Production of clinical grade $^{90}$Y-acetate for therapeutic applications using ultra pure $^{90}$Sr recovered from PUREX HLLW


Nuclear Recycle Group, BARC, Trombay, Mumbai-400085
Radiation Medicine Centre, Parel, BARC, Mumbai-400012
Radiation Safety Systems Division, BARC, Trombay, Mumbai-400085

Abstract

High Level radioactive Liquid waste (HLLW) obtained from reprocessing of spent fuel by PUREX process is a rich source of $^{90}$Sr which is a pure $\beta$- emitter and decays to $^{90}$Y, a very useful radionuclide in nuclear medicine for cancer therapy. A solvent extraction based Plant is being operated in the hot cells of WIP, Trombay, for management of HLLW using indigenously synthesized solvents. The secondary streams from the Plant are being employed for the recovery of many useful radionuclides. One of the streams from this process is found ideal to recover $^{90}$Sr(NO$_3$)$_2$ solution of high specific activity. In view of generating clinical grade carrier-free $^{90}$Y, availability of high purity $^{90}$Sr is most important requirement. In Process Control Laboratories of NRG, multi step separation processes involving solvent extraction, extraction chromatography, radiochemical precipitation and membrane based techniques have been used to purify $^{90}$Sr to generate clinical grade $^{90}$Y. A two-stage Supported Liquid Membrane based $^{90}$Sr-$^{90}$Y generator system developed in-house is used for milking carrier-free $^{90}$Y-acetate. Clinical grade $^{90}$Y-acetate in batches of ~140-160 mCi are separated and transported to Radiation Medicine Centre, Parel, BARC for radiopharmaceutical applications. Approved transport procedure by BARC Safety Council is followed for transporting the activity from Trombay to RMC, Parel.

Introduction

Utilization of radioisotopes for diagnosis and therapy of various diseases in health care is one of the important programme of Department of Atomic Energy. Several radionuclides are produced using research reactors and particle accelerators for applications in nuclear medicine. The High Level radioactive Liquid waste (HLLW) generated during reprocessing of spent fuel by PUREX process is a rich source of many useful radionuclides viz. $^{137}$Cs, $^{90}$Sr, $^{90}$Y, $^{106}$Ru, $^{148}$Pm, $^{146}$Ce, $^{211}$Pa, $^{212}$Np, $^{212}$Am, and $^{252}$Cf etc. It is therefore considered as resource rather than a waste. Separation and purification of these radionuclides from such streams is extensively being explored in Nuclear Recycle Group (NRG), BARC, Trombay. Yttrium-90, a pure $\beta$-emitter ($E_{\text{max}} = 2.28$ MeV, $T_{1/2} = 64.1$ h), is a potential therapeutic radionuclide formed by $\beta$ decay of $^{90}$Sr, which is available in large quantities in HLLW. On separation and purification, it can be used as a long lasting source for the generation of carrier-free $^{90}$Y. To separate $^{90}$Y from $^{90}$Sr, several techniques such as extraction chromatography, electrochemical and supported liquid membrane based generator systems were studied in our laboratory at Trombay [1–6]. Among these, a two-stage supported liquid membrane (SLM) based generator system [5] is extensively pursued in our laboratories at NRG and is found to be a convenient system for milking carrier-free $^{90}$Y.

In view of high purity carrier-free $^{90}$Y to be used in radiopharmaceutical applications, earlier a 2-stage $^{90}$Sr-$^{90}$Y generator system was proposed [5, 7]. Based on the extensive studies the generator system was found suitable in getting the purity of $^{90}$Y with respect to $^{90}$Sr (<10 Ci/Gi of $^{90}$Y i.e. 10% of total activity) as desired for clinical grade $^{90}$Y. As per European Pharmacopeia the purity requirements with respect to a activity are more stringent (10 Ci/Gi of $^{90}$Y) as compared to $^{90}$Sr [8]. Nuclear Recycle Group made a collective effort to separate and purify high specific activity $^{90}$Sr from HLLW.
using a multi stage solvent extraction loop at Waste Immobilization Plant (WIP), Trombay removing bulk of uranium, cesium, lanthanides and actinides. Since a single separation technique is unable to recover $^{90}$Sr of desired radionuclidic purity from such waste solution containing host of minor actinides, fission products and other metallic elements, multi separation techniques viz. solvent extraction, ion-exchange, extraction chromatography and membrane based methods were employed for purification. The purified $^{90}$Sr (NO$_3$)$_3$ was used to generate carrier-free $^{90}$Y by employing two-stage Supported Liquid Membrane (SLM) generator. Various steps employed during separation, purification and assaying its quality to make it suitable for clinical grade $^{90}$Y generation, are discussed in this article.

