Nanomaterial Sorbents for the Preparation of $^{188}W/^{188}Re$ Generator and ^{188}Re Radiopharmaceutical Development

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Abstract: Rhenium-188 is a useful radionuclide for targeted therapy thanks to the high energy (2.12 MeV) β^- emission, low abundance gamma rays (155 keV and 15%) suitable for imaging and availability from the $^{188}W/^{188}Re$ generator. Though considerable amount of work on the development of ^{188}Re-radiopharmaceuticals have been reported in the literature, the clinical uses of them are still low mainly due to the limited availability and high cost of the generators. However, a ^{188}Re radiopharmacy can be successfully run provided the generator is used for the preparation of several ^{188}Re-radiopharmaceuticals. The relatively low radioactive concentration of ^{188}Re from conventional alumina based generators, thereby needing post elution concentration, is one of the limitations for the extended use of the generator. The development of nanomaterials having higher capacity for adsorption of ^{188}W allows it to be used for the preparation of column generators capable of giving high radioactive concentration for the eluted perrhenate. This review provides an overview of the work done at the Bhabha Atomic Research Centre, Mumbai, India, for the development of $^{188}W/^{188}Re$ generator as well as the development of several ^{188}Re-based radiopharmaceuticals.

Keywords: Nanomaterials, Radionuclide generator, Radiopharmaceuticals, Rhenium-188, Targeted therapy.

1. INTRODUCTION

Rhenium belongs to the group 7 of the periodic table, same as that of ^{99m}Tc, the workhorse of nuclear medicine. Rhenium has two important radioisotopes, ^{186}Re [half-life – 3.71 days, $E_{\beta max}$ – 1.09 MeV, E_γ - 136 keV (9%)] and ^{188}Re [half-life – 16.9 h, $E_{\beta max}$ – 2.12 MeV, E_γ - 155 keV (15%)][1], both of which have beta energies suitable for therapy and gamma emissions, though of low abundance, which permits monitoring the distribution of the radiotracer *in vivo*, and potentially, perform image-based dosimetry calculations. While relatively low-energy beta particles of ^{186}Re are useful for therapeutic applications requiring low tissue penetration, high-energy beta from ^{188}Re are particularly useful for therapy of diseases in large organs such as liver. Being in the same group of the periodic table, technetium and rhenium share similar chemistry, which implies, wherever applicable, it is possible to have theranostic pair with ^{99m}Tc and $^{186/188}Re$ radionuclides. However, rhenium being more difficult to reduce than technetium, quite often, technetium chemistry cannot be directly extrapolated for preparing rhenium radiopharmaceuticals. Rhenium generally requires harsher radiolabeling conditions compared to technetium, and therefore, ligands that cannot survive these conditions cannot be used for preparing rhenium radiopharmaceuticals.

Rhenium-186 is a reactor-produced radionuclide from neutron activation of enriched ^{185}Re or natural rhenium. A difficulty associated with the production of ^{186}Re from natural rhenium is the co-production of ^{188}Re. Though mixed radiation therapy with $^{186/188}Re$ is feasible, the approach has not been further pursued. On the other hand, ^{188}Re is a decay product of long lived ^{188}W and hence available from a $^{188}W/^{188}Re$ generator. Like the $^{99}Mo/^{99m}Tc$ generator, which has a major role in making ^{99m}Tc the workhorse of nuclear medicine, $^{188}W/^{188}Re$ generator has the potential to popularize the use of ^{188}Re-radiopharmaceuticals for therapy.

Commercial availability of $^{188}W/^{188}Re$ generator has a significant role to play in popularizing the use of ^{188}Re-radiopharmaceuticals in nuclear medicine. An equally important aspect is to make available new ^{188}Re-radiopharmaceuticals and freeze dried kits for their preparation in hospital radiopharmacy housing the $^{188}W/^{188}Re$ generator. In this review, authors have attempted to cover the recent developments in $^{188}W/^{188}Re$ generator technology and discuss some of the important ^{188}Re-radiopharmaceuticals, which have been used in the clinic or which have clinical potential. These discussions are mainly focused on the developmental activities done at the Bhabha Atomic Research Centre, India.

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2. DISCUSSION

2.1. Nanosorbents for $^{188}W/^{188}Re$ Generator Preparation

$^{188}W/^{188}Re$ generator is an excellent source for availing no-carrier-added (NCA) grade ^{188}Re. Most of the separation methodologies which have been reported for $^{99}Mo/^{99m}Tc$ generators have also been exploited for preparation of $^{188}W/^{188}Re$ generators [2]. Out of these procedures, the alumina based column chromatographic approach wherein ^{188}W is absorbed on bulk alumina matrix and ^{188}Re is selectively eluted using saline solution at regular intervals, has been identified as the most reliable method for the preparation of $^{188}W/^{188}Re$ generator. Owing to the limited sorption capacity of bulk alumina (~50 mg W/g), clinical-scale $^{188}W/^{188}Re$ generator can only be prepared using high specific activity (150-190 GBq/g) ^{188}W that can be produced in only very few high flux (~10^{15} $n.cm^{-2}.s^{-1}$) reactors available (High Flux Isotope Reactor at Oak Ridge National Laboratory in United States and SM Reactor at Dimitrograd in Russia) in the world. Even while using high specific activity ^{188}W produced in these reactors, the $^{188}W/^{188}Re$ generators currently available yield low specific volume (activity/ mL) of ^{188}Re and require post-elution concentration procedures prior to radiopharmaceutical preparation, which is not always very convenient to perform in hospital radiopharmacies [3]. From this perspective, it is desirable to develop a $^{188}W/^{188}Re$ generator where the concentration step can be avoided to simplify the operational procedure for widespread clinical utility.

