4]. This resin absorbs perrhenate ion ReO$_4^-$ with high distribution ratios, particularly from nitrate containing solutions. However, owing to the resin's high affinity to chloride ions, direct absorption of rhenium from an eluate with a high content of NaCl cannot be achieved. To remove bulk quantities of chloride, it was proposed to evaporate the generator produced eluate to dryness, followed by heating the residue with concentrated nitric acid and removing the chloride ions with volatile hydrochloric acid. The residue produced after this treatment is diluted in 0.16 mol/dm^3 nitric acid and is passed through the column filled with the AG-1-X8 resin prewashed with diluted nitric acid. Subsequent washing of the column with 1.6 mol/dm^3 nitric acid removes sodium ions and other metallic impurities. Rhenium is desorbed with 6 mol/dm^3 nitric acid.

The third procedure for [188]Re concentration also provides for the use of a tandem type generator with an anion exchange column, but 0.155 mol/dm^3 ammonium nitrate solution is used as the primary eluent for isolation of [188]Re from the alumina column [19.2, 19.3, 19.5]. The primary eluate is passed through the anion exchange column attached to the generator column to absorb [188]Re. Rhenium is desorbed with 6 mol/dm^3 nitric acid. Use of nitrate containing solutions is the main disadvantage of the second and third approaches; as the nitrate solutions are incompatible with biologically active substances, they cannot be directly used for synthesis of radiopharmaceuticals. Nitrate content in pharmaceuticals is also limited.

An advanced modification of the tandem generator [19.6, 19.7] that is now widely used is also based on rhenium concentration using a highly basic anion exchanger; however, chloride ions are removed using a quite different procedure initially proposed for service life prolongation of ^{99m}Tc generators [19.1, 19.8]. For this purpose, the primary eluate is passed through the cation exchange column with silver ions (Ag Plus, Analtec, Inc.). This column efficiently removes chloride ions, leaving perrhenate ions in the eluate; the secondary eluate is then passed through the anion exchange column (Millipore QMA Sep-Pak or Waters Sep-Pak AccellW Light QMA), which provides isolation of [188]Re from the solution. Washing the anion column with normal saline provides the sodium perrhenate solution with a bulk activity greater than 18.5 GBq/cm^3.

The main advantage of this system is operation of all three columns (the generator itself, the chloride removal column and the concentrating column) in the 'on-line' mode. All flows are switched with three way valves. The use of solenoid valves and the absence of any evaporation make it possible to automate the entire process.

Another procedure for production of [188]Re or ^{99m}Tc solution with a high bulk activity was patented in 1998 [19.9]. It also uses removal of a salt component with a cation exchange resin followed by selective sorption of perrhenate or pertechnetate ions with the anion exchange resin. Unlike the procedures described above, these processes are implemented in solutions of weak acids. It is required that the pK_a ionization constant of the weak acid be above that of perrhenic acid (pK_a = –1.25) or pertechnetic acid (pK_a = 0.3) and below that of the acid produced by the parent radionuclide — tungsten or molybdenum acid. The primary eluate is produced by washing the alumina based generator column with a weak acid solution of 0.1–0.5 mol/dm^3. From the viewpoint of biological compatibility, use of ammonium acetate or ammonium citrate is preferable, but it is also possible to use succinate, fumarate, maleate, tartrate and phthalate of lithium, potassium, sodium and calcium.

The primary eluate is passed through the column with a strongly acidic cation exchanger where the cation (e.g. ammonia) is replaced by protons of the resin, and thus the solution leaving the column contains a weak acid (e.g. acetic and perrhenic or pertechnic acids). Owing to its low degree of dissociation, the weak acid cannot compete with perrhenate or pertechnetate ions in the subsequent passage of the solution through the third column with a strongly basic anion exchanger that provides for efficient concentration of ReO_4^- or TcO_4^- ions. Washing of the third column with NaCl [19.9] solution or just water [19.10] provides for rapid desorption of rhenium or technetium and high concentration factors. The final eluate contains small quantities of the acid anion used for production of the primary eluate. It was estimated in Ref. [19.9] that the content of this impurity is not greater than 0.1% for the acetate system, for example. The presence of the acetate ion in eluate is not a problem, as sodium acetate is often used as a component of solutions used in synthesis of labelled compounds and radiopharmaceuticals.

A disadvantage of this concentration system is the lower yield of [188]Re and ^{99m}Tc when sodium acetate rather than 0.15M saline is used as an eluent. For example, for the 37 GBq generator, the average yield of [188]Re is 70–80% for the 0.9% solution of NaCl and $62 \pm 14\%$ for the 0.3 mol/dm^3 solution of sodium acetate at pH5.5 [19.10]. Thus, a more expensive generator with higher activity of the parent radionuclide may be required to produce equal activities of the eluate.

As previously mentioned, the ^{99m}Tc concentrating system was described for the service life prolongation of [99]Mo/^{99m}Tc generators [19.1]. In this system, technetium is concentrated by sorption on an alumina column after removal of sodium chloride from the primary eluate solution. In this process, the eluate is passed through the cation exchange column with a Dowex 50 type resin containing silver, as described in Refs [19.8, 19.9]. The experimentally measured concentration factors were 10–20.

Since the chemical properties of technetium and rhenium are similar, separation of ^{99m}Tc and [188]Re from the parent radionuclides is performed in similar sorption systems. Thus it is quite logical to assume that the technetium concentration system can be applied for [188]Re concentration. Additional experiments were required in order to evaluate this assumption. Since the conditions for ^{99m}Tc concentration were not described in detail, the possibility of increasing the concentration factor up to 40–50 was not obvious for the case at hand. The parameters of the eluate resulting from concentration also were not described.

Thus the behaviour of [188]Re and eluate components produced with the alumina based generator using the concentration system proposed for ^{99m}Tc was studied experimentally. In particular, the effects of sodium chloride

concentration and solution pH on rhenium sorption were studied using various modifications of the alumina (acid, neutral and base). The desalination efficiency (removal of NaCl) and the contamination level of the final eluate with silver ions were estimated.

19.3. EXPERIMENTAL PROCEDURE

The [188]Re behaviour was studied using the radioactive tracer procedure. The [188]Re solution was produced by eluting a laboratory scale generator loaded in accordance with the recommendations given in Refs [19.3, 19.4]. The NaCl water solution (0.15 mol/dm^3, pH3.5) was used as an eluent. Silver behaviour was studied using [110m]Ag as a tracer, which was produced by irradiation of natural silver in the SM high flux reactor. Activity was measured using an end window counter (SI-3B type) and a BDBS3 scintillation detector with a well type NaI(Tl) scintillator. All reagents were of analytical or higher grade. The alumina intended 'for chromatography' was one of three types — A (acidic), N (neutral) or B (basic) — and the AG-50 cation exchange resin was obtained from Eichrom Inc. (USA). Columns with the alumina and cation exchanger were filled using a suspension procedure. Flow rates of solutions were controlled using an ISMATEC peristaltic pump.

19.4. RESULTS AND DISCUSSION

The prototype system used for ^{99m}Tc concentration is based on the nuclide's sorption by alumina (in acidic or neutral form), followed by its elution with a small volume of physiological saline. It is well known that ^{99m}Tc is efficiently adsorbed by alumina from slightly acidic solutions [19.1, 19.11]. However, its distribution ratio decreases dramatically in the presence of salts (e.g. NaCl); hence salts must be removed from the solution prior to concentration. The initial eluate passage through the exchanger containing silver cations is used for this purpose. The chloride ions produce insoluble silver chloride on the column and sodium is absorbed, replacing the silver in the resin. The eluate solution produced is pertechnic acid, which is slightly acidic, containing almost no salts, and provides for optimal conditions for technetium sorption by alumina.

Rhenium is a chemical analog of technetium, so its behaviour should be similar to that of technetium. Unfortunately, there is no detailed information about rhenium sorption in the available literature. It is known that the maximum sorption of rhenium from water solutions occurs at pH4–6, but there

is practically no sorption in the presence of sodium chloride [19.11, 19.12]. When the sodium chloride concentration is 0.15 mol/dm^3 and at pH3, the rhenium distribution ratio determined under static conditions is 0.08. Under dynamic conditions, at pH3 and with a sodium chloride concentration of greater than 0.15 mol/dm^3, the distribution ratio is an order of magnitude higher (0.8). For dilute solutions of sodium chloride (concentrations of less than 0.015 mol/dm^3), the rhenium distribution ratio increases to 15–20 at pH4–8. No more detailed information can be found in Ref. [19.11].