**Separation and purification of $^{90}$Sr from HLLW**

HLLW obtained from recycling of spent fuel is subjected to three-cycle solvent extraction processes at WIP, Trombay. In first cycle, depletion of residual uranium and plutonium from the waste is carried out using PUREX solvent. Uranium and plutonium from organic phase are stripped in aqueous phase using dilute HNO$_3$ and sent back for recycling. The U/Pu lean raffinate phase from first cycle is subjected to second solvent extraction cycle wherein indigenously synthesized 1,3-diocetyl oxy calix[4] arene-crown-6 (CC8), in isodecanol (IDA) and n-dodecane is used for selective recovery of $^{137}$Cs. Recovered Cs is used for making Cs glass pencils for blood irradiators. Raffinate from the Cs recovery cycle is subjected to tetra 2-ethyl hexyl diglycolamide (TEHDGA) in IDA and n-dodecane. In this third cycle, entire actinides/lanthanides and $^{90}$Sr are extracted quantitatively in organic phase leaving raffinate stream amenable to direct dilution and dispersal. Stripping of the organic phase using dilute nitric acid generates aqueous stream rich in $^{90}$Sr activity. This aqueous phase generated from stripping also contains minor actinides/lanthanides and traces of Cs activity. A solvent extraction based Plant for recovery of radionuclides from HLLW has been operated in the hot cells of WIP, Trombay (Fig. 1). The chemical and radiochemical composition of this aqueous phase used as feed for $^{90}$Sr purification is given in Table 1.

**Table 1. Composition of Feed used for $^{90}$Sr purification**

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Conc.</th>
<th>Constituents</th>
<th>Conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[HNO$_3$]M</td>
<td>4.0</td>
<td>Cr, mg/L</td>
<td>931.4</td>
</tr>
<tr>
<td>Gross α, mCi/L</td>
<td>10-12</td>
<td>Fe, mg/L</td>
<td>4063</td>
</tr>
<tr>
<td>Gross β, Ci/L</td>
<td>20.90</td>
<td>La, mg/L</td>
<td>334</td>
</tr>
<tr>
<td>$^{90}$Sr, Ci/L</td>
<td>9.50</td>
<td>Mg, mg/L</td>
<td>7.8</td>
</tr>
<tr>
<td>$^{137}$Cs, mCi/L</td>
<td>7.50</td>
<td>Mn, mg/L</td>
<td>292.7</td>
</tr>
<tr>
<td>$^{106}$Ru, mCi/L</td>
<td>2.00</td>
<td>Mo, mg/L</td>
<td>550</td>
</tr>
<tr>
<td>Al, mg/L</td>
<td>48.2</td>
<td>Na, mg/L</td>
<td>285.4</td>
</tr>
<tr>
<td>Ba, mg/L</td>
<td>25.0</td>
<td>Ni, mg/L</td>
<td>467.1</td>
</tr>
<tr>
<td>Ca, mg/L</td>
<td>2440</td>
<td>Sr, mg/L</td>
<td>248</td>
</tr>
<tr>
<td>Ce, mg/L</td>
<td>566.4</td>
<td>U, mg/L</td>
<td>35.9</td>
</tr>
</tbody>
</table>

Fig. 1: Solvent extraction plant for separation of radionuclides from HLLW
"Sr Purification steps

In the Process Control Laboratories of NRG, Trombay, a series of steps were followed for purification of "Sr, which are described below.

