**177** Lu-DOTMP, **153** Sm-DOTMP, **175** Yb-EDTMP and **186/188** Re-CTMP: Novel Agents for Bone Pain Palliation and Their Comparison with **153** Sm-EDTMP

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**Abstract**

Designing ideal radiopharmaceuticals for use as bone pain palliatives require the use of a moderate energy \(\beta\) emitter with a stable carrier molecule. Cyclic polyaminophosphonate ligands are known to form complexes with higher thermodynamic stability and kinetic inertness. The present study therefore envisages the use of a few moderate energy \(\beta\) emitters, viz. \(^{177}\)Lu (\(T_{1/2} = 6.71\) d, \(E_{\beta}\)\(\max = 497\) keV), \(^{153}\)Sm (\(T_{1/2} = 46.27\) h, \(E_{\beta}\)\(\max = 810\) keV), \(^{175}\)Yb (\(T_{1/2} = 4.2\) d, \(E_{\beta}\)\(\max = 480\) keV) and \(^{186/188}\)Re (\(T_{1/2} = 90\) h, \(E_{\beta}\)\(\max = 1.07\) MeV) as the radioisotopes and cyclic polyazamacrocyclic tetramethyl phosphonates namely, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (DOTMP) and 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetramethylene phosphonic acid (CTMP), apart from the widely used ethylenediaminetetramethylene phosphonic acid (EDTMP) for the development of potential bone pain palliation agents. All the radionuclides under investigation can be produced with adequate specific activity using moderate flux reactors. The comparatively longer half-lives of \(^{177}\)Lu, \(^{175}\)Yb and \(^{186/188}\)Re will provide much needed logistic advantages in countries with limited reactor facilities. In the present study, \(^{177}\)Lu-DOTMP, \(^{153}\)Sm-DOTMP, \(^{175}\)Yb-EDTMP and \(^{186/188}\)Re-CTMP complexes were prepared with high radiochemical purities (>98%) under optimized reaction conditions. All the radiolabeled complexes exhibited excellent stability at room temperature. Their potential for bone pain palliation could be seen from the biodistribution studies carried out in Wistar rats, wherein selective skeletal uptake (1.82-5.23% of injected activity per gram in tibia at 3 h post-injection) with rapid blood clearance and minimal uptake in any of the major organs was observed. Scintigraphic studies carried out in rabbits also demonstrated significant accumulation of activity in skeleton and insignificant retention of activity in other vital organs. A comparison of the biological behaviour exhibited by the radiolabeled phosphonates under investigation with that of \(^{153}\)Sm-EDTMP has also been made in order to find out the efficacy of the developed agents.
Introduction

Incidences of bone metastases arising in a large number of patients suffering from breast, lung and prostate carcinoma are on an increase [1,2]. Intravenous administration of bone seeking radiopharmaceuticals wherein β- /conversion electron is incorporated constitutes the most suitable modality for palliation of severe pain in patients suffering from bone metastases [1,3-5]. 32P [E_{β(max)} = 1.71 MeV, T_{1/2} = 14.3 d] in the form of sodium orthophosphate [6] was the first radionuclide to be used in bone pain palliation followed by 89Sr [E_{β(max)} = 1.40 MeV, T_{1/2} = 50.5 d] in the form of strontium chloride [7,8]. The major factor in designing effective radiopharmaceuticals for palliative treatment of bone pain is maximizing radiation dose to the bone lesion and minimizing radiation induced bone marrow suppression [9]. Considerable bone marrow suppression due to the presence of higher energy β- particle is the major constraint towards the widespread use of 32P and 89Sr [1,4,10]. The lack of imagable γ photons and long half-life (especially in case of 89Sr) are often sited as drawbacks towards the use of these isotope for bone-pain palliation. 153Sm with its ideally suited decay characteristics, such as, T_{1/2} = 46.27 h, E_{β(max)} = 0.81 MeV and 103 keV (28%) γ photon [1,10-12] has emerged as an efficient and popular candidate. Additionally, the ease of production of 153Sm in large quantities with adequate radionuclidic purity by neutron activation of even natural samarium is an added advantage [13]. However, in the Indian context, due to logistic reasons, 153Sm with 46.27 h half life needs to be produced in adequately high specific activity for administration of required dose to patients, which in turn necessitates handling of high amount of activity during processing. In this context, 177Lu could be regarded as an attractive alternative radioisotope for bone pain palliation. 177Lu decays with a half life of 6.71 d by emission of β- particles with E_{max} of 497 keV (78.6%), 384 keV (9.1%) and 176 keV (12.2%) to stable 177Hf [14]. It also emits γ photons of 113 keV (6.4%) and 208 keV (11%) [17], which is ideally suited for imaging the in vivo localization. Although the physical half life of 177Lu is relatively longer (compared to 153Sm or 186Re), it is within reasonable limits for therapeutic purpose and will in addition provide logistic advantages for facilitating supply to places far away from the reactors. 177Lu can be produced in adequate specific activity by irradiation of natural Lu target (177Lu, 2.6%) in moderate neutron flux (~10^{13} n/cm²/s) owing to the very high reaction cross section (σ = 2100 barns) [14]. In the present work, while various isotopes are being evaluated, we have explored the possibility of the use of 175Yb also as a radionuclide for evaluation of radiopharmaceuticals for bone pain palliation. 175Yb has excellent radionuclidic properties suitable for developing various radiotherapeutic agents [15], and decays by emission of β- particles with E_{max} of 480 keV to stable 175Lu with a half-life of 4.2 days. 175Yb also emits γ photons of 113 keV (1.9%), 282 keV (3.1%), 396 keV (6.5%) which are suitable for carrying simultaneous scintigraphic studies [14]. Owing to significantly large 174Yb thermal neutron cross section of 69 b [14], it is possible to produce 175Yb adequate specific activity for preparing agents for bone pain palliation using medium flux reactors. The lesser decay loss owing to the comparatively longer half-lives during the preparation and transportation of agents prepared using 177Lu and 175Yb, confers a definite advantage. 186Re, a medium energy β- emitter (E_{β} = 1.07 MeV, E_{γ} = 155 keV, [15%;]) [14], could be envisaged as an isotope of choice for treatment of skeletal metastases. With the existing facilities at our end it is possible to produce 186/188Re with moderately high specific activity (~7 TBq/g) without the use of enriched 186Re target.

