Rubidium-82 Generators for Imaging Studies


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Strontium-82, produced by spallation reaction with medium-energy proton beams, was used to evaluate Bio-Rex 70 and Chelex-100 ion-exchange resins for use in a compact Rb-82 generator. Adsorption of Sr-82 to the resin column, Rb-82 elution yields, Sr breakthrough, and ⁸²Rb–Sr separation factors were determined for newly prepared columns and for long-term elution conditions. Separation factors of 10⁷ to 10⁹ were obtained with 2% NaCl elutions from Bio-Rex 70 resin columns while the separation factor was about 5 x 10⁴ with the Chelex-100 resin column.


Recent improvements in positron cameras and the development of ring detectors for traverse-section positron tomography (1–6) have created renewed interest in positron-emitter generators such as ⁶²Zn→⁶²Cu, ⁶⁶Ge→⁶⁸Ga, ⁸⁵Sr→⁸⁵Rb, and ¹²²Xe→¹²²I. These can provide multimillicurie amounts of short-lived positron-emitting radionuclides to nuclear medicine laboratories without immediate access to a cyclotron.

Rubidium-82 can be useful in myocardial studies because it is conveniently available from a 25-day strontium-82 parent, its 75-sec half-life reduces the radiation dose from a high flux of positrons and annihilation photons (192%), and serial scans can be done every 5–10 min.

The potential value of this system has been shown by previous work on the use of ultrashort-lived radionuclides (7) and the use of cyclotron-produced strontium-82 in the development of a generator with a weakly acidic carboxylic cation-exchange resin* (8). Recently a compact version of the Rb-82 generator was developed and evaluated for myocardial imaging (9). Other investigators have used the chelating ion-exchange resin Chelex-100 (containing iminodiacetate functional groups) in another type of ⁸²Sr→⁸²Rb generator (10). The purpose of the present paper is to report an evaluation of the elution characteristics of the two ion-exchange resins and the effect of long-term elutions on the breakthrough of Sr-82 from the Bio-Rex 70 resin column. This work is a part of a collaborative study with Lawrence Berkeley Laboratory (LBL), Los Alamos Scientific Laboratory (LASL), and Massachusetts General Hospital (MGH).

MATERIALS AND METHODS

Bio-Rex 70, 100–200 mesh in the Na form, was converted to the NH₄ form with ammonium acetate; the Chelex-100, 100–200 mesh, was conditioned with NH₄OH–NH₄Cl to pH 9.0.

The Sr-82 was produced by spallation reaction with medium-energy protons on a molybdenum target and separated radiochemically by a method reported previously (11). The processed Sr-82 solution was used to prepare three generators: two using Bio-Rex 70 and one using Chelex-100.

The radionuclidic compositions of the Sr-82 solutions were determined at LASL by quantitative gamma-ray spectrometry and computer analysis; they are shown in Table 1. Considerable amounts of Sr-85 were also produced by the spallation mechanisms, and small quantities of other impurities remained after the hot-cell radiochemistry. About 8 weeks after the molybdenum target irradiation, the ratio of Sr-85 to Sr-82 was 2.3.

For the Bio-Rex resin column, the radiostrontium

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(Sr-82 + Sr-85 = *Sr) solution in HCl was adjusted to pH 8.0 with NH₄OH and to pH 9.2 for the Chelex-100 column. A tenfold dilution was made with sterile distilled water, and the *Sr solution was passed through the specially machined stainless-steel columns shown in Fig. 1. The design of the column permits rapid connection into the compact generator. The resin volumes were 3.92 ml in the main column and 0.68 ml in the trapping column. The total resin volume of 4.6 ml was a necessary compromise between reasonable Rb-82 yields in an injectable volume and minimum breakthrough of radiostrontium. The useful life of the generator can be prolonged simply by replacing the trapping column with a freshly charged resin unit whenever the *Sr breakthrough becomes excessive (>0.5 μCi). All column components were autoclaved where indicated, and the eluant solutions were sterilized by passage through membrane filters. Elutions of Rb-82 from the Bio-Rex 70 generator were done with 2% or 3% NaCl solution, adjusted to pH 8.0, at a flow rate of 0.5–1.0 ml/sec. The Chelex-100 generator was eluted with 0.1 M NH₄OH–NH₄Cl buffer at pH 9.0.