References [19.1, 19.13] describe the behaviour of ^{99m}Tc and [188]Re with the use of acidic alumina, and the possibility of using neutral alumina is mentioned in Ref. [19.1]. No data on the effect of alumina on rhenium sorption were found in the literature. Moreover, the above publications did not consider the influence of a number of parameters (e.g. elution flow rates) on the operation of the entire concentration system, or of the parameters of the solution after its passage through the desalination column, in particular its pH and sodium chloride concentration, on the efficiency of the concentration column. The level of contamination by silver ions after the ^{99m}Tc concentration was not determined. For these reasons, the following were examined in this study:

(a) Factors influencing the rhenium sorption on alumina under static and dynamic conditions (chemical form of the sorbent, eluate pH, solution flow rate and concentration of sodium chloride);

(b) Factors influencing the desalination column capacity provided with the cation exchanger containing silver (conditions of sorbent preparation and solution flow rate).

19.4.1. Static sorption of [188]Re with alumina

The effect of sodium chloride concentration and solution pH on [188]Re sorption was studied for alumina in acidic, neutral and basic forms. The results, shown in Figs 19.1–19.3, demonstrate that only the acidic form adsorbs [188]Re effectively from the solutions at pH3–8. Rhenium distribution ratios (D_{Re}) are close to 100 when sodium chloride is absent, and are lower for neutral alumina than for acidic alumina. When there is no sodium chloride in the solution, the pH value increases from 2 to 4, dramatically decreasing the distribution ratio from 25 to several units, and this ratio remains low when the solution pH is increased. The rhenium distribution ratio for basic alumina is below 1 for the whole range, and in only one case it is equal to 10, at pH2, for the salt free solution. In all cases, the rhenium distribution ratio strongly depends on the salt concentration; D_{Re} decreases twice for the most effective acidic alumina when

the sodium chloride concentration is 0.001 mol/dm^3; it is not higher than 10 at [NaCl] = 0.01 mol/dm^3. Thus ^{188}Re can be efficiently isolated from the eluate by sorption on the acidic alumina from a salt free acidic solution. The desalination factor should not be less than 1.5×10^4. Rhenium can be desorbed from alumina with a 0.15 mol/dm^3 solution of NaCl (saline).
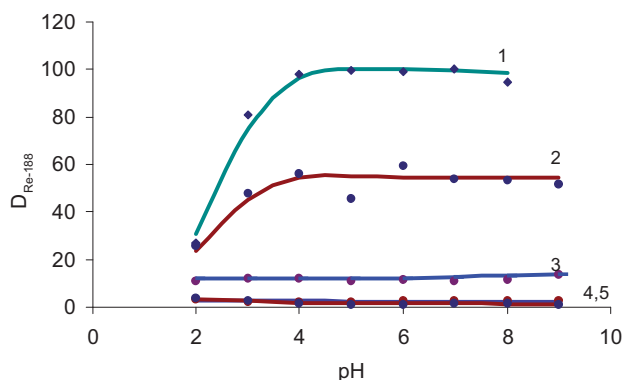
FIG. 19.1.   Sorption of ^{188}Re with acidic alumina (ICN Alumina A, Akt. 1). Curve 1: [NaCl] = 0 mol/L; 2: [NaCl] = 0.001 mol/L; 3: [NaCl] = 0.01 mol/L; 4: [NaCl] = 0.05 mol/L; 5: [NaCl] = 0.1 mol/L.

FIG. 19.2.   Sorption of ^{188}Re with neutral alumina (ICN Alumina N, Akt. 1). Curve 1: [NaCl] = 0 mol/L; 2: [NaCl] = 0.01 mol/L; 3: [NaCl] = 0.05 mol/L; 4: [NaCl] = 0.1 mol/L; 5: [NaCl] = 0.15 mol/L.
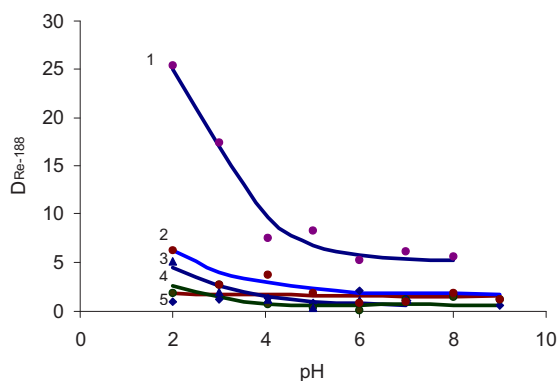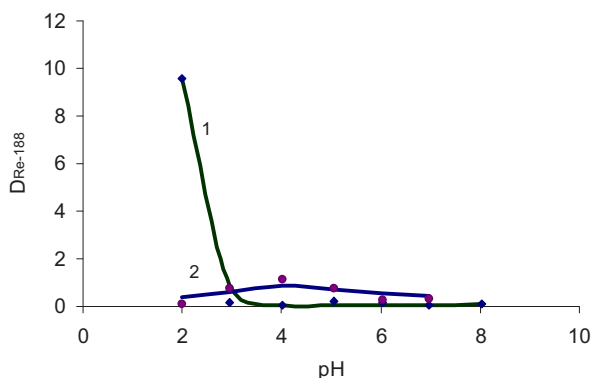
FIG. 19.3. Sorption of ^{188}Re with basic alumina (ICN Alumina B, Akt. 1).Curve 1: [NaCl] = 0 mol/L; 2: [NaCl] = 0.1 mol/L.

19.4.2. Dynamic sorption of ^{188}Re on acid alumina

The ^{188}Re sorption was studied using polypropylene chromatography columns (5 mm in diameter). The column height was 10–11 mm for 0.25 g of alumina. Experiments on sorbent breakthrough capacity estimation demonstrated that ^{188}Re was not detected in the eluate (at pH3.5) after passing 45 and 55 mL of the 'salt free' solution at flow rates of 4.85 and 1.1 mL/min, respectively (Fig. 19.4). Further washing of the column with sodium chloride solution ([NaCl] = 0.15 mol/L, pH3.5) results in complete ^{188}Re elution with 0.6–0.7 mL of eluate (Fig. 19.5). The data presented in Fig. 19.4 show the concentration factor determined as a ratio of volumes of the initial solutions. Under these conditions, the concentration factor of the eluate could be close to 100 at a flow rate of 1.1 mL/min. The eluent flow rate increase up to 4.85 mL/min causes earlier breakthrough of ^{188}Re and reduces the concentration factor to 65–75. Nevertheless, this value is sufficient for practice. It is obvious that the concentration factor can be increased by further decreasing the sodium chloride solution volume that is used for ^{188}Re desorption. However, these experimental results are in good agreement with the results of static sorption experiments and confirm the need for complete removal of sodium chloride before the ^{188}Re concentration procedure. The ^{188}Re elution curve for the acidic alumina column (m = 0.25 g) using 0.15 mol/L solution of NaCl at pH3.5 is shown in Fig. 19.5.
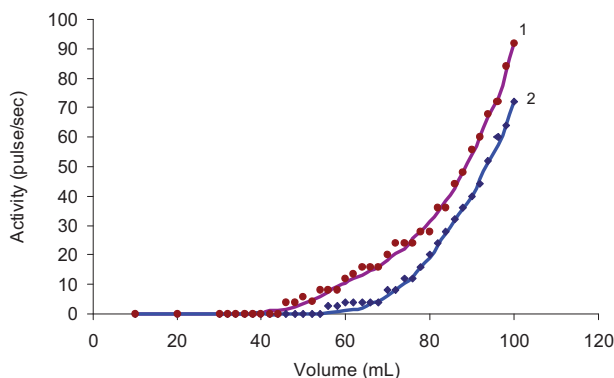
FIG. 19.4. *Frontal elution curve of* ^{188}*Re at various flow rates of eluting solution (for 0.25 g alumina column). Curve 1: flow rate of 4.85 mL/min; 2: flow rate of 1.1 mL/min.*
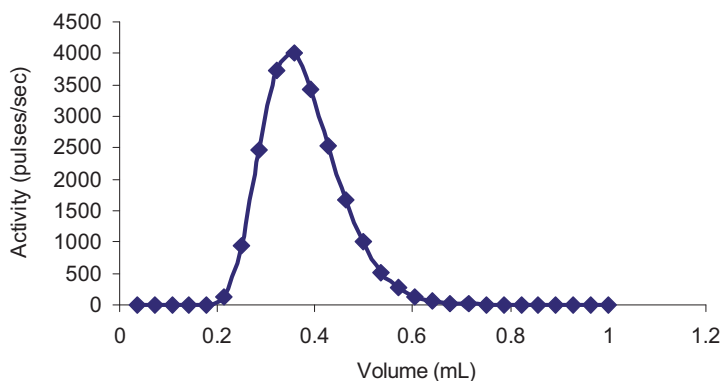
FIG. 19.5. *Rhenium-188 elution curve for acidic alumina column (m = 0.25 g); eluent: 0.15 mol/L solution of NaCl at pH3.5.*

19.4.3. Sorbent preparation for sodium chloride removal

The Eichrom AG-50 cation exchange resin sorbent was prepared in the following way. The resin was soaked in water, after which it was kept in contact with the 0.2 mol/L solution of silver nitrate (1 volume of resin to 10 volumes of solution) for 1 h with continuous stirring with a magnetic stirrer. It was then soaked in the same solution (without stirring) for 1–30 h. The resin was thoroughly washed with water until complete removal of silver ions was achieved (confirmed by chloride testing). The treated resin was transferred to

the chromatography column used for desalination of the eluate. The degree of resin saturation with silver ions depends on the resin contact (soaking) with silver nitrate solution. It was found that the resin exchange capacity relative to the H^+ ions is 1.82 mg eq/mL. The same content of silver (1.8 mg eq/mL) in the resin can be achieved after 8–10 h of soaking. Similar values of silver and proton content (exchange capacity) confirm that protons are nearly replaced by silver ions. The relationship between the resin saturation (dynamic capacity) and the soaking time was estimated by passing NaCl solution through the column at a flow rate of 0.3–0.35 mL/min until chloride ions appeared in the eluate (see Fig. 19.6).

