

Studies on the Labeling of Ethylenediaminetetramethylene Phosphonic Acid, Methylene Diphosphonate, Sodium Pyrophosphate and Hydroxyapatite with Lutetium-177 for use in Nuclear Medicine

Imtiaz Ahmed Abbasi

Directorate of Technology, Pakistan Institute of Nuclear Science and Technology, Nilore, Islamabad, Pakistan

Abstract

For the treatment of skeletal metastasis, a therapeutic radionuclide tagged with a bone seeking ligand is required, while for radiation synovectomy (RS), a therapeutic radionuclide irreversibly attached to pre-formed particles of appropriate size is required. Radio lanthanides are mostly therapeutic, and ligands containing phosphate groups are predominantly bone seekers. Exploiting these facts, number of new therapeutic radiopharmaceuticals could be developed. Labeling of four phosphate containing materials was pursued in the present study. It was hypothesized that various ^{177}Lu -labeled bone-seeking complexes such as ^{177}Lu -ethylenediaminetetramethylene phosphonic acid (EDTMP), ^{177}Lu -methylene diphosphonate (MDP) and ^{177}Lu -pyrophosphate (PYP) could be developed as agents for palliative radiotherapy of bone pain due to skeletal metastases, and ^{177}Lu -Hydroxyapatite (HA) could be developed as an agent for radiosynovectomy of small joints. Lyophilized kit vials of EDTMP, MDP and sodium pyrophosphate (Na-PYP) were formulated. HA particles were synthesized locally and purity was checked by high-performance liquid chromatography (HPLC). ^{177}Lu was labeled with EDTMP, MDP, PYP, and HA and the behavior of all was studied by radio-thin layer chromatography (TLC) radio-HPLC and radio-electrophoresis. Radio-TLC confirmed the labeling. HPLC analysis too verified the labeling. Radio-electrophoresis results depicted peaks for ^{177}Lu -MDP, ^{177}Lu -EDTMP and ^{177}Lu -PYP at 3.37 ± 0.06 cm, 5.53 ± 0.15 cm and 7.03 ± 0.06 cm respectively confirming negative charge on each specie as all migrated toward positive anode. All 3 methods verified the labeling. The study demonstrated that EDTMP, MDP and PYP form stable complexes with ^{177}Lu in injectable solution form. HA particulates could too be labeled with ^{177}Lu with high radiochemical yields (>98%) in suspension form. Former three could be utilized as bone-pain palliation agents for the treatment of bone metastases, and the later could be applied for the treatment of Rheumatoid arthritis of small joints. The study has also indicated the possibility of developing other numerous radiolanthanide analogs with the potentials of possible use in radiation therapy.

Key words: ^{177}Lu -labeled methylene diphosphonate, bone-pain palliation, radiation synovectomy, radio-labeling

Introduction

Phosphate containing ligands like Ethylenediaminetetramethylene phosphonic acid

(EDTMP), methylene diphosphonate (MDP) sodium pyrophosphate (Na-PYP) all labeled with a radionuclide act as bone-seeking radiopharmaceuticals. Structures of EDTMP, MDP and Na-PYP are shown in Figure 1.

Bone scanning using the $^{99\text{m}}\text{Tc}$ -phosphate analogs is an established diagnostic modality for a variety of pathologies.^[1] Complex of MDP with $^{99\text{m}}\text{Tc}$ has been widely used as radiopharmaceutical for bone scintigraphy in cases of metastatic bone disease, Paget's disease, fractures in osteoporosis, and henceforth for the last quarter of a century.^[2-5] Bone scanning

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Address for correspondence:

Dr. Imtiaz Ahmed Abbasi, LEU-Quality Control Group, Pakistan Institute of Nuclear Science and Technology, Nilore, Islamabad, Pakistan.
E-mail: imtiaz_abbasi@yahoo.com

with ^{99m}Tc pyrophosphate is very useful for the detection of soft-tissue lesions that produce extra skeletal ossification.^[6] EDTMP labeled with ^{153}Sm give rise to ^{153}Sm -EDTMP (^{153}Sm labeled EDTMP) a bone-seeking tetraphosphonate, which have been approved by the Food and Drug Administration for the treatment of painful osseous metastases.^[7] Synovectomy by an intra-articular application of a β -emitting radioisotope in colloidal form or radiation synovectomy (RS) was introduced in 1952 for treatment of inflamed synovial membrane.^[8] An ideal agent for RS would be one in which the radionuclide is irreversibly attached to pre-formed particles of appropriate size. The ^{177}Lu -Hydroxyapatite (HA) $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$ is one of the preferred particulates as it is constituent of bone matrix and natural substance known to be biodegradable.^[9]

