2009 International Nuclear Atlantic Conference - INAC 2009
Rio de Janeiro,RJ, Brazil, September27 to October 2, 2009
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR - ABEN
ISBN: **978-85-99141-03-8**

DEVELOPMENT OF A ^{90}Sr/^{90}Y ELECTROCHEMICAL GENERATOR IN BRAZIL

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ABSTRACT

Yttrium-90 based radiopharmaceuticals for therapy are nowadays a powerful tool for cancer treatment. Among their main applications are radioimmunotherapy and radiosynoviortesis. In order to make this radioisotope widely available for research and application, it is necessary an in-house production with the help of a suitable generator. The electrochemical generator is a proper solution because there are no significant effects of the radiation on the generator itself. One of the main advantages of this method is that, by appropriately adjusting the volume of the solution used for final dissolution, ^{90}Y could be obtained at high radioactivity concentrations. The aim of this work is to show the preliminary results coming from the development of a ^{90}Sr/^{90}Y electrochemical generator at IPEN-CNEN/SP. In this generator, on applying a suitable electric potential, ^{90}Y can be selectively deposited at the cathode from a mixture of ^{90}Sr and ^{90}Y. The experiments were performed using a simple electrochemical device, with two Platinum electrodes acting as cathode and anode. Several parameters were varied, such as time and current of the electrodeposition, pH of the solution and cation concentration. After that the experiments were performed using the following gamma emitting radiotracers: ^{88}Y and ^{85}Sr wich were prepared irradiating Y oxide and Sr nitrate at the IEA-R1m Nuclear Reactor, respectively. The results so far showed that Sr is not electroplated in any condition and that up to 40% of Y can be selectively electroplated.

1. INTRODUCTION

Radionuclide generators continue to play an important role in providing radioisotopes for nuclear medicine. The availability of "carrier-free" daughter radioisotopes from generators is an important requirement for radiolabeling many therapeutic agents such as tumor-specific antibodies. Interest in generator systems continues to evolve to meet the needs for availability of radioisotopes to complement advances in other technologies, such as positron emission tomography (PET), radioimmunotherapy (RAIT), and radioimmunodetection (RAID). Advances in these technologies will continue to require the availability of radioisotopes, some which may have been previously considered impractical for use in nuclear medicine.

Use of radioisotopes in nuclear medicine is naturally dependent upon the availability of radioisotope production facilities. Reactor-produced radioisotopes are formed by interaction and/or capture of a neutron by the target nucleus, and often decay by β^- decay. Because of this prevalent decay mode, many reactor-produced radioisotopes thus have therapeutic applications.

An examination of the literature clearly indicates that current research is focused on the development of radioisotope generators which provide daughter radioisotopes for therapy (Table 1). Examples of therapeutic applications include radiolabeled antibodies, fragments, and peptides for radioimmunotherapy of tumors, particles for radiation synovectomy treatment of arthritis of the synovial joints [1], palliative treatment of bone pain from cancer and therapy of nonresectable tumors by administration through the tumor arterial supply [2]. An important requirement, however, is to minimize radiation dose to nontarget organs by modifying the chemical and pharmacokinetic properties of the radiolabeled agent. Although the daughter radioisotopes from a great number of radioisotope generators are either being studied and/or have been proposed for therapeutic applications [3-6, 7].

Table 1. Examples of radionuclide generator systems providing daughter radioisotopes for therapeutic applications

Parent	Half-life	Decay Mode	Emission E_{max}, MeV (%)	Daughter	Half-life	Decay mode	Emission E_{max}, MeV (%)
^{212}Pb	10.6 h	β^-	0.569 (12)	^{212}Bi	60.55 min	β^- (64)	2.27 (55.3)
			0.301 (83)			α (36)	6.09 (9.6)
			0.153 (5)				6.05 (25.2)
							8.78 (64.0)
^{194}Os	6.0 y	β^-	0.096 (67)	^{194}Ir	19.15 h	β^-	2.236 (89)
							1.92 (5.1)
^{103}Ru	39.6 d	β^-	0.064 (92)	^{103m}Rh	65.1 min	IT	Total conversion, X-rays only
^{90}Sr	28.8 y	β^-	0.546 (100)	^{90}Y	64.06 h	β^-	2.288 (100)
^{188}W	69.4 d	β^-	0.349 (99)	^{188}Re	16.9 h	β^-	2.116 (79)
							1.965 (20)