19.4.4.   Estimation of desalination column capacity relative to sodium chloride

The sorbent capacity relative to the sodium chloride was estimated by passing sodium chloride solution (0.15 mol/L, pH3.5) through the column with the help of periodic sampling of the eluate. The pH value was measured for each aliquot. The presence of chloride ions was checked for, using the silver nitrate test. It was found that breakthrough of chloride ions for the 9.5 mm diameter column and V_{sorb} = 1.5 mL at a flow rate of 0.75–5.26 mL/min occurs after passing 8–11 mL of the solution, which corresponds to 0.8–1.1 mg eq/mL capacity.

These data allow estimation of the minimal volume of the desalination column attached to the generator. A column with 6–8 g of alumina is generally used for a 1 Ci generator. In this case, the ^{188}Re eluate volume is 25–30 mL
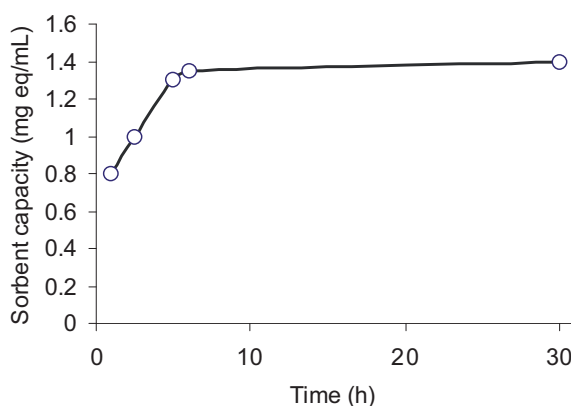

FIG. 19.6. *Relationship between the sorbent capacity relative to sodium chloride and the duration of cationite soaking in silver nitrate solution (measured at a solution flow rate of 0.3–0.35 mL/min).*

[19.10]. So the desalination column volume should not be less than 3 mL at an eluting solution flow rate of 0.75 mL/min and 4 mL at a flow rate of 5 mL/min. To avoid breakthrough of the salt components, an excessive quantity — 7–8 mL — of the sorbent should be used.

The desalination process is described by the following exchange reaction:

$$2R - Ag + Na^+ + 2Cl^- + H^+ \longrightarrow R - Na + R - H + 2AgCl \downarrow$$

where R is a matrix of the ion exchange resin.

As the sorbent capacity is exhausted, the following reaction becomes the dominating one:

$$R - H + Na^+ \longrightarrow R - Na + H^+$$

which results in acidification of the eluate.

The change in the acidity of the solution after passing through the desalination column is shown in Fig. 19.7. Similar to the sorbent capacity, the pH change of the solution flowing from the column depends on the solution flow rate and is correlated with the appearance of the chloride ion in the eluate. This fact confirms the nature of the ion exchange process described above. The acidity (pH) of the eluate produced with the desalination column is within the range of 4 to 5.5 while the sorbent capacity is not exhausted. This provides for efficient sorption of rhenium on the alumina. When the sorbent capacity is exhausted, the solution is acidified and chloride ions appear in it. Both factors decrease the D_{Re} and can lead to [188]Re breakthrough at the stage of concentration using alumina. To ensure reliability of the entire concentration system operation (desalination and concentration columns), 'excessive' capacity of the desalination column seems to be logical, but some other parameters should be controlled as well. One option would be to control the solution acidity (pH); however, on-line control of pH is, unfortunately, rather complicated and requires expensive equipment.

As can be seen from the equations describing the ion exchange processes in the desalination column, the effluent is a water solution with a low ion content. The exhausted capacity of the sorbent increases ion concentration in the eluent; its conductivity increases too. This assumption was confirmed experimentally (Fig. 19.8). The conductivity of the eluate that did not contain chlorine ions was 4–5 mS. The appearance of chloride ions (confirmed by silver chloride testing) led to a 3–4 orders of magnitude increase of electric conductivity. These data allow development of a simple procedure of efficiency control of the desalination column and of the entire concentration system using a very simple electric conductivity sensor (two electrodes attached at the outlet of the
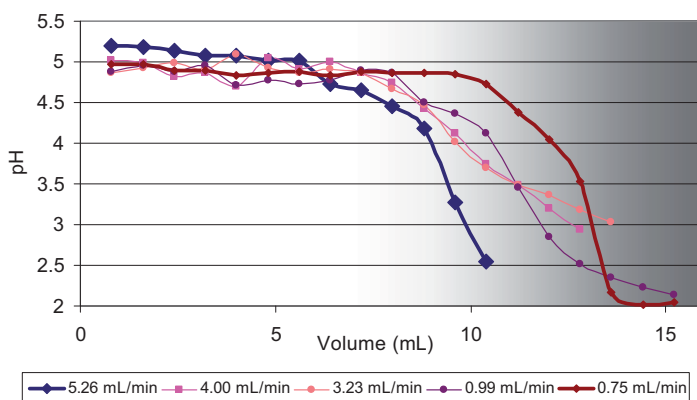
FIG. 19.7. Change of eluate pH at the outlet of the desalination column at various flow rate values. Shadowed area corresponds to a positive silver chloride test.
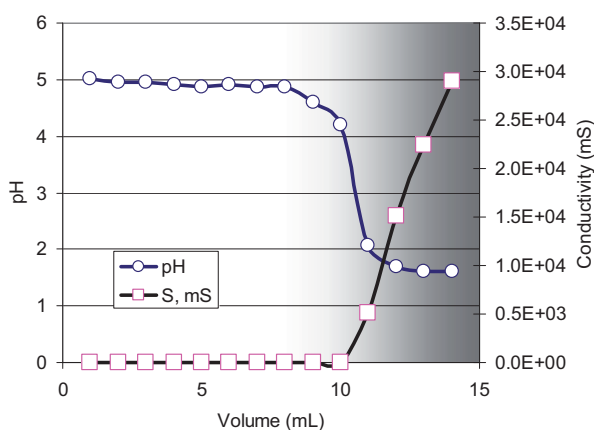
FIG. 19.8. Change of the desalination column eluate pH and conductivity. Shadowed area corresponds to a positive silver chloride test.

desalination column). Low electric conductivity of the eluate indicates normal functioning of all columns. Otherwise, breakthrough of [188]Re is possible while the solution goes through the concentrating column with alumina.

The effect on sorbent capacity of long term storage was also studied. A batch of sorbent was prepared, and its capacity was estimated periodically. The results of measurements are given in Table 19.1. These data show that the AG-50 cation exchange resin saturated with silver can be stored for a long time (at least 4 months) without a change in its capacity.

TABLE 19.1. CAPACITY OF SORBENT RELATIVE TO Cl⁻ ION
VERSUS STORAGE TIME

Storage time (d)	1	2	45	115
Sorbent capacity (mg eq/mL)	1.2	1.2	1.2	1.2

19.4.5. Behaviour of silver

It is obvious that the primary eluate passing through the exchanger containing silver cations can cause the solution to become contaminated with silver ions. This is why the potential level of contamination was estimated using the radioactive tracer ^{110m}Ag. For this purpose, a batch of sorbent was prepared by treating the resin with silver nitrate containing radioactive silver. The ^{110m}Ag activity was measured after passing through the 50 mL column of 0.15 mol/L NaCl solution. It was found that the silver concentration in the eluate was less than 1 mg/mL. It was also found that silver has a very low affinity to alumina under these experimental conditions (water solution, pH5) using the radioactive tracer. On the basis of the ratio of solutions passed through the concentration column with alumina (1.5–2 mL), its free volume (<0.1 mL) and the primary eluate volume (>30 mL), we can affirm that the concentration column decreases the silver content by two orders of magnitude or more. In general, the silver content in rhenium concentrate should not be greater than 0.01 mg/mL.

