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Development of methodology for the preparation of ^{90}Sr-^{90}Y generators

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ABSTRACT

Yttrium-90 is a radioisotope of interest in the Nuclear Medicine field. It is considered one of the most useful and important radionuclides for radioimmunotherapeutic applications, and it is promising for certain applications in cancer therapy. Another important application of ^{90}Y is radiosynoviorthesis. This radionuclide has a half-life of 64 h, long-range beta emissions (maximum energy 2.3 MeV) and it decays to a stable daughter with no undesirable intermediate nuclides. Yttrium-90 can be obtained conveniently and inexpensively, in a carrier free form, as a radionuclide generator product by decay of its 28-yr parent, Strontium-90 (^{90}Sr). ^{90}Sr is a fission product present in large quantities in high level waste generated from the reprocessing of spent nuclear fuel but it requires its processing for recovery followed by purification to very high levels of radionuclidic and chemical purity that can be used as raw material for generator feed. The ^{90}Sr-^{90}Y generators could be used for several months to several years due to the long half-life of ^{90}Sr. Several methods for the separation of ^{90}Y from ^{90}Sr utilizing solvent extraction and ion exchange have been reported in the literature. Because of simplicity, the ion exchange methods are most commonly used in this generator systems. The objective of this work is to develop a methodology for the preparation of ^{90}Sr-^{90}Y generators using a cation exchange resin method. ^{90}Sr is strongly adsorbed in the resin and ^{90}Y is eluted in 0.003M EDTA. The preliminary results will be shown together with the radionuclidic quality control results.

1. INTRODUCTION

In recent years, investigators have developed site-specific delivery of radionuclides for various applications involving the treatment of cancer. Yttrium-90 has a relatively short half-life (*$T_{1/2}$= 64.02 h*) and a stable daughter (^{90}Zr). Moreover, yttrium-90 emits β-radiation (Max. 2.28 MeV) and has no gamma-rays, what makes this nuclide very attractive for therapeutic applications. Yttrium-90 results from the decay of reactor-produced ^{90}Sr according to the following decay scheme[1,3]:

$$^{235}\mathrm{U} \xrightarrow{\text{Fission}} \underset{T_{1/2}=28{,}82\ \mathrm{y}}{^{90}\mathrm{Sr}} \xrightarrow{\beta^-} \underset{T_{1/2}=64{,}06\ \mathrm{h}}{^{90}\mathrm{Y}} \xrightarrow{\beta^-} {}^{90}\mathrm{Zr}(stable)$$

Reactor-produced parents provide radionuclides for therapeutic applications that are readily available at a potentially lower cost. The parent should have a long half-life and decay to a daughter with good yield. Low parent breakthrough without loss of performance is necessary if generators are to be productive for long periods. The production of ^{90}Y through a generator system, from the decay of ^{90}Sr, has many advantages, such as the fact that the final product is carrier-free, is less costly, and has long-term reuse capability. However, one must note that strontium-90 (*$T_{1/2}$= 28.8 y*) as a bone-seeker produces bone marrow depression. Therefore, finding a satisfactory separation method for obtaining yttrium-90 is very important. Only 74kBq of ^{90}Sr fixed in the bone is the current lifetime tolerance.

For these reasons, there is widespread interest in the use of ^{90}Y for various therapeutic applications, including radiolabeled antibodies for tumor therapy, radiolabeled particles for irradiation of malignant tumors in the liver, irradiation of solid tumors and treatment of rheumatoid arthritis of the knee joint. The development of tumor-specific monoclonal antibodies and ^{90}Y labeled particles for radionuclide synovectomy has created a greater demand for ^{90}Y. Table 1 shows the properties of ^{90}Y, along with other reactor-produced radionuclides with wide medical applications [1].

Table 1. Properties of radionuclides for use in radionuclide synovectomy.