Multidentate aminomethylene phosphonic acids form well-characterized stable complexes with different β- emitting radionuclides and have already proven to be very effective for palliation of bone pain [10,16-21]. Localization of those radiolabeled polyphosphonates in bone is attributed to the affinity of phosphate group for calcium present in actively growing bones [21-24]. Ethylenediaminetetramethylene phosphonic acid (EDTMP) is one of the most widely used ligands which forms stable complexes with various radionuclides all of which have shown
high bone affinity and other favorable pharmacological characteristics in biodistribution studies [1,10,12,16,18-21,24]. $^{153}\text{Sm}$-EDTMP (Quadramet) is now considered to be the most promising radiopharmaceutical for pain palliation due to skeletal metastases. This agent shows excellent pharmacokinetics in both animals and humans, such as preferential localization in bone cancer lesion and rapid excretion of the residual activity via the kidneys [9,25]. Since $^{177}\text{Lu}$-EDTMP is well documented [18,19,24], we have explored the possibility of complexation of $^{175}\text{Yb}$ with EDTMP. The choice of cyclic polyamino phosphonic acid for the development of potential agents for bone pain palliation is based on the more pronounced thermodynamic stability and kinetic inertness of their lanthanide complexes compared to that of their acyclic analogues [26,27]. Thermodynamic stability of the metalloradiopharmaceutical is a very important aspect as the dissociation of the radiometal from the chelate in blood circulation is a possible eventuality in presence of a variety of competing chelators and metal ions in plasma [9,27]. This may result in the accumulation of radioactivity in non-target organs. Similarly, kinetic inertness also plays a significant role for the in-vivo stability of a metal chelate. While fast dissociation kinetics are characteristics of lanthanide metal complexes of acyclic chelators, an accumulated body of literature has shown that corresponding complexes containing macrocyclic chelators are much more kinetically inert [27]. In this direction we have explored the possibility of labeling macrocyclic $\alpha$-aminomethylphosphonates viz. DOTMP for labeling with trivalent lanthanides such as $^{153}\text{Sm}$ and $^{177}\text{Lu}$. However, it has been observed that DOTMP does not complex $^{186}\text{Re}$ as it does $^{153}\text{Sm}$ and $^{177}\text{Lu}$. This observation could be attributed to the fact that matching of cavity size of the macrocyclic ligand with the ionic radius of the metal ion is essential for complexation [28] as has been demonstrated earlier on the suitability of TETA ($1,4,8,11$-tetraazacyclotetradecane tetracetic acid) for complexation with Cu(II) ion (ionic radius = 0.72 Å) and not with Y(III) (ionic radius = 0.93Å). Therefore, we have synthesised another cyclic tetraphosphonate, $1,4,8,11$-tetraazacyclo-

Biodistribution studies of a number of lanthanide phosphonate complexes revealed that poor in-vivo stability leads to accumulation of uncomplexed activity in liver due to the formation of colloidal hydroxides in the physiological pH. It is noteworthy that preparation of $^{153}\text{Sm}$-EDTMP for routine clinical applications requires a high ligand-to-metal ratio of $\sim(250-300)$:1. The large ligand excess is employed to prevent uptake of $^{153}\text{Sm}$ in liver. The presence of excess EDTMP in blood prevents the dissociated $^{153}\text{Sm}$ in the plasma from forming colloidal hydroxide [9,29]. It could be presumed that macrocyclic polyamino phosphoninic acids would form highly stable and kinetically inert complex with $^{153}\text{Sm}$ at a considerably lower ligand-to-metal ratio and demonstrate ideal pharmacological characteristics as an agent for bone pain palliation.

Materials and Methods

Natural lutetium oxide, samarium oxide and ytterbium oxide (spectroscopic grade $>99.99\%$ pure) were obtained from American Potash Inc., USA. Natural rhenium metal (spectroscopic grade $>99.995\%$ pure) was obtained from Johnson Matthey Company, UK. Ethylene diamine, 1,4,7,10-tetraazacyclododecane (cyclen), 1,4,8,11-tetraazacyclotetradecane (cyclam), orthophosphoric acid, formaldehyde and stannous chloride dihydrate were obtained from Aldrich Chemical Company, USA. All other chemicals were of AR grade and supplied by reputed chemical manufacturers. Whatman 3 MM chromatography paper was used for paper chromatography and paper electrophoresis studies.

All the radionuclides were produced by neutron irradiation at the Dhruva research reactor at our Institute. All radioactivity measurements were made using NaI(Tl) scintillation counter. The radionuclidic purity of the isotopes after chemical processing was ascertained by high-resolution $\gamma$ ray
spectrometry using a HPGe detector coupled to
a 4 K Multi Channel Analyzer (MCA) system. Energy vs. efficiency calibration of the HPGe
detector was carried out using standard $^{152}$Eu
source obtained from Amersham Inc., USA. A
pre-calibrated well type ion chamber was used to
measure the activity of the radioisotopes
produced on irradiation.

FT-IR spectra of the synthesized ligands were
recorded in a JASCO FT/IR-420 spectrometer
and proton spectra were recorded in a 300 MHz
Varian VXR 300S NMR spectrometer using D$_2$O
as solvent.

Scintigraphic images were obtained using a
single head digital SPECT gamma camera (MPS
GE, USA).