19.4.6. System testing

The system was tested using a laboratory scale generator of 3 mCi activity. Rhenium-188 was eluted from the generator with 50 mL of 0.15 mol/L solution of NaCl at pH3.5. The solution obtained was passed through the column system consisting of a desalination column with 8 g of silver saturated cation exchange resin and a concentration column with 0.25 g of acid alumina. When the primary eluate was passed through, the columns were washed with 2 mL of saline (pH3.5) and detached, and the concentration column was then washed with 1 mL of saline. The solution flow rate was 5 mL/min. Rhenium-188 activity measurements in the concentrate showed that the yield of ^{188}Re is greater than 95% within the experimental error. The bulk activity of ^{188}Re in the primary eluate was 0.06 mCi/mL; in the concentrate it was 3 mCi/mL. Thus the concentration factor achieved was 60. This factor can be further increased by optimizing the columns and piping system. The increase of the concentration factor will be proportional to the decrease of the 'dead' volume of piping and columns.

19.5. SUMMARY AND CONCLUSIONS

Experimental investigation proved the applicability of the [99mTc] concentration system for [188Re] concentration, with concentration factors of not less than 50. The sorption of [188Re] on alumina from NaCl solutions with various concentrations and pH levels was studied. It was demonstrated that only acid alumina can be used for efficient concentration of [188Re]. To provide efficient sorption of [188Re], salts (NaCl) must be removed from the solution prior to concentration, and their concentration should be lower than 0.001 mol/L. The capacity of the AG-50 cation exchange resin in silver form was estimated relative to sodium chloride. It was in the range of 0.8–1.1 mg eq/mL under dynamic conditions. The desalination procedure does not cause any loss of [188Re]. Contamination with silver did not occur, as was experimentally verified. A method of desalination efficiency control based on measuring pH or conductivity of the eluate was proposed. It was proved that the sorbent used on the desalination column can be stored for at least 4 months without a change in its properties.

REFERENCES TO CHAPTER 19

[19.1] RUDDOCK, C.F., Purification of [99mTc] pertechnetate solutions, U.S. Patent 4,123,497 (1978).

[19.2] KNAPP, F.F., LISIC, E.C., MIRZADEH, S., CALLAHAN, A.P., [188W]/carrier-free [188Re] perrhenic acid generator system, U.S. Patent 5,186,913, Feb. 16 (1993).

[19.3] KNAPP, F.F., LISIC, E.C., MIRZADEH, S., CALLAHAN, A.P., Tungsten-188/carrier-free [188Re] perrhenic acid generator system, U.S. Patent 5,275,802, Jan. 4 (1994).

[19.4] LISIC, E.C., CALLAHAN, A.P., MIRZADEH, S., KNAPP, F.F., The 'tandem' [188W]/[188Re] perrhenate/perrhenic acid generator system, Radioact. Radiochem. **3** (1992) 42–46.

[19.5] KAMIOKI, H., et al., [188W]/[188Re] generator for biomedical applications, Radiochim. Acta **65** (1994) 39–64.

[19.6] KNAPP, F.F., et al., Nuclear medicine program progress report for quarter ending December 31, 1996, ORNL/TM-13353, ORNL (1996).

[19.7] SINGH, J., et al., Studies on the preparation and isomeric composition of [186Re]- and [188Re]-pentavalent rhenium dimercaptosuccinic acid complex, Nucl. Med. Commun. **14 (**1993) 197–203.

[19.8] BLOWER, P.J., Extending the life of a [99mTc] generator: a simple and convenient method for concentrating generator eluate for clinical use, Nucl. Med. Commun. **14** (1993) 995–997.

[19.9] KNAPP, F.F., BEETS, A.L., MIRAZADEH, S., GUHLKE. S., Concentration of perrhenate and pertechnetate solutions, U.S. Patent 5,729,821, March 17 (1998).

[19.10] KNAPP, F.F., "Global status of production and quality control of reactor-produced medical radioisotopes", IAEA Consultants' Meeting Report on Updating the Manual on Radioisotope Production and Quality Control, Vienna, Austria, 10–13 November 1997, IAEA, Vienna (1997) 19–28.

[19.11] BRODSKAYA, G.A., GAPUROVA, O.U., Development and study of ^{188}W-^{188}Re generator of high activity, Radiochemistry **3** (1993) 92–97 (in Russian).

[19.12] BRODSKAYA, G.A., GAPUROVA, O.U., GUREYEV, E.S., Chromatography separation of tungsten and rhenium using alumina, Reports of Uzbek Academy of Sciences **10** (1988) 23–24 (in Russian).

[19.13] STEIGMAN, J., Chemistry of the alumina column, Appl. Radiat. Isot. **33** (1982) 829–834.

Chapter 20

PREPARATION OF INORGANIC POLYMER SORBENTS AND THEIR APPLICATION IN RADIONUCLIDE GENERATOR TECHNOLOGY

LE VAN SO*, C.D. NGUYEN**, V.C. BUI**, C.H. VO**

 * Radiopharmaceutical Research Institute, ANSTO,
   Australia

** Nuclear Research Institute,
   Dalat, Vietnam

Abstract

Adsorbents based on poly zirconium compound (PZC) and poly titanium compound (PTC) were synthesized for the preparation of [188]W/[188]Re generators. The chemical composition, molecular structure and physicochemical characteristics of these adsorbents were investigated. The adsorption properties of PZC and PTC sorbents in different tungstate solutions and the elution performance were investigated. Tungsten adsorption capacities of about 520 mg of tungsten per gram of PZC and 515 mg of tungsten per gram of PTC and a [188]Re elution yield greater than 80% for both PZC and PTC sorbents were achieved. A [188]Re eluate concentration process was developed by eluting [188]Re from the tandem system of [188]W-PTC–alumina columns with two different concentrations of saline solution, which gave a concentration factor of about 6. The technology developed can be used for the preparation of clinically applicable [188]W/[188]Re generators using low specific radioactivity [188]W produced in medium flux research reactors.

20.1. INTRODUCTION

Tungsten-188 is produced via the [186]W (nn,γ) [188]W reaction using high neutron flux reactors, which are available in only a handful of countries around the world. However, [188]Re generators can be produced using imported [188]W solution, provided that an appropriate generator technology is used. The literature contains studies of ^{99m}Tc generator technologies using gel or zirconium/titanium polymer based sorbents to produce [188]W/[188]Re radionuclide generators [20.1–20.5]. Here, zirconium and titanium inorganic polymer sorbents were studied for the preparation of [188]W/[188]Re generators.

20.2. MATERIALS AND METHODS

20.2.1. Preparation of PZC and PTC sorbents

PZC and PTC sorbents were synthesized from isopropyl alcohol (iPrOH) and anhydrous metallic chloride under strictly controlled reaction conditions. A given amount of anhydrous metallic chloride ($ZrCl_4$ for PZC; $TiCl_4$ for PTC) was carefully added to different amounts of iPrOH. The temperature of the reaction mixtures immediately reached 96–98°C for iPrOH-$ZrCl_4$ and 92–94°C for iPrOH-$TiCl_4$, where it was maintained. Solutions were stirred gently using a magnetic stirrer in open air until they became viscous. As the reaction temperature increased, a water soluble gel (the intermediate precursor) was formed at 129–131°C for the PZC sorbent and at 111–113°C for the PTC sorbent. The water insoluble, solid PZC or PTC materials of particle sizes from 0.10 to 0.01 mm were formed by maintaining the reaction temperature at 141–142°C (30 min) for PZC and at 124–126°C (45 min) for PTC. The preparation conditions for the different batches of the synthesized PZC and PTC samples are summarized in Tables 20.1 and 20.2.

TABLE 20.1. CONDITIONS FOR THE CHEMICAL SYNTHESIS OF DIFFERENT PZC SAMPLES

Sample	$ZrCl_4$ weight (g)	Volume of isopropyl alcohol (mL)	Reaction temperature at final stage (°C)
PZC$_1$	50	40	141–142
PZC$_2$	50	80	141–142
PZC$_3$	50	100	141–142

TABLE 20.2. CONDITIONS FOR THE CHEMICAL SYNTHESIS OF DIFFERENT PTC SAMPLES

Sample	$TiCl_4$ weight (g)	Volume of isopropyl alcohol (mL)	Reaction temperature at final stage (°C)
PTC$_1$	40.7	40	124–126
PTC$_2$	40.7	80	124–126
PTC$_3$	40.7	100	124–126

20.2.2. Investigation of the chemical composition, structure and physicochemical properties of the PZC and PTC sorbents

The zirconium and titanium contents were analysed by the gravimetric method of ignition of the sorbent samples at 1200°C for 2 h. The ZrO_2 and TiO_2 were weighed, and the zirconium and titanium contents were calculated. The carbon, hydrogen and oxygen contents of the PZC and PTC samples were determined by thermal decomposition of the sorbents on a Perkin Elmer 2400 II instrument. The chlorine content of the sorbents was analysed by thermal decomposition of the samples. The decomposed HCl product was trapped in an alkaline solution and the Cl^- content was determined by ion chromatography. Thermal analysis of the sorbent samples was carried out using an MB-7H derivatographer instrument with an N_2 gas flow rate of 50 mL/min and a heating rate of 10°C/min. Potentiometric titration of PZC and PTC samples was carried out with 0.1 g of PZC or PTC sorbent samples in 60 mL of 0.1M NaCl solution. The titration solution was 0.1M NaOH solution.