The yield of Rb-82 was determined by an ionization-chamber dose calibrator† and corrected for decay of the measured Rb-82 activity to the time of separation. The radiostrontium leakage was determined with a NaI(Tl) detector and a 400-channel analyzer. Total *Sr leakage was measured relative to the 511-keV peak of a standard positron source, the measurement bracketing both the 511-keV peak from Rb-82 in equilibrium with Sr-82 and the 514-keV peak of *85Sr. The samples and standard were counted in a position above the detector.

After testing the Bio-Rex 70 generators for radiostrontium breakthrough, the Rb-82 generators were used for imaging studies with the MGH multicrystal positron camera (9,12).

RESULTS AND DISCUSSION

The retention of *Sr by both Bio-Rex and Chelex-100 was >99% as a result of the column-loading procedures. The elution yield of Rb-82 and the *Sr breakthrough for the first Bio-Rex 70 column are shown in Table 2. The Rb-82 yield was 90–96% with 12 ml of 3% NaCl solution and about 70% with 2% NaCl. The early generator elutions with 3% NaCl contained about 0.001 μCi of *Sr per 12-ml elution. Moving the horizontally mounted resin column over a rough surface apparently caused a physical separation of the packed resin bed, and the breakthrough of *Sr increased to 0.4 μCi. Elution with 1% or 2% NaCl reduced both the radiodubium yield and the *Sr leakage, while elution with 3% NaCl increased both. A trapping column was then added downstream from the main column, after which elution with 2% NaCl gave a 70.5% Rb-82 yield with 0.0013 μCi of *Sr leakage. The breakthrough of *Sr (expressed as μCi *Sr eluate/μCi *Sr resin col) was 10⁻¹ Péter. Further elutions with 200 ml of 2% NaCl did not increase the *Sr leakage. Although the overall yield per elution decreased from about 90% with 3% NaCl to 70% with 2% NaCl, the breakthrough of *Sr could be minimized at about 10⁻¹ Péter.

The second shipment of *Sr was used for experiments with the Chelex-100 resin, first in a Pyrex test column and then in the regular stainless-steel column. The *Sr breakthrough was 1.45 × 10⁻⁴ in the freshly loaded test column. The elution charac-
TABLE 2. ELUTION YIELD OF Rb-82 AND BREAKTHROUGH OF *Sr FROM BIO-REX 70 COLUMN 1

<table>
<thead>
<tr>
<th>*Sr on column (mCi)</th>
<th>Elution number</th>
<th>NaCl in eluant (%)</th>
<th>Volume (ml)</th>
<th>*Rb at T = 0 (mCi)</th>
<th>Yield *Rb (%)</th>
<th>*Sr leakage (µCi)</th>
<th>Breakthrough*</th>
<th>Separation factor†</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.70</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>2.60</td>
<td>96.3</td>
<td>0.0015</td>
<td>1.5 × 10⁻⁶</td>
<td>6.3 × 10⁶</td>
</tr>
<tr>
<td>2.65</td>
<td>8</td>
<td>3</td>
<td>12</td>
<td>2.38</td>
<td>86.8</td>
<td>0.4</td>
<td>4.1 × 10⁻⁵</td>
<td>2.3 × 10⁴</td>
</tr>
<tr>
<td>2.49</td>
<td>15</td>
<td>1</td>
<td>12</td>
<td>0.51</td>
<td>20.5</td>
<td>0.001</td>
<td>1.3 × 10⁻⁴</td>
<td>1.6 × 10⁴</td>
</tr>
<tr>
<td>2.49</td>
<td>19</td>
<td>2</td>
<td>12</td>
<td>1.95</td>
<td>78.3</td>
<td>0.6</td>
<td>6.3 × 10⁻⁴</td>
<td>1.3 × 10⁴</td>
</tr>
<tr>
<td>2.49</td>
<td>20</td>
<td>3</td>
<td>12</td>
<td>2.30</td>
<td>92.4</td>
<td>1.5</td>
<td>1.6 × 10⁻⁴</td>
<td>5.9 × 10⁴</td>
</tr>
<tr>
<td>2.06</td>
<td>28</td>
<td>2</td>
<td>12</td>
<td>1.51</td>
<td>73.3</td>
<td>0.8</td>
<td>9.9 × 10⁻⁴</td>
<td>7.4 × 10⁴</td>
</tr>
<tr>
<td>1.90§</td>
<td>34</td>
<td>2</td>
<td>12.5</td>
<td>1.34</td>
<td>70.5</td>
<td>0.0013</td>
<td>1.7 × 10⁻⁷</td>
<td>4.2 × 10⁶</td>
</tr>
<tr>
<td>1.84</td>
<td>36</td>
<td>2</td>
<td>13</td>
<td>1.28</td>
<td>69.6</td>
<td>0.0007</td>
<td>9.6 × 10⁻⁵</td>
<td>7.2 × 10⁶</td>
</tr>
<tr>
<td>1.84</td>
<td>38</td>
<td>2</td>
<td>16</td>
<td>1.58</td>
<td>85.6</td>
<td>0.0007</td>
<td>9.6 × 10⁻⁵</td>
<td>8.9 × 10⁶</td>
</tr>
</tbody>
</table>