**Experimental**

**Syntheses of ligands**

Ethylene diamine tetramethylene phosphonate
(EDTMP) was synthesized in our laboratory
following a reported procedure [30].

The direct syntheses of cyclic $\alpha$-
aminomethylphosphonic acids, DOTMP and
CTMP, were carried out using Mannich type
reacti The scheme for the synthesis of
DOTMP and CTMP are shown in Figure 1.

![Fig. 1. Schemes for synthesis of DOTMP and CTMP](image-url)
For the synthesis of DOTMP, 2.6 g of cyclen (15 mM) and 4.9 g of anhydrous orthophosphorous acid (60 mM) were dissolved in 10 mL of 37% hydrochloric acid and the resulting solution was refluxed. 1.4 mL of 36% formaldehyde was added drop wise to the refluxing solution and the refluxing was continued for another one hour. The reaction mixture was cooled to room temperature and poured in absolute ethanol with vigorous stirring. The crude product (5.95 g, 80%) was recrystallized from aqueous ethanol whereby pure DOTMP was obtained [m. p. 260°C, dec.].

CTMP was synthesized by drop wise addition of 3.4 mL of 36% formaldehyde to a refluxing solution of 2 g of cyclam (10 mM) and 3.2 g of orthophosphorous acid (40 mM) in 10 mL of 37% hydrochloric acid. The refluxing was continued for another 3 h and the reaction mixture was cooled subsequently whereby precipitate formation was observed. The precipitate was filtered, washed with ice cold water and dried. The crude product (4.7 g, 82%) was recrystallized from aqueous methanol to give a crystalline solid [m. p. 220°C, dec.].

Production of radioisotopes

$^{177}$Lu, $^{153}$Sm and $^{175}$Yb were produced by thermal neutron bombardment of natural Lu$_2$O$_3$, Sm$_2$O$_3$ and Yb$_2$O$_3$ target, respectively in Dhruva reactor at a flux of 3×10$^{13}$ n/cm$^2$/s for about 7 days. A weighed amount (typically 6 mg) of the metal oxide powder was irradiated. Following irradiation the powder was dissolved in 5 mL of 0.1 M HCl by gentle warming. The resultant solution was evaporated to near dryness and reconstituted in 5 mL of double distilled water.

For production of $^{186/188}$Re, 5 mg of natural rhenium metal was irradiated in the Dhruva reactor for 7 days at a thermal neutron flux of 3×10$^{13}$ n/cm$^2$/s. The sample was dissolved in 5 mL of 2 M HNO$_3$. 3 mL (1 mg/mL) of this solution was evaporated by heating to dryness in a beaker. 2 mL of 25% ammonia solution was added to the dry residue. Excess ammonia was removed by heating and the ammonium perrhenate residue was dissolved in 5 mL of 5 M NaOH solution. Rhenium activity was extracted into 5 mL of methyl ethyl ketone (MEK) and the extraction efficiency was estimated by determining the radioactivity in equal aliquots of MEK and aqueous phase. Extraction was repeated with an equal volume of MEK and both the extracts were pooled together. MEK was removed by gentle heating and the residue was dissolved in 5 mL of normal saline.

Radionuclidic purity of all the radionuclides produced was ascertained from the γ ray spectrum of an appropriately diluted sample using a HPGe detector coupled to a 4 K MCA system. Radioactive concentration was also measured using the same system following efficiency calibration with a standard $^{155}$Eu source. Radioactivity assay of high activity samples was carried out by measuring the ionization current obtained when an aliquot of the batch was placed inside a pre-calibrated well-type ion chamber.

Preparation of radiolabeled complexes

$^{177}$Lu-DOTMP: The $^{177}$Lu-DOTMP complex was prepared by dissolving the 2 mg of the ligand in 0.2 mL NaHCO$_3$ buffer (0.5 M, pH 9). To the resulting solutions, 0.1 mL of $^{177}$LuCl$_3$ solution (150-250 MBq, ~100 µg of Lu) was added after the addition of 0.7 mL normal saline. The reaction mixture was incubated at room temperature for 15 minutes after adjusting the pH of the resulting mixtures to 7.

$^{153}$Sm-DOTMP: The $^{153}$Sm-DOTMP complex was prepared by dissolving the 1 mg of the ligand in 0.2 mL of 0.5 M NaHCO$_3$ buffer (pH 9). To the resulting solutions, 0.1 mL of $^{153}$SmCl$_3$ solution (150-200 MBq, ~100 µg of Sm) was added after the addition of 0.7 mL normal saline. The reaction mixture was incubated at room temperature for 15 minutes after adjusting the pH to 7.

$^{175}$Yb-EDTMP: The $^{175}$Yb-EDTMP complex was prepared by dissolving 10 mg of the ligand in 0.4 mL of 0.5 M of NaHCO$_3$ buffer (pH 9). To the resulting solutions, 0.1 mL of $^{175}$YbCl$_3$ solution (80-100 MBq, ~100 µg of Yb) was added after the addition of 0.5 mL normal saline. The pH of the resulting mixture was adjusted to 7 and it was incubated at room temperature for 15 minutes.
For preparation of $^{186/188}$Re-CTMP complex 50 mg of CTMP was dissolved in 0.5 mL of NaHCO$_3$ buffer (0.5 M, pH 9) followed by the addition of 0.3 mL of saline. To the resulting solution 20 µL SnCl$_2$.2H$_2$O solution (in concentrated HCl, 100 mg/mL) and 0.2 mL $^{186/188}$ReO$_4$ (50-350 MBq, ~100 µg Re) were added. The pH of the reaction mixture was adjusted to 2 using 1 M HCl. Finally the reaction mixture was purged with nitrogen for 2 minutes and heated in a boiling water bath for 30 min.

**Quality control techniques**

The radiolabeling yields were determined by employing paper chromatography and paper electrophoresis techniques.