Use of nanomaterials as adsorbents for $^{188}W/^{188}Re$ generator holds promise as they take advantage of the unique physiochemical properties realized at nanoscale that cannot be anticipated from bulk counterparts of the same chemical composition. The defining feature of a nanomaterial is that its properties depend not only on composition but also on its size and shape. One of the specific properties of this class of material is that a high percent of the atoms lies on the surface and the material possesses high surface area. These surface atoms are unsaturated and possess high chemical activity. Therefore, such materials demonstrate high sorption capacity and enhanced selectivity for ^{188}W resulting in elution of ^{188}Re with adequate radioactive concentration and high radionuclidic purity. The above properties make nanomaterials an exciting platform to develop into the realm of $^{188}W/^{188}Re$ generator technology with properties that are difficult to achieve using bulk materials.

The ability of three nanomaterial based sorbents (nanocrystalline titania (TiP), zirconia (ZrO_2) and alumina (γ-Al_2O_3)) have been comprehensively studied and profusely explored for the development of $^{188}W/^{188}Re$ generators by our group [4-7]. Taking advantage of the new physical properties uniquely associated with nanomaterials, $^{188}W/^{188}Re$ generators were prepared using ^{188}W having specific activity of 3-5 Ci/g. A scrutiny of the results depicted in Table **1** reveals that all these sorbents are suitable for preparation of $^{188}W/^{188}Re$ generators. Though testing of these nanomaterials was done by using lower load of ^{188}W, the capacity of the generator can easily be scaled up to >37 GBq (1 Ci) activity levels as the capacity of the nanomatarials are very high. Among all the sorbents used, γ-Al_2O_3 was found to exhibit the highest sorption capacity under dynamic conditions as compared to TiP and ZrO_2 and is therefore the most appropriate sorbent for the preparation of clinical-scale $^{188}W/^{188}Re$ generator. The performance of these generators was studied for more than 6 months and reported to be satisfactory. Not only were the ^{188}Re elution yields appreciably high but also the level of radionuclidic, radiochemical and chemical impurities in the ^{188}Re obtained from all these generators were well within the acceptable limits prescribed in the pharmacopoeias [8].

The mechanism of uptake of ^{188}W and elution of ^{188}Re from the nanosorbent based chromatographic columns could be explained on the basis of pH dependent surface charge on nanosorbents. There are various anionic species of tungsten depending on the pH of the medium. At pH 6, the predominant species is $W_{12}O_{41}^{10-}$ and between pH 2 and 4 the species $W_{12}O_{39}^{6-}$ predominates. Owing to electrostatic attraction, highly negatively charged tungsten anion is taken up on the positively charged surface of the nanosorbent under mildly acidic conditions. Subsequently, it may form a stable complex of the type $[AlW_6O_{24}]^{8-}$, similar to that reported for bulk alumina. As these tungstate ions start transforming into perrhenate ion ($^{188}ReO_4^-$), which has only the mononegative charge, the binding gets weaker and an easy displacement of $^{188}ReO_4^-$ is expected from the nanosorbent.

The performance of the $^{188}W/^{188}Re$ generators prepared using nanomaterial based sorbents is comparable with conventional alumina based generators in terms of ^{188}Re elution yield and the purity of the eluate. However, due to higher sorption capacity

of nanomaterials, relatively lower specific activity ^{188}W produced in medium flux research reactors can also be used for preparation of clinical-scale $^{188}W/^{188}Re$ generators while using such materials as the sorbent matrix. It is also pertinent to point out that agglomerated nanomaterials (comprising of nanosized crystallites) are used as sorbents for preparation of radionuclide generators. Typically, the size of the agglomerates is in the range of 50-100 mesh size (149-297 µm), which is comparable to the size of bulk alumina particles used in preparation of conventional generators. Controlled agglomeration of nanoparticles is essential in order to use them as sorbents for radionuclide generators, as fully dispersed nanoparticles would exhibit issues such as increased back pressure during the elution process and might also result in breakthrough of nanoparticles in the ^{188}Re eluate. While using agglomerated nanomaterial based sorbents, no change in the generator design and the elution procedure is required.

Adoption of nanosorbents (especially γ-Al_2O_3) for preparation of $^{188}W/^{188}Re$ generator would reduce reliance on the two high flux reactors for ^{188}W-production. There are a number of research reactors in the world having thermal neutron flux >5 × 10^{14} n cm^{-2} s^{-1} which could be used for the production of ^{188}W for making $^{188}W/^{188}Re$ generators. Also if the existing generator manufacturers can shift to γ-Al_2O_3 as adsorbent, the generator capacity can be increased. Simultaneously the activity per mL can also be increased by using smaller bed size for the column and lower volume of eluent.

2.2. ^{188}Re Based Radiopharmaceuticals

The Radiopharmaceuticals Division of the Bhabha Atomic Research Centre has been carrying out research on the development of ^{188}Re radiopharmaceuticals for over 25 years. The following sections give details of some of the important developments.