STEP-1: In this step, trace impurity of \(^{113}\)Cs is removed using granulated ammonium molybdo phosphate (AMP) column. Quantitative removal of \(^{113}\)Cs was found in this step which not only helped in the purification of "Sr but also in the reduction of manrem exposure in the subsequent purification steps.

STEP-2: To remove a emitters viz. minor actinides and traces of U and Pu, TRUEX solvent was used both in liquid-liquid extraction as well as in extraction chromatography mode. Extraction chromatography was found simpler as compared to liquid-liquid extraction. This step also removed lanthanides completely from the solution.

STEP-3: Raffinate/effluent containing "Sr in ~3-4M HNO\(_3\), from STEP-2 was subjected to Sr extraction step using di-(t-butyl cyclohexano)-18-Crown-6 in DDA and n-dodecane. "Sr from organic phase was stripped quantitatively using dilute nitric acid.

STEP-4: The stripped "Sr product obtained from Step-3 was collected and passed through a glass column containing polymeric resin (XAD) to remove dissolved organic if any. The resultant solution was evaporated to get the concentrated "Sr product using a specially designed oven having a vent connected to the hood of fume-hood to avoid contamination in the fume-hood. Radiochemical composition of the "Sr product is shown below in Table 2.

Further purification of "Sr from the above feed solution was carried out using radiochemical precipitation method [9] after some modification. Two Fe scavenging step at pH ~9.4 by alkali followed by SrCO\(_3\), precipitation after adding appropriate concentration of Fe and Sr carrier were carried out which recovered more than 80% "Sr. The final SrCO\(_3\), washed in water, is dissolved in a minimum volume of 2M HNO\(_3\), and adjusted to a pH of 1-2. Purified "Sr(NO\(_3\))\(_3\) solution was allowed to reach equilibrium and used for "Y milking by employing two stage SLM generator. "Y acetate product thus generated was found to have alpha activity of 10 \(^{13}\)CiCi of "Y as assayed at RSD, BARC at low background ZnS(Ag) scintillator counting system which was ten times higher than that required for clinical grade "Y.

Further purification of this "Sr(NO\(_3\))\(_3\) solution was carried out by KSM 17 based SLM technique. In this technique Sr(NO\(_3\))\(_3\), solution purified by radiochemical precipitation method adjusted to a pH 1-2 was used as feed and 4M HNO\(_3\),as receiver phase. After about 8 h, the receiver compartment was replaced at least 6 times with fresh 4M HNO\(_3\),each time retaining same "Sr(NO\(_3\))\(_3\), in the feed compartment. This purified "Sr-nitrate solution by SLM technique was used as feed for "Y generation after the growth of "Y activity. "Y (10 \(^{13}\)Ci \(\alpha/\text{Ci}\)) detected earlier in "Y acetate product could be reduced to less than 10 \(^{13}\)CiCi of "Y as desired for clinical applications. This "Sr-nitrate solution was preserved and used for "Y milking as and when required after allowing it to reach radioactive secular equilibrium.

Separation of carrier-free "Y using two-stage SLM generator

A two-stage SLM based generator system developed in-house [5] is used for the separation of carrier-free "Y, which is principally based on the solvent extraction properties of two ligands, namely 2-ethylhexyl 2-ethylhexyl phosphonic acid (KSM-17) and octyl phenyl-N, N-diisobutyl carbamoyl methyl phosphate oxide (CMPO) under optimum conditions. The system was operated in sequential modes with each cell having 5mL capacity. In the first stage, the equilibrium mixture of "Sr and "Y adjusted to a pH of 1-2 was used in the feed compartment and the receiver compartment contained 4 M HNO\(_3\), KSM-17 based SLM was used for selective transport of "Y to the receiver phase in about 4 h. The product from this stage was taken out and placed in the feed compartment of the second stage, whereas the "Y depleted lean "Sr left out in the feed compartment of the first stage was
transferred back to the feed reservoir for next cycle. CMPO based SLM was used for transport of $^90$Y in second stage where 1M acetic acid was used as receiver phase. Stage 1 and 2 of the generator system are shown in Fig. 2. Beta activity transported after 4h are given in Table 3.