**Paper Chromatography**: 5 µL of the test solutions were applied at 1.5 cm from one end of Whatman 3 MM chromatography paper strips (12×2 cm). The strips were developed in suitable solvents, dried, cut into 1 cm segments and activity was measured.

**Paper Electrophoresis**: 5 µL of the complex solutions prepared were applied on pre-equilibrated Whatman 3 MM (35×2 cm) chromatography paper at 15 cm from the cathode. Paper electrophoresis was carried out for 1 h under a voltage gradient of ~10 V/cm using 0.025 M phosphate buffer of pH 7.5. The strips were dried, cut into 1 cm segments and activity was counted.

**Stability studies**

The stability of all the complexes was studied at room temperature by determining the radiochemical purities of the complexes at regular time intervals after their preparation by employing standard quality control techniques mentioned above.

**Biodistribution studies**

Biodistribution studies of the complexes were performed in Wistar rats weighing 200-300 g. 0.15-0.2 mL (3-4 MBq) of the complex solutions were injected through tail veins and the animals were sacrificed by anesthetizing (using chloroform) followed by cardiac puncture, at different time intervals post-injection. Three rats were used for each time point. The tissues and the organs were excised and activity associated with organs/tissues was measured in a flat type NaI(Tl) scintillation counter. Distribution of the activity in different organs was calculated as percentage of injected activity per gram of organ. All the biodistribution studies were carried out in strict compliance with the national laws related to the conduct of animal experiments.

**Imaging studies**

150-200 MBq of $^{177}$Lu-DOTMP, $^{153}$Sm-DOTMP and $^{186}$Re-CTMP preparations were injected intravenously into healthy adult New-Zealand white rabbits weighing 3-4 kg through ear vein. Serial scintigrams were taken in a single head digital SPECT gamma camera (MPS GE, USA) using a low energy high-resolution (LEHR) collimator. Sequential images were recorded at 30 min, 1 h, 3 h, 24 h and 48 h post injection. All the images were acquired using a 256×256 matrix with 500 kilocounts with appropriate window settings for the respective radioisotopes.

**Results and Discussions**

**Characterization of ligands**

The synthesized ligands were characterized by FT-IR and $^1$H-NMR spectroscopy. The FT-IR and $^1$H-NMR spectral data of synthesized ligands are given below. The peak integrations in the $^1$H-NMR spectrum correspond to the expected number of protons.

**EDTMP**

IR (KBr, ν cm$^{-1}$): 3308, 2633, 2311, 1666, 1436, 1356.

$^1$H-NMR (D$_2$O, δ ppm): 3.55 (d, J = 12.3 Hz, 8H, -N-[CH$_2$-P(O)(OH)$_2$]), 3.86 (s, 4H, >N-CH$_2$-CH$_2$-N<).

**DOTMP**

IR (KBr, ν cm$^{-1}$): 3244, 2953, 2366, 1455, 1216.

$^1$H-NMR (D$_2$O, δ ppm): 3.24-3.32 (s, 8H, -N-[CH$_2$-P(O)(OH)$_2$]), 3.32-3.44 (s, 16H, >N-CH$_2$-CH$_2$-N<).
CTMP

IR (KBr, ν cm\(^{-1}\)): 3400, 2984, 2826, 1630, 1487.

\(^1\)H-NMR (D\(_2\)O, δ ppm): 2.05-2.07 (m, 4H, >N-CH\(_2\)-CH\(_2\)-N<), 2.91-3.57 (m, 24H, >N-CH\(_2\)-CH\(_2\)-N<, >N-[CH\(_2\)-P(O)(OH)\(_2\)]\(_2\)].

Production of radioisotopes

\(^{177}\)Lu: 15–20 GBq (405-540 mCi) of \(^{177}\)Lu activity was obtained at 6 h post EOB from 6 mg of natural Lu\(_2\)O\(_3\) powder irradiated for 7 days at a thermal neutron flux of 3×10\(^{13}\) n/cm\(^2\)/s, corresponding to a specific activity of 3-4 TBq/g (81-108 Ci/g). The radionuclidic purity of \(^{177}\)Lu was ~100% as obtained by analyzing the γ-ray spectrum. The major peaks observed were at 72, 113, 208, 250 and 321 keV, all of which correspond to the photopeaks of \(^{177}\)Lu [14]. It is worthwhile to note there is a possibility of the formation of \(^{177m}\)Lu (T\(_{1/2} = 160.5\) d) [14] on thermal neutron bombardment of natural Lu\(_2\)O\(_3\) target. However, the γ-ray spectrum did not show any significant peak corresponding to \(^{177m}\)Lu (at 128, 153, 228, 378, 414 and 418 keV). This is expected as the radioactivity due to \(^{177m}\)Lu produced will be too insignificant on 7 d irradiation owing to its long half life and comparatively low cross section (σ=7 barns) for its formation [14].

