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Review Article

Emerging role of electrochemistry in radiochemical separation of medically important radiometals: state of the art

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Abstract: Electrochemical separation technology has brought a renaissance in the field of nuclear medicine towards obtaining clinical-grade radiometals for preparation of a wide variety of radiopharmaceuticals. This article is a comprehensive summary of the electrochemical processes developed for the separation of radiometals that could be used for diagnostic or therapeutic applications in nuclear medicine. For using electrochemistry as a tool for the separation of radiometals, intricate knowledge is essential to understand the basic parameters of electrochemical separation processes which include applied potential, selection of electrolyte, choice of the electrode, the temperature of the electrolyte, pH of the electrolyte and time of electrolysis. The advantages of the electrochemical separation approach over the other conventional methodologies such as solvent extraction, column chromatography, sublimation, etc., have also been discussed. The latest research and development from our laboratory on electrochemical methodologies developed for separation of ^{90}Y from ^{90}Sr, ^{188}Re from ^{188}W, ^{99m}Tc from ^{99}Mo, ^{47}Sc from ^{46}Ca, ^{45}Ca from ^{46}Sc,^{153}Sm from ^{154}Eu, ^{169}Er from ^{169}Yb, ^{177}Lu from Yb and $^{132/135}$La from Ba have been described. In all the cases, the final product is obtained either in a 'no-carrier-added' (NCA) form or free from inextricable impurities and thus found suitable for formulation of radiopharmaceuticals.

Keywords: Applied potential, electrochemical separation, no-carrier-added, nuclear medicine, radionuclidic purity, radiopharmaceuticals, separation technology

Introduction

Over the last few decades, application of radiometals for preparation of various diagnostic and therapeutic radiopharmaceuticals has remained at the center stage of nuclear medicine [1, 2]. In general, radioisotopes are produced in two different ways: the first is the direct route and the other is the indirect route. In the direct route, radioisotopes are generally obtained in carrier added (CA) form with low specific activity while the indirect route leads to production of radioisotopes in 'no-carrier-added' (NCA) form and hence obtained with very high specific activity. The major challenge in the indirect route is the separation of miniscule quantity of NCA radioisotopes from its bulk irradiated target precursor. Conventionally, various strategies like solvent extraction, column chromatography, sublimation, selective precipitation, etc. have been employed in the past to separate the radiometals from their bulk irradiated target materials but in most of the cases, these approaches involved multistep separation with low to moderate separation factor, compromised chemical purity and in some cases, the extracted radionuclide was obtained in a form incompatible for radiopharmaceutical formulation [3-6]. In order to circumvent these challenges, electrochemical separation has been used as an attractive strategy for the separation of medically important radiometals for preparation of radiopharmaceuticals [7-14]. The basic tool used in this approach is 'electrochemistry'. The development of an electrochemical strategy advanced the progress of nuclear medicine because the NCA radiometals are obtained in a form which is suitable for preparation of clinically useful target specific radiopharmaceuticals [9-14].

Advantages of electrochemical process

The electrochemical separation strategy has not only circumvented the limitations discussed above but also has the following advantages:

(i) In this approach, electron transfer is a process involved without using any external hazardous chemical and so the strategy is consistent with the principles of 'green chemistry'.

(ii) In electrochemical separation process, no organic or inorganic matrices are utilized and hence the radiolytic damage of the column matrix which is often observed during the course of separation using column chromatography or solvent extraction techniques can be avoided.

(iii) Since this method precludes radiolytic damage, high linear energy transfer (LET) radioisotopes can be used for separation.

(iv) In the electrochemical method, extractants or adsorbents are not used, and therefore the capability of this method is independent of the amount of extractants or adsorbents.

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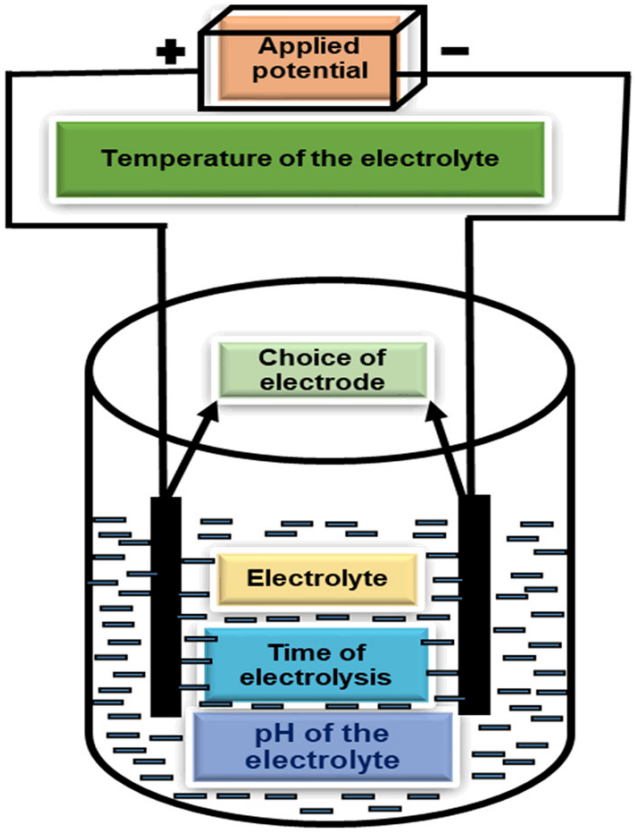

Figure 1. Schematic of electrochemical separation set up.

(v) In this method, purity of the final product and the separation efficiency of the process remain consistent upon repeated operations.

(vi) This approach is flexible and versatile, and therefore easy to scale up or down according to the product demand.

Limitations of electrochemical process

Despite excellent attributes of the electrochemical process, it also has some limitations which are discussed below.

(i) The main limitation of this method is that this can be applied only when there is a significant difference in redox potential between the desired radiometal and its precursor except in few cases where the hydroxide of one of the nuclide ions possesses extremely low solubility product and get selectively deposited on one of the electrodes [15, 16]. To circumvent this, the complexation behavior between radiometal ions and ionic liquids (ILs) may be evaluated to provide insights towards designing more efficient radiochemical separation methods [17, 18]. The selective complexation of one metal with the ionic liquid would reduce the energy gap between the highest occupied and lowest unoccupied molecular orbitals, forming more reducible structures for energy-efficient electrochemical separations of radiometals for use in nuclear medicine. This is based on widening the potential window between the desired radiometal and its precursor for selective electrodeposition of the desired radiometal on the electrode surface.

(ii) This process cannot be applied when radionuclide ion or its precursor makes alloy with the electrodes. Preferably, noble metal electrodes such as Au or Pt are chosen which are chemically inert during the electrochemical process to prevent alloy formation [9, 11, 15].

(iii) Highly skilled personnel are required to operate this process.

(iv) Radionuclide deposited is sometimes held strongly on the surface of the electrode and cannot be retrieved easily in a desired medium. Therefore, noble metal electrodes are preferred which do not form a strong adherent bonding with the radiometal deposited on the electrode surface.

(v) Sometimes, it is difficult to make an automated facility for this process which could be operated in a shielded glove box fitted with remotely operable tongs to minimize the radiation exposure to the working personnel.

Factors influencing the electrochemical separation process

The schematic diagram of the set up generally used in electrochemical separation process is shown in **Figure 1**. The separation efficiency of the electrochemical process has been influenced by various factors such as applied potential, choice of electrolyte, pH of the electrolyte, choice of the electrode, temperature of the electrolyte solution, and time of the electrolysis (**Figure 1**).

Applied potential

Among various parameters which govern the potential of the electrochemical separation process, the applied potential is the foremost and it depends on the formal electrode potential of the radiometal ions which are to be separated. In general, the applied potential should be more negative than the formal electrode potential of the metal ion which is to be reduced and deposited on the cathode and more positive than the formal electrode potential of the metal ion which would remain in the solution.