^{90}Y is the daughter formed by decay of ^{90}Sr and is a pure β-emitter with no gamma photons in its decay, although slow-down of beta particles in tissue results in formation of abundant "bremsstrahlung" radiation. A major advantage is that essentially unlimited amounts of the longlived ^{90}Sr parent (half-life, 28.8 years) are available from processing of reactor fission products. Because of its ready availability and high radiation dose, the clinical use of yttrium-90 for radioimmunotherapy has been widely explored. A disadvantage to the use of ^{90}Y is the absence of gamma photons for imaging; this is important for evaluation of biodistribution, tumor targeting and pharmacokinetics, which are important for safety, efficacy, and dosimetry estimation. The biodistribution of ^{90}Y can be evaluated, however, by detection of the bremsstrahlung radiation.

The ^{90}Sr/^{90}Y generator system has been of interest for a number of years, and several modifications have been reported for use in a radiopharmacy [8]. The interest for radiopharmaceuticals for the direct management of serious illness and specially cancer and rheumatism has increased during the last decade. At the moment radioisotopes of ^{89}Sr, ^{186}Re, ^{177}Lu, ^{153}Sm, ^{90}Y and ^{166}Ho are used in the routine practice of medical clinics. Yttrium-90 based radiopharmaceuticals for therapy are nowadays a powerful tool for cancer treatment. Among their main applications are radioimmunotherapy and radiosynoviortesis. Several favorable characteristics of this radioisotope make it an attractive candidate for such applications, such as suitable physical half-life (64.2 h), a LET useful for therapy ($E_{\beta max}$ 2.28 MeV), stable daughter (^{90}Zr) and simple chemistry. One important requirement for safe clinical use of ^{90}Y is the near-complete removal of ^{90}Sr, because it is a bone seeker and will cause bone marrow depression. Only 74 kBq (2μCi) of ^{90}Sr fixed in the bone is the current lifetime tolerance [9].

In order to make this radioisotope widely available for research and application, it is necessary an in-house production with the help of a suitable generator. Unlike ^{99}Mo/^{99m}Tc and ^{188}W/^{188}Re generators, there is not a ^{90}Sr/^{90}Y generator at the present time (at least not commercially available) that can give a “ready-to-use” ^{90}Y eluate. Most of the current separation techniques involves multiple steps such as solvent extraction, ion exchange or extraction chromatography either alone or in combination [10-17]. The electrochemical generator is a proper solution because there are no significant effects of the radiation on the generator itself. One of the main advantages of this method is that, by appropriately adjusting the volume of the solution used for final dissolution, ^{90}Y could be obtained at high radioactivity concentrations.

The aim of the present work is to show the preliminary results of a ^{90}Sr-^{90}Y electrochemical generator in development at IPEN-CNEN/SP. For this study, ^{85}Sr and ^{88}Y, both of which emit γ-rays, were used as tracers to investigate the separation efficiency.

2. EXPERIMENTAL

2.1. Materials

In this generator, the difference between the electrochemical potentials of Y^{+3} and Sr^{+2} is employed to achieve a clean and quick separation of ^{90}Y from ^{90}Sr. On applying a suitable electric potential, ^{90}Y can be selectively deposited at the anode from a mixture of ^{90}Sr and ^{90}Y. The experiments were performed using a simple electrochemical device (Figure 1), with two Platinum electrodes acting as cathode and anode. The apparatus was based on the reports of Rubel et al [18]. A stabilized DC power source (potentiostat unit) was used with the characteristics: 15 V compliance, 15 Ω resistance, a maximum current of 150 mA and 60 Hz for impedance (Tectrol, model TC 15-0015, BRAZIL).