\(^{153}\)Sm: The yield of \(^{153}\)Sm was around 9.2-10 TBq/g (250-270 Ci/g) at 6 h EOB when natural Sm\(_2\)O\(_3\) was irradiated at a thermal neutron flux of 3×10\(^{13}\) n/cm\(^2\)/s for a period of 7 d. This value is in excess of the theoretically calculated yield of \(^{153}\)Sm (6 TBq/g, 160 Ci/g) under identical irradiation conditions. This could perhaps be attributed to the contribution from epithermal neutrons, which is not accounted in the theoretical calculations [13]. The use of commercially available enriched Sm target (99.2% \(^{155}\)Sm) could yield around 4 fold higher specific activity of \(^{153}\)Sm. However, the specific activity obtained by using natural Sm target is adequate for preparation of agents for bone pain palliation and hence the use of costly enriched target is not essential. The analysis of γ-ray spectrum of the processed \(^{153}\)Sm samples revealed the presence of \(^{154}\)Eu [T\(_{1/2} = 8.5\) y, E\(_γ\) = 123.1 keV (40.5%)], \(^{155}\)Eu [T\(_{1/2} = 4.68\) y, E\(_γ\) = 86.5 keV (32.7%)] and \(^{156}\)Eu [T\(_{1/2} = 15.2\) d, E\(_γ\) = 811.8 keV (10.3%)] [14] as radionuclidic impurities. For the determination of activities of the long-lived impurities such as \(^{154}\)Eu and \(^{155}\)Eu, samples assayed initially for \(^{153}\)Sm were preserved for complete decay of \(^{153}\)Sm (20 T\(_{1/2}\), i.e. around 40 days) and re-assayed for \(^{154}\)Eu and \(^{155}\)Eu. The average radionuclidic impurity burden was found to be 185 Bq (5 nCi) of \(^{154}\)Eu, 3 kBq (81 nCi) of \(^{155}\)Eu and 24 kBq (650 nCi) of \(^{156}\)Eu per 37 MBq (1 mCi) of \(^{153}\)Sm at 6 h post EOB. This implies that the radionuclidic purity of \(^{153}\)Sm at 6 h post EOB is ~99.93%.

\(^{175}\)Yb: 1.3-1.5 TBq/g (35-40 Ci/g) of \(^{175}\)Yb activity was obtained at 6 h post EOB after 7 d irradiation at a flux of 3×10\(^{13}\) n/cm\(^2\)/s using natural Yb\(_2\)O\(_3\) target. Irradiation of natural Yb also results in the formation of \(^{169}\)Yb and \(^{177}\)Lu as radionuclidic impurities. The γ photopeaks observed in the γ-ray spectrum of irradiated ytterbium after chemical processing correspond to \(^{175}\)Yb (113, 144, 286 and 396 keV), \(^{169}\)Yb (63, 110, 130, 177, 198, 261 and 307 KeV) and \(^{177}\)Lu (208 and 250 keV) [14]. By analyzing the γ-ray spectra the radionuclidic purity of \(^{175}\)Yb was found to be 96.2% with the presence of 2.1% \(^{169}\)Yb and 1.7% \(^{177}\)Lu as radionuclidic impurities. However, radionuclidically pure \(^{175}\)Yb can be obtained by using enriched target available at reasonable cost. At the same time, the use of enriched target will provide ~3 fold higher specific activity (~ 4.5 TBq/g).]

\(^{186/188}\)Re: 6.7-7.4 TBq/g (180-200 Ci/g) of \(^{186/188}\)Re activity was obtained when the radiochemical processing was carried out immediately after end of bombardment (EOB) and it was observed from the radionuclidic purity determination that ~60% of the total activity was in the from of \(^{188}\)Re. On the other hand, it was observed that when the radiochemical processing was done after 3 d of cooling, 1.5-1.85 TBq/g (40-50 Ci/g) of the \(^{186/188}\)Re activity was obtained out of which only ~13% of the total activity was contributed by \(^{188}\)Re.
Characterization of the radiolabeled ligands

$^{177}$Lu-DOTMP, $^{153}$Sm-DOTMP and $^{175}$Yb-EDTMP complexes were characterized by employing paper chromatography technique using normal saline as the eluting solvent. It was observed that all the complexes moved towards the solvent front ($R_t = 1.0$) while uncomplexed radiometals under identical conditions remained at the point of spotting ($R_t = 0$). The paper electrophoresis patterns in phosphate buffer showed the movement of all the complexes towards anode indicating that they are negatively charged. On the other hand, uncomplexed radiometals did not show any movement from the point of application under identical conditions.

On the other hand, characterization of $^{186/188}$Re-CTMP complex was carried out by paper chromatography studies in saline as well as acetone. In paper chromatography using acetone as the solvent, the major activity remained at the point of spotting ($R_t = 0$). An estimation of the unreacted $^{186/188}$ReO$_4^-$ could be made since, under identical conditions $^{186/188}$ReO$_4^-$ was found to move towards the solvent front ($R_t = 0.9$). In paper chromatography using saline as the solvent, the major activity was observed at the solvent front. Since no significant activity at the point of spotting was observed, the absence of hydrolyzed Re could be inferred. In paper electrophoresis carried out under identical conditions as mentioned above, the $^{186/188}$Re-CTMP complex showed a migration towards anode indicating the complex is anionic in nature.

The results of paper chromatography and paper electrophoresis were used to ascertain both the yield and radiochemical purity of all the complexes.

Optimization studies

In order to maximize the complexation yields, several experiments were carried out by varying reaction parameters, such as, ligand concentration, pH of the reaction mixture, reaction time and temperature.

The effect of ligand concentration on complexation yield was determined by carrying out complexation studies at various ligand concentrations. It was observed that >99% complexation yield was obtained by using 2 mg/mL and 1 mg/mL of DOTMP concentrations in case of $^{177}$Lu-DOTMP and $^{153}$Sm-DOTMP complexes, respectively. In case of $^{175}$Yb-EDTMP, the optimum ligand concentration yielding a maximum complexation yield (~98%) was found to be 10 mg/mL. On the other hand, the optimum ligand concentration for $^{186}$Re-CTMP complexation was found to be 50 mg/mL.

The effect of variation of pH on complexation yields was studied by varying the pH of the reaction mixtures from 2 to 10 using either 0.1 M HCl or 0.1 M NaOH solution. Complexation yields were comparatively lower at the acidic pH and became maximum at pH ~7 for all the lanthanide phosphonate complexes viz. $^{177}$Lu-DOTMP, $^{153}$Sm-DOTMP and $^{175}$Yb-EDTMP. In case of $^{186}$Re-CTMP, however, maximum complexation yield (>98%) was obtained at pH 2 and it decreased sharply with increase of pH of the reaction mixture.

