Process for Separation of Y-90 from Sr-90 in HNO\textsubscript{3} Using Combined Solvent Impregnated Resins of D2EHPA/Dodecane and CMPO/TBP

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ABSTRACT

Yttrium-90 (Y-90) is a radioisotope having a short half-life of 64 hours and emitting high energy beta radiation at 2.28 MeV. It becomes one of the radionuclides being used for the targeted cancer treatment. Y-90 can be generated from radioactive decay of strontium-90 (Sr-90), which is one of the fission products of uranium fuel in the nuclear reactor. Y-90 must be highly pure and free from Sr-90 and other metal ions to achieve high efficient uses. Process for separation and purification of Y-90 from Sr-90 by extraction chromatographic technique has been investigated using two columns packed with different types of solvent impregnated resins namely, 0.3 M di(2-ethylhexyl) phosphoric acid (D2EHPA) in dodecane and 1.0 M n-octyl(phenyl)-N,N-diisobutylcarbamoyl-methylphosphine oxide (CMPO) in tri-n-butyl phosphate (TBP). Feed solutions used in the study were the mixture of the stable isotopes Y and Sr in HNO\textsubscript{3} at the concentration ratio Y:Sr of 0.18:756 simulating the equilibrium composition ratio of their radionuclides, Y-90 and Sr-90. Yttrium product yield and recovery of Sr were compared with the separation using a set of commercially available Sr resins and RE resin. High purity of Y product could be obtained from combined columns of D2EHPA and CMPO resins and yield of Y higher than 75% could be achieved. Performance of the in-house prepared resins was evaluated by separation the sample of \textsuperscript{90}Sr-\textsuperscript{90}Y radionuclides in equilibrium. The extracted Y-90 was quantified for Sr-90 contamination by recounting after 30 days decayed with about 1x10\textsuperscript{-5} Bq \textsuperscript{90}Sr per Bq of \textsuperscript{90}Y. The extraction chromatographic process was found to be easy to operate continuously and there is no need for the treatment of the intermediate solution in the process.

Keywords: solvent impregnated resin, yttrium-90, strontium-90, Sr resin, RE resin

1. INTRODUCTION

Targeted therapy using radiopharmaceuticals has been increasingly used for the treatment of various types of cancer. The carrier molecules such as peptides and antibodies usually have biological half-lives of a few hours to a few days. Hence, radioisotopes having short half-lives ranging from a few hours to a few days are useful for radionuclide therapy [1]. The use of short-lived radioisotopes has several advantages for radionuclide therapy, which includes higher rates of dose delivery and shorter hospital stay for the patients. However, the use of short-lived
radioisotopes for radionuclide therapy can also have some constraints such as issues associated with their delivery to the hospital and the need for frequent shipments. Then, radionuclide generators can provide the opportunity for in-house use on the needed basis and the cost of unit dose will be dramatically reduced.

Among the generator derived radioisotopes used for therapy, yttrium-90 (Y-90) has become a widely-used radionuclide in cancer therapy due to its physical properties which include a pure high energy β-emission at 2.28 MeV, while it has a short half-life of 64 hours which is comparable with the pharmacokinetics of many tumor targeting molecules. Moreover, the product of Y-90 decay is zirconium-90 (Zr-90) which is a stable isotope. The effectiveness of Y-90 in conjunction with antibodies for the treatment of several kinds of cancer has been reported [2,3]. Y-90 can be generated from the beta decay of strontium-90 (Sr-90), which is one of the main fission products of uranium in the nuclear reactor and Sr-90 can be obtained from the reprocessing of spent nuclear fuels [4,5]. A regular production of Y-90 from a purified Sr-90 solution is then possible. However, Y-90 must be highly pure and free from Sr-90 and other metal ions to have high efficient uses as Sr-90 can be accumulated in bones causing depression of marrow and the metal ions can interfere with the compound labeling [6]. Thus, the process for the separation and purification of Y-90 from Sr-90 is of great interest.

Different methods such as precipitation, solvent extraction, ion exchange and extraction chromatography [7-11] have been employed to separate and purify Y-90 from Sr-90. The extraction chromatography using solvent impregnated resins has been applied widely for trace metal separation and recovery. This method combines the advantages of both solvent extraction and ion exchange technique to increase mass transfer rate of target ions, high distribution and selective factors, simplicity of equipment and operation, and applicability for the processing of dilute solutions [12,13]. Such solvent impregnated resin can be used for preferential extraction of a species of interest, by impregnating the resin with a solvent containing a ligand specific for the species. It was reported that the organic solvent used to preferentially extract Y-90 from a solution at pH 1–2 to a solution of higher acidity was Di-(2-ethylhexyl) phosphoric acid (D2EHPA) and the solvent used to extract Y-90 from a highly acidic solution to a solution of much lower acidity was n-octyl(phenyl)-N,N-diisobutylcarbamoyl-methylphosphine oxide (CMPO) [14-16].

