การพัฒนาการเตรียมไอโซโทปรังสี ^{188}Re จาก ^{188}W/^{188}Re เจเนเรเตอร์

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บทคัดย่อ

ได้พัฒนาการผลิตไอโซโทปรังสี^{188}Re ความแรงรังสีต่ำ เพื่อใช้ในงานวิจัยการติดฉลากสารไอโซโทปรังสี^{188}Re ทางการแพทย์ โดยเตรียมในรูป ^{188}W/^{188}Re เจเนเรเตอร์ ด้วยเทคนิคโครมาโทกราฟี ซึ่งมีตัวคอลัมน์บรรจุตัวดูดซับอลูมินา น้ำหนัก 1.74 กรัม วางในกระบอกพลาสติกและวางในถ้ำตะกั่วหนา 30 มิลลิเมตรอีกชั้นหนึ่ง ทำการบรรจุไอโซโทปรังสี ^{188}W ในคอลัมน์ของเจเนเรเตอร์ทั้งสามตัวความด้วยความแรงรังสี 25, 25 และ 30 มิลลิคูรี หลังจากนั้นตรวจสอบคุณสมบัติทางเคมีและรังสีของเจเนเรเตอร์ทั้งสามตัว ได้แก่ ร้อยละการถูกชะของไอโซโทปรังสีตัวลูก ความบริสุทธิ์ทางเคมีรังสี การเจือปนด้วยธาตุอลูมิเนียม และความบริสุทธิ์ทางเรดิโอนิวไคล์ หลังจากการใช้งานนาน 6 เดือน เจเนเรเตอร์ทั้งสามตัวยังคงมีคุณสมบัติที่ดี ทั้งทางกายภาพและเคมี โดยมีค่าร้อยละการถูกชะของไอโซโทปรังสีตัวลูกมากกว่า 90%, ความบริสุทธิ์ทางเคมีรังสีสูงมากกว่าร้อยละ 99.7 การเจือปนของไอโซโทปรังสีตัวแม่ (W-188) และอื่นๆ (^{192}Ir และ ^{191}Os) พบในระดับต่ำมากๆ การเจือปนของทังสเตนแคริเออร์ (W-186) อยู่ในระดับน้อยกว่า 1 พีพีเอ็ม และ Al อยู่ในระดับน้อยกว่า 3 พีพีเอ็ม

คำสำคัญ: ^{188}W/^{188}Re, เจเนเรเตอร์, ไอโซโทปรังสี, ^{188}Re

In-house Preparation of ^{188}W/^{188}Re Generators

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Abstract

Low activity ^{188}W/^{188}Re generators were developed for the purpose of routinely supplying rhenium-188 for laboratory experiments and research works. Chromatography technology was applied in the construction of the generators. The chromatography columns containing 1.74 g alumina (Al_2O_3) were housed in plastic (PE) shielding inside the 30mm thick lead shield. Three generators were loaded with three different ^{188}W activities; 25mCi (RG1), 25 mCi (RG2) and 50 mCi (RG3). Generator performances were determined in terms of elution yields, radiochemical purity, Al-breakthrough, ^{188}W-breakthrough, and radionuclidic purity of the eluted products. These generators can be used for more than 6 months with average elution yields greater than 90 %. Radiochemical purity of $^{188}ReO_4^-$ was high (> 99.7 % by ITLC), low level of ^{188}W –breakthrough and low contamination of ^{192}Ir and ^{191}Os. There were only less than 1 ppm of ^{186}W carrier and less than 3 ppm of Al-breakthrough.

Key words: ^{188}W/^{188}Re, Generator, ^{188}Re, Radionuclide

1. Introduction

Rhenium-188(Re-188) is one of the most attractive radioisotope being used in therapeutic nuclear medicine application. In the last 15 years, a number of therapeutic ^{188}Re-radiopharmaceuticals have been developed and some of them are now being introduced into clinical applications such as ^{188}Re-HEDP for bone pain palliation, ^{188}Re-Sn/Colloil for synovectomy, 188Re-Antibodies for tumor therapy or ^{188}Re-Perrhenate for inhibition of restenosis after PTCA-Liquid-filled Balloon Approach for Coronaries.