2.3. $^{188}Re(V)DMSA$ (DMSA – Dimercapto Succinic Acid)

$^{99m}Tc(V)DMSA$ is a widely used radiopharmaceutical for diagnostic imaging of medullary carcinoma of thyroid [9-11], head and neck tumors, [12, 13], soft tissue tumors and metastatic bone lesions and osseous metastasis from breast cancer [14-16]. Rhenium being the therapeutic analogue of ^{99m}Tc, which shares similar chemistry, envisaging use of $^{186/188}Re(V)DMSA$ for therapeutic applications is obvious. Bisunadan *et al*. reported the first study on the preparation and use of $^{186}Re(V)DMSA$ for tumor therapy [17]. Subsequently, several others reported the preparation and use of $^{186/188}Re(V)DMSA$ for different cancers [18-20]. General approach for the preparation of $^{186/188}Re(V)DMSA$ involves heating DMSA with $Na^{186/188}ReO_4$ in presence of Sn^{2+} at 100°C. Following this method, Kothari *et al*. reported the preparation of $^{186}Re(V)DMSA$ and its biological evaluation in Wistar rats [21]. They observed significant uptake of the radiotracer in kidneys, which limited wide spread application of this therapeutic agent in the clinic. Attempts to reduce the kidney uptake of $^{186/188}Re(V)DMSA$ using blocking agents were not successful [22]. Later, Kothari *et al*. found that signify-cant reduction in kidney uptake of $^{186/188}Re(V)DMSA$ could be achieved by modifying the method of preparation of the radiotracer. The $^{186/188}Re(V)DMSA$ prepared using sodium metabisulphite ($Na_2S_2O_5$) as reducing agent in place of stannous chloride ($SnCl_2$), showed significant reduction in kidney uptake (only 0.68±0.06 %ID/g at 24 h post injection (p.i.)). It is pertinent to note that kidney uptake observed with $^{186/188}Re(V)DMSA$ prepared by conventional method, using stannous chloride as reducing agent, was 2.93±0.93 %ID/g at the same time point [23]. Though the reason for this observation was not understood, authors observed a noticeable change in the isomeric ratio of the $^{186/188}Re(V)DMSA$ complex. The high-performance liquid chromatography (HPLC) analysis of $^{186/188}Re(V)DMSA$ prepared by conventional method using stannous chloride as reducing agent showed three major peaks representing anti, syn-endo and syn-

Table 1: Summary of $^{188}W/^{188}Re$ Generators Developed Using Nanosorbents

Sorbent	Dynamic Sorption Capacity (mg/g)	Activity of ^{188}W Loaded (GBq)	Elution Yield of ^{188}Re (%)	Maximum Radioactive Concentration of ^{188}Re (GBq/mL)	Level of ^{188}W Impurity in ^{188}Re (%)	Radiochemical Purity of $^{188}ReO_4^-$ (%)	Consistency in Generator Performance
TiP	100	1.85	> 80	0.37	< 10^{-3}	>99	Consistent performance for 6 months
ZrO_2	120	1.85	> 78	0.33	< 10^{-4}	>99	
γ-Al_2O_3	326	11.1	> 80	1.85	< 10^{-3}	>99	

exo isomers, respectively, as shown in Figure **1**(**A**) [24]. Apart from these major peaks, a minor peak representing an unknown structure was observed between the anti and syn-endo isomeric forms. Kothari *et al*. observed significant contribution from this peak in $^{186/188}$Re(V)DMSA prepared using sodium metabisulphite reducing agent [Figure **1**(**B**)] [23]. However, it is not clear whether it has any correlation with reduction in kidney uptake and the phenomenon is worth investigating.

Recently, our group developed a lyophilized kit for the preparation of ^{188}Re(V)DMSA at room temperature [unpublished results]. It is known that presence of oxalate facilitate reduction of rhenium, therefore the room temperature kit (RT kit) contained sodium oxalate in addition to other ingredients of conventional kit, *i.e*. DMSA and stannous chloride. Using this kit ^{188}Re(V)DMSA could be prepared in >98% yield at room temperature in 15 min. Though HPLC analysis of ^{188}Re(V)DMSA prepared using RT kit showed similar isomeric peak patterns, the isomeric ratios were different. The ^{188}Re(V)DMSA prepared following the conventional method, by heating at 100°C for 30 min, had the anti, syn-endo and syn-exo isomers in the ratio 48:39:13, whereas, the ^{188}Re(V)DMSA prepared using RT kit at room temperature had the isomeric ratios 48:29:23, respectively. It is interesting to note that experimental conditions had effect only on the syn-endo and syn-exo isomeric ratio and percentage contribution from the anti isomer remained same. This apparently small change in the isomeric ratio of ^{188}Re(V)DMSA prepared using RT kit, however, had profound influence on the overall biodistribution pattern in Swiss mice bearing fibrosarcoma tumor. With ^{188}Re(V)DMSA prepared following conventional method, we observed uptake in bone (15 %ID/g), kidney (3.2 %ID/g) and tumor (2.2 %ID/g) at 60 min p.i. Subsequently, the activity cleared from all organs and at 24 h p.i., the activity in bone, kidney and tumor were 2.8 %ID/g, 1.5 %ID/g and 0.2 %ID/g, respectively. Similarly, biodistribution of ^{188}Re(V)DMSA prepared using RT kit showed initial uptake of 6 %ID/g, 1.8 %ID/g and 1.4 %ID/g in bone, kidney and tumor, respectively, at 60 min p.i. It could be noted that uptake values in these organs/tissue are relatively lower compared to the distribution of ^{188}Re(V)DMSA prepared by conventional method at the same time point. However, at 24 h p.i. a significant increase in bone uptake (22 %ID/g) was observed, while the uptake values in kidney (1.2 %ID/g) and tumor (0.4 %ID/g) were similar to that of ^{188}Re(V)DMSA prepared by conventional method.