In this work, the suitable operating conditions for the separation process of Y-90 from Sr-90 by extraction chromatography was studied using individual and combined columns of in-house prepared solvent impregnated resins. Extraction yield of Y and recovery of Sr were compared with a couple of commercial solvent impregnated resins namely Sr resin and RE resin [9,17]. Yttrium-90 product was measured for contamination of Sr-90 by recounting after 30 days decayed and half-life confirmation.

2. MATERIAL AND METHODS

The experiments were carried out first using feed of stable isotopes of yttrium and strontium to determine the proper operating conditions for the separation process. Then the feed of radioisotopes Sr-90 in secular equilibrium with Y-90 (Sr-90/Y-90) was investigated at the selected conditions.

2.1 Feed of Y and Sr

Feeds of the stable isotope Y and Sr mixture in nitric solution were prepared from standard Y solution of 1,000 mg/L in 2% HNO₃ supplied by PlasmaCAL and standard Sr solution of 1,000 mg/L in 0.5 M HNO₃ supplied by Merck. Acidity of feed solution was adjusted to 0.3, 4 and 7 M HNO₃ and the concentrations of Y and Sr were set at 0.18 mg/L and 756 mg/L,
respectively. The concentration ratio of Y:Sr in the feed was fixed at 0.18:756 to simulate the composition ratio of their radionuclides, Y-90 and Sr-90, at equilibrium mixture used in the actual separation process. Sample of Sr-90/Y-90 radionuclides to be used as a starting feed solution was supplied by Polatom.

2.2 D2EHPA/Dodecane resin and CMPO/TBP resin

Amberlite XAD 16 resin from Sigma Aldrich with the particle size 560-710 µm was used as polymeric support in the preparation of solvent impregnated resins. Two solvents, 0.3 M D2EHPA in dodecane and 1 M CMPO in TBP, were employed. D2EHPA was supplied by Sigma Aldrich and dodecane was supplied by Merck. The reagents CMPO and TBP (tributyl phosphate) were supplied by Strem Chemicals and BDH Chemicals, respectively. All reagents were used as received. The in-house preparation of resin impregnated with each solvent was carried out in the following steps. The resins were first washed with deionized water followed by acetone and then dried in an oven at 60 °C before being used. After that, the dried resins were immersed in each solvent to which 20% hexane was added and stirred for 2 hours. The resulting impregnated resins were filtered and washed with deionized water. Then, the obtained 0.3 M D2EHPA/dodecane and 1 M CMPO/TBP impregnated resins were dried at 60 °C for 2 hours to let all the dissolved hexane and the attached water evaporated. The dried solvent impregnated resins were weighed to determine the amount of solvent adsorbed on the resins.

2.3 Sr resin and RE resin

Sr resin and RE resin used in the study having the size of 50-100 µm were obtained from Eichrom Industries. The first resin is polymeric resin impregnated with 1.0 M crown-ether (4,4'(5')-di-t-butylcyclohexano-18-crown-6) dissolved in octanol and the second resin is impregnated with 1.0 M n-octyl(phenyl)-N, N-diisobutylcarbamoyl-methylphosphine oxide (CMPO) dissolved in tri-n-butyl phosphate (TBP). Sr resin is Sr-selective resin while RE resin is rare-earths selective resin.

2.4 Extraction Chromatography

Each solvent impregnated resin was packed separately in 2-mL polyethylene columns with an inner diameter of 1 cm and a height of 3 cm. D2EHPA column and CMPO column was packed with 0.3 M D2EHPA/dodecane impregnated resin and 1 M CMPO/TBP impregnated resin, respectively. Both in-house solvent impregnated resins were prepared from 0.25 g of dry XAD 16 resin. Each column was tested for the proper conditions in separation of Y from Sr in nitric solution. Then, D2EHPA column and CMPO column were connected in series as shown in Figure 1. The set of combined Sr columns and RE column used for the separation of Y from Sr was also set as shown in Figure 2. The involved solutions were flowed through the columns according to the diagram shown in Figures 1-2. Feed was first loaded into first column followed by rinse solution and elute solution, respectively. All solutions were fed continuously at a constant flow rate of 0.3 mL/min. The effluent from the column was collected in 2-mL or 5-mL fraction and analyzed with ICP-AES (Perkin Elmer model Optima 5300 DV). For the feed of radioisotopes Sr-90/Y-90, the effluent was separately collected in fractions according to the solution acidity. The purity of yttrium in the product fraction was determined from its beta activity before and after one month storage which was about 10 half-lives of Y-90. The beta activity and count rate of the sample were measured using a dose calibrator (Capintec CRC-15 beta) and a scaler rate meter with GM detector (Ludlum model 2200 with 44-1 probe), respectively.
Figure 1. Diagram of Y and Sr separation with combined columns D2EHPA/dodecane resin and CMPO/TBP resin.