Rhenium-188 is of much interest because of its 16.9 hour half-life, emission of a beta particle with maximal energy of 2.12 MeV and a gamma photon of 155 keV (15 %abundance) suitable for imaging and dosimetry estimation. Rhenium-188 (Re-188) is obtained from decay of its parent Tungsten-188(W-188) which is prepared from high flux (>2 x10^{15} n/cm^{2}x s) reactor[1,2] by the process of double neutron capture of W-186: ^{186}W(n,r)^{187}W(n,r)^{188}W (Figure 1).

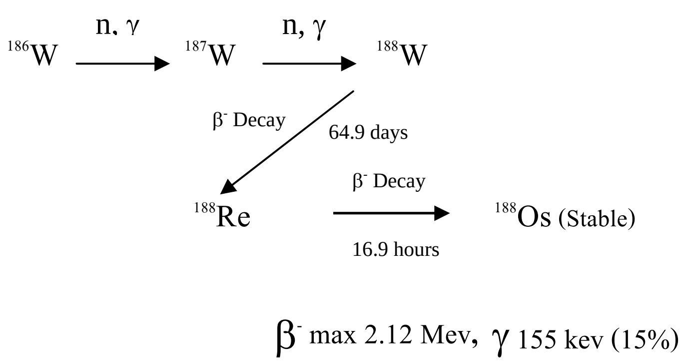


Figure 1. Production and decay mode of Tungsten-188 to Rhenium-188

Unfortunately, There are only 2 High Flux Reactors: one is the High Flux Isotope Reactor, HFIR (flux∼2.5 x 10^{15}n.cm^2.s^{-1}) at Oak Ridge National Laboratory(ORNL)[1], USA and the other one is High Flux Reactor SM-3 (flux∼5x10^{15} n.cm^{-2}.s^{-1}) at Reasearch Institure for Atomic Reactor (RIAR)[3]. ORNL usually supply Re-188 in the form of ^{188}W/^{188}Re-generator commercially but the production schedule may be limit in 1 batch a year and its cost is relatively high for developing countries while RIAR produce W-188 and distribute in the chemical form tangstate ($^{188}WO_4^{2-}$) in more economic price per mCi ordered and the production is schedulely at approximately every two month in the year which is a better source supply of W-188 for the production of Re-188 radioisotope.

By the advantage of isotope generator technology, the chromatographic type $^{188}W/^{188}Re$-genertors have been developed in the same way as $^{99}Mo/^{99m}Tc$-genertor. In fabrication of generator, $^{188}W/^{188}Re$-generator is much more differ from $^{99}Mo/^{99m}Tc$-generator which is produced from high specific activity fission ^{99}Mo while $^{188}W/^{188}Re$ –generator use low specific activity W-188 ranging 1-7 mCi/mg W resulting the large amounts of alumina absorbing media and required high elution volume of Re-188 product. ORNL has produced this type of generator with activity level 500 mCi and above which required the bolus volume as much as 10-30 ml

0.9%NaCl eluant [3,4]. In research and development sectors of nuclear medicine, a daily or weekly supply of small volume Re-188 with activity amount ranging 50-200 mCi is enough for experiments, quality controls or other research works. So the $^{188}W/^{188}Re$-Generator with low activity and small size of alumina bed, in order to minimize elution volume, is required. In this work we have developed low activity $^{188}W/^{188}Re$-generators for routine used in our laboratory and evaluated their performances and quality controls.