The initial experiments were performed using non-irradiated materials (strontium nitrate, $Sr(NO_3)_2$, and yttrium oxide, Y_2O_3) and radioactive tracers (these salts were irradiated at the Nuclear Reactor IEA-R1m, producing ^{88}Y and ^{85}Sr as radiotracers). Nitric acid, ammonium hydroxide, acetone, and other reagents were analytical grade. For the electrolysis using materials non-irradiated, the analysis were performed through the mass difference $Sr(NO_3)_2$ and Y_2O_3 between the electrolysis, using a digital balance (Shimadzu, model AU220D). The gamma activity of ^{85}Sr and ^{88}Y was analyzed using a HPGe detector (Canberra, model 747, USA).

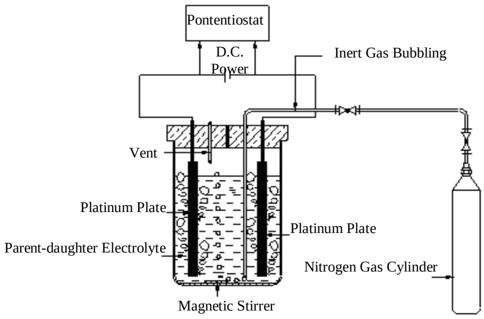

Figure 1. Schematic diagram of the electrochemical device used in experiments.

The electrolysis was performed in two stages: the first one aiming the electrodeposition of the desirable element (Y) and the second one, also called recovering stage, aiming the removal of Y from the electrode.

2.2. Electrolysis with non-irradiated materials

The electrodeposition stage used ~ 30 mL of a solution containing $Sr(NO_3)_2$ or Y_2O_3 in 1 M HNO_3. During the experiments, N_2 gas was gently bubbled in the electrolytic solution which was also stirred all the time using a magnetic stirrer. The parameters studied were: time of electrodeposition (between 30-240 minutes), current and voltage applied (60 and 120 mA; 3.0-6.0 V, respectively); pH of the electrolyte solution (1.5-5.0 using 1 M NaOH to adjust) and the concentration of Y. The effect of the presence of N_2 was also studied. The Pt electrodes were weighted before and after the electrodeposition in order to evaluate the electrodeposition yield.

The second stage (recovery) was performed removing the electrodes from the electrodeposition experiment, placing them into a clean 0.001-1 M HNO_3 solution, reverting the polarity with constant potential and current for a time ranging from 5 to 30 minutes. There was no N_2 bubbling, nor stirring in this stage. Again, the electrodes were weighted after the experiments, to evaluate the recovery yield of Y.

2.3. Electrolysis with radiotracers materials

The electrolysis process was performed with a mixture of irradiated $Sr(NO_3)_2$ and irradiated Y_2O_3. These materials were irradiated at the Nuclear Reactor IEA-R1m (IPEN/CNEN-SP), producing ^{88}Y (gamma emitter, $t_{1/2}$=106.64 days) and ^{85}Sr (gamma emitter, $t_{1/2}$=64 days).

The electrodeposition and reversion stages were performed in the same way as discussed in 2.2. The electrodeposition was made at pH 3.5-4.0, current of 60 mA and average voltage of 4.0 V. The electrodeposition time varied between 30 and 90 minutes. The solutions were analyzed by γ-spectroscopy before and after the electrodeposition in order to evaluate the electrodeposition yield, using a HPGe detector. The recovering stage was performed during 10 minutes, and the recovery yield was evaluated measuring the solutions before and after the process in a HPGE detector.

At the end of an experiment, the electrodes were washed with 3 M HNO_3 and acetone to clean them up.

3. RESULTS AND DISCUSSION

3.1 Electrolysis with non-irradiated material

The results of the electrodeposition of Y as function of the electrodeposition time, variation of pH and applied current are shown in Figures 2, 3 and 4, respectively.

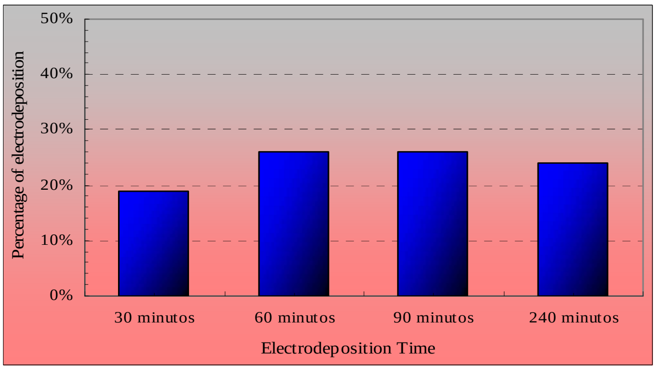

Figure 2. Electrodeposition of yttrium as a function of electrodeposition time.

