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Classic Radionuclide $^{188}W/^{188}Re$ Generator (Experiments, Design and Construction)

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Abstract

Rhenium-188 belongs to the group of beta-gamma emitters. A radiometric characteristic of radiation emitted by Rhenium-188 creates advantageous conditions for medical applications of this radionuclide. The Radioisotope Center Polatom Poland has developed and implemented the technology for routine production of carrier free ^{188}Re. A production line for the preparation of sterile, isotonic solution carrier-free ^{188}Re sodium perrhenate (VII) has been constructed. On the basis of collected experiences, the manufacturing of $^{188}W/^{188}Re$ generators, in which chromatographic column is loaded with alumina has been established. At the present time the generators with activity of 3.7-37 GBq are available.

Keywords: 188W/188Re generator; Rhenium-188; Radioisotope generator

Introduction

Rhenium-188 is an important beta-gamma emitter, which emits beta particles with an average energy of 784 keV and a maximal energy of 2.11 keV as well as gamma photons with energy of 155 keV (15%) and a half-life time of 17 hours. There are important properties which make this radioisotope of interest for clinical use. The beta particles have a penetration range in soft tissues of about 8-10 mm which is convenient for the destruction of tumor tissue. In addition the gamma emission permits quantitative gamma camera imaging for evaluation of biokinetics and dosimetric estimations.

Rhenium -188 exhibits chemical reactivity similar to technecium-99m and can be converted to chemical forms required for preparation of various therapeutic radiopharmaceuticals.

A number of important therapeutic applications of rhenium-188, which have been developed over the two decades, have demonstrated uses of rhenium-188 as a cost effective alternative to more expensive and/or less readily available therapeutic radioisotopes. Clinical trials include the use of ^{188}Re-HEDP and -DMSA for the treatment of metastatic bone pain and various ^{188}Re-labeled HDD/Lipiodol and DEDC/Lipiodol agents for radioembolytic therapy of Hepatocellular Carcinoma (HCC) [1-12].

More recently, the use of ^{188}Re colloid for radionuclide synovectomy has been found effective for treatment of refractory disease [13-15].

Rhenium-188 is produced from the decays of tungsten-188. The ^{188}W parent is obtained by double neutron capture of ^{186}W in a nuclear reactor following the reaction scheme:

$$^{186}W \xrightarrow{n,\gamma(\sigma=37,9b)} {}^{187}W \xrightarrow{n,\gamma(\sigma=64\ b)} {}^{188}W \xrightarrow{n,\gamma(\sigma=12\ b)} {}^{189}W$$

Because this reaction proceeds in two steps and the intermediary product ^{188}W is short lived ($T_{1/2}$ = 23,8 h), the reaction requires a thermal neutron flux >$1^{*}10^{15}$ n/cm^2. Such conditions are available at the SM in Dimitrovgrad the Russian Federation and HFIR in Oak Rige, Tennessee USA. In Figure 1 Dependence of ^{188}W specific activity versus time of irradiation and the flux of thermal neutrons is presented.

The radionuclide generator is an efficient and convenient device for obtaining ^{188}Re solution. Several types of $^{188}W/ ^{188}Re$ generators have been described in the literature in which different material, Dowex, zirconium oxides, alumina, tungstate of Zr, Ti, Co, Mo were used [13,16]. Some other sorbents with high content of tungsten such as gel metal oxide composites, hydroxyapatites and Polymeric Zirconium Compounds (PZC), as well as new nanomaterials have been employed in the preparation of $^{188}W/^{188}Re$ generators also a simple electrochemical method for the separation of ^{188}Re from ^{188}W and obtained ^{188}Re suitable for radiolabeling biomolecules has been presented [17-24]. However the best elution efficiency was obtained when the aluminium oxide was applied for loading of the generator column [25-27].

Material and Methods

Laboratory works

In our experiments the adsorption of tungstate solution on two types of alumina (50-200 µm and 63-200 µm) were investigated for a wide range of pH from 9.7 to 2.5 and temperature values from 0 to 34°C. After loading of a generator column the alumina was activated using 0.9% NaCl in 0,001m HCl to obtain a final pH 3. Tungsten-188 in the form of tungstenic acid was slowly fed onto the column. After tungsten deposition, the alumina column was washed with 0.9% NaCl. Next the ^{188}Re was eluted with 0.9% NaCl. The obtained sodium perrhenate solution was purified and concentrated in the chromatographic system. The system consists of two columns with ion-exchange resins. The solution first passed through the column with cation exchanger AG-50W-X4 (Bio-Rad) resin, 200-400 mesh hydrogen form. The Ag^+ cations deposited on the bed react with Cl^- anions to form unsoluble AgCl, whereas the Na^+ cations replace H^+. This column essentially "traps" all of the chloride anions. The second column is filled with the anion exchanger Sem-Pack Plus QMA Light resin. The $^{188}ReO_4^-$ ions pass through the column and are trapped. The column is the eluted with 1-2ml of saline and concentrated solution of sodium perrhenate is obtained [26].