^{177}Lu ($t_{1/2}=6.71$ d) is an adequate radionuclide for therapy, which has both beta particle emissions with $E_{\text{max}} = 497$ keV (78.6%), 384 keV (9.1%) and 176 keV (12.2%) for therapeutic effect and gamma emissions 113 keV (6.4%) and 208 keV (11%) for imaging. ^{177}Lu decays to stable ^{177}Hf and its long half-life provides logistic advantage for facilitating the supply to places far away from the reactor.^[9-11] The major advantage of ^{177}Lu lies in the feasibility of its large-scale production with excellent radionuclide purity and adequate specific activity owing to the high thermal neutron capture cross-section of ^{176}Lu (2100 b) using moderate flux reactors.^[12]

For the treatment of skeletal metastasis, a therapeutic radionuclide tagged with a bone seeking ligand is required while, for RS, a therapeutic radionuclide irreversibly attached to pre-formed particles of appropriate size is required. Radio lanthanides are mostly therapeutic, and ligands containing phosphate groups are predominantly bone seekers. Fortunately, lanthanides have a strong affinity towards ligands containing phosphate groups. Exploiting these facts, number of new therapeutic radiopharmaceuticals could be developed. Complex formation of four phosphate containing materials was pursued in the present study. It was hypothesized that various ^{177}Lu -labeled bone-seeking complexes such

as ^{177}Lu -EDTMP, ^{177}Lu -MDP and ^{177}Lu -PYP could be developed as agents for palliative radiotherapy of bone pain due to skeletal metastases, and ^{177}Lu -HA could be developed as an agent for radiosynovectomy.

Materials and Methods

Methylene Diphosphonic acid (99.0%), Tetra Na-PYP (95.0% F. Wt. =265.9) and EDTMP all of Aldrich Chemistry were used in the study.

Natural Lu_2O_3 (99.9% chemically pure, 2.6% ^{176}Lu) powder from A Johnson Mathey Company (UK) was used as a target for the production of ^{177}Lu . $^{177}\text{LuCl}_3$ solution was prepared by dissolving irradiated natural Lu_2O_3 powder in 0.1 M HCl with a little heating. Normally, vials containing 10 mg/ml MDP, 28 mg/ml Na-PYP and 35 mg/ml EDTMP (except reported) were used for labeling studies. $^{177}\text{LuCl}_3$ solution was used for labeling of kit vials. HA $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$, was synthesized locally. Kits of EDTMP, MDP and Na-PYP were formulated by dissolving appropriate amounts of the ligands in double distilled water with adjustment of relevant pH. These solutions were dispensed in vials. Vials were placed in a freeze dryer. Freeze drying was performed for 24 h with a shelf temperature of -80°C and 0.630 mbar pressure. Vials were capped under vacuum and stored at room temperature. Composition of each freeze dried kit is mentioned in Table 1.

Natural Lu_2O_3 (10 mg) target was irradiated at a thermal flux $\sim 8.0 \times 10^{13}$ n/cm²/s for 12 h for the production of ^{177}Lu . The irradiated target was dissolved in 1 M HCl with gentle heating and filtered inside a home-made lead-shielded plant. Specific activity of the product

Table 1: Composition of freeze dried kits

Kit	Weight/mg	mg/ml	Number of vials	$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (mg)	CaCO_3 (mg)	pH
PYP	560	28	20	Nil	Nil	10
MDP	400	10	40	Nil	Nil	6
EDTMP	1750	35	50	705	375	7.5

PYP: Pyrophosphate; MDP: Methylene diphosphonate; EDTMP: Ethylenediaminetetramethylene phosphonic

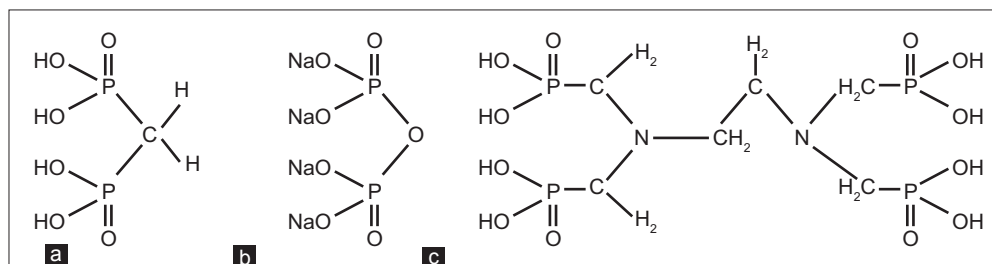


Figure 1: Structure of (a) ^{177}Lu -Methylene diphosphonate, (b) Sodium pyrophosphate and (c) ^{177}Lu -ethylenediaminetetramethylene phosphonic acid

was ~25.3 mCi/mg at EOB. Analysis of the gamma ray spectrum of the irradiated target revealed major γ -peaks at 72, 113, 208, 250 and 321 keV, which correspond to the photopeaks of ^{177}Lu as per literature^[43] and the radionuclide purity of ^{177}Lu more than 99%. Analysis of the gamma ray spectrum was carried out by using a p-type coaxial HPGe detector (Eurisy Mesures, France) coupled through a 570 ORTEC made spectroscopy amplifier to Trump PCI, 8 k ADC/MCA card with Gamma Vision-32 ver. 6 software (ORTEC, USA).