* Breakthrough = Sr eluate/Sr resin (3.12 mCi of Sr-82 + 7.09 mCi of Sr-85 on 2/6/75).
† Separation Factor = Fraction Rb-82 ÷ breakthrough.
§ 3.9 ml of Bio-Rex 70 in stainless-steel column loaded with Sr-82.
Resin column after transport over rough surface.
§ 0.7 ml of Bio-Rex 70 in trapping column connected to main column.

TABLE 3. ELUTION YIELD OF Rb-82 AND BREAKTHROUGH OF *Sr FROM CHELEX-100 AND BIO-REX 70 COLUMNS

<table>
<thead>
<tr>
<th>Elution number</th>
<th>Yield of *Rb (mCi)</th>
<th>*Sr leakage (µCi)</th>
<th>Breakthrough†</th>
<th>Separation factor‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-C</td>
<td>0.68</td>
<td>1.1 × 10⁻²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-C</td>
<td>1.51</td>
<td>2.5 × 10⁻²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-C</td>
<td>5.10</td>
<td>1.74</td>
<td>2.9 × 10⁻⁴</td>
<td>2.6 × 10⁴</td>
</tr>
<tr>
<td>7-C</td>
<td>4.64</td>
<td>1.87</td>
<td>3.1 × 10⁻⁴</td>
<td>2.3 × 10⁴</td>
</tr>
<tr>
<td>9-C</td>
<td>4.09</td>
<td>2.24</td>
<td>3.2 × 10⁻⁴</td>
<td>1.9 × 10⁴</td>
</tr>
<tr>
<td>10-C§</td>
<td>2.92</td>
<td>0.68</td>
<td>1.1 × 10⁻⁵</td>
<td>4.4 × 10⁴</td>
</tr>
<tr>
<td>12-C</td>
<td>3.22</td>
<td>0.67</td>
<td>1.1 × 10⁻⁵</td>
<td>4.9 × 10⁴</td>
</tr>
<tr>
<td>5-BⅠ</td>
<td>7.03</td>
<td>0.0012</td>
<td>1.9 × 10⁻⁴</td>
<td>5.2 × 10⁷</td>
</tr>
<tr>
<td>6-B</td>
<td>5.56</td>
<td>0.0003</td>
<td>4.9 × 10⁻⁴</td>
<td>1.5 × 10⁵</td>
</tr>
<tr>
<td>7-8</td>
<td>5.70</td>
<td>0.0004</td>
<td>6.9 × 10⁻⁴</td>
<td>1.1 × 10⁶</td>
</tr>
</tbody>
</table>

* Sr-82 and Sr-85.
† Breakthrough = *Sr eluate/*Sr resin (6.8 mCi of Sr-82 + 53.3 mCi of Sr-85 for Chelex and 7.2 mCi of Sr-82 + 55.6 mCi of Sr-85 for Bio-Rex).
‡ Separation Factor = Fraction Rb-82 ÷ breakthrough.
§ Elutions from Chelex-100 with NH₄OH-NH₄Cl, pH 9.0 (12 ml).
§ New resin in trapping column.
† Elutions from Bio-Rex 70 with 2% NaCl, pH 8.0 (20 ml).