Infrared spectra of sorbent samples were recorded on a Brucker-IFS 48, Carlo Erba-GC 6130 instrument. X ray diffraction patterns of sorbent samples were recorded on a Rigaku Miniflex diffractometer with a CuKα ray and CuNi filter at 40 KV/20 mA.

20.2.3. Adsorption and elution patterns of ^{188}W/^{188}Re generators

A radioactive ^{188}W solution with a concentration of 25.6 mg W/mL at pH7 was added to the PZC or PTC sorbent samples (0.75 g weight), which were then gently shaken in a water bath at 50°C overnight. After shaking, the samples were allowed to stand and a portion of clear supernatant solution was removed to measure the ^{188}W radioactivity. The remaining solution was decanted to obtain the solid sorbent portion. These solid PZC or PTC samples were packed on 8 mL glass columns and washed with 50 mL of water followed by 10 mL of saline. Activity levels of 5–10 mCi of ^{188}W were used in all column experiments. Elution yield, ^{188}W breakthrough and tungsten elemental content were determined for each elution.

20.2.4. PZC or PTC sorbent based ^{188}Re elution concentration systems

Investigation of the ^{188}Re concentration process was carried out by eluting ^{188}Re from the ^{188}W-PTC column with a 0.005% saline solution; this eluate was passed through a small alumina column where all ^{188}ReO$_4^-$ was retained. The ^{188}ReO$_4^-$ was subsequently eluted with a small volume of physiological saline.

20.3. RESULTS AND DISCUSSION

20.3.1. Synthesis and specification of PZC and PTC sorbents

Both the PZC and the PTC sorbents were light brown in colour and changed to white when soaked in water. These particles swelled in water and were hydrolyzed to give an acidic solution, while the solid matrix of the sorbents remained insoluble. The volume of swollen PZC was 1.25 and that of the PTC bed was 1.35 times that of the dry gel. The adsorption capacities of both PZC and PTC sorbents decreased with an increase of the reaction temperature, whereas an increase of the molar ratio of the reactants (isopropyl/$MeCl_4$) resulted in a higher degree of swelling of sorbent particles in aqueous solution. This swelling phenomenon favoured diffusion of the tungstate ions into the solid matrix of the sorbents during the adsorption process. However, the swelling of particles also gives rise to a decrease of their mechanical stability. For further investigations, the PZC2 and PTC2 sorbent samples were used owing to their favourable stability.

20.3.2. Chemical composition and molecular formula of PZC and PTC sorbents

The results of chemical and thermal analysis are given in Tables 20.3 and 20.4. Based on these results, the molecular structure of the PZC and PTC sorbents was calculated. The molecular weight (including organic residue) was determined to be M = 5901.3. Organic residue in the PZC molecule was equivalent to 9.63% of the PZC molecular weight, as was seen with thermal analysis. Because the organic substance in this formula was attributed to a residual organic by-product of the chemical synthesis reaction and was completely released from the polymer matrix in aqueous solution, the segment unit of the real polymer compound is assumed to have the following formula: $[Zr_{15}(OH)_{30}Cl_{30}(ZrO_2) \cdot 126\,H_2O]_n$.

TABLE 20.3. CHEMICAL COMPOSITION OF PZC SORBENT

Element	Cl	H	Zr	O	H_2O	(H + O + C) Organic
Content (% weight)	17.90	0.505	24.92	8.74	38.31	9.63
Atomic ratio	1.87	1.87	1	2	7.83	(Not calculated)

TABLE 20.4. CHEMICAL COMPOSITION OF PTC SORBENT

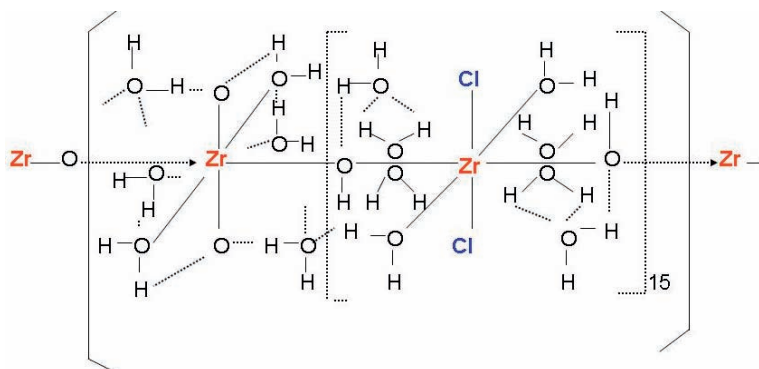| Element	Cl	H	Ti	O	H_2O
Content (% weight)	18.965	0.535	43.87	29.33	7.3
Atomic ratio	0.584	0.584	1.0	2.001	0.443

FIG. 20.1. *Proposed arrangement of atoms in PZC polymer.*

The proposed steric arrangement of atoms in the PZC molecule is shown in Fig. 20.1.

The ion exchange capacity derived from the above chemical formula offers an adsorption capacity of 517.1 mg of tungsten per gram of PZC by assuming that tungstate ions are adsorbed on PZC in the form of WO_4^{2-}. In addition, it is assumed that one molarity of WO_4^{2-} ion consumes 2 equivalents of ion exchange capacity of PZC and PTC sorbents (one equivalent of WO_4^{2-} ion is 91.92 g). This type of strong adsorption suggests a covalent bond between tungstate ions and the zirconium metal atom.

The molecular formula of the PTC sorbent was calculated to be $[Ti_{40}Cl_{80}(OH)_{80}(TiO_2)_{97} \cdot 60H_2O]_n$. The proposed molecular structure of PTC is depicted in Fig. 20.2.

The chlorine content of the PTC sorbent is 5.35 millimole per gram of PTC sorbent (18.96% of chlorine element in 1 g of PTC). This is equivalent to the ion exchange capacity of 5.35 meq per gram of PTC sorbent and consequently offers a very high adsorption capacity of 491.8 mg of tungsten per gram of PTC by assuming that the tungstate ions are adsorbed on PTC in the form of WO_4^{2-}, and that one molarity of WO_4^{2-} ion consumes 2 equivalents of ion exchange capacity of PTC sorbent. This type of strong adsorption gives a covalent bond between molybdate or tungstate ions and the titanium metal atom.
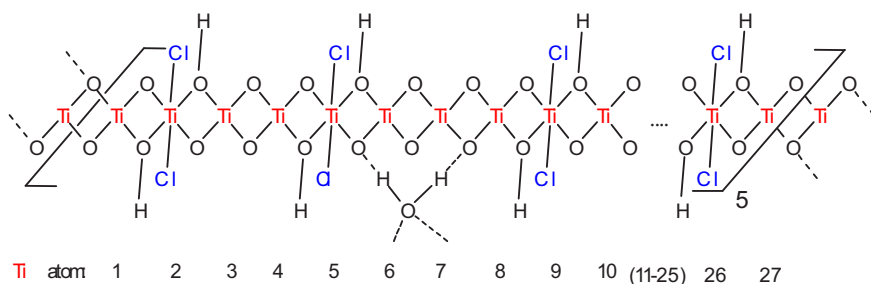
FIG. 20.2. *Proposed arrangement of atoms in PTC polymer.*

The adsorption capacity of both sorbents was varied depending on the temperature, reaction time and gel ageing process before the solid PZC and PTC polymers were formed. The actual adsorption of PZC and PTC sorbents, which is to some extent higher than the values mentioned above, accounted for the non-covalently adsorbed tungstate ions and/or for adsorption of small amounts of polytungstate ions. These polyanions could be formed at the beginning stage of adsorption owing to the strongly acidic medium resulting from the hydrolysis of the -Zr-Cl (or -Ti-Cl) groups of the backbone of the PZC or PTC molecules. These types of weak adsorption of the polytungstate ions result in higher tungstate breakthrough when loaded with high tungstate concentration. The infrared adsorption patterns of PZC and PTC are given in Table 20.5.

Good agreement was found between these results and the infrared absorption data of the $ZrO_2 \cdot xH_2O$ and $TiO_2 \cdot xH_2O$ samples. The organic trace amount retained in the PZC and PTC, detected at 2900 cm^{-1}, is assigned to

TABLE 20.5. INFRARED ADSORPTION OF PZC AND PTC SORBENTS

Wave number (cm^{-1})	Intensity	Chemical bond characteristics	Specified group
3353	Very strong (broad)	ν (OH)	OH in Zr-OH, Ti-OH and in -CH$_2$-CH(OH)-CH$_3$
3300	Very strong	ν (OH$_3^+$)	
2900	Very strong	ν (CH)	-CH$_2$-CH$_2$-
2900	Weak	ν (H$_3$O$^+$)	
1619	Medium	δ (H$_2$O)	
666	Medium	ν (Zr-O)	

organic by-products of the chemical synthesis reaction, but not to the isopropyl alcohol reactant. X ray diffraction analysis results showed an amorphous structure of the PZC and PTC sorbents.

