Effective and Economically Viable Rhenium-188 Radiopharmaceuticals for Liver Cancer Therapy and Bone Pain Palliation: BARC Contributions to Rhenium-188 Radiopharmaceuticals Program in India

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Abstract
Rhenium-188 is an important therapeutic radioisotope, available from a commercial Tungsten-188/Rhenium-188 generator (188W/188Re generator). Its high energy beta emission \[E_{\beta_{\text{max}}} - 2.12 \text{ MeV}, \ E_\gamma - 155 \text{ keV (15%)}, \ \text{half-life} - 16.9 \text{ h}\] is especially useful for the therapy of large tumors in organs such as liver. Trans arterial radioembolization (TARE) using rhenium-188 labeled lipiodol is an effective and economically viable alternative to imported radiotherapeutic agents for liver cancer therapy. The 188ReN(DEDC)2 complex (hence forth written as 188ReN-DEDC complex, DEDC – diethyl dithiocarbamate) extracted into lipiodol is one such radiopharmaceutical, which has proven its clinical efficacy for the therapy of liver cancer. 188Re-HEDP (1-Hydroxy Ethylidene-1,1-Diphosphonic Acid) is another effective radiopharmaceutical for palliation of bone pain due to osseous metastasis. In-house development of freeze-dried kits for the preparation of 188ReN-DEDC/lipiodol and 188Re-HEDP will eliminate the dependence on imported kits, that had been a major impediment for its wide spread clinical application in India. This article highlights the contributions from BARC to clinical 188Re-radiopharmaceutical program in India.

Key words: Rhenium-188, Radiopharmaceuticals, Therapy, Theranostic isotope, Liver cancer, Bone pain palliation, 188ReN-DEDC, 188Re-HEDP, Freeze-dried kits.

INTRODUCTION
Rhenium belongs to group-VII of the periodic table, same as that of technetium-99m, the isotope which is called the workhorse of nuclear medicine. It has two important radioisotopes, 186Re [half-life - 3.71 days, \(E_{\beta_{\text{max}}} - 1.09 \text{ MeV}, \ E_\gamma - 136 \text{ keV (9%)\}] \] and 188Re [half-life - 16.9 h, \(E_{\beta_{\text{max}}} - 2.12 \text{ MeV}, \ E_\gamma - 155 \text{ keV (15%)\}] \[1\]. Both radioisotopes have beta energies suitable for therapy with associated gamma emissions, which permits monitoring the distribution of the radiotracer in vivo. While relatively low-energy beta particles of 186Re are useful for therapeutic applications requiring low tissue penetration, high-energy beta emissions from 188Re are particularly useful for therapy of cancer in large organs like liver.
Being in the same group of the periodic table, technetium and rhenium may be expected to share similar chemistry. For example, pertechnetate (TcO$_4^-$) and perrhenate (ReO$_4^-$), in which both the metals are in their most stable oxidation state of +7, are isostructural. With suitable ligands, both metals form complexes in +5 oxidation state. Both metals form $\text{fac}$-tricarbonyl complexes, $\langle [\text{M(CO)}_3]^+; \text{M} = \text{Tc}, \text{Re} \rangle$, in which the metal is in +1 oxidation state. Similarity in chemistry of technetium and rhenium prompt us to believe it is possible to have theranostic radiopharmaceutical pair with $^{99m}$Tc and $^{188}$Re radionuclides, wherein the $^{99m}$Tc-radiopharmaceutical will be used for diagnosis and corresponding $^{188}$Re-analogue for therapy. However, practically, rhenium in +7 oxidation is more difficult to reduce than technetium. Rhenium often requires acidic conditions for its efficient reduction, while technetium can be reduced under neutral or slightly acidic/basic conditions, ideally suited for radiopharmaceutical preparation. This is one of the reasons, we do not see rhenium analogue of all successful technetium radiopharmaceuticals.