SnCl$_2$.2H$_2$O was used as the reducing agent for the preparation of $^{186/188}$Re-CTMP complex and its concentration was optimized by carrying out complexation using different concentrations of reducing agent keeping other parameters of radiolabeling at the optimized value. The use of 2 mg SnCl$_2$.2H$_2$O was found to be necessary for achieving ~98% complexation.

In order to optimize the reaction time and reaction temperature, the reaction mixtures were incubated at various temperatures for different time periods and the complexation yields were determined. It was observed that all the radiolanthanide complexes were formed in excellent yields within 15 min incubation at room temperature. The effect of higher reaction temperature on the complexation yields was not studied as sufficiently high yields were achieved at room temperature. On the other hand, for $^{186/188}$Re-CTMP complex, the complexation must be carried out at higher temperature in order to achieve high complexation yield within a reasonable time limit. It was observed that, heating the reaction mixture for 30 min in a boiling water bath yielded >98% complexation.
Stability studies
The stability of all the radiolabeled phosphonates were studied up to 3 half-lives of the respective radionuclides used for its preparation and it was observed that all the complexes were highly stable at room temperature as no appreciable degradation was observed for any of them within the above said time limit.

Biodistribution studies
The uptake in the different organs expressed as %ID/g of the organs for all the radiolabeled phosphonate complexes are shown in Table 1-4. The results of the biodistribution studies revealed significant bone uptake within 3 h post-injection. Tibia was taken as a representative of the skeleton and observed uptake in tibia were 4.23%/g, 3.94%/g, 4.37%/g and 1.80%/g for $^{177}$Lu-DOTMP, $^{153}$Sm-DOTMP, $^{175}$Yb-EDTMP and $^{186/188}$Re-CTMP, respectively at 3 h post-injection. Almost all the activity from the blood was cleared at this time point for all the complexes and no significant accumulation of activity was observed in any of the major organs except in kidneys and liver. However, the uptake observed in kidneys and liver were found to reduce with time. ~30-50% of the injected activity was cleared via urinary excretion within 3 h post-injection for all the complexes. No leaching of the activity from bone was observed as there was no increment of the uptake in any of the organs and tissues. It may be possible that the retention of activity could be even higher in metastatic lesion site as compared to normal cells owing to the hypoxic nature of the cells [31]. Thus it is pertinent to evaluate the potential of these radiolabeled phosphonates in metastatic lesion sites.

Table 1: Biodistribution pattern of $^{177}$Lu-DOTMP complex in Wistar rats

<table>
<thead>
<tr>
<th>Organ</th>
<th>3 h</th>
<th>1 d</th>
<th>2 d</th>
<th>7 d</th>
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<tr>
<td>Blood</td>
<td>0.01 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Liver</td>
<td>0.13 (0.02)</td>
<td>0.07 (0.01)</td>
<td>0.08(0.00)</td>
<td>0.05 (0.02)</td>
</tr>
<tr>
<td>Intestine</td>
<td>0.43 (0.19)</td>
<td>0.15 (0.02)</td>
<td>0.13 (0.01)</td>
<td>0.07 (0.02)</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.35 (0.08)</td>
<td>0.26 (0.03)</td>
<td>0.27 (0.03)</td>
<td>0.20 (0.04)</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.05 (0.06)</td>
<td>0.00 (0.00)</td>
<td>0.03 (0.02)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Heart</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.00 (0.00)</td>
<td>0.01 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Tibia</td>
<td>5.23 (0.77)</td>
<td>5.50 (0.59)</td>
<td>6.54 (0.12)</td>
<td>5.10 (0.05)</td>
</tr>
<tr>
<td>Muscles</td>
<td>0.01 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.06 (0.02)</td>
<td>0.05 (0.02)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Excretion#</td>
<td>47.79 (1.30)</td>
<td>55.99 (1.51)</td>
<td>55.99 (0.95)</td>
<td>59.29 (2.84)</td>
</tr>
</tbody>
</table>

Figures in the parenthesis represents standard deviations
At every time point 3 animals had been used

*Excretion has been calculated by subtracting the activity accounted in all the organs from the total activity injected
Table 2: Biodistribution pattern of $^{153}$Sm-DOTMP complex in Wistar rats

<table>
<thead>
<tr>
<th>Organ</th>
<th>%ID/g</th>
<th>3 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.09 (0.05)</td>
<td>0.08 (0.01)</td>
<td>0.01 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Intestine</td>
<td>0.08 (0.05)</td>
<td>0.05 (0.03)</td>
<td>0.08 (0.06)</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>0.27 (0.05)</td>
<td>0.10 (0.02)</td>
<td>0.10 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>0.04 (0.03)</td>
<td>0.02 (0.02)</td>
<td>0.02 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Tibia</strong></td>
<td><strong>3.94 (0.50)</strong></td>
<td><strong>3.72 (0.10)</strong></td>
<td><strong>3.72 (0.27)</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>0.02 (0.01)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Excretion#</strong></td>
<td><strong>40.13 (5.92)</strong></td>
<td><strong>43.46 (4.46)</strong></td>
<td><strong>48.77 (7.28)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Figures in the parenthesis represents standard deviations
At every time point 3 animals had been used

#Excretion has been calculated by subtracting the activity accounted in all the organs from the total activity injected