2. Material and Method

-Alumina adsorbent and chromatographic column: plastic column with glass fritz and aluminium oxide, Al_2O_3 active acidic were used as adsorbing media

-W-188: Irradiated Tungstate-188 in the form WO_4^{2-} with specific activity 6.4 mCi/mg W in 0.15 M NaOH was purchased from Radioisotope Centre, POLATOM, Poland (Produced by RIAR, Dimitrovgrad, Russia)

-Dose calibrator: Victoreen-Calibration II was calibrated for Re-188 and used for measurement of Re-188 eluted products

2.1. Preparation of alumina column

The column used is the alumina column containing active acidic of 1.74 g. Al_2O_3 form. The alumina was reactivated by eluting the column with nitric acid 0.001 N at flow rate 0.8 ml/min for 6 hours and then ready for use

2.2. Generator housing

The generator housing compose of two shielding layers as show in figure 2, the inner shielding is plastic (PE) capsule with 17 mm. ID and 10 mm. thick while the outer is 30 mm. thick lead pig. Two small holes were made for insertion of extension tubing. The generator column (15 mm. OD and 40 mm. high) is attached with plastic tubing (Tygon) to the upper inlet and lower outlet connection. One 0.22 μ millipore filter was connected in-line to the outlet tubing for trapping of alumina fines or other particles which may be eluted from the generator.

Figure 2. Arrangement of $^{188}W/^{188}Re$ -Generator

2.3. Conditioning of W-188

To ensure that W-188 is to be in the form which be completely adsorbed on the alumina, the W-188 solution was added 0.3 ml. H_2O_2 and the pH was adjusted with dilute HCl to pH 3-4. The pH was accurately checked with pH meter using micro pH-probe and the solution was made to 5.0 ml. with 0.9% NaCl.

2.4. Loading of W-188 into the generator

Because of low activity(<100 mCi) of W-188 to be loaded and the Re-188 product intented for laboratory use only, fumehood was used as working station together with 2 inchs thick lead brick as radiation shielding. The generators and W-188 solution were brought into the fumehood behind lead shielding and the desired W-188 activity amounts for each generator were dispensed in to glass vials under lead shield. The W-188 activity was loaded into each generator by mean of peristaltic pump with a flow rate less than 1.0 ml/min as showed in figure 3 then followed by washing with 50 ml.0.9%NaCl. After that, the generators were eluted for at least two times on day 3 and day 7 and all the eluted solution were kept for quality control.

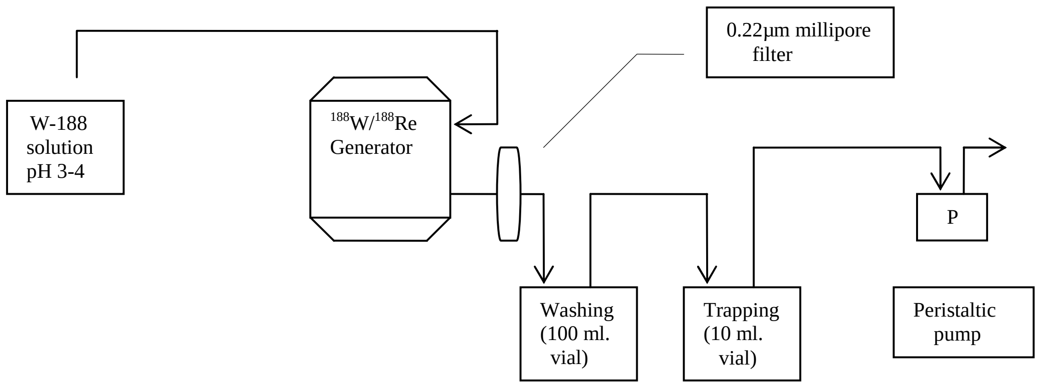


Figure 3 Diagram show loading of W-188 into the generator

2.5. Quality control

A series of quality controls were evaluated as follow

2.5.1 Elution Profile and determination of elution yield.

The elution profile of each generator was determine by eluting the generator with 10 ml 0.9%NaCl and each 1 ml fraction was collected and measured the radioactivity in dose calibrator. The fraction activities were plotted against elution volume or fraction number eluted.