Like the $^{99}$Mo/$^{99m}$Tc generator, which had a significant role in making $^{99m}$Tc the workhorse of nuclear medicine, the $^{188}$W/$^{188}$Re generator has the potential to popularize the use of $^{188}$Re-radiopharmaceuticals for therapy. Commercial availability of $^{188}$W/$^{188}$Re generator fulfils the primary criteria to achieve this objective. However, unlike a $^{99}$Mo/$^{99m}$Tc generator, a $^{188}$W/$^{188}$Re generator is several times costlier. At present in India, cost of a 500mCi $^{188}$W/$^{188}$Re generator is approximately 18 lakhs. For any nuclear medicine centre, economic viability of the services they provide is vital for their existence. Initial investment, a $^{188}$W/$^{188}$Re generator, necessary to start $^{188}$Re-therapy program in a nuclear medicine centre being high, availability of sufficient number of effective $^{188}$Re-radiopharmaceuticals for prime oncological applications is essential for efficient utilization of $^{188}$Re-activity from the generator, which will make the therapy program sustainable.

Freeze-dried kits remarkably simplify the preparation of radiopharmaceuticals in a busy hospital radiopharmacy. Radiopharmaceutical division, BARC, recognized the importance of in-house development of freeze-dried kits for the preparation of $^{188}$Re-radiopharmaceuticals to boost $^{188}$Re-therapy program in India. By carefully analyzing the trends in clinical nuclear medicine scenario, two $^{188}$Re-radiopharmaceuticals, which could provide an effective and economically viable alternative to existing nuclear medicine practice, were selected. The first one was $^{188}$ReN-DEDC/lipiodol for the therapy of unresectable primary liver cancers such as hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC) [2]. The second radiopharmaceutical was $^{188}$Re-HEDP, a palliating agent for pain arising from bone metastasis [3]. At the time of conceptualizing this work, freeze-dried kits for the preparation of both of these $^{188}$Re-radiopharmaceuticals were not available commercially. In this article, author briefly describe the development of freeze-dried kits for the preparation of the two selected radiopharmaceuticals starting from laboratory bench, culminating in its application in the clinic.

**THERAPY OF LIVER CANCER**

**Background**

HCC and ICC are the two most common primary liver cancers and represents the second most common causes of cancer death worldwide [4]. Patients presented with late stage HCC/ICC are often unresectable, and therefore, recommended for loco-regional therapies such as Trans arterial chemoembolization (TACE), TARE or sorafinib therapy, depending on the stage of the disease [5]. TARE is one of the minimally
invasive, image-guided loco-regional liver therapies in clinical practice today [6]. Primarily, this procedure embolizes the blood vessels feeding the tumor to deny vital nutrients and oxygen. Additionally, the radiotherapy agent in the embolizing medium delivers effective loco-regional therapy while sparing neighboring normal liver cells.

Some of the clinically available options for TARE include $^{90\text{Y}}$-labeled microparticles [7, 8], $^{131\text{I}}$-lipiodol [9, 10] and $^{188\text{Re}}$-lipiodol [2, 11, 12]. Recent studies have proved the efficacy and safety of $^{90\text{Y}}$-microparticles for TARE [13]. However, high cost of $^{90\text{Y}}$-microparticle therapy limits its application to a small fraction of patients who can afford it. Though $^{131\text{I}}$-lipiodol therapy provides an economically viable alternative, long half-life, low β-energy [$E_{\beta^{\text{max}}} - 0.61 \text{ MeV (89.3%)}, 0.33 \text{ MeV (7.3%)}, 0.25 \text{ MeV (2.1%)}, \text{half-life – 8.02 days}] and the need for isolation of the patient post therapy, makes it a less preferred clinical choice.

$^{188\text{Re}}$-Radiopharmaceuticals for TARE

Rhenium-188 radiopharmaceuticals for liver cancer therapy combine the low-cost benefit of $^{131\text{I}}$-lipiodol therapy and, the safety and efficacy of $^{90\text{Y}}$-microparticle therapy. Rhenium-188 has beta energy comparable to that of $^{90\text{Y}}$ [$E_{\beta^{\text{max}}} - 2.28 \text{ MeV}, \text{half-life - 64.1 h}$] and hence comparable tissue penetration range could be expected. As mentioned earlier, presence of gamma emission, which permits monitoring the localization of radiopharmaceutical in the target tissue, is an added advantage of $^{188\text{Re}}$-radiopharmaceutical over $^{90\text{Y}}$-counterpart.