Figure 2. Diagram of Y and Sr separation performed with combined 3 columns of Sr resin and RE resin according to Horwitz et al. [9] and Pichestapong et al. [18].

2.5 Radiolytic Stability of D2EHPA/Dodecane and CMPO/TBP resins

Two sets of resins impregnated with 0.3 M D2EHPA in dodecane and 1.0 M CMPO in TBP were packed separately in 2-mL columns (D2EHPA resin and CMPO resin) and irradiated. Gamma irradiation was carried out with Co-60 at doses of 5, 10, 20 and 50 kGy. For beta irradiation, solution of $^{90}$Sr/$^{90}$Y mixture at secular equilibrium was used as beta radiation source and loaded into the resin packed columns. The radiation activity in each column was about 1 mCi and the exposure time was 96 and 168 hours which are equivalent to absorbed doses of 320 and 440 Gy, respectively. The irradiated and non-irradiated columns of both solvent impregnated resins were used individually to separate Y from Sr in HNO$_3$ as described earlier.

2.6 Separation of $^{90}$Y from Sample Mixture of $^{90}$Sr/$^{90}$Y in Secular Equilibrium

Strontium-90/Yttrium-90 with activity of 14.77 mCi (measured with Capintec CRC15 beta dose calibrator) in 4 mL of 0.3 M HNO$_3$ was loaded into the set of D2EHPA and CMPO columns. The columns were rinsed and eluted as described according to Figure 1.

3. RESULTS

The experiments were carried out with each individual column of solvent impregnated resin and two sets of combined columns.

3.1 Separation of Y from Sr with D2EHPA/Dodecane resin

The separation of Y from 10 mL feed in 0.3 M HNO$_3$ using one column packed with 0.3 M D2EHPA/dodecane impregnated resins prepared from 0.10–0.30 g of dry resin were shown in Figure 3 and Table 1. Most of Sr was not adsorbed in the column, but Y was adsorbed and eluted into 7 M HNO$_3$ fraction. More than 99.9% of Sr remained in 0.3 M HNO$_3$ resulting in high separation efficiency and high purity of Y was obtained. However, traces of Sr were still found in 7 M HNO$_3$ fraction depending on the amount of resin used in the column. The recovery of Y in 7 M HNO$_3$ fraction depended on the amount of resin used in the column. The recovery of Y was increased from 45.79 to 89.69% as the amount resin used was raised from 0.1 to 0.3 g.

3.2 Separation of Y from Sr with CMPO/TBP resin

The feed used for a column of 1 M CMPO/TBP impregnated resin prepared from 0.10–0.20 g of dry resin was in 7 M HNO$_3$ and the concentration was similar to the feed used for RE resin. The separation results
are shown in Figure 4 and Table 2. Similarly, most of Sr in 7 M HNO₃ feed was also seen to flow through the column and only Y was adsorbed by this resin and eluted with 0.1 M HNO₃. More than 99% of Sr was separated in 7 M HNO₃ and traces of Sr were found in 0.1 M HNO₃. Although high purity of Y could be obtained from this process but some of Y was seen to be retained in 7 M HNO₃ resulted in moderate recovery of Y. The recovery of Y from the columns containing 0.1 and 0.2 g CMPO/TBP impregnated resin were 59.56 and 68.09%, respectively.

Table 1. Portions of Sr and Y in the effluent fractions from a column packed with 0.3 M D2EHPA/dodecane impregnated resin prepared from dry resin of 0.10, 0.20 and 0.30 g.

<table>
<thead>
<tr>
<th>Dry resin (g)</th>
<th>Fraction</th>
<th>Sr portion (%)</th>
<th>Y portion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>0.3 M HNO₃</td>
<td>100.00</td>
<td>54.21</td>
</tr>
<tr>
<td></td>
<td>7 M HNO₃</td>
<td>0.00</td>
<td>45.79</td>
</tr>
<tr>
<td>0.20</td>
<td>0.3 M HNO₃</td>
<td>99.995</td>
<td>23.08</td>
</tr>
<tr>
<td></td>
<td>7 M HNO₃</td>
<td>0.005</td>
<td>76.92</td>
</tr>
<tr>
<td>0.30</td>
<td>0.3 M HNO₃</td>
<td>99.97</td>
<td>10.31</td>
</tr>
<tr>
<td></td>
<td>7 M HNO₃</td>
<td>0.003</td>
<td>89.69</td>
</tr>
</tbody>
</table>

Table 2. Portions of Sr and Y in the effluent fractions from a column packed with 1 M CMPO/TBP impregnated resin prepared from dry resin of 0.10 and 0.20 g.