In another experiment, ^{188}Re(V)DMSA prepared using RT kit was heated at 100°C for 10 min. Subsequent HPLC analysis of the sample revealed that isomeric ratios changed from 48:29:23 to 48:38:14, which was very close to that of ^{188}Re(V)DMSA prepared using conventional kit. This experiment possibly indicated higher thermodynamic stability of syn-endo isomer vis-à-vis syn-exo isomer. Proceeding further, we carried out biodistribution of ^{188}Re(V)DMSA prepared by RT kit at room temperature and then heating it again at 100°C for 10 min. As expected, the biodistribution results were similar to the one obtained with ^{188}Re(V)DMSA prepared by conventional method. These results indicate that higher bone uptake observed in the case of ^{188}Re(V)DMSA prepared using RT kit at room temperature may be due to the syn-exo isomer. This interesting results advocate further investigation to understand the distribution of individual

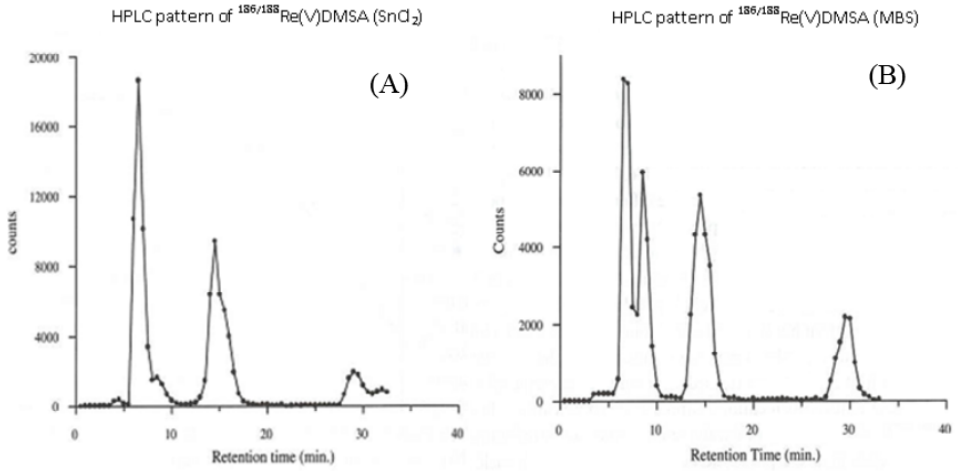

Figure 1: HPLC elution profile of $^{186/188}$Re(V)DMSA prepared using different reducing agents (**A**) stannous chloride and (**B**) metabisulphite [23].

isomers. If an isomer was found to be suitable for a particular application, modification of reaction conditions to maximize the yield of that isomer could be the next logical step forward.

2.4. $^{186/188}$Re-HEDP (HEDP – Hydroxyethane 1,1-Diphosphonic Acid)

$^{186/188}$Re-HEDP is a clinically established palliating agent for bone pain due to osseous metastasis [25-31]. Initial HEDP studies were carried out using ^{186}Re radioisotope. Rhenium-186 is a reactor produced radioisotope from neutron radiative capture (n,γ) reaction on enriched ^{185}Re or natural rhenium (37.4% enriched in ^{185}Re).

Kothari *et al.* reported preparation and evaluated ^{186}Re-HEDP from ^{186}Re produced from natural rhenium [32]. This was probably the first study, which used ^{186}Re produced from natural rhenium in a medium flux (6 x 10^{13} neutrons/cm^2/s) reactor. The ^{186}Re-HEDP prepared under optimized conditions (pH - 2, $SnCl_2.2H_2O$ - 10 mg, HEDP – 50 mg, reaction temperature - 100ºC, time – 30 min) was evaluated in normal Wistar rats. The distribution study showed significant uptake of ^{186}Re-HEDP in bone (30.7 ± 0.04 %ID/organ at 3 h p.i.) and retention thereafter, throughout the duration of the study (29.5 ± 4.0 %ID/organ at 48 h p.i.). There was no significant uptake of activity in any other major organs. During optimization studies, authors observed that >98% radiochemical purity could be achieved with HEDP amount as low as 1.25 mg/mL, stannous chloride 0.4 mg and total rhenium content 100 µg, rest of the reaction conditions remaining the same. However, to achieve stability of ^{186}Re-HEDP for extended periods, significantly higher amounts of the reactants were necessary. This observation was in agreement with a study reported by Elder *et al*., which established the influence of amounts of HEDP, stannous chloride and the total rhenium content on the final structure of Re-HEDP, and consequently, its biodistribution [33]. Use of natural rhenium resulted in, unavoidable, co-production of ^{188}Re (Half-life – 16.9 h). Therefore, the authors cooled the irradiated sample for four days to reduce the activity of ^{188}Re to ~6% of the total activity. Authors noticed, and highlighted, the practical difficulty with this approach of ^{186}Re-HEDP preparation, since it resulted in significant reduction in ^{186}Re-activity during the cooling period. By this approach, preparation of clinical dose of ^{186}Re-HEDP was virtually impractical. As an alternative, authors proposed mixed radionuclide therapy with $^{186/188}$Re-HEDP, which could eliminate the 4 day cooling requirement. However, dosimetry of mixed radionuclide therapy approach with $^{186/188}$Re-HEDP was challenging, which probably limited its clinical applications.