Table 3: Biodistribution pattern of $^{175}$Yb-EDTMP complex in Wistar rats

<table>
<thead>
<tr>
<th>Organ</th>
<th>%ID/g</th>
<th>3 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.03 (0.01)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.05 (0.02)</td>
<td>0.05 (0.01)</td>
<td>0.05 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Intestine</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>0.28 (0.04)</td>
<td>0.19 (0.03)</td>
<td>0.11 (0.01)</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>0.11 (0.01)</td>
<td>0.07 (0.02)</td>
<td>0.05 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>0.02 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Lungs</td>
<td>0.06 (0.02)</td>
<td>0.04 (0.01)</td>
<td>0.03 (0.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Tibia</strong></td>
<td><strong>4.37 (0.60)</strong></td>
<td><strong>4.71 (0.21)</strong></td>
<td><strong>4.69 (0.19)</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>0.03 (0.02)</td>
<td>0.01 (0.00)</td>
<td>0.00 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>0.15 (0.07)</td>
<td>0.12 (0.05)</td>
<td>0.09 (0.03)</td>
<td></td>
</tr>
<tr>
<td><strong>Excretion#</strong></td>
<td><strong>30.20 (1.58)</strong></td>
<td><strong>28.46 (9.02)</strong></td>
<td><strong>29.13 (5.09)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Figures in the parenthesis represents standard deviations
At every time point 3 animals had been used

#Excretion has been calculated by subtracting the activity accounted in all the organs from the total activity injected
Table 4: Biodistribution pattern of \(^{186/188}\text{Re-CTMP}\) complex in Wistar rats

<table>
<thead>
<tr>
<th>Organ</th>
<th>3 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.05 (0.01)</td>
<td>0.03 (0.02)</td>
<td>0.03 (0.02)</td>
</tr>
<tr>
<td>Liver</td>
<td>0.04 (0.01)</td>
<td>0.02 (0.01)</td>
<td>0.07 (0.02)</td>
</tr>
<tr>
<td>Intestine</td>
<td>0.50 (0.22)</td>
<td>0.07 (0.03)</td>
<td>0.10 (0.03)</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.91 (0.22)</td>
<td>0.30 (0.09)</td>
<td>0.20 (0.03)</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.20 (0.07)</td>
<td>0.10 (0.03)</td>
<td>0.01 (0.00)</td>
</tr>
<tr>
<td>Heart</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.02 (0.01)</td>
<td>0.01 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Tibia</td>
<td>1.82 (0.48)</td>
<td>1.31 (0.20)</td>
<td>1.42 (0.22)</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.03 (0.00)</td>
<td>0.01 (0.01)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.02 (0.01)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Excretion#</td>
<td>65.84 (6.28)</td>
<td>77.50 (5.69)</td>
<td>73.94 (7.55)</td>
</tr>
</tbody>
</table>

Figures in the parenthesis represents standard deviations
At every time point 3 animals had been used

#Excretion has been calculated by subtracting the activity accounted in all the organs from the total activity injected

Table 5: Comparison of uptakes of the radiolabeled phosphonates with \(^{153}\text{Sm-EDTMP}\) in bone and other major organs in rats

<table>
<thead>
<tr>
<th>Complex</th>
<th>(^{153}\text{Sm-EDTMP})</th>
<th>(^{177}\text{Lu-DOTMP})</th>
<th>(^{153}\text{Sm-DOTMP})</th>
<th>(^{175}\text{Yb-EDTMP})</th>
<th>(^{186/188}\text{Re-CTMP})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>0.002 (0.002)</td>
<td>0.007 (0.002)</td>
<td>0.003 (0.000)</td>
<td>0.027 (0.009)</td>
<td>0.050 (0.008)</td>
</tr>
<tr>
<td>Liver</td>
<td>0.027 (0.005)</td>
<td>0.131 (0.022)</td>
<td>0.090 (0.052)</td>
<td>0.052 (0.024)</td>
<td>0.042 (0.005)</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.147 (0.022)</td>
<td>0.352 (0.078)</td>
<td>0.269 (0.047)</td>
<td>0.283 (0.041)</td>
<td>0.908 (0.222)</td>
</tr>
<tr>
<td>Muscles</td>
<td>0.003 (0.001)</td>
<td>0.008 (0.002)</td>
<td>0.002 (0.001)</td>
<td>0.026 (0.014)</td>
<td>0.028 (0.007)</td>
</tr>
<tr>
<td>Bone</td>
<td>3.720 (0.259)</td>
<td>5.230 (0.768)</td>
<td>3.942 (0.480)</td>
<td>4.373 (0.602)</td>
<td>1.823 (0.481)</td>
</tr>
<tr>
<td>Bone/Blood</td>
<td>1860.00</td>
<td>747.14</td>
<td>1314.00</td>
<td>161.96</td>
<td>36.46</td>
</tr>
<tr>
<td>Bone/Muscles</td>
<td>1240.00</td>
<td>653.75</td>
<td>1971.00</td>
<td>168.19</td>
<td>65.11</td>
</tr>
<tr>
<td>Time p.i.</td>
<td>2 h</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
<td>3 h</td>
</tr>
<tr>
<td>Animal strain</td>
<td>Sprague-Dawley</td>
<td>Wistar</td>
<td>Wistar</td>
<td>Wistar</td>
<td>Wistar</td>
</tr>
<tr>
<td>Reference</td>
<td>1</td>
<td>Present study</td>
<td>Present study</td>
<td>Present study</td>
<td>Present study</td>
</tr>
</tbody>
</table>
Although the bone and other organ uptakes $^{153}$Sm-EDTMP complex have been reported earlier [1], its comparison with the radiolabeled phosphonates under investigation is difficult due to the heterogeneity in animal models used, as well as the difference in post-injection times wherein the respective uptakes have been determined. However, to evaluate the potential of presently studied agents, an attempt to compare their biodistribution patterns with that of $^{153}$Sm-EDTMP have been attempted and the results are depicted in Table 5.

**Imaging studies**

The scintigraphic images of rabbits recorded at 3 h post-injection for $^{177}$Lu-DOTMP and $^{153}$Sm-DOTMP are given in Figure 2 and 3, respectively. The uptake of the activity in the skeleton was observed within 1 h post-injection and it became quite significant at 3 h. At this time point, the total skeleton was clearly visible in spite of some uptake observed in the kidneys. The images clearly show no appreciable accumulation of activity in any other soft tissues. The hot bladder visible in the scintigram at this time point indicates the major renal excretion of the administered activity.