Type of electrolyte

The choice of electrolyte is another salient factor that can alter the separation efficiency of the process. The primary condition for the selection of electrolyte is that the metal ion has to be completely soluble in the electrolyte medium and the electrolyte should be reluctant towards radiolysis in presence of intense radiation. Also, depending upon the type of electrolyte, the formal electrode potential of the metal ions would be changed due to the com-

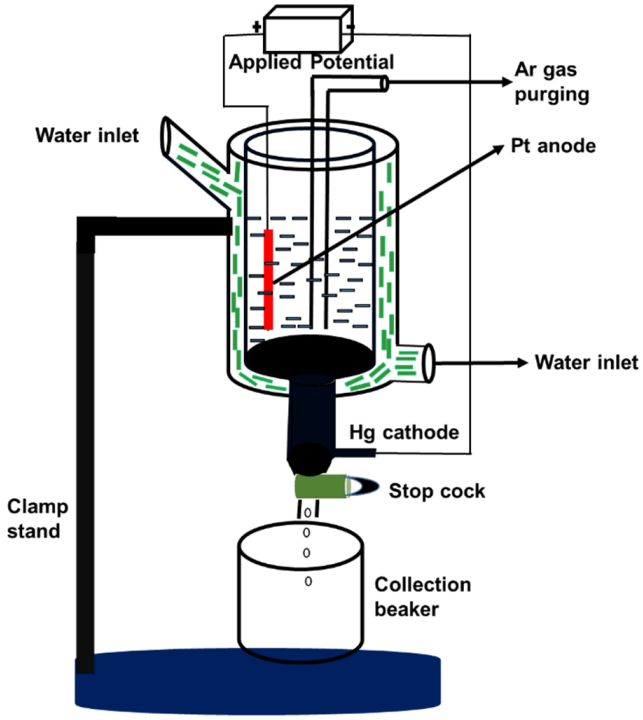

Figure 2. Schematic diagram of the water-jacketed electrochemical cell for maintaining the temperature of the electrolyte during electrolysis.

plex formation ability of the electrolyte, changing the ionic strength of the medium, pH of the medium, etc. [19]. Within the given applied potential window, the electrolytic degradation of electrolytes should not occur [20]. Recently, organic electrolytes or room temperature ionic liquids (RTIL) have been used due to their wide electrochemical potential windows and high conductive behavior [21, 22]. Although use of these novel electrolytes has brought a paradigm shift in the electrochemical separation process, their organic framework which as such resists electrolysis because of high impedance of the organic moiety might be susceptible towards radiolysis in the presence of intense radiation. Additionally, the radiolytic products generated might alter the efficacy of the electrochemical separation process. Therefore, it is of paramount importance to select the appropriate electrolyte for electrochemical separation of medically important radiometals.

pH of the electrolyte

The pH of the electrolyte is a critical parameter for electrolysis in an aqueous medium because of the evolution of H_2 gas at the cathode due to the loss of H^+ ions would increase the pH of the electrolyte. Sometimes the enhancement in the pH would help to separate the radionuclides which demonstrate large difference in their solubility products as metal hydroxides [15, 16]. But in most of the cases, pH of the electrolyte needs to be maintained using an appropriate buffer so that the electrolysis process is not hampered.

Temperature

During the course of electrolysis, the temperature of the electrolyte medium is kept well below the boiling point of the electrolyte and sometimes the electrolysis is carried out in a water-jacketed electrochemical cell (**Figure 2**), where a provision for the circulation of cold water has to be made to prevent the elevation of the temperature during the process [11, 23].

Type of electrodes

The electrode which is used in electrolysis should withstand oxidation/reduction and resist intense radiation. In short, the electrode material should possess high conductance value, excellent radiation stability, and proven chemical inertness.

Time of electrolysis

The time of the electrolysis also needs to be optimized to minimize the decay loss of the deposited product during the electrochemical separation process. Sometimes, prolonged electrolysis might convert the cathodic deposit into a new phase which is strongly adherent to the surface of the cathode and makes the stripping process extremely difficult [10, 24].

Electrochemical separation of medically important radiometals

Based on the electrochemical process, various radiometals were separated from their bulk irradiated target material. Also, using this approach some clinically useful radionuclide generator systems were prepared and evaluated. This section provides an overview of these developments using the electrochemical separation method.

Separation of ^{90}Y from ^{90}Sr

Yttrium-90 (^{90}Y) is used as a therapeutic radionuclide in targeted cancer therapy as well as in radiation synoviorthesis of painful arthritis because of its decay to stable ^{90}Zr with emission of high energy β^- ($E_{\beta\text{-max}}$ = 2.28 MeV) and having suitable half-life ($T_{½}$ = 64.1 h) [25-32]. NCA ^{90}Y is the decay product of ^{90}Sr, which is having a very long half-life ($T_{½}$ = 28.8 y) and is also a bone seeker with maximum permissible body burden (MPBB) of only 74 kBq (2 μCi) in the entire lifetime of the patient [33-35]. The unintentional presence of ^{90}Sr has to be avoided before using ^{90}Y and the only possible way is to isolate ^{90}Y very selectively from ^{90}Sr. For effective separation of ^{90}Y, a two-step electrochemical process was found attractive with high decontamination factor and in both steps platinum (Pt) metal was used as electrodes [9]. A schematic of the electrochemical process is shown in **Figure 3**.

In the first step of electrolysis, the applied potential was -2.5 V (100-200 mA current) with respect to the saturated

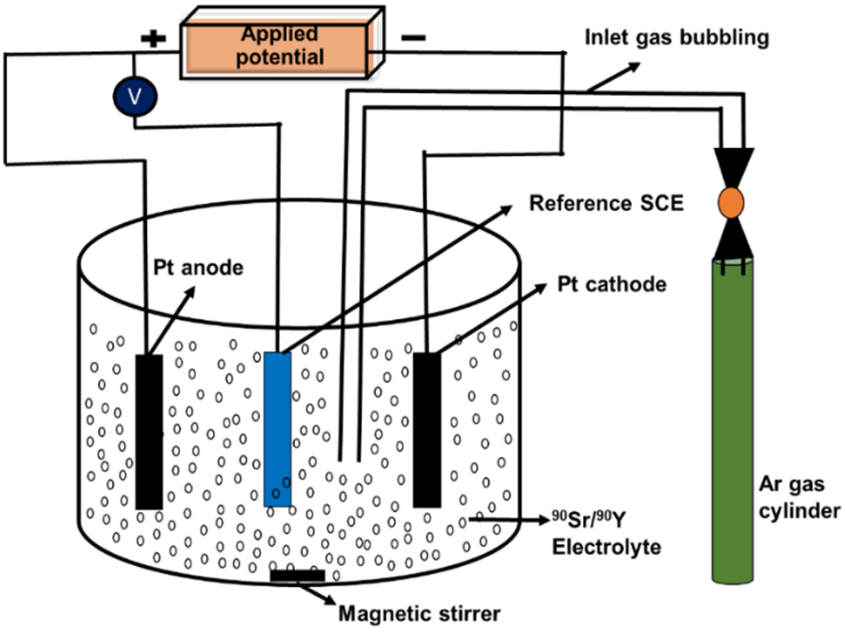

Figure 3. Schematic of the electrochemical cell for the separation of ^{90}Y from ^{90}Sr.

calomel electrode because the standard reduction potential of the Y^{+3}/Y couple and Sr^{+2}/Sr couple were -2.27 V and -2.89 V, respectively. The electrolysis was carried out in $^{90}Sr(NO_3)_2$ feed solution for 90 min at the pH 2-3. During the course of electrolysis Y^{3+} would be reduced to Y(0) and deposited at the Pt-cathode. The deposited Y was stripped off in 0.003 M HNO_3 medium without switching off the voltage in the second step of electrolysis. In the next step, the electrolysis was carried out for 45 min by reversing the polarity of the electrode and hence the leached ^{90}Y would be deposited onto another Pt cathode. At the end of the electrolysis, the deposited ^{90}Y onto Pt-plate was dissolved into acetate buffer as ^{90}Y acetate, which was suitable for preparation of radiopharmaceuticals. The overall separation yield of this process was > 90% and the processed was scaled up to ~4.4 GBq activity of ^{90}Sr. It has also been demonstrated in several batches that the amount of ^{90}Sr after the electrochemical separation was 30.2 ± 15.2 kBq (817 ± 411 nCi) of ^{90}Sr per 37 GBq (1 Ci) of ^{90}Y, corresponding to (0.817 ± 0.411 ppm) of ^{90}Sr which was well below the permissible limit for clinical use.