With commercial availability of $^{188}W/^{188}Re$ generator, several studies using ^{188}Re-HEDP were reported. A comparative clinical study of ^{188}Re-HEDP, ^{186}Re-HEDP, ^{153}Sm-EDTMP and ^{89}Sr by Liepe *et al*. demonstrated similar efficacy of these agents for palliation of pain from osseous metastasis [30]. The authors concluded that efficacy being comparable, choice of therapeutic radionuclide may be decided based on availability of the radioisotope and logistics. In this respect, ^{188}Re-HEDP enjoyed clear advantage over the other pain-palliating agents based on reactor produced radioisotopes, since it can be prepared *on demand* in any hospital radiopharmacy housing a $^{188}W/^{188}Re$ generator.

The growth of nuclear medicine can be partly attributed to the availability of lyophilized radiopharmaceutical kits and $^{99}Mo/^{99m}Tc$ generator. For a hospital radiopharmacy having a $^{188}W/^{188}Re$ generator, availability of lyophilized kits for the preparation of ^{188}Re-radiopharmaceuticals is an advantage. Verdera *et al*. reported the first lyophilized kit for the preparation ^{188}Re-HEDP [35]. Preparation of ^{188}Re-HEDP requires addition of carrier rhenium to carrier-free $Na^{188}ReO_4$ from $^{188}W/^{188}Re$ generator. This is essential to obtain the ^{188}Re-HEDP species which shows the pharmacokinetics necessary for a bone pain palliating agent. Along with HEDP (10 mg), gentisic acid (3 mg) and stannous chloride dihydrate (3.7 mg), Verdera *et al*., included carrier potassium perrhenate (300 µg, ~1 µmol) in their lyophilized HEDP kit. Though the authors have not mentioned the shelf-life of such lyophilized HEDP kits, presence of stannous and carrier perrhenate together in the kit could significantly shorten the shelf-life of the kit.

Mallia *et al*. circumvented this problem of short shelf-life of the kit by excluding the carrier perrhenate from the HEDP kits [36]. While rest of the kit components and their amounts remained similar to that of the kit reported by Verdera *et al*., preparation of ^{188}Re-HEDP using this kit required addition of 1µmol of carrier perrhenate along with freshly eluted $Na^{188}ReO_4$ from $^{188}W/^{188}Re$ generator. Subsequently, heating the kit vial at 100°C for 20 min resulted in the formation of ^{188}Re-HEDP in more than 98% radiochemical purity. After adjusting the pH of the preparation to physiological conditions (using sterile sodium acetate

provided with the kit), the preparation is ready for patient administration. Shelf-life of this kit was one year from the date of production. Clinical evaluation of ^{188}Re-HEDP prepared using these kits are being carried out in different nuclear medicine centres in India. The development of lyophilized HEDP kit in BARC is well-timed considering the increasing number of nuclear medicine centres in India offering ^{188}Re-therapy.

2.5. ^{188}ReN-DEDC/Lipiodol (DEDC – Diethyl Dithiocarbamate)

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and represents the second most common causes of cancer death worldwide [37]. Patients presented with late stage HCC, which are unresectable, are recommended for loco-regional therapies such as transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT) or sorafinib therapy, depending on the stage of the disease [38]. SIRT is also called TARE or transarterial radioembolization. TARE is similar to TACE, the only difference being the use of radiation emitted from radioisotopes for therapy in former, while the latter uses chemotherapeutics. TARE using radiolabelled particles and colloids are one of the options for inoperable HCC patients. There are several options for doing TARE, which include ^{90}Y-labeled particulates based on glass (TheraSphere®) or resin (SIR-Spheres®) and ^{131}I- or ^{188}Re-labeled lipiodol. Especially in India, high cost of ^{90}Y-microspheres and non-availability of local substitutes has limited this mode of therapy to a very small group of patients who can afford it.

Wang *et al*. reported the preparation of ^{188}Re-labeled lipiodol for TARE [39]. Their approach involved preparation of ^{188}Re-EDTB (EDTB - N,N,N",N"-tetrakis(2-benzymidazolylmethyl)-l,2-ethanediamine) and subsequent incubation with EDTB-lipiodol at 70ºC for 2h. This procedure resulted in ^{188}Re-lipiodol >98% yield. Biodistribution studies carried out in Sprague Dawley rats showed slow clearance of activity from liver, however, accumulation of significant levels of activity in lungs and kidneys severely limited its clinical applications.

Jeong *et al*. reported preparation and use of a lipiodol solution of ^{188}Re-TDD (TDD - 2,2,9,9-Tetramethyl-4,7-diaza-1,10-decanedithiol) for therapy of liver cancer [40]. This method involved preparation of a lipophilic complex, ^{188}Re-TDD, and subsequent extraction into lipiodol. Due to the lipophilic nature of the ^{188}Re-TDD complex, it is retained in lipiodol phase. This radioactive lipiodol solution was used for TARE procedure. Though ^{188}Re-TDD could be prepared in good yields and extracted into lipiodol, authors noticed that its retention in liver is not good enough to treat liver cancer patients. The same group subsequently reported a modified form of ^{188}Re-TDD, ^{188}Re-HDD (HDD - 4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol), which showed higher retention in liver. Kumar *et al*. reported an IAEA-sponsored clinical study, which concluded that TARE with ^{188}Re-HDD is safe and effective option for the therapy of inoperable hepatocellular carcinoma [41]. Lyophilized kits for the preparation of ^{188}Re-HDD are available commercially.