A common approach for the preparation of $^{188\text{Re}}$-radiopharmaceutical for liver cancer therapy involves preparation of a stable, lipophilic complex of $^{188\text{Re}}$ and its extraction into lipiodol (poppy seed oil). Subsequently, $^{188\text{Re}}$-loaded lipiodol is used for TARE.

Jeong et al. reported a freeze-dried kit procedure for the preparation of a lipiodol solution of $^{188\text{Re}}$TDD (TDD - 2,2,9,9-Tetramethyl-4,7-diaza-1,10-decanedithiol) for therapy of liver cancer [11]. This method involved preparation of a lipophilic $^{188\text{Re}}$TDD complex and its extraction into lipiodol. Though $^{188\text{Re}}$TDD/lipiodol could be prepared in good yields, its retention in liver was not good enough for the therapy of liver cancer. The same group subsequently reported a modified form of $^{188\text{Re}}$TDD, the $^{188\text{Re}}$HDD (HDD - 4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol), which showed higher retention in liver. In an IAEA-sponsored clinical study, Kumar et al. concluded that TARE with $^{188\text{Re}}$HDD/lipiodol is a safe and effective option for the therapy of inoperable hepatocellular carcinoma [12].

Though $^{188\text{Re}}$HDD/lipiodol is clinically used for the therapy of liver cancer, efficiency of extraction of $^{188\text{Re}}$HDD into lipiodol is poor (~50%). Lower extraction efficiency is an impediment to prepare higher patient doses of $^{188\text{Re}}$HDD/lipiodol and, quite often, the radiopharmacist is forced to do multiple preparations of $^{188\text{Re}}$HDD to obtain the required patient dose. Moreover, freeze-dried HDD kits are not available locally and have to be imported.

The $^{188\text{ReN}}$-DEDCC complex reported by Boschi et al. had higher extraction efficiency into lipiodol (>80%) and combined with excellent clinical efficacy for the therapy of HCC and ICC by TARE, it presents itself as an effective alternative to existing clinical option. Based on these facts, we decided to develop these kits in-house to ensure uninterrupted local availability at an affordable cost.

$^{188\text{ReN}}$-DEDCC/lipiodol for liver cancer therapy

Preparation of $^{188\text{ReN}}$-DEDCC complex involves two steps [2]. First step involves the preparation of $[^{188\text{ReN}}]^{2+}$ (rhenium nitride) intermediate, the precursor for the preparation
Figure 1. Preparation of $[^{188}\text{Re}N]^{2+}$ intermediate

The preparation of $[^{188}\text{Re}N]^{2+}$ intermediate involves the reduction of $[^{188}\text{ReO}_4^-]$ by stannous chloride dihydrate ($\text{SnCl}_2\cdot2\text{H}_2\text{O}$) followed by attack of the nitride ($\text{N}^{3-}$) ion from $\text{N}$-methyl-$\text{S}$-methyl dithiocarbazate (DTCz). This reaction is highly facilitated under acidic conditions ($\text{pH} = 3$) and kinetics of $[^{188}\text{ReO}_4^-]$ reduction is enhanced in the presence of oxalate ligand. Therefore, glacial acetic acid and disodium oxalate are added in the reaction mixture while preparing $[^{188}\text{Re}N]^{2+}$ intermediate.

The $[^{188}\text{Re}N]^{2+}$ intermediate has square pyramidal structure with ‘N’ atom occupying the apex of the square pyramid and four labile ligands (L) occupying the four corners of the basal plane. It should be noted that nitride ion donor, DTCz, itself can act as a ligand in the present case.