Radioisotope	Half-life	Emissions	Maximum β energy (MeV)	Soft-tissue range (mm) Max	Soft-tissue range (mm) Mean
Dysprosium-165	2.3 h	β	1.3	5.0	1.4
Erbium-169	9.5 d	β	0.34	1.0	0.3
Gold-198	2.7 d	β	3.6	3.6	1.2
Phosphorus-32	14.0 d	β	1.7	7.9	2.6
Rhenium-186	3.7 d	β	0.98	3.6	1.2
Rhenium-188	16.9 h	β	2.1	11.0	3.0
Yttrium-90	2.7 d	β	2.2	11.0	3.6

Recently developed yttrium generators can provide ^{90}Y that is chemically and radiochemically acceptable for therapeutic applications. Numerous methods for the separation of ^{90}Y from ^{90}Sr utilizing ion exchange, solvent extraction, precipitation, filtration of colloidal yttrium hydroxides and “residue adsorption” of yttrium hydroxide have been reported in the literature[4]. Among these, because of simplicity, the ion exchange methods are most commonly used in the generator systems for the separation of ^{90}Y from ^{90}Sr in very pure form. Most of these generators have been using the Dowex-50 cation exchange resins, that can retain strontium-90 while the yttrium-90 daughter is eluted in various solvents such as citrate, oxalate, acetate, and ethylenediaminetetraacetic acid (EDTA)[2,3].

The objective of this work is to develop a methodology for the preparation of ^{90}Sr-^{90}Y generators using a cation exchange resin method. ^{90}Sr is strongly adsorbed in the resin and ^{90}Y is eluted in 0.003M EDTA. The preliminary results will be shown together with the radionuclidic quality control results using also strontium-85 (gamma-rays emitter) as a tracer to investigate separation efficiency.

2. MATERIAL AND METHODS

Two generators were developed, both using cation exchange resins in order to separate ^{90}Y from ^{90}Sr. Solution containing the pair ^{90}Sr/^{90}Y was prepared in 1M HNO_3 and ethylenediaminetetraacetic acid (EDTA) was used as the eluant. For the development this work, all reagents used were of analytical grade and all experiments were accomplished at Radiopharmacy Center at IPEN/CNEN-SP.

2.1. Standardization of the samples of $^{90}Sr/^{90}Y$ and ^{90}Y.

A liquid scintillation analyzer (LSC) (Tri-Carb 1900 TR, Packard Canberra Company) and a liquid scintillation cocktail (Ultima Gold XR) were available for determination of the $^{90}Sr/^{90}Y$ and ^{90}Y samples standards. A pure sample of ^{90}Y which was available at the Institution was analyzed and the spectrum was recorded. The samples were counted for 60 minutes.

2.2. First ^{90}Sr-^{90}Y generator

The first generator consisted of a glass chromatographic column with a 1cm diameter and 2cm high fitted with a glass frit at the bottom and fitted ends with plugs. The column was assembled vertically.

Before being loaded into the column, the AG 50W-X4 (100 – 200 mesh, H^+ form) cation exchange resin was first washed in a Becker with distilled water, 0.1M HCL and 0.1M NaOH and finally washed with distilled water, for its activation. The whole process was repeated three times. After the activation, the resin was loaded into 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 pH= 4.8.

The loading solution was prepared diluting 0.1 ml (185MBq) of ^{90}Sr in 100 ml HNO_3 1M. From this solution, 2 ml (3.7MBq) were percolated into the column followed by 5 ml of EDTA solution. After allowing 24 hr for adsorption, the column was washed with EDTA twice and after three days the generator was eluted with 15 ml of EDTA solution and successively every week from then on. The flow rate was 1.63 mL/min. Activities of ^{90}Y in the samples were determined by liquid scintillation counting (LSC) for 30 minutes for the recovered.

2.3. Second ^{90}Sr-^{90}Y generator

The second generator consisted of a glass chromatographic column with a 1cm diameter and 8cm high and was assembled vertically. In this generator, gamma-ray emitter ^{85}Sr, was used as a tracer to investigate the separation efficiency.