Separation of ^{188}Re from ^{188}W

In the last several years, there has been an increase in the use of rhenium-188 (^{188}Re) in therapeutic nuclear medicine because of its acceptable nuclear decay characteristics such as reasonable half-life ($T_{½}$ = 16.9 h), high energy β^- particles ($E_{\beta\text{-max}}$ = 2.118 MeV), emission of a 155 keV γ-ray (15%) compatible for imaging purpose [32, 36]. Therefore, ^{188}Re is used in various fields of nuclear medicine such as radionuclide synovectomy, bone pain palliation, liver cancer therapy, radioimmunotherapy, etc. [37-40]. ^{188}Re is the decay product of ^{188}W and hence it is possible to obtain ^{188}Re in NCA form but the only difficulty is to develop a separation method which can effectively separate ^{188}Re from the bulk irradiated ^{188}W target. As the chemistry of ^{188}Re is similar to that of ^{99m}Tc, the wide variety of biomolecules that are used for radiolabeling with ^{99m}Tc can also be used with ^{188}Re once it is obtained in a NCA form. Thanks to the electrochemical method which is capable of effective separation of ^{188}Re with a very high decontamination factor and hence possible to obtain ^{188}Re in a NCA form. The separation of ^{188}Re from the ^{188}Re/^{188}W mixture was based on the difference in standard reduction electrode potential of the two couples and hence selective electrodeposition of ^{188}Re onto the Pt-cathode was possible.

$$WO_3 + 6H^+ + 6e \rightarrow W + 3H_2O$$
$$E^o = -0.090 \text{ V}$$

$$ReO_4^- + 8H^+ + 7e \rightarrow Re + 4H_2O$$
$$E^o = +0.362 \text{ V}$$

The electrodeposition of W onto the Pt electrode is not possible in aqueous solution as the standard reduction potential is close to zero. This is because of high discharge potential of W in an aqueous medium and low hydrogen over voltage [41]. But in the alkaline medium the electrodeposition of a very thin film of W is possible. Therefore, in order to inhibit the electrodeposition of W, electrolysis of ^{188}Re/^{188}W mixture was carried out in an appropriate acidic medium so that ^{188}Re could be selectively deposited onto Pt-cathode. It has been observed that electrolysis in common mineral acid medium exhibit poor electrodeposition yield of ^{188}Re with significant co-deposition of ^{188}W despite long operation time. So, the electrolysis was performed in oxalic acid medium where oxalate ions expedited the reduction of ReO_4^- ion through 1:1 complex formation that changed the formal reduction potential of ReO_4^-/Re couple [42]. The electrochemical set up for ^{188}Re/^{188}W is similar to that of ^{90}Sr/^{90}Y (**Figure 3**), but only difference is that here 'two-electrode system' was employed instead of 'three-electrode system' for the sake of maintaining constant applied potential. The electrolysis was conducted in 0.1 M oxalic acid medium at constant potential 7 V for 60 min. Subsequently the deposited ^{188}Re was stripped out in 0.1 M HCl medium as perrhenic acid without switching off the voltage. Then the solution was passed through the alumina column so that a trace amount of ^{188}W impurity (0.05-0.1%) was trapped into the column. The overall batch yield of the process was > 70% with > 99% radiochemical purity and > 99% of radionuclide purity [10]. The performance of the ^{188}W/^{188}Re generator was investigated over a period of 6 months and consistency in the elution yield of ^{188}Re was observed in all batches (**Figure 4**).

Separation of ^{99m}Tc from ^{99}Mo

From several decades, ^{99m}Tc ($T_{½}$ = 6 h) has remained as the 'work horse' in nuclear imaging because of the emis-

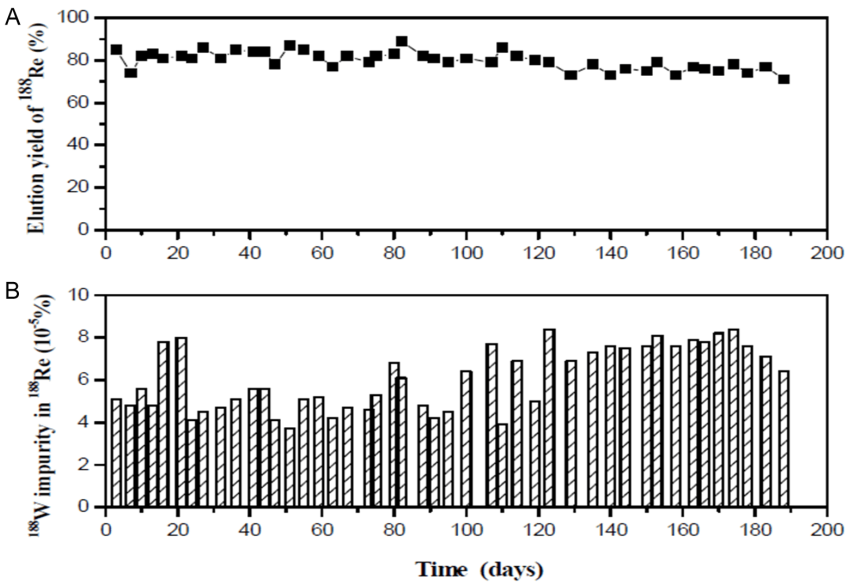

Figure 4. Performance of the electrochemical ^{188}W/^{188}Re generator over a period of 6 months. Adapted from reference [10] with permission.

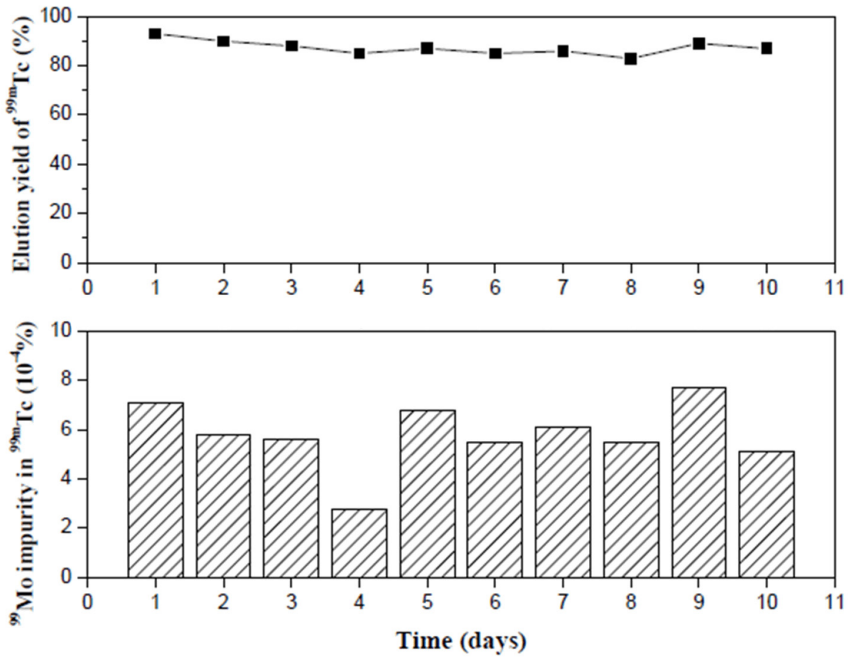

Figure 5. Performance of the electrochemical ^{99}Mo/^{99m}Tc generator over a period of 10 d. Adapted from reference [49] with permission.