**Conclusion**

Four different radiolabeled phosphonates based on moderate energy $\beta^-$ emitters and polyaza tetramethylene phosphonic acids have been prepared in very high radiochemical purity. All the complexes exhibited excellent stability on storage at room temperature. Preliminary biodistribution studies in Wistar rats revealed selective skeletal uptake with rapid renal clearance along with insignificant accumulation of activity in any non-target organ or tissues. Imaging studies in rabbits also demonstrated significant skeletal localization with no appreciable uptake in the soft tissues. A favourable comparison of the target to non-target ratio exhibited by the radiolabeled phosphonates with that of $^{153}$Sm-EDTMP indicates the potential of developed agents for use in bone pain palliation. These studies warrant the detailed evaluation of the agents under investigation in higher animal models.
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References


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Dr (Ms) Sharmila Banerjee joined the Radiopharmaceuticals Division, BARC, in 1996. Prior to that, she obtained her M.Sc. in Organic Chemistry from the University of Calcutta and Ph.D. degree from Indian Institute of Technology, Mumbai, in 1992. Her current areas of interest include research in the field of radiopharmaceuticals chemistry aiming at the development of new diagnostic and therapeutic radiopharmaceuticals. She is a recognized guide for M.Sc. and Ph.D. degree under the University of Mumbai. She has about 90 publications in international journals including review articles.
Mr Sudipta Chakraborty is a gold medalist of Jadavpur University (West Bengal) and obtained M.Sc. (Chemistry) in 1997. He graduated from BARC Training School in 1999 (42nd Batch, Chemistry discipline) and joined Radiopharmaceuticals Division, BARC. Since then he has been actively involved in the research and development work on therapeutic radiopharmaceuticals. He has to his credit about 35 publications in various national and international journals.

Dr Tapas Das obtained M.Sc. (Chemistry) from Kalyani University (West Bengal) in 1997. After graduating from BARC Training School in 1998 (41st Batch, Chemistry discipline), he joined Radiopharmaceuticals Division, BARC. Since then he has been actively involved in the research and development work on diagnostic and therapeutic radiopharmaceuticals. He has obtained Ph.D. degree in Chemistry from University of Mumbai in 2004. He has published about 40 papers in various national and international journals.

Dr (Ms) Kanchan Kothari joined the Radiopharmaceuticals Division (earlier Isotope Division) in 1974 after obtaining her B.Sc. (Chemistry) from Mumbai University. She has been associated with R & D activities in the field of radiopharmaceutical chemistry for the last 30 years. She was awarded the Ph.D. degree (Chemistry) in 1990 for work carried out on immunoassay development. She has worked as a Post Doctoral Research Fellow at the University of Missouri, Columbia (USA) in 1999-2000. She has 70 publications in national and international journals.

Dr (Ms) Grace Samuel obtained M.Sc. and Ph.D. in Chemistry from Mumbai University. She joined the Radiopharmaceuticals Division in 1976. She is actively involved in the radiolabeling of various molecules with different diagnostic and therapeutic radioisotopes for use in radiopharmaceuticals. She has been instrumental in the development of radioimmunoassay procedures for several hormones and drugs. She has served as an IAEA expert in thefield of radioimmunoassay. She has published more than 90 papers in several national and international journals.

Dr (Ms) Meera Venkatesh joined the Training School of BARC in the year 1976 after completing Bachelor’s Degree in Chemistry from Bombay University. She joined the Radiopharmaceuticals Division in 1977 and has been engaged in the research and development of Radiopharmaceuticals and radiometric assays since then. Dr. Meera obtained her doctorate degree from the Bombay University in 1986 for her work in the field of Radioimmunoassays. She did her post-doctoral fellowship at the University of Missouri, USA, during 1992-94 in the field of therapeutic radiopharmaceuticals and later in 1999 served as a visiting professor at the same university. Currently, Dr. Meera is heading the Radiopharmaceuticals Division, BARC, and concurrently serves in the capacity of General Manager of Quality Control at the Board of Radiation and Isotope Technology. She has published over 150 papers in the international journals, international and national symposia/conferences and has authored a few invited articles. She has served as an expert in the field of Radiopharmaceuticals and Radiometric assays for the International Atomic Energy Agency.

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Dr Boby Mathew joined the Radiation Safety Systems Division in 1991 after successful completion of the Health Physicist’s Stipendiary Training Course. He completed his doctorate degree in the field of radiopharmaceuticals in 2003 and is currently working as a post-doctoral fellow at the Thomas Jefferson University, USA.

Dr Haladhar D. Sarma is Head of Laboratory Animal Facility and Radioisotope Laboratory in Radiation Biology and Health Sciences Division, BARC. He obtained M.V.Sc. with distinction from Assam Agricultural University, Guwahati, in 1989. His major research interest concerns radiation carcinogenesis and application of nuclear technology in human and animal health. Prior to joining BARC in 1994, Dr. Sarma was Assistant Professor in the faculty of Veterinary Sciences, Assam Agricultural University. He has published more than 50 publications in various national and international journals.

Dr Pradip R. Chaudhari obtained M.V.Sc. from Bombay Veterinary College, Mumbai, in 1994 and joined Radiation Medicine Centre (RMC), BARC, in 1994. Currently, he is working in Laboratory Nuclear Medicine Section (LNMS) and is actively involved in the bio-evaluation of newer radiopharmaceuticals. He is the recipient of many awards—Young Scientist Award of Indian Society for Nuclear Technology in Animal Sciences, Young Surgeon Award of Indian Society for Veterinary Surgery and BOYSCAST fellowship of Department of Science and Technology, Government of India, to name a few. He has published about 35 papers in various journals.