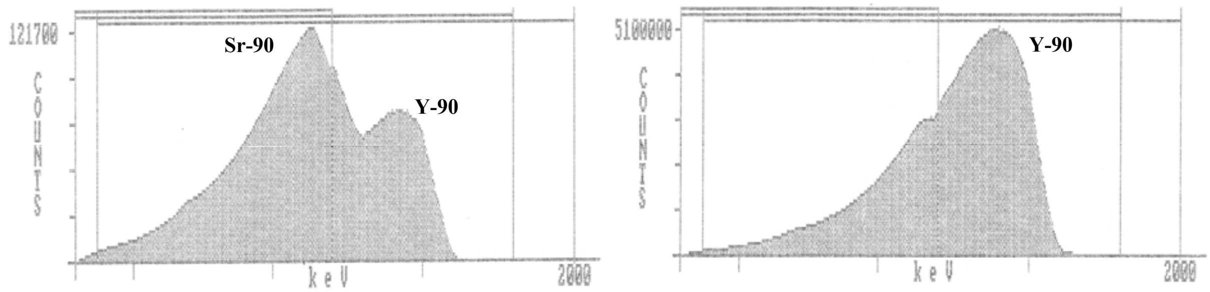
Before being loaded into the column, the AG 50W-X8 (200 – 400 mesh) resin was converted to the Na^+ form with 1M NaOH and then washed with distillated water. The whole process was repeated three times. After the activation, the resin was loaded into column and conditioned with 100 ml of EDTA solution at pH= 4.8.

The loading solution was prepared with 20 µl of ^{90}Sr (*55.5MBq*) in 1M HNO_3 solution and 300 µL of ^{85}Sr (*28.7MBq*). This solution was percolated into the column and 4 ml of EDTA solution was percolated. Immediately after this process, the column was washed five times with the EDTA solution with the same volume. After two days, a 15 ml weekly elution was performed. In this condition the flow rate was 0.48 mL/min. Activities of ^{90}Y in the samples were determined by liquid scintillation counting (LSC) for 30 minutes and the activity of ^{85}Sr determined by gamma ray spectroscopy using a HPGe detector. A paper chromatographic method was also performed for the quality control of this generator system, where a small aliquot of the elution obtained is spotted on a paper (Whatman 3) and then chromatography is carried out by dipping the spotted strip into an appropriate solvent (0.9% NaCl solution) contained in a jar. In this case, the R_f of ^{90}Y is zero and the R_f of ^{90}Sr is about 1.0.

3. RESULTS AND DISCUSSION

3.1. Standardization of the samples of ^{90}Sr/^{90}Y and ^{90}Y.

Figs. 1 (a) and (b) show the beta spectrum of pair ^{90}Sr/^{90}Y and ^{90}Y. According to Fig. 1a, it was observed that the two beta components in the compound spectra (^{90}Sr/^{90}Y) can be easily resolved. In Fig. 1b it was recorded a single beta spectra from ^{90}Y to be used as a reference in order to check the elution efficiency of the generator. The energy channel used was between 50 – 800 keV.



(a) **(b)**

Figure 1. Beta spectra of ^{90}Sr/^{90}Y (a) and ^{90}Y (b).

3.2. First ^{90}Sr-^{90}Y generator

Fig. 2 shows the beta spectrum of the elution of this generator.

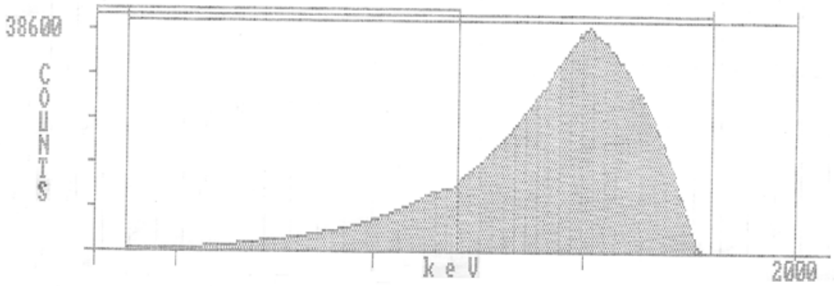


Figure 2. Beta spectrum of the elution of the first ^{90}Sr/^{90}Y generator.

The elution curves for this generator are illustrated in Fig. 3. The behavior of the generator as a function of eluted volume can be analyzed through these curves. An increase in the ^{90}Y with the increasing volumes is observed. This increasing is due the ^{90}Sr radioactive decay and ^{90}Y growth. The overall yield of the generator was very low.