sion of single gamma ray having energy of 140 keV (89.1%) [3, 43]. ^{99m}Tc is the decay product of ^{99}Mo which can easily be produced by the neutron bombardment on natural MoO_3 via ^{98}Mo (n, γ) ^{99}Mo reaction. However, the specific activity of ^{99}Mo produced by (n, γ) reaction in a medium flux research reactor varies in the range of 300-1000 mCi g^{-1} rendering it unsuitable for preparation of clinical-scale ^{99}Mo/^{99m}Tc generators [44]. In this premise, electrochemical separation process is an attractive method as ^{99m}Tc can be selectively electrodeposited on the surface of an electrode without depending on the specific activity of ^{99}Mo. This is mainly possible because of the large difference of standard reduction potential value of MoO_4^{2-}/Mo (-1.05 V) and TcO_4^-/TcO_2 (0.738 V) couple in alkaline medium as per the reactions below.

$$MoO_4^{2-} + 4H_2O + 6e \rightarrow Mo + 8OH^-$$
$$E^o = -1.05\ V$$

$$TcO_4^- + 4H^+ + 3e \rightarrow TcO_2 + 2H_2O$$
$$E^o = +0.738\ V$$

It is reported that along with the electrodeposition of ^{99m}Tc, there has been simultaneous electrodeposition of ^{99}Tc (2.2×10^5 y), which cannot be avoided [45]. However, the percentage of ^{99}Tc in ^{99m}Tc is negligibly small to demonstrate any adverse effect [46, 47]. Electrodeposition of ^{99}Mo is precluded in aqueous solution because of small hydrogen over-voltage and high discharge potential of MoO_4^{2-} in aqueous solution [48]. The electrodeposition of ^{99m}Tc was carried out in sodium molybdate medium and the electrolysis was carried out at Pt-electrode under the constant potential of 5 V for 50 min [49]. The deposited ^{99m}Tc on the cathode was stripped out in 500 μL saline solution by reversing the polarity of the electrode. The trace amount of ^{99}Mo impurity was removed by passing the solution through an alumina column and the overall yield of ^{99m}Tc was found to be > 80% with > 99% radiochemical purity and > 99.9% of radionuclide purity. Since ^{99m}Tc is produced continuously in the electrolyte medium due to nuclear decay of ^{99}Mo, repeated electrodeposition was carried over a prolonged period of 10 d to obtain ^{99m}Tc from the same electrolyte solution (**Figure 5**).

Separation of ^{47}Sc from ^{46}Ca

Scandium-47 ($T_{½}$ = 3.35 d) is an emerging radioisotope for potential application in cancer theranostics because of its favorable nuclear decay properties such as emission of 159 keV (68.3%) gamma energy which could be used for single photon emission computed tomography (SPECT) imaging and the emission of moderate energy beta particle (600 keV) compatible for small tumor therapy [50, 51]. Additionally, the co-ordination chemistry of Sc^{3+} ion with chelators is well established for preparation of a wide variety of radiopharmaceuticals [2, 51]. NCA ^{47}Sc can be produced in a cyclotron and also in reactor. In the cyclotron, ^{47}Sc can be produced by (p, 2p) reaction using enriched ^{48}Ti target [2],

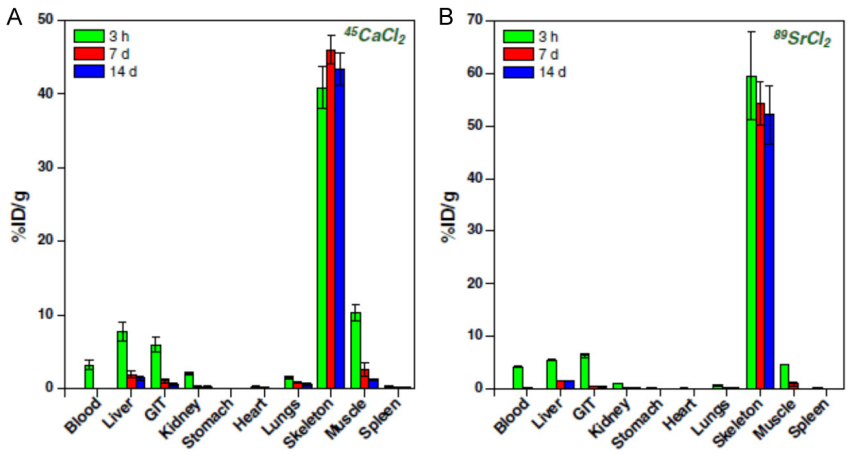

Figure 6. Ex vivo biodistribution study of (A) $^{45}CaCl_2$, (B) $^{89}SrCl_2$. Adapted from reference [57] with permission.

but in this case very high proton beam energy is required (> 45 MeV) and across the world, there are few cyclotron facilities accessible to provide such high energy proton beam. While in the reactor ^{47}Sc could be obtained by two different routes (a) ^{47}Ti (n, p) ^{47}Sc reaction and (b) ^{46}Ca (n, γ) $^{47}Ca \rightarrow {}^{47}Sc$ reaction [52]. The first route required the bombardment of the ^{47}Ti target material with a fast neutron (E_n > 1 MeV), which is inaccessible in most of the research reactors across the world. So, the most favourable way for the production of ^{47}Sc is the irradiation of ^{46}Ca by a thermal neutron. The only disadvantage of this route is the requirement of a large amount of target due to the low thermal cross-section of ^{46}Ca (σ = 0.7 b). After the production and radiochemical processing of ^{47}Sc, it is mandatory to separate ^{47}Sc from its bulk irradiated target material, and for this selective electrodeposition of Ca^{2+} on the mercury (Hg) pool cathode as Ca-Hg amalgam was carried out [53]. For the electrodeposition, ^{47}Sc/Ca mixture was re-constituted in lithium citrate solution and transferred to a water-jacketed glass cell (34 × 70 mm, 30 mm internal diameter) fitted with a stop cock. The schematic of the electro-amalgamation process was similar as **Figure 2**. In order achieve the maximum separation yield the applied potential was adjusted to 7 V for 35 min at pH ~6. After the electrolysis, the Ca-Hg amalgam was drained away and the electrolyte consisting ^{47}Sc was passed through Whatman filter paper (No. 50). The filtrate was evaporated to near dryness and reconstituted in 2 mL deionized water. The separation yield of the process was > 90% with > 99.95% radionuclide purity, and > 97% radiochemical purity.