The second step involves the preparation of $^{188}\text{ReN}$-DEDC complex from $[^{188}\text{Re}N]^{2+}$ intermediate prepared in the first step (Figure 2) by incubating with DEDC ligand at 70°C for 20 min. The pH of the reaction mixture was maintained at 6.

The neutral, lipophilic, $^{188}\text{ReN}$-DEDC complex thus prepared was subsequently extracted into lipiodol and used for TARE procedure for the therapy of liver cancer.

Kit procedure for the preparation of $^{188}\text{ReN}$-DEDC/lipiodol

Freeze-dried kits are designed to prepare radiopharmaceuticals in minimum time, following simple procedures, in a busy hospital radiopharmacy. A freeze-dried kit contains all the necessary reagents, except radioactivity, for the preparation of a radiopharmaceutical. A two-vial freeze-dried kit for the preparation of $^{188}\text{ReN}$-DEDC complex was made in-house following a previously optimized procedure. Kit vial 1 for the preparation of $[^{188}\text{Re}N]^{2+}$ intermediate contained DTCz (2 mg), disodium oxalate (28 mg) and stannous chloride dihydrate (0.8 mg). Kit vial 2 contained DEDC ligand and carbonate buffer. To prepare the complex using freeze-dried kits, glacial acetic acid (0.1 mL) and freshly eluted Na$^{188}\text{ReO}_4$ (3 mL, $\sim$185 MBq) from a $^{188}\text{W}/^{188}\text{Re}$ generator was mixed and transferred into kit vial 1. The vial was gently shaken to dissolve the contents and then incubated at room temperature for 30 min to obtain $[^{188}\text{Re}N]^{2+}$ intermediate. In step two, kit vial 2 was reconstituted with sterile saline (2 mL) and 1.5 mL of the reconstituted solution was transferred into vial 1 containing $[^{188}\text{Re}N]^{2+}$ intermediate. The two solutions are thoroughly mixed and incubated at 70°C for 20 min to obtain $^{188}\text{ReN}$-DEDC complex. After cooling the vial to room temperature, lipiodol (3 mL) was added to kit vial 1. The contents of
the kit vial were thoroughly agitated in a vortex mixture to effect maximum extraction of the lipophilic $^{188}$ReN-DEDC complex into the lipiodol phase. The lipiodol phase containing $^{188}$ReN-DEDC complex is used for therapy of liver cancer by TARE procedure. Using this kit, $^{188}$ReN-DEDC complex could be prepared in $>$80% radiochemical purity and $>$95% extraction in lipiodol phase could be achieved.

The two-vial kit for the preparation of $^{188}$ReN-DEDC/lipiodol is in the process of obtaining regulatory approval from Radiopharmaceuticals Committee (RPC) for its production and supply to various nuclear medicine centers across India through Board of Radiation and Isotope Technology (BRIT), Vashi.

**Limited clinical Evaluation**

After obtaining necessary hospital ethical committee clearance, limited clinical trials of $^{188}$ReN-DEDC/lipiodol, prepared using the two-vial kits developed in BARC, was carried out in Tata Memorial Hospital (TMH), Mumbai, and, Kovai Medical Centre and Hospital (KMCH), Coimbatore. Preliminary results of the clinical trials are satisfactory and as per expectations. Typical clinical images of a liver cancer patient obtained at different time intervals during the course of therapy are shown in Figure 3.

From Figure 3, it could be noted that activity deposited in liver by tare procedure is retained even after 50h post injection (blue arrow). It is
also important to note that there is no significant accumulation of activity in any other part of the body, especially the lungs and kidneys. At present, extensive dosimetric studies of this agent is being carried out at KMCH, Coimbatore.

Making the two-vial kit more user-friendly!