To determine the actual activity of W-188 or Re-188, a sample of reference standard in equilibrium was counted in multi-channel analyzer using HPGE detector (G&G, ORTEC Model

672). The generator was eluted at every week interval in the first 3 months with bolus volume 4-7 ml and measured Re-188 activity eluted in dose calibrator. After that the generators were checked for their performances for 6 months.

2.5.2 ^{188}W breakthrough and Radionuclidic impurities

^{188}W breakthrough and radionuclidic impurities were determined by aging the elutes for one week (after most of Re-188 decayed) and their spectroscopy were detected and counted in multi-channel analyzer (MCA) with HPGE detector (G&G, ORTEC Model 672). A more rapid method was done by using alumina Sep-Pak® to remove most of Re-188 activity in the sample to be detected while W-188 was trapped in the column. After thorough washing of the Sep-Pak® with 0.9% saline, the Sep-Pak® was then counted in multi-channel analyzer for photo peak 227 keV and 290 keV of W-188.

2.5.3 Chemical purity; Aluminium breakthrough assessment and determination of inactive Tungsten (W-186)

-To control the contamination of aluminium in the eluted Re-188 product, the elutes were checked for Al-breakthrough by the method as follows;

Dispensed 1.0 mL acetate buffer pH 4.6 into 10 mL vial 10 vials, vial 1-6 added 0.5 mL standard Al solution 0.1, 0.2, 0.5, 1, 2, and 3 ppm. Vial 7-9 added 0.5 mL decayed solution of eluted product. A few drops of 0.1% mordant blue R1 was added in to each vial and diluted to 3.0 mL with distillate water. After color developed, the concentrations of Al in the sample were checked by comparing to that of standard references.

- Determination of inactive tungsten; a decayed Re-188 eluted product (> 2 months ageing) waschecked forW-186 byICP-MS technique using ICP-MS,PerkinElmer,Optima 5300 DV.

2.5.4 Radiochemical Purity

The radiochemical purity of $^{188}ReO_4$- products were determined by both ITLC/MEK as mobile phase system to confirm the chemical form of Re-188 Perrhenate ($^{188}ReO^-_4$) and by detecting its photo peak 155 keV on multi-channel analyzer (MCA).

3. Experimental results

3.1 Elution profile and yields

Three ^{188}W/^{188}Re-generators with low activity W-188 loaded were made with successful performance and high quality Re-188 product obtained. The 1st and 2nd ^{188}W/^{188}Re-generators (Gen.1and Gen.2) were loaded with 25 mCi W-188 while the 3rd one (Gen.3) was 50 mCi W-188. All the generators were eluted with 4-6 ml 0.9% NaCl at every week (figure 4-5) in the first 3 months by using peristaltic pump, and after that once a month until most of W-186 activity was decayed for 6 months. The elution time interval is enough for the in growth of Rhenium-188 from the decay of Tungsten-188 to get equilibrium, resulting the elution yields for each generator in the first month were greater than 90% (22.5-27.6 mCi for Gen1, 22.3-27.4 mCi for Gen2 and 44.2-53.7 mCi for Gen3)