Although, ^{188}Re-HDD complex could be prepared in high yields with commercially available kits, extraction of the complex into the lipiodol phase was not satisfactory. Boschi *et al*. reported preparation of a lipiodol solution of ^{188}ReN-DEDC (DEDC – diethyl dithiocarbamate) complex [42]. This approach was very similar to that of Jae Min Jeong *et al*. wherein a lipophilic ^{188}Re-complex was prepared and extracted into lipiodol. The complex ^{188}ReN-DEDC is prepared in two steps. First step involved preparation of ^{188}Re-nitrido core, which was subsequently used for radiolabeling DEDC ligand to obtain ^{188}ReN-DEDC complex. By this method, ^{188}ReN-DEDC complex could be prepared in >97% radiochemical purity and >96% extraction of the complex into lipiodol could be achieved. Clinical trials with ^{188}ReN-DEDC/lipiodol showed retention of activity in liver with no activity accumulation seen in lungs, kidneys or any other vital organs.

Considering increasing number of liver cancer incidences in India, a need for locally available, effective and economical TARE agent was felt. Following the procedure reported by Prof. Duatti's group, we developed a two-vial kit for the preparation of ^{188}ReN-DEDC. First kit vial used for the preparation of ^{188}ReN core, contained 2 mg of DTCz (N-methyl-S-methyl-dithiocarbazate), 28 mg of sodium oxalate and 0.8 mg of stannous chloride dihydrate. The second kit contained 27 mg of DEDC and carbonate buffer (1 M). The procedure involved addition of up to 3 mL of freshly eluted $Na^{188}ReO_4$ containing 150 μL of glacial acetic acid to the kit vial 1. Upon incubating at room temperature for 30 min, ^{188}ReN core could be prepared in >90% yield. In the second step, kit vial 2 was reconstituted with 2 mL of sterile saline and 1.5 mL of the solution is aseptically transferred to kit vial 1.

Subsequently, kit vial 1 was heated at 70ºC for 20 min to obtain ^{188}ReN-DEDC complex. Analysis of the reaction mixture showed that ^{188}ReN-DEDC complex was formed in >80% purity. In the third step, 1-2 mL of sterile lipiodol was added to kit vial 1, the contents were thoroughly mixed for 5 min and subsequently centrifuged for 10 min to effect separation of the two layers. The lipiodol layer containing the ^{188}ReN-DEDC complex was carefully separated and used for TARE. The SPECT/CT images obtained during preliminary clinical trials using ^{188}ReN-DEDC/lipiodol, carried out in Tata Memorial Hospital, Mumbai, showed retention of the ^{188}Re-activity in liver 24 h p.i., with no detectable accumulation of activity in lungs or kidneys. A regulatory clearance to manufacture and supply the kits in India is underway.

2.6. ^{188}Re-Agents for Radiation Synovectomy

Radiation synovectomy is an effective treatment for rheumatoid arthritis [43-46]. This modality, which is an alternative to surgical intervention, involves intra-articular injection of beta emitting radiopharmaceutical to control the synovial inflammation. A critical requirement of radiation synovectomy agents is their ability to localize at the point of injection, since leaching of the agent will render the therapy ineffective. A general approach to minimize the effect of leaching is to use a short-lived radioisotope such that therapeutic dose can be delivered at the point of inflammation in a short span of time. Another approach to minimize leaching is to use radiolabeled particles with larger size [47].

Yttrium-90 and ^{32}P are two radioisotopes commonly used for the preparation of synovectomy agents [48, 49]. Both radioisotopes have high-energy beta emissions suitable for synovectomy applications. However, being pure beta emitters, both radioisotopes exclude the possibility of imaging to assess localization of the injected radiopharmaceutical. Additionally, the 14 day half-life of ^{32}P is too long and in the event of leaching it may result in radiation dose to other organs/tissues. In this context, ^{188}Re has significant advantages over both ^{90}Y and ^{32}P, owing to its favorable physical and chemicals properties described in section 1. Additionally, it has relatively short half-life (16.9 hours) and it is a generator produced radioisotope. Preparation and evaluation of ^{188}Re labeled microspheres and ^{188}Re-suphur colloids was reported earlier [50-53]. However, significant leaching from the site of injection severely limited their application. Hydroxyl apatite (HA), a major component of the bone matrix, had been radiolabeled with $^{186/188}$Re for synovectomy applications [54, 55]. However, these agents exhibited poor *in vitro* stability, which limited their application.

Kothari *et al*. reported direct labeling of HA with ^{188}Re [47]. Their method involved incubation of freshly eluted $Na^{188}ReO_4$ with HA (10 mg), sodium oxalate (10 mg) and stannous chloride (10 mg) at room temperature for 1 hour. The pH of the solution was maintained at 1.4 using hydrochloric acid. Subsequently, the ^{188}Re-HA particles were washed with ascorbic acid to remove free perrhenate and re-suspended in ascorbic acid medium. By this method, ^{188}Re-HA particles could be prepared in >98% yield. Authors observed that presence of oxalate significantly reduced the dissolution of HA under acidic conditions. Particle size of cold Re-HA, determined by laser diffraction, was found to be between 2-20 μm (>90%). ^{188}Re-HA particles were found to be stable in ascorbic acid medium for up to 4 days. Upon intraarticular injection of ^{188}Re-HA particles in rat joints, extra-articular leakage of only 2.5% was observed even after 2 days post injection. Overall, this study demonstrated the potential of ^{188}Re-HA particles for therapy of inflamed synovial joints.