Production line to provide carrier-free rhenium-188

Based on the previously developed procedures for loading and eluting of the generator, and also taking into account the requirements

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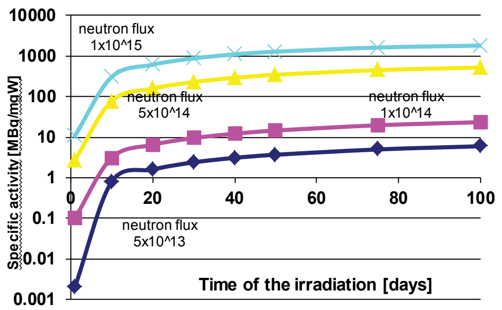

Figure 1: Dependence of the W-188 specific activity rests on the time of the irradiation and the flux of thermal neutrons

formulated for the final product, a production line for processing of sodium tungstate was constructed.

The line consists of five lead-shielded chambers in which the following operations are performed:

1. Unloading of active material

2. Preparation of ^{188}W solution and loading of ^{188}W solution onto the alumina column

3. Elution of ^{188}Re in the form of sodium perrhenate

4. Concentration of the elute and dispensing ^{188}Re solution in to vials.

5. Sterilization and removal of vials from production line.

The ^{188}Re solution is recommended for medical applications as a precursor for radiopharmaceuticals production, therefore the air inside the production chambers must meet GMP purity requirements.

The air in chamber 1 and 5 should be classified as Class C. Also the air inside the room where the production line is installed should fulfil the D-class requirements of purity [28].

Quality control

An important aspect of the production is Quality Control of the final product, especially when the product is intended for medical purposes.

Radiochemical purity of eluated ^{188}Re perrhenate solution was evaluated by means of paper chromatography using 0.9% NaCl as a developing solution. Chemical purity was determined using ICP-Optical Emission Spectrometer (Optima 33000XL, Perkin-Elmer). Radionuclide purification of the eluates was checked by γ-spectrometry with HPGe detector, which included the overall assessment of radionuclide impurities related to the ^{188}Re activity and ^{188}W breakthrough. The quantitative specifications of sodium perrhenate (VII) solution are summarized in Table 1.

Radionuclide 188W/188Re generator

On the basis of our development study and availability of necessary facilities the production of $^{188}W/^{188}Re$ generators has been undertaken at the Radioisotope Centre POLATOM Poland. 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, with diameter of 7.5 mm and length of 40 mm, 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.

The tungsten oxide irradiated in SM nuclear reactor at Dimitrovgrad (Russian Federation) with specific activity of between 27 and 133 GBq per gram of tungsten is dissolved in NaOH and converted to sodium tungstate. Directly before the adsorption of tungstate on the generator alumina column, the solution of sodium tungstate is heated and sodium hypochlorite (0.5 ml NaOCl 0.5 M per gram of tungsten), 80% acetic acid (1 ml CH_3COOH per gram of tungsten) and 32% hydrochloric acid is added in order to lower the solution pH to 2.5. In Figure 2 the pH changes of sodium tungstate solution during acidification are illustrated.

The purpose of this operation is to transform the sodium tungstate into tungstenic acid solution at pH 2-3. The acid solution is slowly passed (flow 0.1 ml/min) onto the generator column placed in a lead shield. Under such conditions the adsorption of tungstenic acid solution on the alumina column achieved a value up to 99%. The column was washed with 20-50 ml of 0.9% NaCl solution (pH 5.0-5.5) at flow rate of 0.1 ml/min in order to remove the unbound ^{188}W. Two methods were evaluated for the elution of the generator. The first involves use of a peristaltic pump to pass saline through the generator column under positive pressure. Application of this solution enables as to join a few generators and increase the total activity of rhenium solution up to 74 GBq. In the second method the vacuum technique was applied. The saline is removed at the generator column outlet under negative pressure using evacuated vials as in the $^{99}Mo/^{99m}Tc$ generator which is a simple and reliable method. The example of the elution profile of a generator is shown in Figure 3.