As mentioned in the previous section, the preparation of $^{188}$ReN-DEDC complex using two-vial kit required addition of stipulated volume of glacial acetic acid for efficient preparation of the $[^{188}\text{ReN}]^{2+}$ intermediate. An error by the radiopharmacist in this step can potentially affect the formation of $[^{188}\text{ReN}]^{2+}$ intermediate as well as the optimum pH required for the reaction mixture in the crucial second step, leading to low radiochemical purity of $^{188}$ReN-DEDC complex. In routine conventional radiopharmacy operations, an “acetic acid free” procedure for the preparation of $^{188}$ReN-DEDC complex could be more reliable and reproducible, thus helping to avoid any inappropriate usage of the radiopharmaceutical.

In Radiopharmaceuticals division, we devised a simple strategy to solve this problem by including a buffer of pH 3 in the kit vial itself to create a conducive environment for $[^{188}\text{ReN}]^{2+}$ intermediate formation. The basis of this strategy was the observation that disodium oxalate, salt of oxalic acid, is a constituent of kit vial 1 discussed above [2] and by including calculated amount of oxalic acid, it is possible to construct a buffer of pH = 3, which would then eliminate the need of adding glacial acetic acid.

We prepared a freeze-dried oxalate buffer kit of strength 0.5M and used it for the preparation of $[^{188}\text{ReN}]^{2+}$ intermediate. The only difference in the procedure for the preparation of $[^{188}\text{ReN}]^{2+}$ intermediate using oxalate buffer kit was that there is no need to add glacial acetic acid. The formation of $[^{188}\text{ReN}]^{2+}$ intermediate using oxalate buffer kit and its radiochemical purity was determined by HPLC. Figure 4 shows the formation of $[^{188}\text{ReN}]^{2+}$ intermediate as a function of incubation time at room temperature. For comparison, $[^{188}\text{ReN}]^{2+}$ intermediate prepared by glacial acetic acid method is also shown in Figure 4. It could be noted that using 0.5M oxalate buffer kit, ~96% formation of $[^{188}\text{ReN}]^{2+}$ intermediate was complete as early as 5 min. No further improvement in RCP was observed. By conventional method, however, only about 28% $[^{188}\text{ReN}]^{2+}$ intermediate formation was complete during the same time interval. After 30 min incubation at room temperature, RCP of $[^{188}\text{ReN}]^{2+}$ intermediate prepared by conventional method approached that of 0.5M oxalate buffer kit. Typical HPLC elution profile of $[^{188}\text{ReN}]^{2+}$ intermediate prepared by glacial acetic acid method and oxalate buffer method is shown Figure 5. It could be noted that there is no difference in the HPLC elution profile of $[^{188}\text{ReN}]^{2+}$ intermediate prepared by either methods.
observed that $^{188}$ReN-DEDC complex could be consistently prepared in $>$80% RCP. In addition, the $^{188}$ReN-DEDC complex prepared by both methods showed $>$95% extraction into lipiodol phase.

The novel oxalate buffer method has led to a significant simplification of the procedure required for in-house production of this therapeutic agent. Considering that routine manipulation of high-energy $\beta$-emitters always constitutes a significant health hazard for operators involved in this type of radiopharmaceutical preparations, the more user-friendly kit described here could contribute to drastically decrease the radiation exposure, particularly when used in a busy hospital radiopharmacy. Process to obtain regulatory clearance for the manufacture and supply of oxalate buffer kits for the preparation of $^{188}$ReN-DEDC/lipiodol has been initiated.

**BONE PAIN PALLIATION**

$^{188}$Re-HEDP for bone pain palliation

Bone metastasis is common in patients with cancer of prostrate, breast, lung, bladder and thyroid. Problems associated with bone metastasis include severe pain, pathological fracture, spinal cord compression etc., which can compromise the quality of life of the patient by affecting mobility and sleep. Clinical management of pain itself can significantly improve the quality of life of the patient. Radionuclidic therapy is one of the modalities widely being practised for bone pain palliation. This involves selective delivery of radiation dose to the affected bone lesions, which are responsible for pain to the patient.