<table>
<thead>
<tr>
<th>Dry resin (g)</th>
<th>Fraction</th>
<th>Sr portion (%)</th>
<th>Y portion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>7 M HNO₃</td>
<td>99.89</td>
<td>40.44</td>
</tr>
<tr>
<td></td>
<td>0.1 M HNO₃</td>
<td>0.11</td>
<td>59.57</td>
</tr>
<tr>
<td>0.20</td>
<td>7 M HNO₃</td>
<td>99.27</td>
<td>31.91</td>
</tr>
<tr>
<td></td>
<td>0.1 M HNO₃</td>
<td>0.73</td>
<td>68.09</td>
</tr>
</tbody>
</table>
3.3 Separation of Y from Sr with Combined D2EHPA resin and CMPO resin

The combination of 1 column packed with 0.3 M D2EHPA/dodecane resin and 1 column packed with 1 M CMPO/TBP resin, both prepared from 0.2 g dry resin, was able to separate Y from Sr in feed of 0.3 M HNO₃ effectively as shown in Figure 5 and Table 3. It could be seen that most of Sr was not adsorbed while most of Y was adsorbed by both solvent impregnated resins in the columns. More than 99.9% of Sr went through the column of D2EHPA/dodecane resin and was collected in the 0.3 M HNO₃ fraction. This first column plays an important role in separation most of Y from Sr. The second column containing CMPO/TBP resin then can be used to purify Y in 7 M HNO₃ which is the eluent from the first column as traces of Sr still contaminate this solution. The recovery of Y in 0.1 M HNO₃ of 77.40% was lower than that from the Sr-RE combined columns. The trace of Sr in the Y product in 0.1 M HNO₃ was also non-detectable.

3.4 Separation of Y from Sr with Combined Sr resin and RE resin

The adsorption behaviors of Sr resin and RE resin were reported in our previous studies [18]. The combination of 3 Sr columns and 1 RE column was found to be able to separate Y from Sr in 4 M HNO₃ effectively as shown in Figure 6 and Table 4. The recovery of Y in 0.1 M HNO₃ fraction or fraction of Y product was 83.81%. Trace of Sr in the Y product was non-detectable as the Sr concentration may be lower than 0.0003 mg/L which is the detection limit of the ICP-AES spectrometer for Sr species.

3.5 Radiolytic stability of D2EHPA/dodecane and CMPO/TBP resins

Yield of Y and Sr in each effluent fraction from the γ-irradiated resins of 0-50 kGy were calculated from their concentration and shown in Tables 5 and 6. It was seen that most Y in the feeds were adsorbed by both resins and later eluted with resulting in high separation efficiency (more than 92%) and high purity of Y could be obtained. Only γ-irradiated D2EHPA resin at 50 kGy has lost some adsorption ability of Y and then yielded less Y product. This indicated that γ-radiation dose below 20 kGy seems to have no effect on the separation efficiency of these resins.

Yield of Sr and Y portions in each effluent fraction from the β-irradiated D2EHPA resin
and CMPO resin were determined from their concentration and shown in Tables 7 and 8. It was seen that in the case of D2EHPA resin, the adsorption capacity was very similar as more than 98% of Y was adsorbed and separated from Sr. In the case of CMPO resin, the adsorption of Y was seen to decrease from 96 to 90% on the β-irradiation at 320 and 440 Gy. This means that exposure to β-radiation more than 320 Gy the CMPO resin seemed to have decreasing Y adsorption ability.

3.6 Separation of Y-90 from Sample Mixture of $^{90}$Sr/$^{90}$Y in Secular Equilibrium

The combined columns of D2EHPA resin and CMPO resin was used to separate radioisotope Y-90 from Sr-90 in 0.3 M HNO$_3$ with a gross activity of 546.49 MBq (14.77 mCi). The Y-90 obtained in the 0.1 M HNO$_3$ fraction had a gross activity of 286.75 MBq (7.75 mCi). The purity of Y-90 product was determined from its count rate measurement before and after 30-day storage which were 250,000 and 3 cpm, respectively. Then, the activity ratio of Sr-90 to Y-90 was calculated to be about 1.2 x 10$^{-5}$ Bq. This $^{90}$Sr/$^{90}$Y activity ratio was well in the limitation for approval of Ytracis® (Y-90 product of CIS, France), 0.74 MBq $^{90}$Sr per 37 GBq $^{90}$Y (or 2 x 10$^{-5}$ Bq $^{90}$Sr / Bq $^{90}$Y) [6].
3.7 Half-life determination of the extracted Y-90 product