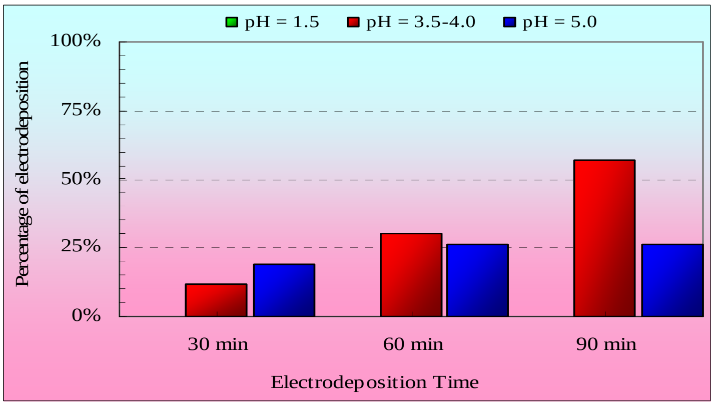

Figure 3. Electrodeposition of yttrium as a function of electrodeposition time and different values of pH.

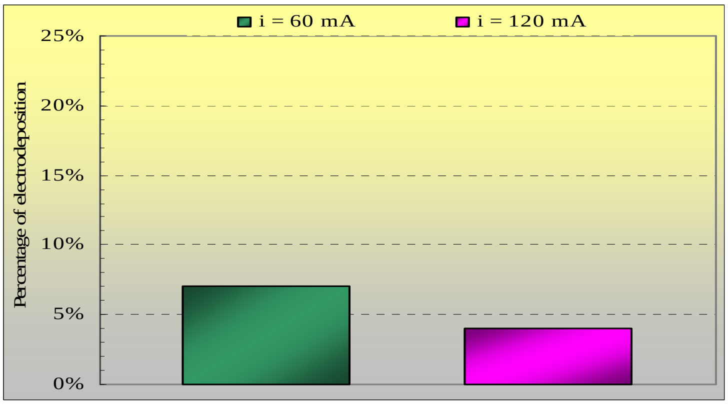

Figure 4. Electrodeposition of yttrium as a function of applied current.

The best results were achieved with electrodeposition time between 60 and 90 minutes, pH between 3.5 and 4.0 and current of 60 mA with an average voltage of 5.0 V. Longer electrodeposition times can lead to the removal of Y from the electrode, whereas short times gave reduced electrodeposition yields. The effect of the best pH conditions also increased the electrodeposition yields for a 90 minutes length. The overall best electrodepositions yield was about 60 % for Y.

The study of different concentrations of Y in the electrolytic solution is show in Figure 5. The results show that the three concentrations studied gave yields higher than 80 %. The best results of electrolysis were obtained with low concentrations of Y_2O_3, with yield for Y of about 95 %.

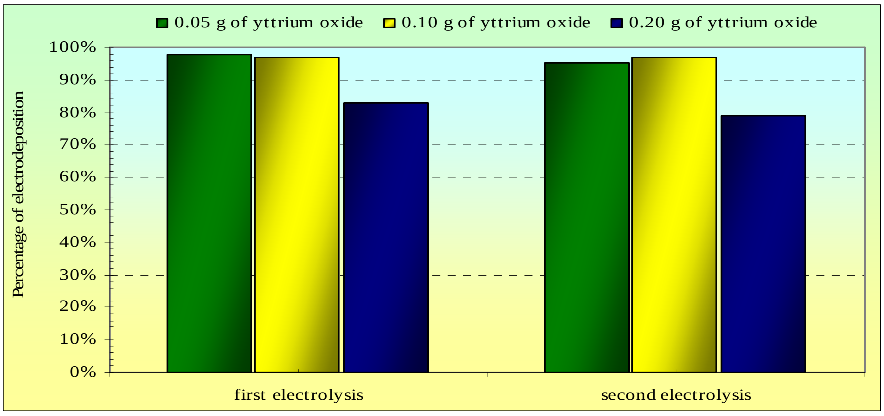

Figure 5. Electrodeposition of yttrium as a function of electrodeposition time and different quantities of yttrium oxide.