20.3.3. Behaviour of PZC and PTC sorbents in the aqueous solution

The results of potentiometric titrations of PZC and PTC sorbents are shown in Fig. 20.3. An ion exchange capacity of 5.65 meq H^+ per gram of PZC was found at pH11. This amount is equivalent to 5.65 meq Cl^- per gram of PZC and agrees with the chlorine content of PZC found in the thermal analysis mentioned above. There is good agreement between the ion exchange capacity values as estimated by titration results and the molecular formulas of the PZC and PTC compounds.

The behaviour of PZC in aqueous solution can be summarized as follows: PZC sorbent is hydrolyzed, but not dissolved, in aqueous solution and gives an acidic solution (pH1.6) in water. This PZC product is mainly composed of (-ZrO-) and (-ZrO$^+$Cl$^-$) groups bonded together. The HCl formed during hydrolysis makes the water strongly acidic.

In open air, the PZC adsorbs water molecules from the humid environment and a very strong acidic medium is formed in the PZC particles. This acidity destroys the -ZrO-(ZrO)$_n$-ZrO- bonds and, after three weeks of standing in open air at room temperature, makes the PZC sorbent soluble in water. The PZC sorbent contains a minor quantity of unidentified organic compounds (2.53% carbon, 1.96% hydrogen and 5.14% oxygen). This organic substance is released when PZC adsorbent is hydrolyzed in aqueous solution.

Potentiometric titration of PTC sorbents gave similar results: 5.35 meq H^+ per gram of PTC capacity was found for PTC sorbent at pH11. The hydrolysis property of the PTC sorbent is similar to that of the PZC sorbent.
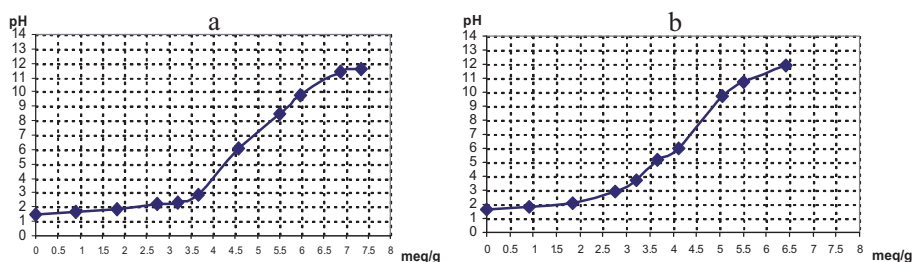

FIG. 20.3. Potentiometric titration curve of PZC (a) and PTC (b) sorbents.

20.3.4. Tungsten adsorption and [188]Re elution performance of PZC and PTC sorbents

Tungsten adsorption capacity and other characteristics of PZC and PTC samples versus adsorption time are given in Table 20.6. Rhenium-188 elution profiles using PTC and PZC columns loaded with 1 g of sorbents are shown in Figs 20.4 and 20.5, respectively. These studies demonstrate that the sorbents fulfill the requirements in use for preparation of chromatographic [188]W/[188]Re generators.

20.3.5. Effect of tungsten content on adsorption capacity, [188]Re elution yield and tungsten breakthrough

Table 20.7 summarizes the results of the effect of the tungsten content in the solution used for adsorption by the sorbents. Adsorption of tungsten increased with increasing concentration of tungsten, indicating higher capacity at higher tungsten concentrations. However, the percentage of adsorption decreased with an increase of tungsten concentration. Tungsten breakthrough from [188]W-PZC and [188]W-PTC columns increased with the increasing tungsten content of adsorption solution. This is attributed to the weakly bound tungstate ion on the sorbent particle surface. Rhenium-188 elution yields showed lower yields at both low and high tungsten load concentrations with both sorbents.

TABLE 20.6. TUNGSTEN ADSORPTION CHARACTERISTICS OF THE PZC2 AND PTC2 SORBENTS

Sorbent sample	Tungsten adsorption capacity (mg of tungsten per g of sorbent)[a]	Particle size of sorbent (mm)	Swelling in H_2O (% volume)	Reaction time (min)	Re-188 elution yield (%)
PZC2-1	515.2	0.1–0.001	22.5	30	90.3
PZC2-2	520.1	0.1–0.001	24.4	45	91.2
PZC2-3	541.2	0.1–0.001	29.3	50	88.3
PTC2-1	492.2	0.1–0.001	23.5	35	89.2
PTC2-2	515.1	0.1–0.001	26.3	45	90.4
PTC2-3	521.3	0.1–0.001	28.5	60	93.4

[a] The tungsten adsorption capacity of the PZC and PTC sorbents in tungstate solution at a concentration of 25.6 mg W/mL at pH7 (the pH of the post-adsorption solution was 4.5).

FIG. 20.4. ^{188}Re elution profiles of three different ^{188}W-PTC columns loaded with 1.0 g of sorbent samples (PTC2); elution performed with 0.9% saline.

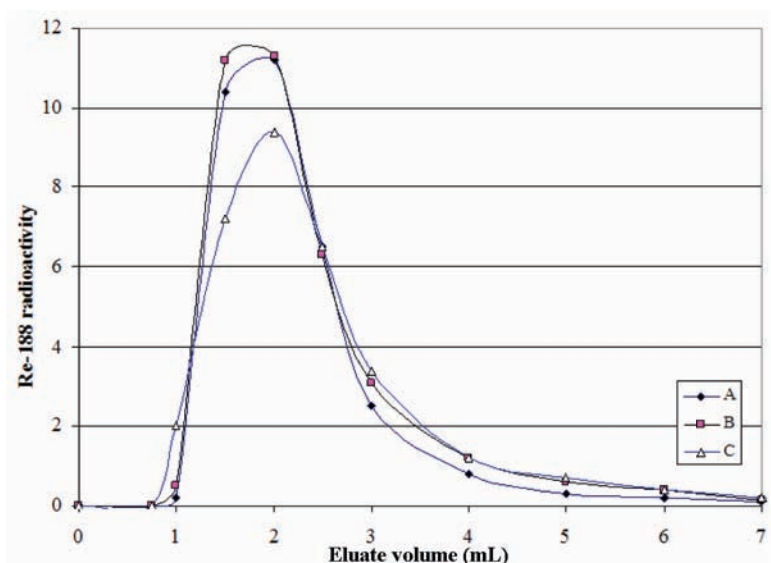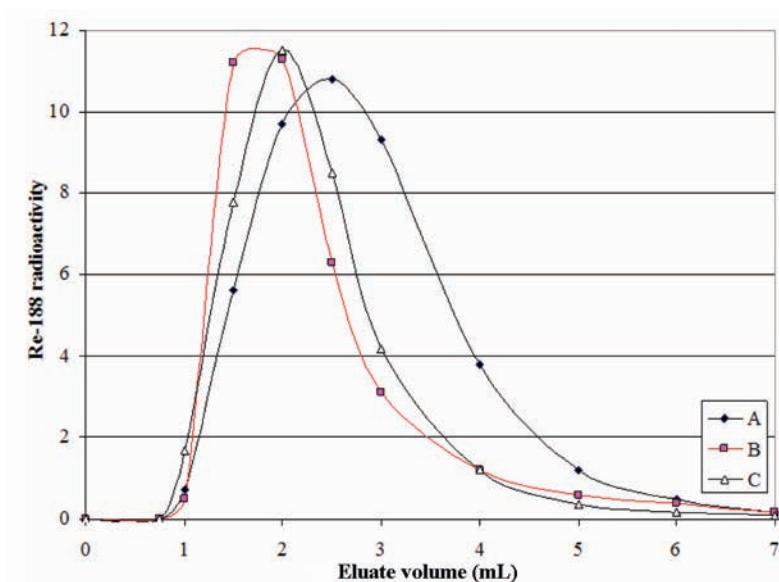FIG. 20.5. ^{188}Re elution profiles of three different ^{188}W-PZC columns loaded with 1.0 g of sorbent samples (PZC2); elution performed with 0.9% saline.