Separation of ^{45}Ca from ^{46}Sc

The primary component of the bone is hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] which consists of Ca^{2+}, PO_4^{3-} and OH^- and hence a radiometal mimicking Ca while possessing appropriate decay characteristics could be used for the metastatic bone pain palliation. In this regard, the first United States Food and Drug Administration (US FDA) approved radiometal was ^{89}Sr ($T_{½}$ = 50.5 d, $E_{βmax}$ = 1.49 MeV) in the form of $^{89}SrCl_2$ because of chemical similarities of Sr^{2+} with Ca^{2+} [54, 55]. But, across the world there is limited production of ^{89}Sr which makes this formulation expensive and inaccessible [56]. In order to circumvent the problem, ^{45}Ca ($T_{½}$ = 163 d, $E_{βmax}$ = 0.3 MeV) has been proposed for use in bone pain palliation because it could be easily produced from enriched ^{44}Ca target by (n, γ) reaction in a medium flux nuclear reactor. Despite its easy production, complexity arise from co-produced ^{46}Sc [$T_{½}$ = 84 d, $E_{βmax}$ = 0.357 MeV, $E_γ$ = 0.89 MeV (99%) and 1.12 MeV (99%)] and therefore separation of ^{45}Ca from ^{46}Sc is essential for use of ^{45}Ca in nuclear medicine. Electroamalgamation is an efficient method for isolation of ^{45}Ca from the radionuclidic impurity, ^{46}Sc [57]. In this approach, ^{45}Ca/^{46}Sc mixture was reconstituted in 0.15 M lithium citrate medium in which Ca^{2+} could selectively be deposited at the mercury pool cathode in the form of Ca-Hg amalgam when the applied potential was 7 V, pH of the electrolyte was ~6 and the operation time was 30 min. The ^{45}Ca was recovered from Ca-Hg amalgam using HCl (> 5 M) as an extractant and obtained in the form of $^{45}CaCl_2$ which could directly be utilized for bone pain palliation purpose like $^{89}SrCl_2$. The schematic diagram of the electroamalgamation process was similar to that represented in **Figure 2**. To compare the efficacy of [^{45}Ca]$CaCl_2$ with that of clinically established [^{89}Sr]$SrCl_2$, biodistribution studies were performed in normal Wistar rats after intravenous administration of both these radiotracers in different groups (**Figure 6**). The biodistribution patterns were almost comparable even though a slightly lower bone uptake was observed for [^{45}Ca]$CaCl_2$ due to the soft $β^-$ of ^{45}Ca which was attenuated by the bone and hence less count was registered in the detector. Overall, the biodistribution study established the potential of [^{45}Ca]$CaCl_2$ for targeting bone metastases.

Separation of ^{177}Lu from Yb target

Lutetium-177 (^{177}Lu, $T_{½}$ = 6.65 d) is an established therapeutic radioisotope because of its appropriate nuclear decay characteristics such as emission of gamma ray of energy 113 keV (11%), 208 keV (6.4%) which are suitable for SPECT imaging and maximum beta energy of 497 keV (79.3%) having maximum soft tissue penetration range of ~2.5 mm which is useful for treatment of small lesion metastases [58]. In a nuclear reactor, ^{177}Lu could be produced by two routes (i) direct route and (ii) indirect route. Direct route involves irradiation of ^{176}Lu by (n, γ) reaction and it would produce ^{177}Lu together with trace amount of ^{177m}Lu (160.3 d). The indirect route involves the irradiation of the ^{176}Yb target which would produce ^{177}Yb followed by $β^-$ decay to obtain NCA ^{177}Lu [58]. The main advantage of

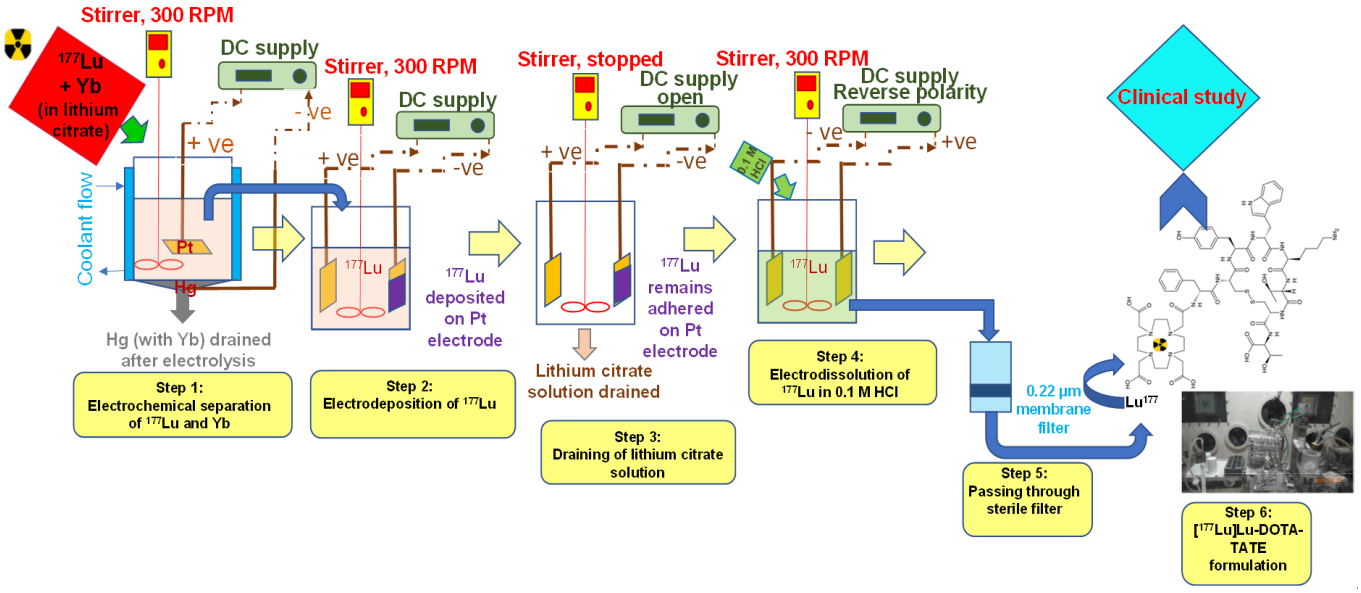

Figure 7. Schematic diagram of the electrochemical setup of ^{177}Lu/Yb. Adapted from reference [11] with permission.

indirect route is that it precludes the co-production of ^{177m}Lu and ^{177}Lu is obtained with high specific activity (~5 times more than the direct route). But the ^{177}Lu produced by the indirect route has to be separated from its bulk irradiated target and for this selective electroreduction of Yb^{+3} to Yb^{+2} followed by deposition of Yb^{+2} on the Hg pool cathode was performed [11]. Since Yb^{+2} is having [Xe]$4f^{14}$ electronic configuration which is stable and therefore it behaves like alkaline earth metal and is hence reversible and replaceable with the alkali metal amalgam solution. While Lu^{3+} could not be reduced to Lu^{2+} because of the lack of stable electronic configuration, so Lu would not deposit as Lu-Hg amalgam. For the electrolysis, the radiochemically processed ^{177}Lu/Yb solution was re-constituted in 0.15 M lithium citrate medium and subsequently, the solution was taken in a water-jacked electrochemical cell fitted with a stop cock. The schematic diagram of the processes involved in ^{177}Lu/Yb separation is shown in **Figure 7**. During the course of electrolysis, the applied potential was kept at 8 V (500 mA) for 45 min at pH ~6. At the end of electrolysis, the Yb-Hg amalgam was drained off and ^{177}Lu solution was transferred to another beaker where ^{177}Lu was selectively electrodeposited on the Pt-cathode under the applied potential of 10 V for 55 min at pH ~6-7. The deposited ^{177}Lu was stripped out in 0.1 M HCl solution by reversing the polarity of the electrode and passed through 0.22 µM Millipore filter paper to trap the trace amounts of impurities like colloidal Hg. The overall batch yield of the process was > 70% with > 99.99% radionuclide purity, and > 98% radiochemical purity. The specific activity of the NCA ^{177}Lu was obtained by titrimetric method using DOTA as a complexing agent and found to be 89 ± 2 Ci/mg. A therapeutically relevant dose of [^{177}Lu]Lu-DOTATATE (7.4 GBq activity) was prepared, intravenously administered in a 67 y old male patient with neuroendocrine tumor and SPECT images were acquired 4 h after injection (**Figure 8**) to demonstrate selective uptake in the cancerous cells. Since, enriched ^{176}Yb target which is quite expensive was used in large quantities in the production process, recovery and reuse of the target material is the cornerstone for the cost-effective sustainability of this approach. In order to recover the enrich target, the decayed Yb-Hg amalgam was washed with ethanol and then added 7 M HCl solution. The mixture was shaken vigorously for 15 min at room temperature. Then the aqueous solution was separated and evaporated to dryness followed by re-constitution in HPLC water. Subsequently, 20 mL of 1 M oxalic acid solution was added to precipitate Yb as ytterbium oxalate. The precipitate was dried under IR-lamp and heated in a furnace at 500°C. Then the sample was collected and taken for characterization using XRD (**Figure 9A**) that prove formation of Yb_2O_3 and XRF (**Figure 9B**) which demonstrated the high purity of Yb_2O_3. In this process, the overall recovery of the enriched target was > 85%. This retrieved Yb_2O_3 target would be irradiated for production of ^{177}Lu which could be separated again using electroamalgamation method followed by recovery of bulk irradiated target. This cycle can be continued till the retrieved Yb_2O_3 is depleted (depletion of ^{176}Yb) to such an extent that production of ^{177}Lu becomes inadequate and in this way 'indirect route' for production of ^{177}Lu becomes economically sustainable.