**Experimental condition**

Cell volume: 5 mL for each compartment, Feed: pH 1.24, Gross β-activity: 82.96 Ci/L, Receiver phase in 1st stage: 4M HNO₃, Receiver phase in 2nd stage: 1M CH₃COOH. Thus, carrier-free $^90$Y product of ~40 Ci/L in acetic acid medium could be generated under optimized conditions and supplied to RMC, Mumbai.

Special shielding containers were fabricated for transporting batches of ~140-160 mCi $^90$Y from BARC, Trombay to RMC, BARC in public domain. Approved transportation procedure by regulatory authority was followed during transportation of each lot.

**Quality Control of the $^90$Y Product**

Quality Control of the final product with respect to $^{89}$Sr was carried out as per “BARC Method for Quality Control of $^90$Y” which is based on Extraction Paper Chromatography (EPC) [10]. Paper chromatography pattern of $^90$Y is shown in Fig. 4. The contamination of $^{89}$Sr in all batches of $^90$Y-acetate product was found within

---

**Fig. 2: SLM based two stages for generation of carrier-free $^90$Y**

**Table 3: Transport of β-activity after 4h in two stages**

<table>
<thead>
<tr>
<th>STAGE-1</th>
<th>STAGE-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-activity (Ci/L)</td>
<td>β-activity (Ci/L)</td>
</tr>
<tr>
<td>Feed</td>
<td>Product</td>
</tr>
<tr>
<td>41.48</td>
<td>40.86</td>
</tr>
<tr>
<td>Yield ~98.5%</td>
<td>Yield ~97.01%</td>
</tr>
</tbody>
</table>
Production of clinical grade $^{90}$Y-acetate for therapeutic applications...

the permissible level. Fig. 4 shows the decay curve of $^{90}$Y activity as a function of time. $T_{1/2}$ as calculated from the slope of the line plotted between ln (β- activity) vs time in hour is found to be 64.17h indicating the purity of the product.

The $^{90}$Y-acetate product was subjected to various quality control tests as per the requirements of Radiopharmaceuticals Committee. Typical β spectrum of $^{90}$Y before and after complete decay is shown Figs. 5 & 6.

The elemental concentrations in six separated batches of $^{90}$Y-acetate products as carried out at FRD laboratory by Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) are given in Table 4. These analysis results were validated by carrying out the analysis at WMD laboratory. Presence of elements in each batches were observed to be same as in reagent blank (1M acetic acid) indicating presence of no metallic impurities in the $^{90}$Y-acetate product.

Gross impurity analyses in six $^{90}$Y-acetate batches (each about 140-160 mCi in 4 mL at the time of supply) after near complete decay as assayed by RSSD, BARC using low background ZnS (Ag) scintillator counting system are given in Table 5 (next page). For validating the results, one particular batch (Batch 11) of

![Fig. 5: β spectrum of $^{90}$Y](image)

![Fig. 6: β- Spectrum of decayed $^{90}$Y acetate sample](image)

<table>
<thead>
<tr>
<th>Element</th>
<th>*Blank</th>
<th>Batch-1</th>
<th>Batch-2</th>
<th>Batch-3</th>
<th>Batch-4</th>
<th>Batch-5</th>
<th>Batch-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al</td>
<td>0.052</td>
<td>0.069</td>
<td>0.074</td>
<td>0.055</td>
<td>0.056</td>
<td>0.049</td>
<td>0.056</td>
</tr>
<tr>
<td>Ca</td>
<td>0.900</td>
<td>0.807</td>
<td>0.878</td>
<td>0.890</td>
<td>0.940</td>
<td>0.910</td>
<td>0.940</td>
</tr>
<tr>
<td>Fe</td>
<td>0.020</td>
<td>0.024</td>
<td>0.027</td>
<td>0.020</td>
<td>0.022</td>
<td>0.021</td>
<td>0.022</td>
</tr>
<tr>
<td>Cu</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Zn</td>
<td>&lt;0.020</td>
<td>&lt;0.020</td>
<td>&lt;0.020</td>
<td>&lt;0.020</td>
<td>&lt;0.020</td>
<td>&lt;0.020</td>
<td>&lt;0.020</td>
</tr>
<tr>
<td>Zr</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Pb</td>
<td>&lt;0.025</td>
<td>&lt;0.025</td>
<td>&lt;0.025</td>
<td>&lt;0.025</td>
<td>&lt;0.025</td>
<td>&lt;0.025</td>
<td>&lt;0.025</td>
</tr>
</tbody>
</table>