TABLE 20.7. EFFECT OF SOLUTION'S TUNGSTEN CONTENT ON ADSORPTION CAPACITY OF SORBENT AND ON ELUTION YIELD AND TUNGSTEN BREAKTHROUGH OF Re-188 ELUATE

Sample[a]	PZC2-1	PZC2-2	PZC2-3	PZC2-4	PTC2-1	PTC2-2	PTC2-3	PTC2-4
Weight of sorbent (g)	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Volume of tungsten solution (mL)	3.75	4.50	5.25	6.00	3.75	4.50	5.25	6.00
Tungsten content of adsorption solution (mg of tungsten per g of sorbent)	478.6	574.3	670.0	765.7	478.6	574.3	670.0	765.7
Tungsten adsorption capacity (mg of tungsten per g of sorbent)	448.0	520.3	544.7	601.8	435.7	515.2	545.1	595.2
Adsorption percentage (%)[b]	93.60	90.60	81.3	78.60	91.0	89.9	81.4	77.7
Re-188 elution yield (%)	72.50	85.30	81.20	79.00	75.1	86.2	85.6	81.5
Tungsten breakthrough in first elution (µg of tungsten/mL)	82.0	125.0	323.0	375.0	98.5	121.5	401.3	405.7
Tungsten breakthrough in second–fifth elutions (µg of tungsten/mL)	10.4 ± 0.4	27.1 ± 0.6	52.4 ± 0.7	60.2 ± 0.5	12.3 ± 0.2	28.2 ± 0.4	58.5 ± 0.5	65.7 ± 0.3

[a] PZC2 and PTC2 samples used; elution volume: 5 mL of 0.9% NaCl.
[b] Adsorption percentage (%) = 100 × (tungsten adsorption capacity/tungsten content of solution).

20.3.6. Effect of the composition of tungsten solution on adsorption and ^{188}Re elution

Studies of the tungsten adsorption and ^{188}Re elution performance of ^{188}W-PZC and ^{188}W-PTC sorbents in different solutions were carried out. It was found that, when NaOCl is added to the tungsten solution, both tungsten adsorption capacity and ^{188}Re elution performance improve. Maximum tungsten adsorption capacities of about 520 mg of tungsten per gram of PZC and 515 mg of tungsten per gram of PTC were achieved. The capacities varied depending on the adsorption conditions. The adsorption of tungstate in acetate buffer solution showed a better integrity of PZC and PTC sorbent particles than did adsorption of tungsten in pure water solution of tungstate. Sterilizing the ^{188}W-PZC and ^{188}W-PTC columns in the autoclave reduced the elution yield of ^{188}Re to some extent, but did not affect the tungsten breakthrough of column.

20.3.7. ^{188}Re concentration for ^{188}W-PZC or ^{188}W-PTC generator

Since low specific activity ^{188}W was used in the above studies, the ^{188}Re obtained required post-elution concentration. The ^{188}ReO$_4^-$ concentration process was carried out by eluting ^{188}Re from the ^{188}W-PZC and/or ^{188}W-PTC columns with a dilute (0.005%) saline solution. The ^{188}Re eluate collected was then passed through a small alumina column where all the ^{188}ReO$_4^-$ was retained; the ^{188}ReO$_4^-$ was then eluted from the alumina column with a small volume of physiological saline. Results of these studies are presented in Table 20.8 and Figure 20.6. A concentration factor greater than 6 was achieved with this concentration technique.

20.4. CONCLUSION

The PZC and PTC sorbents for the preparation of chromatographic ^{188}W/^{188}Re generators were synthesized and their chemical composition and molecular structure were determined. Tungsten adsorption capacities of about 520 mg of tungsten per gram of PZC and 515 mg of tungsten per gram of PTC, and a ^{188}Re elution yield greater than 80% were achieved with both PZC and PTC sorbents. A ^{188}W breakthrough of 0.015% and tungsten element breakthrough of less than 5 µg of tungsten per millilitre were found in the ^{188}ReO$_4^-$ eluate. A ^{188}Re concentration process was developed by eluting ^{188}Re from the tandem system of ^{188}W-PTC–alumina columns with different concentrations of saline solutions. A concentration factor greater than 6 was achieved with this concentration technique.

TABLE 20.8. ELUTION PERFORMANCE OF [188]W-PTC COLUMN WITH [188]Re CONCENTRATION SYSTEM

First column (W-188-PTC column) elution (0.005% NaCl eluant)			
Eluant volume (mL)	Re-188 elution yield (%)	Re-188 radioactivity retained on alumina column (mCi)	Tungsten breakthrough in the eluate
20	0	5.5 mCi (91.6% of Re-188 radioactivity of W-188-PTC column)	Not detected

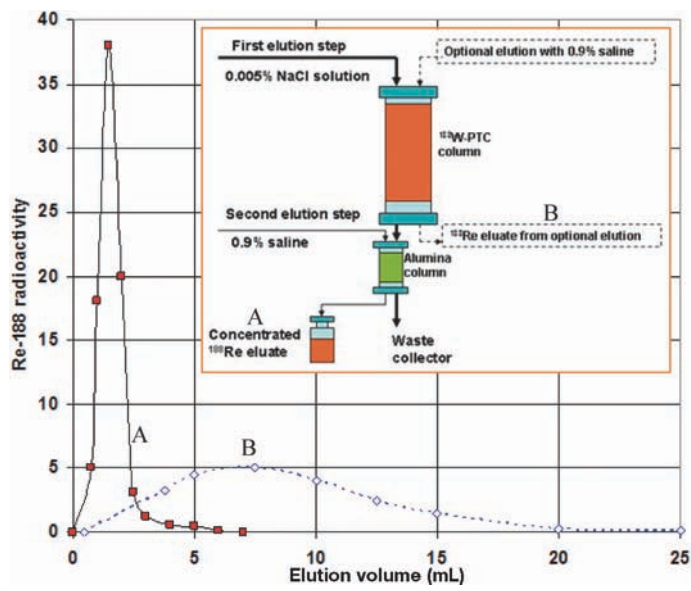| Second column (alumina) elution (0.9% NaCl eluant)				
Re-188 radioactivity and elution yield	Re-188 radioactivity retained on alumina column (mCi)	Tungsten breakthrough in the eluate	Eluant volume (mL)	Concentration factor
5.0 mCi (83.0% of Re-188 radioactivity of W-188-PTC column)	0.5	Not detected	3	6.7

FIG. 20.6. Concentration system and elution profiles: (A) elution profile from the alumina column after concentration; (B) elution profile from the PTC column without concentration; PTC sorbent weight: 4 g; alumina weight: 1.5 g; tungsten weight loaded onto PTC column: 2.1 g; [188]W radioactivity: 6 mCi.

REFERENCES TO CHAPTER 20

[20.1] TANASE, K., et al., ^{99m}Tc generator using a new inorganic polymer adsorbent for (n, γ) ^{99}Mo, Appl. Radiat. Isot. **48** (1997) 607–611.

[20.2] LE VAN SO, LAMBRECHT, R.M., Development of alternative technologies for a gel-type chromatographic ^{99m}Tc generator, J. Labelled Compd. Radiopharm. **35** (1994) 270–272.

[20.3] INTERNATIONAL ATOMIC ENERGY AGENCY, Alternative Technologies for ^{99}Tc^{m} Generators, IAEA-TECDOC-852, IAEA, Vienna (1995).

[20.4] DADACHOV, M.S., LE VAN SO, LAMBRECHT, R.M., DADACHOVA, E., Development of a titanium tungstate-based ^{188}W/^{188}Re gel generator using tungsten of natural isotopic abundance, Appl. Radiat. Isot. **57** (2002) 641–646.

[20.5] LE VAN SO, "Standard procedure for the preparation of PZC based chromatographic Tc-99m generator to be available for clinical application", Proc. Workshop on The Utilization of Research Reactors, JAEA–Conf–2006-001, Japan Atomic Energy Agency, Tokaimura (2006) 229–256.

PAPERS PUBLISHED BY THE PARTICIPANTS RELATED TO THE CRP

BECKFORD, D.A., XIQUES, A., LEYVA, R., PÉREZ, M., CASANOVA, E., ZAMORA, M., New radioimmunoconjugate ^{90}Y-DOTA-hR3: Synthesis and radio-labeling, Nucleus **41** (2007) 3–8.

CHAKRAVARTY, R., PANDEY, U., MANOLKAR, R.B., DASH, A., VENKATESH, M., PILLAI, M.R.A., Development of an electrochemical ^{90}Sr-^{90}Y generator for separation of ^{90}Y suitable for targeted therapy, Nucl. Med. Biol. **35** (2008) 245–253.

DHAMI, P.S., NAIK, P.W., DUDWADKAR, N.L., KANNAN, R., ACHUTHAN, P.V., MOORTHY, A.D., JAMBUNATHAN, U., MUNSHI, S.K., PANDEY, U., VENKATESH, M., DEY, P.K., Studies on the development of a two stage SLM system for the separation of carrier-free ^{90}Y using KSM-17 and CMPO as carriers, Sep. Sci. Technol. **42** (2007) 1107–1121.

SATPATI, D., KORDE, A., PANDEY, U., DHAMI, P.S., BANERJEE, S., VENKATESH, M., Synthesis and evaluation of ^{90}Y-DOTA-colchicine conjugate in murine fibrosarcoma model, J. Labelled Compd. Radiopharm. **49** (2006) 951–958.