Separation of ^{153}Sm from ^{154}Eu impurity

Among the various US FDA approved bone seeking agents used for palliative care of metastatic bone pain, [^{153}Sm] Sm-EDTMP is the most widely employed radiopharmaceutical because of reasonable half-life of ^{153}Sm ($T_{½}$ = 46.3 h) with the emission of soft beta ($E_{\beta max}$ = 233 keV) possessing effective tissue penetration range of 2-3 mm and the associated gamma energy [E_{γ} = 103.2 keV (28%)] which

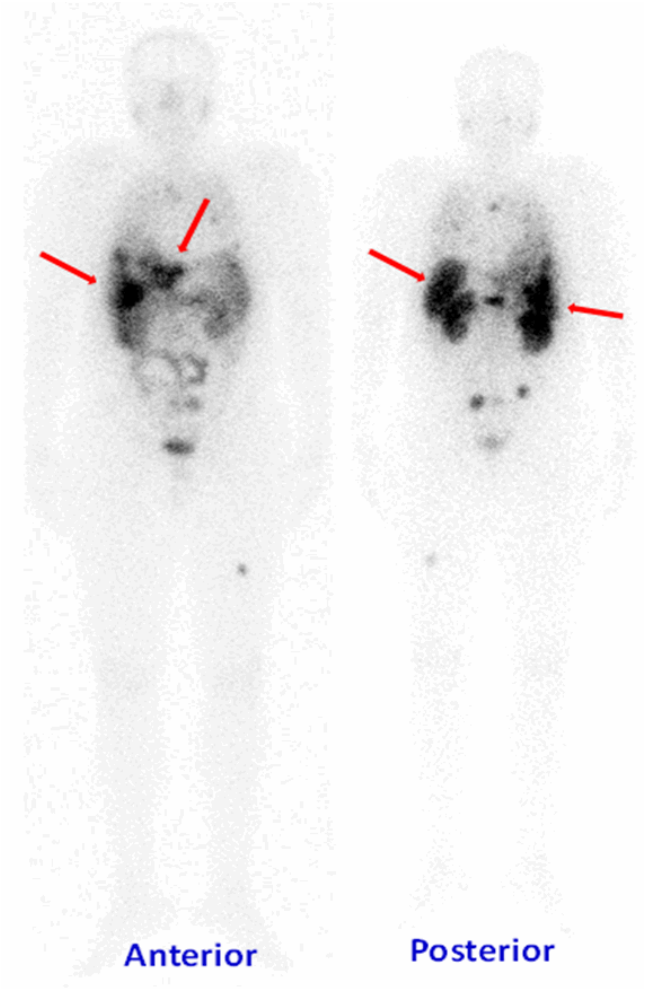

Figure 8. Typical SPECT image of a 67 y old male patient after at 4 h post-injection of [^{177}Lu]Lu-DOTA-TATE. Adapted from reference [11] with permission.

could be utilized for scintigraphic imaging [57, 59]. ^{153}Sm can be produced from ^{152}Sm by (n, γ) reaction and it decays to ^{153}Eu which would produce ^{154}Eu ($T_{½}$ = 8.6 y) upon neutron capture. Preferably, after radiochemical processing of ^{153}Sm and prior to the application in human health care ^{153}Sm must be separated from the long-lived impurity, ^{154}Eu. In this regard, electroamalgamation method was employed for selective deposition of ^{154}Eu in the pool type Hg cathode by amalgam formation [60]. The mechanism of this method was selective reduction of Eu^{3+} to Eu^{2+}, which is possible because of the stable half-filled 4f electronic configuration of Eu^{2+}. Once Eu^{2+} is formed, it would immediately amalgamate with Hg while Sm^{3+} remained in the solution. In this approach, 0.15 M lithium citrate was used as electrolyte and at the optimal condition the applied potential was 6 V, pH of the electrolyte was ~6, operation time was ~30 min and more 85% of ^{153}Sm could be separated with > 99% radionuclide purity. The schematic of this process was similar to **Figure 2**. Ex vivo biodistribution study was performed in normal Wistar rats with the separated ^{153}Sm in the form of [^{153}Sm]Sm-EDTMP and compared the result with unpurified ^{153}Sm (**Figure 10A**). Presence of ^{154}Eu impurities could be seen in the γ-ray spectra of bone samples of Wistar rats administered with [^{153}Sm]Sm-EDTMP (prepared without purification of ^{153}Sm) 15 days after intravenous administration (**Figure 10B**). On using [^{153}Sm]Sm-EDTMP using electrochemically purified ^{153}Sm, the extraneous peaks were not seen in the γ-spectrum of the bone samples (inset of **Figure 10B**). Adoption of this robust separation technology would ensure the widespread clinical utility of ^{153}Sm without regulatory hurdles for maximum benefit of cancer patients.

Separation of ^{169}Er from ^{169}Yb impurity

Radiation synovectomy (RSV), is a minimally invasive treatment modality in which microparticles (1-10 μm size range) are radiolabeled with beta-emitting radioisotopes and administrated intra-articularly into inflamed synovial joints of the patients suffering from rheumatoid and degenerative joint disorder [61-63]. Depending upon the type of synovial joint in human body, various beta-emitting radiometals have been recommended based on their optimal tissue penetration range. For this reason, ^{169}Er ($T_{½}$ = 9.4 d) could be used for RSV of the small digital joints because of the emission of low energy beta particles [342 keV (45%) and 351 keV (55%)] having tissue penetration depth of ~0.3 mm which preclude damage to the surrounding healthy tissues [64]. ^{169}Er with adequate specific activity could be produced by (n, γ) reaction from enriched ^{168}Er (> 98%) target. It has been observed that during the production of ^{169}Er there is a co-production of ^{169}Yb ($T_{½}$ = 32 d) as an impurity which can't be prevented because of presence of trace level impurity of Yb (~20 ppm) in the target material. During the enrichment of ^{168}Er, the ^{168}Yb impurity also get enriched. Owing to its rather large cross section (~2300 b), ^{168}Yb produces long-lived ^{169}Yb which decays to ^{169}Tm by electron capture followed by emission of gamma rays of different energies [$E_{γ}$ = 109.8 (17.4%), 177 keV (22.5%),197 keV (35.9%)]. Therefore, it is necessary to separate ^{169}Er from the ^{169}Yb impurity to avoid the unnecessary dose delivered to healthy organs/tissues surrounding the synovial joints. A feasible separation yield could be achieved adopting the electroamalgamation method [65]. In this process, Yb could be selectively deposited at the Hg-pool cathode. The schematic of this process was similar to **Figure 2**. The radiometal mixture was taken in 0.15 M lithium citrate medium and maximum separation yield (> 95%) was obtained when electrolysis was carried out for 20 min at applied potential ~8 V at pH ~6. After the electrochemical separation, the ^{169}Yb impurities could be completely removed from ^{169}Er solution. The purified radioactivity could be utilized for preparation of ^{169}Er labelled hydroxyapatite which is an established agent for radiation synovectomy of small joints.