*1M Acetic acid
Table 5: Alpha assay of decayed $^{90}$Y product

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>$^{90}$Y β - activity in separated product (Ci/L)</th>
<th>$\alpha$ activity in decayed $^{90}$Y solution (Ci $\alpha$/Ci $^{90}$Y)</th>
<th>$^{90}$Sr activity (Ci $^{90}$Sr/Ci $^{90}$Y) (β after EPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>38.90</td>
<td>$1.65 \times 10^{-9}$</td>
<td>$1.5 \times 10^{-7}$</td>
</tr>
<tr>
<td>11</td>
<td>38.56</td>
<td>$0.55 \times 10^{-9}$</td>
<td>$1.4 \times 10^{-7}$</td>
</tr>
<tr>
<td>12</td>
<td>37.48</td>
<td>$1.07 \times 10^{-9}$</td>
<td>$1.2 \times 10^{-7}$</td>
</tr>
<tr>
<td>13</td>
<td>37.60</td>
<td>$0.66 \times 10^{-9}$</td>
<td>$1.4 \times 10^{-7}$</td>
</tr>
<tr>
<td>15</td>
<td>35.46</td>
<td>$0.34 \times 10^{-9}$</td>
<td>$1.3 \times 10^{-7}$</td>
</tr>
<tr>
<td>16</td>
<td>34.96</td>
<td>$0.15 \times 10^{-9}$</td>
<td>$1.4 \times 10^{-7}$</td>
</tr>
</tbody>
</table>

[Permissible limit-$\alpha$: $<1 \times 10^{-7}$ Ci $\alpha$/Ci $^{90}$Y, $^{90}$Sr:$<10^{-7}$ Ci/Ci of $^{90}$Y] *RSSD - Radiation Safety System Division
*RCSD - Radiochemistry Division

decayed $^{90}$Y solution was also assayed at Radiochemistry Division, BARC, using Solid State Nuclear Track Detector (SSNTD). The result of analysis is given in the same Table. Good agreement is observed between the results obtained from both the laboratories using different counting systems.

A $^{90}$Sr-$^{90}$Y generator system housed in Fume-hood is shown in Fig. 7.

Conclusions

- HLLW is a good source for recovery of $^{90}$Sr. Purification of $^{90}$Sr could be done using a series of in-house developed extractants and optimized steps to achieve the level of purity required for milking of $^{90}$Y.
- Carrier-free $^{90}$Y could be successfully recovered from Sr and have a good potential use for therapeutic applications.
- The carrier-free $^{90}$Y-acetate product having specific activity $\sim 40$ Ci/L can be used for radiopharmaceutical applications. At a time, about 140-160 mCi activity could be obtained by the generator system.
- To meet the rising demand for $^{90}$Y activity, such multiple generator systems may be employed in multiple fume hoods keeping in mind that not more than 500 mCi of $^{90}$Sr activity can be handled in a particular fume-hood.

Corresponding author and email: Shri C.P. Kaushik (cpk@barc.gov.in)

Acknowledgements

Authors are thankful to Shri. P. A. Bhosale, Shri. Sanjay Achare, Shri. Sunil Solankar, Dr. K. Sreenivasa Rao and Shri. R. Sankar for their valuable
contribution during the course of the work.

References