The characteristics of Chelex-100 in the stainless-steel column are shown in Table 3. After the passage of 108 ml of the NH₄OH-NH₄Cl buffer, the breakthrough of *Sr increased from 0.68 µCi (1.1 × 10⁻⁵) to 2.2 µCi (3.7 × 10⁻⁵). The elution yield of Rb-82 was 55% for an elution volume of 12 ml.

The *Sr was then stripped from the Chelex-100 resin and placed on an identical stainless-steel column loaded with Bio-Rex 70. The results of the early elutions performed with 2% saline from this Bio-Rex 70 resin column are also shown in Table 3. The leakage of *Sr activity was about 0.004 µCi per 20-ml elution (breakthrough 7 × 10⁻⁹ or a separation factor of 10⁸). Long-term elution data obtained at MGH, plotted in Fig. 2, show that *Sr breakthrough has increased to 0.02 µCi by 0.9 liter and to 0.3 µCi after passage of 1.4 liters (70 elutions) through the column over a period of about 1 month. The elution yield of Rb-82 was about 75% at zero time. Sterility and pyrogen testing of the column eluates by an independent laboratory gave negative results.

The Rb-82 generators were used in studies with the fast-count-rate MGH positron camera, which can function in a high radiation field and collect a high count rate from the myocardium after the
Rb-82 activity has cleared from the blood but before it has decayed away. Human studies were also done with the LBL scintillation camera (with a heavy lead pinhole collimator) for the purpose of evaluating the potential of Rb-82 relative to Tl-201 for myocardial imaging. The two radionuclides gave comparable images of a septal infarct.

CONCLUSIONS

This study of the two different ion-exchange resins loaded with spallation-produced Sr-82 indicated that the Bio-Rex 70 saline system was superior to the Chelex-100 NH₄Cl-NH₃OH system for the separation of Rb-82. Not only was the observed separation factor higher with Bio-Rex 70 resin, but a 2% saline solution is a better eluant for intravenous infusion than the 0.1 M NH₄OH-NH₄Cl buffer. The discrepancies between the results of this study and those of earlier generator experiments (8,10) are thought to be related to the amount of carrier strontium present in the system. This possibility is currently being investigated.

The radiation dose, delivered to bone and marrow, is ten times greater for Sr-82 than for Sr-85 because of the positron emission associated with the Rb-82 daughter; the total-body dose is three times greater for Sr-82 relative to Sr-85. The radiation dose from 0.1 μCi of Sr-82 is 40 mrad to total bone, 38 mrad to red marrow, and 4 mrad to total body (13). A comparable administration of Sr-85 delivers a radiation dose of 4 mrad to total bone, 3 mrad to red marrow, and 1.4 mrad to total body. Thus, the increasing ratio of Sr-85 to Sr-82 with time is not an important factor, at least through 1–2 months of useful generator life. The radiation dose from 10 mCi of Rb-82 is primarily to the kidneys, which receive 740 mrad.

The favorable elution characteristics of the Bio-Rex 70 ion-exchange chromatographic separation system, enclosed in a readily portable generator, is a potential asset for myocardial and bloodflow imaging when it is used in conjunction with a fast-response tomographic positron-imaging system. The behavior of spallation-generated Sr-82 and its initial use in a Rb-82 generator system indicate a potential application for the large amounts of Sr-82 that can be generated by the medium-energy proton beams of large linear accelerators.

ACKNOWLEDGMENTS

The authors express their appreciation to L. G. Stang, Jr., F. Richards, and F. Horn of Brookhaven National Laboratory for irradiating one of the molybdenum targets used in this study. Portions of this work were performed under the auspices of the U.S. Energy Research and Development Association.

FOOTNOTES

* Bio-Rex 70.
† The ion-exchange resins used in this study were obtained from Bio-Rad Laboratories (Richmond, Calif.).
‡ Squibb CRC-A (Princeton, N.J.).

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