DU, J., CHINOL, M., SAVONEN, A., HILTUNEN, J., Simple and safe production of yttrium-90 from a new type of ^{90}Sr/^{90}Y generator, Radiochim. Acta **93** (2005) 111–113.

FERRARI, M., CREMONESI, M., BARTOLOMEI, M., BODEI, L., CHINOL, M., FIORENZA, M., TOSI, G., PAGANELLI, G., Dosimetric model for locoregional treatments of brain tumors with ^{90}Y-conjugates: Clinical application with ^{90}Y-DOTATOC, J. Nucl. Med. **47** (2006) 105–112.

ILLER, E., ZELEK, Z., KONIOR, M., SAWLEWICZ, K., STANISZEWSKLA, J., MIKOŁAJCZAK, R., KARCZMARCZYK, U., "Technological line for production of carrier free ^{188}Re in the form of sterile isotonic solution of sodium perrhenate (VII)", Trends in Radiopharmaceuticals (ISTR-2005), Vol. 1 (Proc. Int. Symp., Vienna, 2005), IAEA, Vienna (2007) 323–331.

JEONG, J. M., KNAPP, F.F., Jr., Use of the Oak Ridge National Laboratory tungsten-188/rhenium-188 generator for preparation of the rhenium-188 HDD/lipiodol complex for trans-arterial liver cancer therapy, Semin. Nucl. Med. **38** (2008) S19–S29.

MARCZEWSKI, B., DIAS, C.R., MORAES, V., OSSO, J.A., Jr., Liquid Kit for Preparation of ^{188}Re-etidronate, Brazilian Arch. Biol. Technol. **48** (2005) 137–140.

MIKOŁAJCZAK, R., ZUCHLINSKA, M., PAWLAK, D., "Optimized alumina column for preparation of ^{188}W/^{188}Re generator", Technetium, Rhenium and Other Metals in Chemistry and Nuclear Medicine, Vol. 7 (Proc. Sixth Int. Symp. on Technetium in Chemistry and Nuclear Medicine), SGE Editoriali, Padova (2006) 601–604.

MONROY-GUZMAN, F., BADILLO ALMARAZ, V.E., FLORES DE LA TORRE, J.A., COSGROVE, J., KNAPP, F.F., Jr., "Hydroxyapatite based ^{99}Mo–^{99m}Tc and ^{188}W–^{188}Re generator systems", Trends in Radiopharmaceuticals (ISTR-2005), Vol. 1 (Proc. Int. Symp., Vienna, 2005), IAEA, Vienna (2007) 333–347.

MONROY-GUZMAN, F., HERNANDEZ PAZ, M., GALICO COHEN, L., ROSALES, C.J., Tungsten and rhenium sorption study on alumina to prepare ^{188}W/^{188}Re generators, Sep. Sci. Technol. **44** (2009) 1120–1143.

PANDEY, U., BANERJEE, S., MUKHERJEE, A., SARMA, H.D., VENKATESH, M., ^{90}Y-DOTA-Lanreotide: A potential agent for targeted therapy, J. Radioanal. Nucl. Chem. **273** (2007) 719–723.

PANDEY, U., BAPAT, K.N., SAMUEL, G., SARMA, H.D., CHAUDHARI, P.R., DHAMI, P.S, KANNAN, R., VENKATESH, M., Evaluation of ^{90}Y phosphate particles as a possible radiation synoviorthesis agent, Nucl. Med. Comm. **26** (2005) 459–464.

PANDEY, U., DHAMI, P.S., JAGESIA, P., VENKATESH, M., PILLAI, M.R.A., Extraction paper chromatography technique for the radionuclidic purity evaluation of ^{90}Y for clinical use, Anal. Chem. **80** (2008) 801–807.

PARK, S.H., DEMBERELNYAMBA, D., JANG, S.H., BYUN, M.W., Ionic liquid-type crown ether as a novel medium for a liquid/liquid extraction of radioactive metal ion ^{85}Sr^{2+}, Chem. Lett. **35** (2006) 1024–1025.

PARK, S.H., SEIFERT, S., PIETZSCH, H.-J., Novel and efficient preparation of precursor $[^{188}$Re$(OH_2)_3(CO)_3]^+$ for the labeling of biomolecules, Bioconjug. Chem. **17** (2006) 223–225.

SARKAR, S.K., VENKATESH, M., RAMAMOORTHY, N., Evaluation of two methods for concentrating perrhenate (^{188}Re) eluates obtained from ^{188}W-^{188}Re generator, Appl. Radiat. Isot. **67** (2009) 234–239.

SO, LE VAN, NGUYEN, C.D., PELLEGRINI, P., BUI, V.C., Polymeric titanium oxychloride sorbent for ^{188}W/^{188}Re nuclide pair separation, Sep. Sci. Technol. **44** (2009) 1074–1098.

URBANO, N., PAPI, S., GINANNESCHI, M., DE SANTIS, R., PACE, S., LINDSTEDT, R., FERRARI, L., CHOI, S.J., PAGANELLI, G., CHINOL, M., Evaluation of a new biotin-DOTA conjugate for pretargeted antibody-guided radio-immunotherapy (PAGRIT®), Eur. J. Nucl. Med. Mol. Imaging **34** (2007) 68–77.

LIST OF PARTICIPANTS

Castillo, A.X.	Isotope Centre, Cuba
Chinol, M.	European Institute of Oncology, Italy
Jin Xiao-Hai	China National Nuclear Corporation, China
Knapp, F.F., Jr.	Oak Ridge National Laboratory, United States of America
Kuznetsov, R.	Research Institute of Atomic Reactors, Russian Federation
Le Van So	Nuclear Research Institute, Vietnam
Mikolajczak, R.	POLATOM, Poland
Monroy-Guzman, F.	Instituto Nacional de Investigaciones Nucleares, Mexico
Osso, J.A., Jr.	Nuclear and Energy Research Institute, Brazil
Park, S.H.	Korea Atomic Energy Research Institute, Republic of Korea
Pillai, M.R.A.	International Atomic Energy Agency
Venkatesh, M.	Bhabha Atomic Research Centre, India
Wagner, G.	Hans Wälischmiller GmbH, Germany

Research Coordination Meetings

Vienna International Centre, Vienna, 10–14 October 2004
European Institute of Oncology, Milan, Italy, 21–24 April 2006
Korea Atomic Energy Research Institute, Daejeon, Republic of Korea,
8–12 October 2007

CYCLOTRON PRODUCED RADIONUCLIDES:
GUIDELINES FOR SETTING UP A FACILITY
Technical Reports Series No. 471
STI/DOC/010/471 (forthcoming)
ISBN 978–92–0–103109–9   Price: €45.00

CYCLOTRON PRODUCED RADIONUCLIDES:
PHYSICAL CHARACTERISTICS AND PRODUCTION METHODS
Technical Reports Series No. 468
STI/DOC/010/468 (279 pp.; 2009)
ISBN 978–92–0–106908–5   Price: €52.00

TECHNETIUM RADIOPHARMACEUTICALS:
MANUFACTURE OF KITS
Technical Reports Series No. 466
STI/DOC/010/466 (202 pp.; 2008)
ISBN 978–92–0–100408–6   Price: €50.00

CYCLOTRON PRODUCED RADIONUCLIDES:
PRINCIPLES AND PRACTICE
Technical Reports Series No. 465
STI/DOC/010/465 (230 pp.; 2008)
ISBN 978–92–0–100208–2   Price: €45.00

COMPARATIVE EVALUATION OF THERAPEUTIC
RADIOPHARMACEUTICALS
Technical Reports Series No. 458
STI/DOC/010/458 (310 pp.; 2007)
ISBN 92–0–115106–3   Price: €56.00

LABELLING OF SMALL BIOMOLECULES USING NOVEL
TECHNETIUM-99M CORES
Technical Reports Series No. 459
STI/DOC/010/459 (312 pp.; 2007)
ISBN 92–0–101607–7   Price: €70.00

TRENDS IN RADIOPHARMACEUTICALS (2 VOLUMES)
STI/PUB/1294 (Vol. 1: 408 pp.; Vol. 2: 464 pp.; 2007)
ISBN 92–0–101707–3   Price: €120.00

DEVELOPMENT OF ^{99M}TC AGENTS FOR IMAGING CENTRAL
NEURAL SYSTEM RECEPTORS
Technical Reports Series No. 426
STI/DOC/010/426 (197 pp.; 2004)
ISBN 92–0–115303–1   Price: €33.00

Radionuclide generators are efficient means to enhance the availability of short lived radioisotopes used in medicine and industry. Technologies for the preparation of ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generator systems developed through an IAEA coordinated research project are presented in this publication. Analytical methods that are essential for evaluating the safety of radionuclides used in therapy are also described. By adapting the technologies described in this publication, these generators can be fabricated to cost effectively provide ^{90}Y and ^{188}Re for basic research and radiopharmaceutical preparation.