From Figure 7, the relationship of count rate of Y-90 sample in ln-function versus time was linear with $r^2$ of 0.9991 and the slope of the graph indicated the decay constant value ($\lambda$). The calculated half-life of Y-90 according to the decay equation was 64.77 hours or 2.70 days which was slightly longer than 64.2 hours, the usual half-life of Y-90. The longer half-life value of Y-90 product indicated a trace of Sr-90 contamination.

$$y = -0.0107x + 10.226$$
$$R^2 = 0.9991$$

**Figure 7.** Decay curve of extracted Y-90; half-life determined from slope of the linear curve.

### Table 7. Sr and Y portions in the effluent fractions from β-radiated D2EHPA resin column.

<table>
<thead>
<tr>
<th>β-radiated D2EHPA resin, Gy</th>
<th>Sr portion %</th>
<th>Y portion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 M HNO$_3$</td>
<td>99.83</td>
<td>0.17</td>
</tr>
<tr>
<td>7 M HNO$_3$</td>
<td>1.87</td>
<td>98.13</td>
</tr>
<tr>
<td>320</td>
<td>99.97</td>
<td>0.03</td>
</tr>
<tr>
<td>0.3 M HNO$_3$</td>
<td>0.31</td>
<td>99.69</td>
</tr>
<tr>
<td>7 M HNO$_3$</td>
<td>0.32</td>
<td>99.68</td>
</tr>
<tr>
<td>440</td>
<td>99.92</td>
<td>0.08</td>
</tr>
</tbody>
</table>

### Table 8. Sr and Y portions in the effluent fractions from β-radiated CMPO resin column.

<table>
<thead>
<tr>
<th>β-radiated CMPO resin, Gy</th>
<th>Sr portion %</th>
<th>Y portion %</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 M HNO$_3$</td>
<td>95.30</td>
<td>4.70</td>
</tr>
<tr>
<td>0.1 M HNO$_3$</td>
<td>3.45</td>
<td>96.55</td>
</tr>
<tr>
<td>7 M HNO$_3$</td>
<td>96.75</td>
<td>3.20</td>
</tr>
<tr>
<td>0.1 M HNO$_3$</td>
<td>9.42</td>
<td>90.58</td>
</tr>
<tr>
<td>320</td>
<td>96.31</td>
<td>3.69</td>
</tr>
<tr>
<td>9.25</td>
<td>90.75</td>
<td></td>
</tr>
</tbody>
</table>

4. DISCUSSION AND CONCLUSION

The performance of in-house prepared D2EHPA resin and CMPO resin used to separate Y from Sr in HNO$_3$ was carried out with individual column and combined columns. Separation of Y from Sr with the combined resins was comparable to the use of combined Sr resin and RE resin, however it has slightly lower recovery yield. On exposure with γ radiation, Y adsorption property of the D2EHPA impregnated resin was decreased at activity more than 50 kGy. Beta irradiation more than 320 Gy moderately affected the CMPO impregnated resin. Radiolytic stability of the CMPO impregnated resin was consistent with the work of Horwitz et al [9]. From our results, increase activity of Sr-90 to curies amount would be degrade the impregnated resin. Therefore, the resins should be use for small scale (approx. below 100 mCi) or limit multiple cycles use. Considering the cost of using Sr resin and D2EHPA resin, Sr resin available from Eichrom® is an expensive resin whereas D2EHPA is commercially available reagent with tenth-times cheaper. The separation of Y-90 from Sr-90 was also tested. High recovery and purity of Y product were achieved with $2 \times 10^{-4} - 1 \times 10^{-5}$ Bq $^{90}$Sr/Bq $^{90}$Y contamination level [19]. This contamination value is correlated with D2EHPA impregnated support liquid membrane done by P.W. Naik et al. [14]. In addition, Y-90 separated from organo-phosphate hybrid to ceramic material done by Jun Sig Lee [20] contained Sr in the range of $1.2 \times 10^{-7}$ that is similar to our work. With this contamination level of Sr-90, the $^{90}$Y product could be used to prepare $^{90}$Y-synovectomy for rheumatoid arthritis. The process was found to be easy to operate continuously and there is no need for the treatment of the intermediate solution in the process.
ACKNOWLEDGEMENTS

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