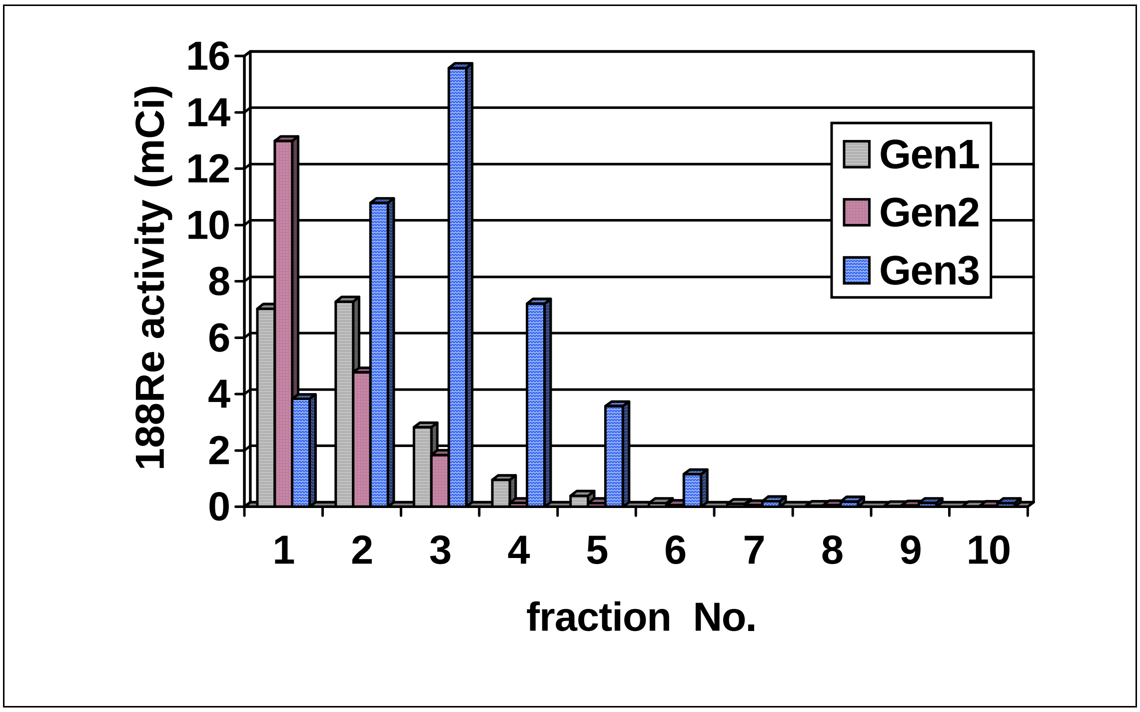


Figure 4. Elution profile of three ^{188}W/^{188}Re-genertors (1 ml/fraction)