Separation of $^{132/135}$La from Ba target

Among various emerging theranostic radiometals, $^{132/135}$La pair is one of the most attractive one because of

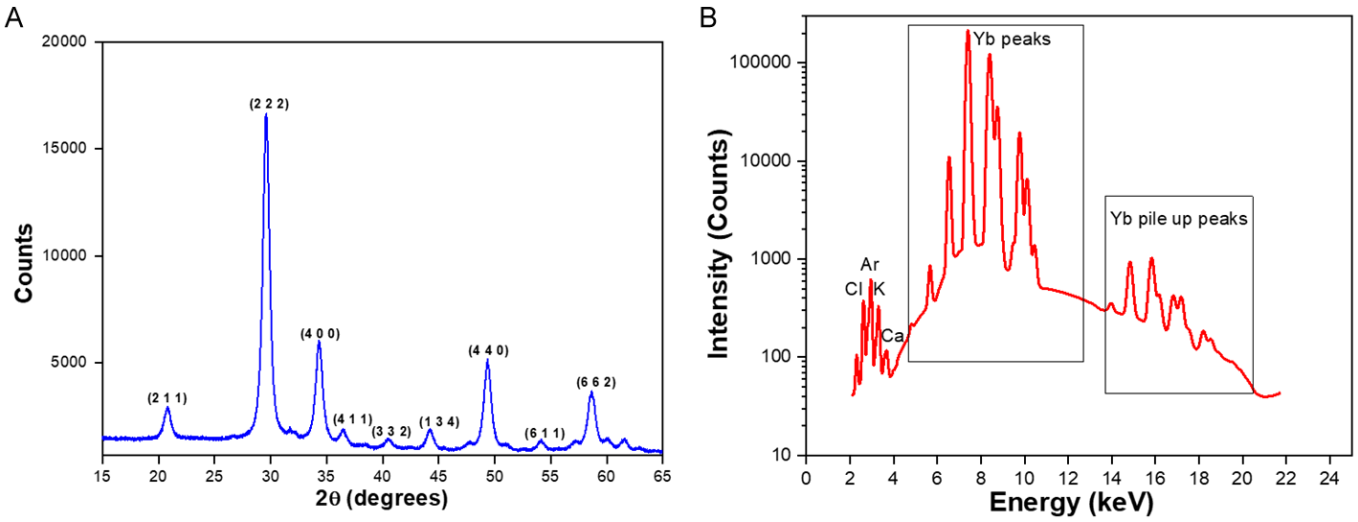

Figure 9. (A) XRD, (B) XRF pattern of enriched [^{176}Yb]Yb_2O_3 target after recovery from the mercury electrode subsequent to radiochemical separation. Adapted from reference [11] with permission.

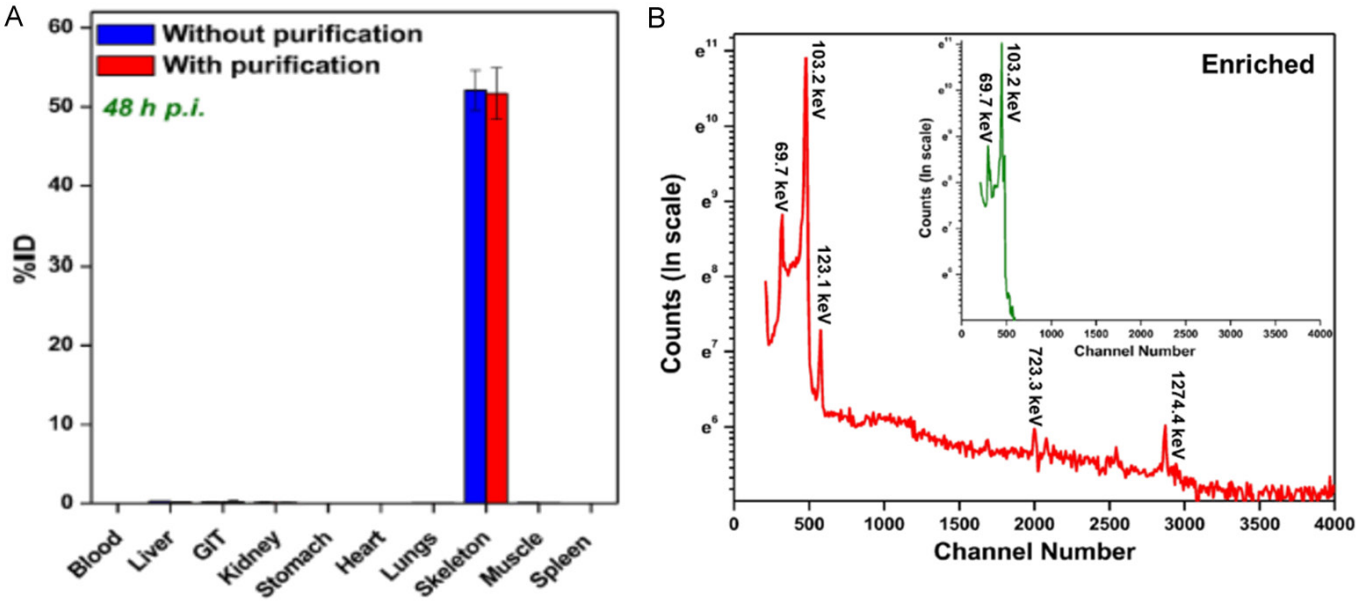

Figure 10. A. Ex-vivo biodistribution of [^{153}Sm]Sm-EDTMP at 48 h of post injection; B. γ-spectra of bone samples of Wistar rats recorded 15 days after intravenous administration of [^{153}Sm]Sm-EDTMP. Inset shows γ-spectra of bone samples of Wistar rats when electrochemically purified ^{153}Sm was used for the preparation of [^{153}Sm]Sm-EDTMP. Adapted from reference [60] with permission.

its excellent nuclear decay characteristics. ^{132}La ($T_{½}$ = 4.59 h) decays by positron emission and so it can be used for PET imaging while ^{135}La ($T_{½}$ = 19.93 h) decays by electron capture emitting Auger electrons (LET ~4-26 keV/μm) and so it could be used as a potential therapeutic agent. Together, $^{132/135}$La pair can be used as a potential theranostic agent [66]. As the co-ordination chemistry of $^{132/135}$La resembled ^{90}Y and ^{177}Lu, the same bifunctional chelators which are used for ^{90}Y and ^{177}Lu could also be used for $^{132/135}$La labeling. The $^{132/135}$La pair was produced from the proton irradiation of natural Ba target by (p, xn) reaction and for this reaction, the proton beam energy was 15 MeV with 200 nA beam current for 84 h [15]. The irradiated target was radiochemically processed and reconstituted in 0.1 M HCl solution. The $^{132/135}$La was separated from the bulk irradiated Ba target by an electrochemical process where $^{132/135}$La was deposited as $^{132/135}La(OH)_3$ at the Pt-cathode while Ba would remain in the solution [15]. During the course of electrolysis, the applied potential was kept at 6 V for 20 min at pH ~3-4. The deep negative standard potential ($E^0_{La+3/La}$ = -2.38, $E^0_{Ba+2/Ba}$ = -2.73) precludes the deposition of La^{+3} and Ba^{+2} at their metallic state onto the cathode. Under the influence of applied potential, both La^{+3} and Ba^{+2} migrated towards the cathode where H_2 evolved due to the loss of H^+, and hence the pH at cathode proximity increases. So, both La^{+3} and Ba^{+2} would form their corresponding hydroxide at cathode proximity. As the solubility product