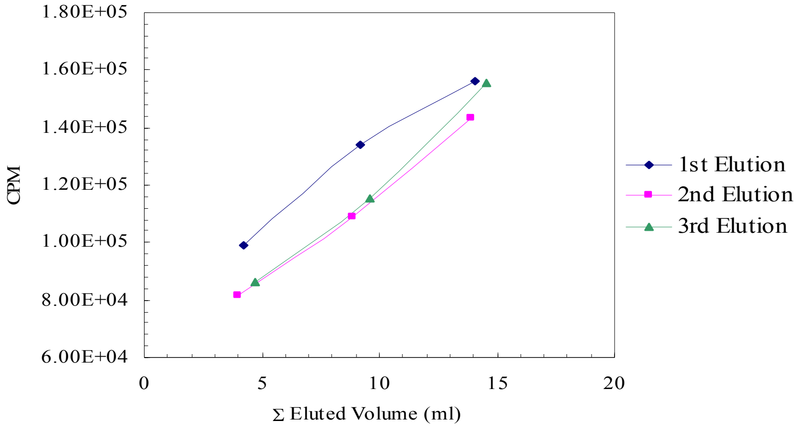


Figure 3. Elution curves of the first ^{90}Sr/^{90}Y generator.

3.3. Second ^{90}Sr-^{90}Y generator

Fig. 4 shows the beta spectrum of the elution of this generator.

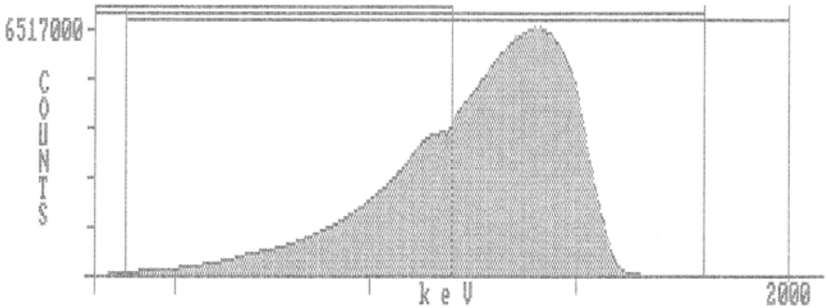


Figure 4. Beta spectrum of elution of the second ^{90}Sr/^{90}Y generator.

The elution curves for this generator are shown in Fig. 5.

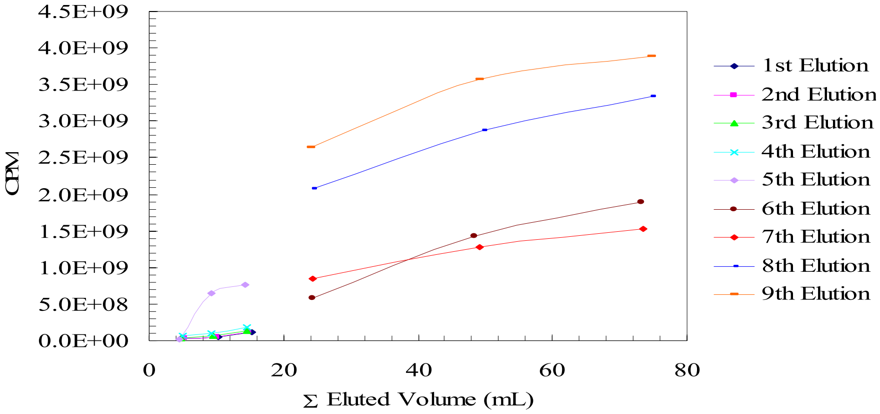


Figure 5. Elution curves of second ^{90}Sr/^{90}Y generator.

It can be seen an increase in the ^{90}Y activity with increasing elution volume. Between the 1st and 4th elution with the activity remained nearly constant. From the 5th elution on, an abrupt increase in the activity was noticed leading to an increase in the elution volume. Efficiency yields greater than 65% were achieved with this generator. The quality control showed that ^{90}Y had no ^{90}Sr or ^{85}Sr impurities, inside the detection limits of the detectors used in the paper chromatography technique.

4. CONCLUSIONS

A methodology for the preparation of ^{90}Sr-^{90}Y generators was developed using a cation exchange resin method. In this method, ^{90}Sr is strongly adsorbed in both generators, and ^{90}Y eluted using 0.003M EDTA as eluent. The preliminary results presented here are very promising, showing that the present methodology is able to separate these two nuclides. Further experiments must be performed in order to improve the ^{90}Y yields of the whole process in order to gradually increase the generator activity.

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