2.7. Miscellaneous ^{188}Re-Radiopharmaceuticals

2.7.1. ^{188}Re-Skin Patches

Application of radioactive skin patches is an effective mode of therapy for skin cancers and superficial tumors [56]. This modality is an alternative to teletherapy, brachytherapy or kilo voltage x-ray therapy for the treatment of superficial cancers. Papers or skin patches incorporating beta emitting radionuclides such as ^{188}Re or ^{166}Ho has been reported earlier [57-59].

Mukharjee *et al*. reported a modified procedure for the preparation of ^{188}Re-bandage patch [60]. Their method involved preparation of ^{188}Re-tin colloid followed by trapping of the radioactive colloidal particle on to a 0.22 μm Millipore filter by passing the solution through the filter. The filter paper was subsequently sandwiched between two nitrocellulose membranes and then placed on an adhesive bandage for therapeutic applications. Radioactive bandages thus prepared were evaluated in melanoma tumor bearing C57BL/6 mice. The study conclusively demonstrated the efficacy and potential of ^{188}Re-bandages for the therapy of superficial tumors [Figure **2**].

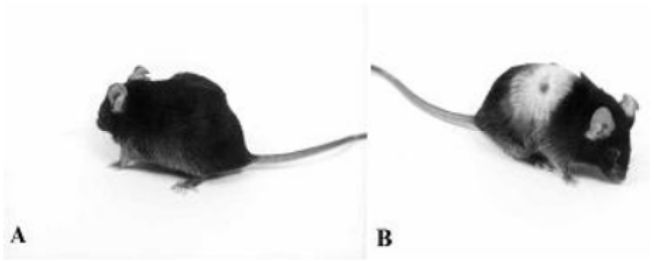

Figure 2: Control mouse (**A**) bearing melanoma (25 day old tumor); and mouse treated with skin patch application after five months (**B**) [60].

2.7.2. ^{188}Re-EC (EC-Ethylene Dicystene) for Endovascular Therapy

Restenosis is an event with significant probability following coronary angioplasty [61, 62]. One of the procedures followed to avoid/minimize restenosis of dilated artery by balloon angioplasty is by local delivery of radiation dose to the dilated arteries [63-65]. Dose delivery is generally achieved using balloon filled with radioactive solution by a procedure similar to balloon angioplasty. One of the inherent risks in this procedure is the rupture of balloon during the procedure leading to leakage of the radioactive liquid into circulation. Therefore, the pharmacokinetics of the radiotracer should be such that in the event of a balloon rupture, the activity should clear from the body within a short period of time, such that dose burden on the patient could be minimized. A comparison between $Na^{188}ReO_4$, ^{188}Re-MAG_3 and ^{188}Re-DTPA for this application revealed that ^{188}Re-MAG_3 is most suitable for the purpose [64]. However, the long-term stability of ^{188}Re-MAG_3 is doubtful [66].

Das *et al*. [67] reported the preparation of $^{186/188}$Re-EC, an analogue of ^{99m}Tc-EC, which is a clinically used renal agent, as a substitute for ^{188}Re-MAG_3. Optimized procedure for the preparation of $^{186/188}$Re-EC involved incubation of a mixture of 10 mM solution of EC with stannous chloride (2 mg) and $Na^{186/188}ReO_4$ at 100ºC for 20 min. The pH of the reaction mixture was maintained at 2. By this method, ^{188}Re-EC could be prepared in >98% radiochemical purity. Biodistribution studies of $^{186/188}$Re-EC carried out in Wistar rats indicated that in terms of clearance and dose delivered to other vital organs, $^{186/188}$Re-EC had distinct advantages over other rhenium agents used for endovascular brachy therapy applications. In addition, $^{186/188}$Re-EC was also found to retain its radiochemical purity for a longer time compared to ^{188}Re-MAG_3.

2.7.3. ^{186}Re-CTMP (CTMP – 1,4,8,11-Tetraaza Cyclotetradecyl-1,4,8,11-Tetramethylene Phosphonic Acid) for Bone Pain Palliation

Phosphonates have shown good affinity for bone matrix and they have been utilized to deliver therapeutic dose of radiation to pain causing metastatic or primary bone lesions to obtain palliative effect to the patients. A number of phosphonates radiolabeled with beta emitting radionuclides such as ^{186}Re, ^{188}Re, ^{153}Sm, ^{177}Lu etc. have been prepared and evaluated [25-34]. A number of such phosphonate radiopharmaceutials are in clinical use today.