Results and Discussion

As observed from the data of Figure 3, 99% of ^{188}Re activity is collected in 2-3 ml of eluted solution. Such results allow obtaining of high specific activity ^{188}Re and indicate the possibility of avoiding of concentrated eluate post elution. Standard elutions of the $^{188}W/^{188}Re$ generator were performed using 8 ml of saline solution (2 × 4 ml). Evaluation of the prototype generator has been conducted over six months.

As shown in Figure 4, maximum activity of ^{188}Re we can be obtained after 72 hours from the previous elution, but an elution yield of 60% is available after 24 hours. In the case of consistence in eluate of considerable amount of ^{188}W (breakthrough) the obtained solution could be purified by adsorption of tungstenic anions on additional alumina columns. In our experiments the ^{188}W concentration in

Tests	Requirement	Method
Identification Characters Identity Gamma-ray spectrum	colourless, clear solution Presence of specifics γ lines: Eγ=155.06 Eγ=477.96 Eγ=633.00	Visual inspection Gamma-ray spectrometry
pH	5.5-7.5	Potentiometry
Radionuclide purity	>99.9%	Gamma-ray spectrometry
Radiochemical purity	≥ 98%	Paper chromatography
Chemical purity	Not more than: 5 ppm Pb, Al, Ba, Ni 10 ppm B, Zn 15 ppm W 20 ppm Si, Mg, Ca	ICP-OES
Sterility	Sterile	Direct inoculation
Bacterial endotoxins	<0.125 EU/ml	LAL test

Table 1: Specifications of 188Re sodium perrhenate (VII) solution

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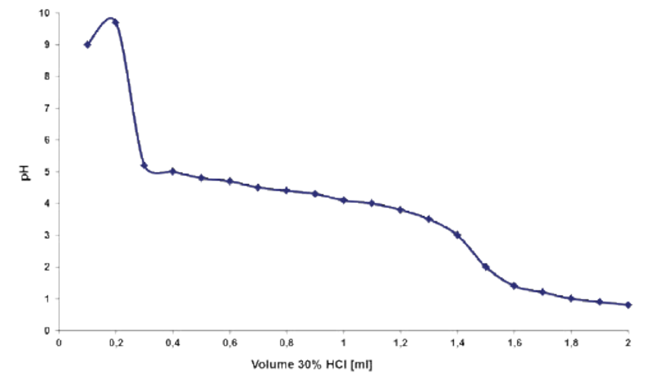

Figure 2: Graph of pH changes of the sodium tungstate solution while adding hydrochloric acid

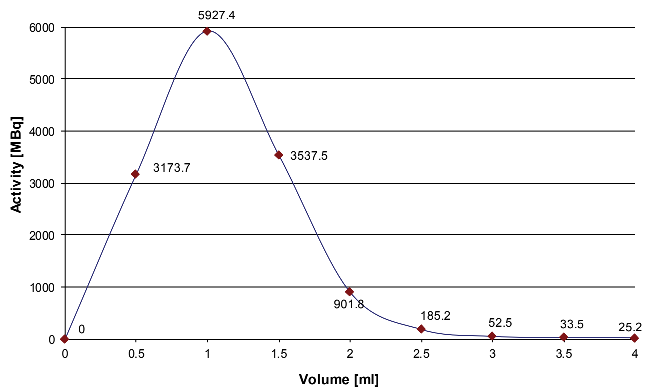

Figure 3: Elution profile of generator

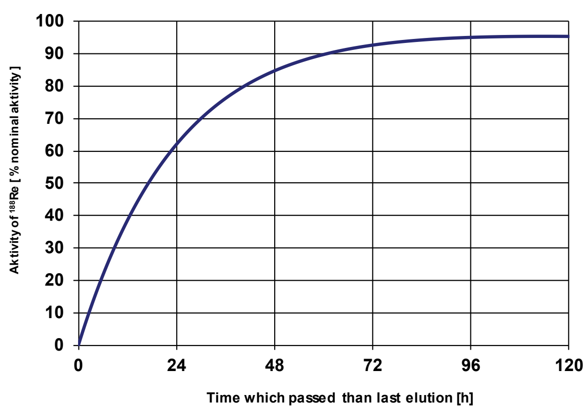

Figure 4: Increase activity of ^{188}Re on the generator

sodium perrhenate did not exceed 10.0 ppm; therefore the application of a purification column was unnecessary.