Bisphosphonates are by far the most widely explored molecules for preparing bone seeking radiopharmaceuticals [14]. HEDP is one such phosphonate which has shown strong adsorption on hydroxyapatite, the major constituent of bone, in vitro [15]. Liepe et al. reported a comparative study of surface bone-seeking radiopharmaceuticals $^{186}$Re-HEDP, $^{188}$Re-HEDP, $^{153}$Sm-EDTMP (EDTMP – ethylene diamine tetramethylene phosphonic acid) and the volume seeker $^{89}$Sr (as $^{89}$SrCl$_2$) for the treatment of skeletal metastases [15]. This study concluded that all the radiopharmaceuticals are helpful in rendering pain relief to the patient with no significant

**Figure 5.** Typical HPLC elution profile of $[^{188}\text{ReN}]^{2+}$ intermediate prepared by (Top) glacial acetic acid method and (Bottom) 0.5M Oxalate buffer after 30 min incubation at room temperature.
difference in their therapeutic efficacy or toxicity [15]. The clinical efficacy of the above radiopharmaceuticals for bone pain palliation being similar, the choice may be made on the basis of relative logistical advantage and cost factor of the radiopharmaceutical. In this context, \(^{188}\text{Re-HEDP}\) enjoys advantage since it can be prepared “on demand” in any hospital radiopharmacy housing a \(^{188}\text{W}/^{188}\text{Re}\) generator. In this context, availability of a freeze-dried kit for the preparation of \(^{188}\text{Re-HEDP}\) would be of great help for easy and efficient preparation of this radiopharmaceutical in a busy radiopharmacy.

**Freeze-dried HEDP kits**

Formulation of a lyophilized HEDP kits for the preparation of \(^{188}\text{Re-HEDP}\) was initially reported by Verdera et al [16]. Later, Marczewski et al. reported a liquid kit preparation for the same purpose [17]. Practical difficulty associated with liquid kit formulation involved its shelf-life (approximately 9 days) and logistics associated with its transport to distant places.

There is a wide variation in the amount of HEDP, gentisic acid and stannous chloride dihydrate in the freeze-dried HEDP kits reported by different groups for the preparation of \(^{188}\text{Re-HEDP}\) [16-18]. In the present work, although the amount of reagents used were similar to that reported by Verdera et al., there is significant difference between the two formulations. While rhenium carrier (300 µg potassium perrhenate; total rhenium metal content 193 µg) was included in the lyophilized kit formulated by Verdera et al., no rhenium carrier is included in the kit vial reported herein. This was done to avoid the possibility of the Sn\(^{2+}\) ions being consumed by carrier rhenium in the kit, which could ultimately affect the shelf-life of the kit.

Procedure for the preparation of freeze-dried HEDP kits without carrier rhenium was optimized. Six consecutive batches of freeze-dried HEDP kits were prepared to demonstrate the robustness of the procedure. Randomly selected kits from all the six batches were subjected to thorough quality control tests before declaring fit for use in clinical applications. A proposal was submitted to RPC to obtain regulatory approval for the manufacture and supply of these kits to various nuclear medicine centres through BRIT, Vashi. Freeze-dried HEDP kit is now a RPC approved radiopharmaceutical kit for the preparation of \(^{188}\text{Re-HEDP}\) for bone pain palliation (Fig. 6).

**Kit procedure for the preparation of \(^{188}\text{Re-HEDP}\)**

Typical procedure for the preparation of \(^{188}\text{Re-HEDP}\) using freeze-dried HEDP kit is as follows. About 1 µmol (in ~100 µL) of perrhenic acid (HReO\(_4\)) or ammonium perrhenate (NH\(_4\)ReO\(_4\)) supplied along with the freeze-dried HEDP kit was thoroughly mixed with 1 mL of freshly eluted Na\(^{188}\text{ReO}_4\) from a \(^{188}\text{W}/^{188}\text{Re}\) generator. This solution was aseptically transferred to the sterile HEDP kit vial. Subsequently, the kit vial was heated at 100°C for 15 min. After cooling the vial to room temperature, pH of the preparation was adjusted to physiological level by adding sodium acetate solution (0.5 mL) supplied with the kit. The \(^{188}\text{Re-HEDP}\) complex thus prepared should pass the necessary quality control tests before it can be injected into the patient.
Table 1. Quality control check list for $^{188}$Re-HEDP prepared using lyophilized kit