The presence of bubbling gas N_2 in the solution during the electrodeposition was studied. According to the Table 2, it's possible to notice that N_2 bubbling is necessary during the electrodeposition, independent of the quantity of Y_2O_3 in solution, because it releases the gases produced during electrolysis as well as it keeps the solution in dynamic form. The table also shows the advantage of the use of low concentrations of Y_2O_3 in the solution.

Table 2. Effect of the N_2 bubbling during the electrodeposition of Y.

Electrolysis	Mass of yttrium oxide	Percentage of Y electroplated
With N_2	0,20 g	11%
	0,05 g	27%
Without N_2	0,20 g	8%
	0,05 g	6%

The results of the experiments of recovery of Y from the electrode are shown in Table 3. The best results were achieved using a clean solution of 1 M HNO_3 even in shorter times, when compared to the use of 0.001 M HNO_3.

Table 3. Recovery yields for Y in clean solution with different concentrations of HNO_3.

0.001 M HNO_3	
Time of recovering	Percentage of recovery
15 minutes	83%
30 minutes	79%
1 M HNO_3	
Time of recovering	Percentage of recovery
5 minutes	97%
10 minutes	97%

The experiments of electrodeposition of Sr showed that in all conditions studied there was no significant electrodeposition of Sr. This is the basis of the proposal method for preparation of the ^{90}Sr-^{90}Y generator.

3.2 Electrolysis with radioactive materials

After the parameters established with non radioactive compounds, a electrolysis was performed with a mixture of ^{85}Sr and ^{88}Y, using the best conditions of electrodeposition: current of 60 mA, initial pH = 3.5-4.0 with final pH = 2.5 in each electrolysis, bubbling N_2, low concentration of yttrium oxide in the solution and recovery with 1 M HNO_3 with the same pH of the previous solution (Figure 5). It can be observed that in the first 30 minutes of electrolysis, there was no yttrium electrodeposition. Only after 60 minutes, yttrium was obtained with a electrodeposition yield of 30 % and recovery of 70 % and less than 10 % of ^{85}Sr being electroplated together with ^{88}Y. There was no significant electrodeposition with a length of 90 minutes.

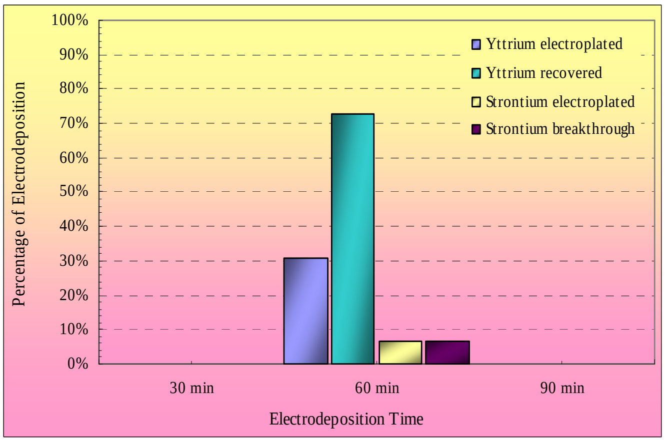

Figure 5. Percentage of electrodeposition of mixture (^{85}Sr+^{88}Y) radioactive solution as function of electrodeposition time.

4. CONCLUSIONS

An electrochemical separation procedure has been successfully demonstrated for the separation of Y from Sr, with low contamination with Sr. These preliminary results are useful for planning the next experiments involving the use of the pair ^{90}Sr/^{90}Y. This particular method has practical application and is susceptible to the experimental conditions, so one must be very careful during all the process. The operational cost of such a generator will be very low and could provide a permanent supply of ^{90}Y suitable for therapeutic application.

ACKNOWLEDGMENTS

This work is performed as part of the International Atomic Energy Agency (IAEA) CRP on "Development of Generator Technologies for Therapeutic Radionuclides." The authors wish to acknowledge CNPq for granting a fellowship for this work.

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