Table 2 compares the requirement parameters of eluates and obtained data during examinations of Polish $^{188}W/^{188}Re$ generators are listed. In the Figure 5 the cross section of $^{188}W/^{188}Re$ generator is presented. Table 3 presents the technical parameters of the generator. All plastic parts which are used for generator construction were examined for resistance to long-time irradiation of beta particles. For generators which allow us to obtain ^{188}Re solution with activity of 18.5 GBq, the radiation dose on lead shield is less than 1 mSv/h.

Conclusion

Radioisotope Centre Polatom, Poland to develop the technology for manufacturing of $^{188}W/^{188}Re$ generators. The production line for preparation of carrier-free ^{188}Re in form of sterile, isotonic solution of sodium perrhenate (VII) has been constructed.

The ^{188}Re sodium perrhenate solution is obtained from a single stationary generator or from a series of generators attached in tandem. The total activity of ^{188}Re eluate achieved value 74 GBq with radiochemical purity of 99.9%.

On the basis of collected experiences, during operations of the production line, the manufacturing of $^{188}W/^{188}Re$ generators, in using alumina has been established. At the present time, 37 GBq level generators are available, from RC Polatom. Maximum activity of ^{188}Re we can be obtained after 72 hours from the previous elution, but an elution yield of 60% is available after 24 hours. In the case of consistence in eluate of considerable amount of ^{188}W (breakthrough) the obtained solution could be purified by adsorption of tungstenic anions on additional alumina columns. The radiopharmaceuticals and radiochemicals containing rhenium-188 are used in clinical trials of cancer radioimmunotherapy, palliation of skeletal bone pain, endovascular brachytherapy as well as in the development of novel radiopharmaceuticals in pre-clinical stage. Its high energy beta radiation with soft tissues penetration range of about 8-11 mm is suitable for irradiation of medium or large tumors, while the low energy and abundance of gamma photons make the isotope suitable for quantitative gamma camera imaging for evaluation of biokinetics and dosimetric estimations. References

Parameter		Requirement	Result	Method
Radionuclide purity	188W	< 0.5 %	< 0.01 %	ICP-OES
	others	< 0.1 %	< 0.1 %	
Radiochemical purity		>98%	99,8%	
Chemical purity	Al	<10.0 ppm	5.5 ppm	
	W	<10.0 ppm	<10.0 ppm	
pH of the elute		4.5-6.0	5.0	potentiometry
Elution yield	in first 4 ml	>90%	98.0%	ionization chamber
	in first 8 ml	>95%	99.7%	

Table 2: Monitoring parameters of generator elute

Chemical form	**sodium perrhenate $Na^{188}ReO_4$ in 0.9% NaCl solution**
Nominal activity of ^{188}Re	3.7 GBq-37 GBq (100-1000 mCi) 2 generators can be coupled serially to be eluted in a single procedure
Elution yield	> 90 % of nominal activity in first 4 ml fraction of elute > 95 % of nominal activity in first and second 4 ml fractions of elute
Radiochemical purity	> 98%
Chemical purity	Al <10.0 ppm W <10.0 ppm
Radionuclide purity	^{188}W <0.5 % others <0.1 %
pH of the eluate	4.5-6.0
Weight of the generator	16 kg
Expiration time	at least 6 months from the day of calibration
Calibration	maximal 7 days after production

Table 3: Technical parameters of generator $^{188}W/^{188}Re$

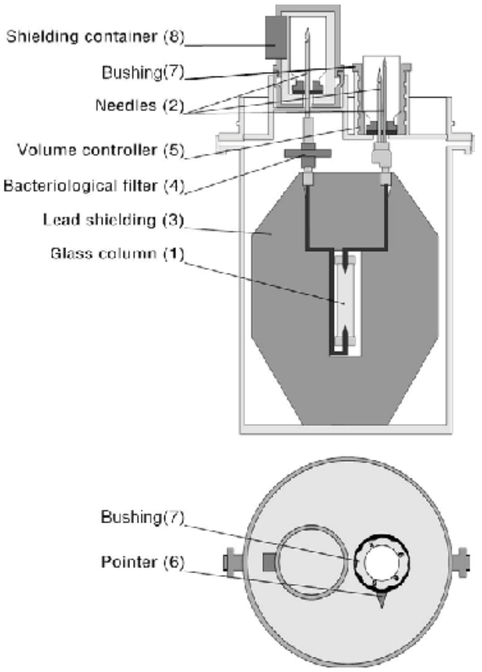

Figure 5: Cross section of $^{188}W/^{188}Re$ generator

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