<table>
<thead>
<tr>
<th>QC parameter</th>
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<th>Determined by</th>
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<tbody>
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<td>Appearance</td>
<td>Clear</td>
<td>Visual inspection</td>
</tr>
<tr>
<td>Colour</td>
<td>Pale yellow - amber</td>
<td>Visual inspection</td>
</tr>
<tr>
<td>pH</td>
<td>5 - 6</td>
<td>Non-bleeding pH paper</td>
</tr>
<tr>
<td>Radiochemical purity</td>
<td>$&gt;95%$</td>
<td>ITLC-SG</td>
</tr>
</tbody>
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Figure 7. Typical ITLC-SG pattern of $^{188}$Re-HEDP in acetone and saline

Fig. 8. Typical whole-body scan of a patient obtained 24 hours after $^{188}$Re-HEDP injection. The scan shows extensive bone metastasis.
Quality control parameters (Table 1) for \(^{188}\text{Re}\)-HEDP include visual inspection of the preparation to determine clarity and colour, followed by determination of pH and RCP. The RCP of \(^{188}\text{Re}\)-HEDP should be >95\% to pass the quality control check. Typical ITLC-SG pattern of \(^{188}\text{Re}\)-HEDP in saline and acetone is shown in Figure 7.

**Clinical evaluation**

Clinical evaluation of \(^{188}\text{Re}\)-HEDP prepared using freeze-dried HEDP kits were carried out in various nuclear medicine centers in India, including, Tata Memorial Hospital, Mumbai, Radiation Medicine Center, Mumbai and Kovai Medical Centre and Hospital, Coimbatore. The clinical results are satisfactory and in expected lines. Patients injected with \(^{188}\text{Re}\)-HEDP experienced the onset of pain relief within a week and pain-free period lasted for several weeks. A typical clinical image obtained with \(^{188}\text{Re}\)-HEDP is shown in Figure 8.

A significant advantage with BARC HEDP kits discussed here compared to the commercial HEDP kits is that the former kit can be used with up to 5 mL of freshly eluted \(^{188}\text{Re}\)-activity while the latter is restricted to use only 2 mL of activity. This feature of BARC HEDP kits comes in handy at the fag end of generator-life when radioactive concentration (RAC) or activity per millilitre available from the generator decreases drastically. It can be explained further with a real scenario in a hospital radiopharmacy. A hospital radiopharmacy having access to \(^{188}\text{Re}\)-activity of RAC 10 mCi/ml requires just a single BARC HEDP vial to prepare a patient dose of ~50 mCi (5 mL x 10 mCi). At the same time, due to volume limitation in commercial HEDP kit vial which is 2 mL, the radiopharmacist will be forced to use two HEDP vials to prepare the same patient dose. This may result in escalation of cost of therapy as well as dose received by the radiopharmacist during radiopharmaceutical preparation.

**Conclusions**

In a nuclear medicine centre, initial investments required to start a diagnostic or therapeutic program and the returns expected from the program are prime considerations. Considering relatively high cost of \(^{188}\text{W}/^{188}\text{Re}\) generator, it is important to use the generator for as many applications as possible so that the program is self-sustainable. Therefore, improving the \(^{188}\text{Re}\)-radiopharmaceutical portfolio for therapeutic applications is very essential. The rhenium radiopharmaceuticals development program in Radiopharmaceuticals Division, Bhabha Atomic Research Centre, is essentially aimed at improving the \(^{188}\text{Re}\)-radiopharmaceutical portfolio at an affordable cost. Development of freeze-dried DEDC kits for the preparation of \(^{188}\text{Re}\)-N-DEDCC/lipiodol for the therapy of inoperable HCC, along with other freeze-dried kits such as HEDP kits, is a timely step in the right direction, which will help boosting \(^{188}\text{Re}\)-radiopharmaceuticals program in India.

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