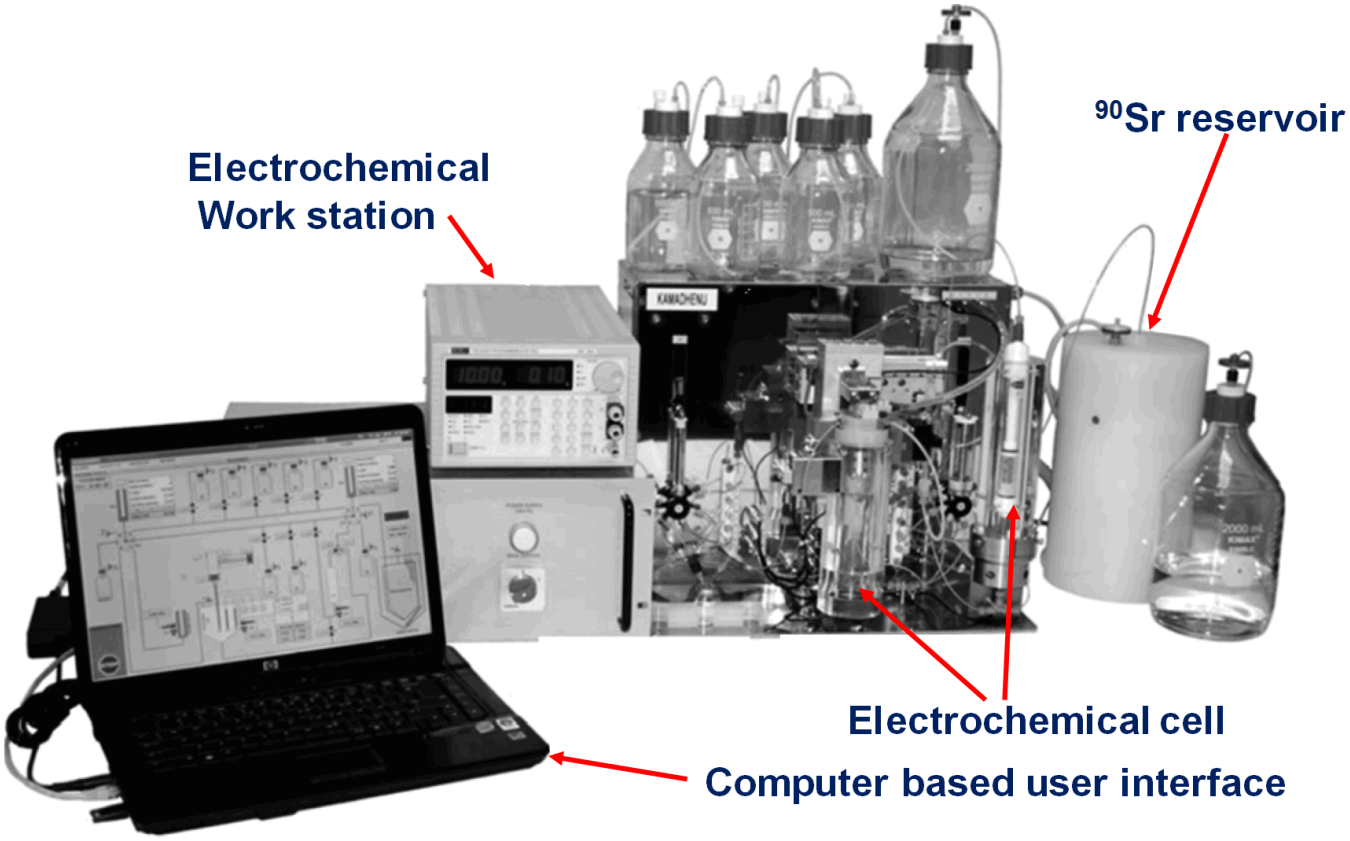

Figure 11. Fully automated ^{90}Sr/^{90}Y generator (Kamadhenu) commercially available from Isotope Technologies Dresden (Germany). Adapted from reference [7] with permission.

of $La(OH)_3$ (K_{sp} = 2.1 × 10^{-21}) is extremely small as compared to $Ba(OH)_2$ (K_{sp} = 5 × 10^{-3}), therefore at the optimized condition $Ba(OH)_2$ would be soluble and unable to deposit at the cathode while $La(OH)_3$ would be deposited onto the Pt-cathode [67, 68]. After the electrolysis, the electrodes were pulled out without switching off the voltage and $La(OH)_3$ layer onto Pt-cathode was stripped by reversing the polarity of the electrodes in 0.1 M HCl. The overall batch yield of the process was > 90% with > 99% radionuclide purity and > 98% radiochemical purity. The specific activity of $^{132/135}$La was determined using DOTA as a complexation agent and found to be 25.8 ± 2.2 MBq $nmol^{-1}$ [69]. The schematic of this electrochemical process is similar to **Figure 3**, without the reference electrode. Electrochemically purified $^{132/135}$La could be utilized towards formulation of target specific radiopharmaceuticals with high (> 95%) radiolabeling yields.

Scaling up of the electrochemical separation process and automation of the system for routine use in nuclear medicine

The future of electrochemical separation process for obtaining radiometals for use in nuclear medicine is inextricably linked to the scale up of the procedure to a clinically relevant level which is easily executable in a centralized radiopharmacy set up. This necessitates the development of an automated system which can perform the electrochemical procedure for large-scale radiochemical separation in a shielded facility. The primary advantages of automation in electrochemical separation process of radiometals include minimization in radiation dose to the working personnel, process robustness as well as reproducibility of the product quality, consistent performance of the separation process, traceability of the overall process, including documentation of all process parameters and functions while maintaining regulatory standards for clinical translation. From this perspective, scale-up and automation is essential for the ongoing research efforts to create a foundation as well as advancement of this technology for routine use in nuclear medicine. Successful implementation of automation would not only ensure a sustained growth in the field of nuclear medicine but also empower future developments with the availability of newer radiometals for imaging and therapy.

Designing an automated module which can function efficiently in a shielded glove box facility might be challenging, technology intensive and require significant capital investment which would increase the overall production cost. Nevertheless, the electrochemical separation process provides ample opportunities to mitigate the limitations of the present generation radiochemical separation methodologies. Moreover, it is a one-time investment as

the electrochemical process system is expected to be minimally affected in the intense radiation environment over prolonged use. This cost can easily be recovered in the long run by expanding the applications of the radiometals obtained from these electrochemical separation systems for use in the burgeoning fields of nuclear medicine and molecular imaging. To advance automation, operation steps of each electrochemical process need to be examined scrupulously, and the feasibility for automation has to be appropriately explored. In the past, the efforts of commercial companies in devising an automated ^{90}Sr/^{90}Y electrochemical separation system have been fruitful and a module has been designed for the production of up to 37 GBq of ^{90}Y per day (**Figure 11**) [70]. This automated module is already in use in certain countries through the efforts of the International Atomic Energy Agency (IAEA) and is a noteworthy step in the right direction to meet the global demand for ^{90}Y in cancer therapy. Similar approach can be applied for other systems which in turn may take a giant leap in closing the gap between requirements of radiometals for preparation of radiopharmaceuticals and the production capabilities.

Conclusions

The electrochemical technique has manifested itself as an attractive strategy for the separation of radiometals and in this article, some depiction of the separation of medically important radiometals using this method has been discussed. The reproducibility and high purity of the final product with remarkable yield make this approach superior to the conventional chromatographic and solvent extraction methods. Moreover, when the enriched target is used for the production of desired radioisotope, recovery of the enriched target is essential to make the process economically viable for routine use in clinical context. In an electrochemical method it is easy to retrieve the enriched irradiated target with a significant yield which make the process cost effective. Although all radiometals could not be separated by this method, this strategy has surely opened up an alternative path for the separation of many radiometals which are very cumbersome to separate by conventional methods. The superiority of the electrochemical process has been acknowledged in the recent past and a paradigm shift towards radiochemical separation of medically important radiometals is noticed. However, regulatory approvals for the final product obtained from this relatively newer method is required so that the final product could actually be utilized for the treatment of cancer patients. Arguably, the development of the electrochemical process and its implementation in separation of radiometals inextricably enhance the progress in nuclear medicine. Although electrochemical method has paved the milestone in separation of radioisotopes, responsibility has to be taken by all stakeholders including clinicians, research scientists and regulatory authorities to exploit the full potential of this process in order to make it a predominant radiochemical separation model for routine clinical usage.

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Disclosure of conflict of interest

None.

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