Kothari *et al*. had earlier reported the preparation and evaluation of $^{186/188}$Re-HEDP for bone pain palliation [32]. The same group reported synthesis, radiolabeling and evaluation of a cyclic phosphonate for bone pain palliation [68]. Starting from cyclam (1,4,8,11-tetraaza cyclotetradecane), formaldehyde and orthophosphoric acid, a tetra phosphonate ligand, 1,4,8,11-tetraaza cyclotetradecyl-1,4,8,11-tetramethylene phosphonic acid or CTMP, was synthesized. This ligand was subsequently radiolabeled with $Na^{186}ReO_4$ by heating at 100ºC for 30 min in presence of stannous chloride as reducing agent. The pH of the reaction mixture was maintained at 2. By this procedure, ^{186}Re-CTMP could be prepared in >97% RCP. Authors observed that ^{186}Re-CTMP complex remained stable at room temperature for up to 6 days post preparation. Biodistribution of ^{186}Re-CTMP in normal Wistar rats showed significant uptake and retention of the complex in skeleton with fast clearance from other non-target organs. A comparison with ^{186}Re-HEDP indicated that the pharmacokinetic parameters of ^{186}Re-CTMP are either similar or superior to the former [Figure **3**]. Overall, ^{186}Re-CTMP complex demonstrated its potential as a possible bone pain-palliating agent.

2.7.4. $^{186/188}$Re-Labeled Porphyrin for Targeted Radiotherapy

Porphyrin is a structural unit central to the oxygen transporter in our body, the hematoporphyrin. Porphyrins have shown preferential accumulation in neoplastic tissues, lymph nodes, embryonic and traumatized tissues [69-72]. This property made them potential molecules for diagnosis and therapy of various diseases such as cancer [69-77]. Wong *et al*. reported a ^{99m}Tc-hematoporphyrin for *in vivo* imaging applications [78]. In this complex, ^{99m}Tc was tagged at the periphery of the porphyrin ring. Thereafter, several studies were reported wherein different derivatives of porphyrins were radiolabeled with radioisotopes such

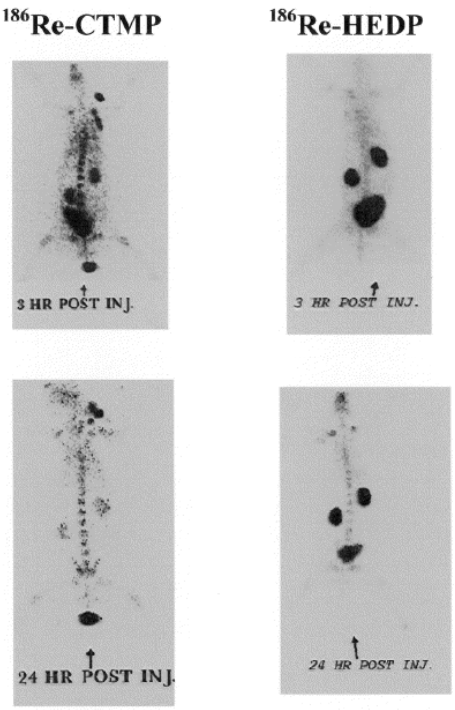

Figure 3: Scintigraphic images of ^{188}Re-CTMP and ^{188}Re-HEDP [68].

as ^{57}Co, ^{64}Cu, ^{109}Pd etc. [79-81]. A notable difference between the ^{99m}Tc-hematoporphyrin and the ^{57}Co/^{64}Cu/^{109}Pd-porphyrins is that in the latter, the metal atom (^{57}Co, ^{64}Cu or ^{109}Pd) occupied the centre of the porphyrin ring. However, ^{57}Co/^{64}Cu/^{109}Pd-porphyrin derivatives failed to show selective uptake in target tissue. This observation possibly indicates that the porphyrin significantly lose its ability to accumulate in tumor ones a metal atom occupy its core.

Banerjee *et al*. reported the synthesis of a water-soluble porphyrin, meso-tetrakis[3,4-bis(carboxy methyleneoxy)phenyl] porphyrin, and subsequently radiolabeled it with $^{186/188}$Re [82]. Radiolabeling was carried out under basic conditions (pH 9) in presence of stannous tartarate as reducing agent. Upon heating the reaction mixture at 100ºC for 30 min, the $^{186/188}$Re-porphyrin complex could be prepared in >98% yield. Biodistribution studies of $^{186/188}$Re-porphyrin complex in Swiss mice bearing fibrosarcoma tumor showed uptake in tumor (~3.5% ID/g), and retention till the duration of the study (24 h). Authors observed no significant accumulation of activity in any other vital organ. Major clearance of activity was through renal route.

CONCLUSIONS

Availability of radionuclides at affordable cost is one of the important considerations for the growth of nuclear medicine. The initial investments needed to start a program and adequate revenue returns from it are prime considerations. Considering relatively high cost of ^{188}W/^{188}Re generator it is important to use the generator for as many applications as possible. Therefore, improving ^{188}Re-radiopharmaceutical portfolio is highly essential. Despite the fact that the rhenium radiopharmaceuticals development program was initiated at the Bhabha Atomic Research Centre in the early nineties, clinical utility was limited due to the lack of interest shown by nuclear medicine departments. A new fillip to the program was provided by the entry of Kovai Institute of Medical Sciences (KMCH) which started the routine clinical use of ^{188}W/^{188}Re generator for the treatment of HCC and a collaborative program between BARC and KMCH. One of the newer developments thanks to this collaboration is the development of lyophilized DEDC kits for the preparation of ^{188}ReN-DEDC/lipiodol for the therapy of inoperable HCC. Along with lyophilized DEDC kits, other lyophilized kits for the preparation of ^{188}Re-HEDP, ^{188}Re-DMSA etc. will help in effective utilization of ^{188}Re-activity from ^{188}W/^{188}Re generator. The authors also feel it appropriate that the commercial manufacturers explore the utility of high capacity adsorbents discussed in this paper for making generators with higher load of 188W which will provide high activity per mL for the eluted perrhenate solution.

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