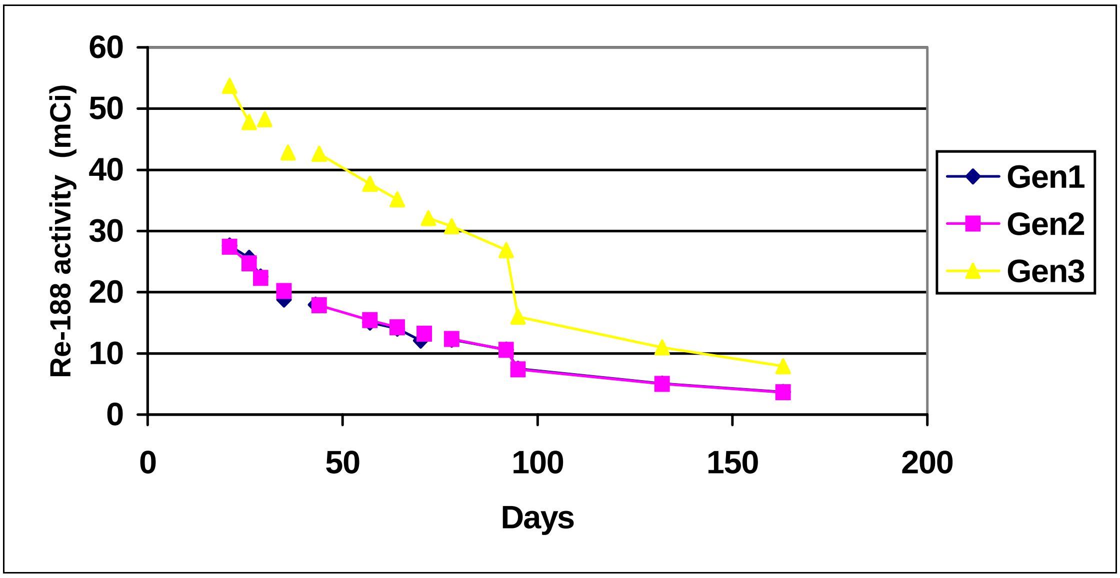


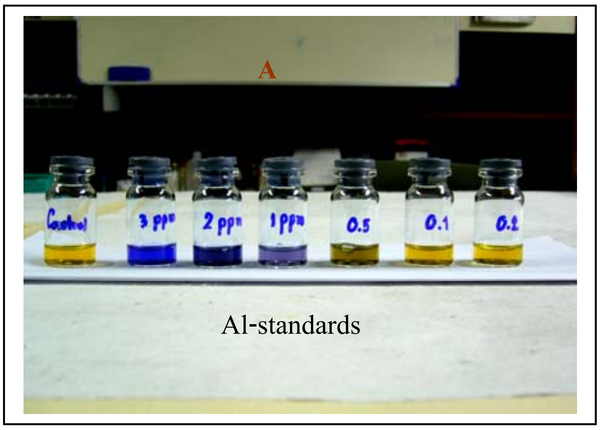
Figure 5. Elution yields of $^{188}W/^{188}Re$ genertors

3.2. Radionuclidic purity

The determination of Tungsten-188 breakthrough by the method describe earlier, the W-188 breakthrough in the Re-188 products were less than 3 x 10^{-3}% while other radionuclide impurity like Os-191or Ir-192 were found in low level (< 2 x 10^{-4}% and< 3 x10^{-5}%, respectively).

3.3. Chemical purity

Chemical purity determinations for Al-breakthrough and W-186 (inactive) contamination were found to be less than 0.5 ppm Al (figure 6, A and B) and 1 ppm W-186 by ICP-MS.



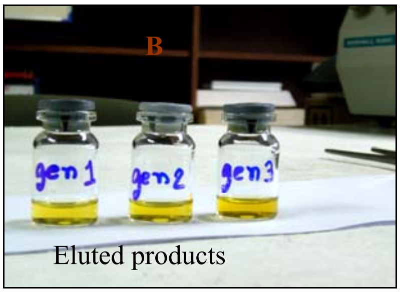


Figure 6. Determination of aluminium breakthrough of three generators was assessed by colorimetric of Re-188 eluted products (B) compared with Al standards (A).

3.4 Radiochemical purity

Radiochemical purity analysis of Re-188 products by ITLC-SG/MEK (figure 7) showed that more than 99.7% in the chemical form of perrhenate ($^{188}ReO_4^-$) and its photo peak 155 keV of Re-188 by MCA revealed more than 99.9% Re-188.

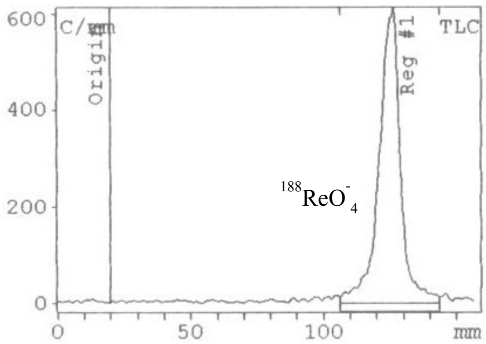


Figure 7. Re-188 product analyze by ITLC-SG/MEK system .

4. Conclusion

From the elution profile, more than 80% of Re-188 activity was obtained in the first 4 ml for Gen1 and Gen2 and the first 6 ml for Gen3 respectively. All generators were working well up to 6 months.

Results from quality controls indicated that the generators have good elution yields and high quality of Re-188 products with low contamination of W-186 and Al- breakthrough (USP allow < 10 ug Al/ml in an injection), radiochemical purity grater than 99.7% by ITLC (> 99.9% by MCA), W-188 - breakthrough was less than 3 x 10^{-3}% and low contamination of other nuclides. The Re-188 product, in the chemical form perrhenate ($^{188}ReO_4^-$), was suitable for research, laboratory experiments and/or medical applications, if the generator is prepared by aseptic technique.

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