Desired volume of $^{177}\text{LuCl}_3$ solution (containing required activity) was taken in the vials containing MDP 10 mg/ml Na-PYP 28 mg/ml and EDTMP 35 mg/ml. Resulting solutions were incubated for ½ h at room temperature. 1 ml NaHCO_3 (0.5M) and 1 ml normal saline were added to 100 mg of HA in a vial. A volume of 1 ml NaOH was added to make the pH > 7. $^{177}\text{LuCl}_3$ (solution in HCl) was injected to the vial and shaken for 30 min. The shaken mixture was centrifuged at 3500 rpm for 10 min. Supernatant was removed carefully and again saline was added for washing. Centrifugation was carried out for another 5 min. Supernatant was removed again to have ^{177}Lu -labeled hydroxyapatite (^{177}Lu -HA), which was used for further studies.

The centrifuged shaken mixture of $^{177}\text{LuCl}_3$ and HA in 1 ml saline in the form of suspension was used for radiochemical purity check by thin layer chromatography (TLC) system using EDTA as mobile phase. Aliquots from the vial were spotted on Whatman 3 MM paper strips and eluted to develop actigrams.

The kit vials (MDP, PYP and EDTMP) containing $^{177}\text{LuCl}_3$ solution (0.5–1.0 mCi/vial) were shaken and kept at room temperature, and the radiochemical purity check was carried out by TLC system using ammonium hydroxide: Methanol: Water (1:20:20) as mobile phase. Aliquots from the vials were spotted on Whatman 3 MM paper strips of 2 × 14 cm and eluted up to 12 cm. The chromatograms were dried and after drying the strip was subjected to 2π -scanner Berthold coupled with NaI detector to get actigrams depicting the labeling yield.

All the 4 Lu labeled complexes were incubated for >24 h at room temperature. To observe the stability of the complexes, aliquots from the vials containing ^{177}Lu -PYP, ^{177}Lu -MDP, ^{177}Lu -EDTMP and ^{177}Lu -HA complex at different time intervals (1 h–24 h) were also spotted on paper strips, eluted and processed likewise by virtue of which *in vitro* stability of the labeled preparations were ascertained.

To determine the effect of temperature on labeling yield, ^{177}Lu -MDP, ^{177}Lu -PYP and ^{177}Lu -EDTMP solutions were heated in three vials with temperature monitoring and

aliquots from the vials at various temperatures 20, 40, 60, and 80°C (each vial was heated at the specified temperatures other than 20°C for 1 min) were spotted on paper strips and eluted and subjected to 2π -scanner Berthold coupled with NaI detector to get actigrams depicting the labeling yield and hence the effect of temperature on the labeling yield was determined. Vial containing ^{177}Lu -HA particulates in 1ml saline was also subjected to high temperatures likewise and aliquots from the vials at various temperatures were spotted on paper strips and eluted with EDTA and actigrams were developed. The centrifuged shaken mixture of $^{177}\text{LuCl}_3$ and HA in 1 ml saline in the form of suspension was used for radiochemical purity check by TLC system using EDTA as mobile phase. Aliquots from the vial were spotted on Whatman 3 MM paper strips and eluted to develop actigrams.

To verify the complex formation and to determine the retention time of ^{177}Lu -PYP, ^{177}Lu -MDP and ^{177}Lu -EDTMP complexes, the reaction mixtures were analyzed by high performance liquid chromatography (HPLC). First 20 μl of $^{177}\text{LuCl}_3$ (10 mCi) solution was injected (thrice) into the column, and the elution was monitored by observing the radioactivity profile. Similarly, 20 μl of the test solution of each type was injected (thrice) into the column and the elution was monitored. Chromatograms were obtained on Hitachi L6200 HPLC system with NaI crystal detector using C-18 reversed phase (25 × 0.5 cm) column utilizing (1:1) mixture of water and methanol as the mobile phase. Both results of TLC/TLC and HPLC were compared for the said reaction mixture.

To determine the charge on the ^{177}Lu -PYP, ^{177}Lu -MDP and ^{177}Lu -EDTMP complex, radio-electrophoresis was conducted. 10.0 μl of each solution (^{177}Lu -PYP, ^{177}Lu -MDP and ^{177}Lu -EDTMP and $^{177}\text{LuCl}_3$) was spotted in the center of 30 cm strip of Whatman 3 MM chromatography strips (30 × 2 cm) at 15 cm from each electrode. Paper electrophoresis was carried out for 1 h under a voltage of 300 V using 0.025M phosphate buffers pH 6.9 and 45 mA current. Wet paper strips were removed and placed on a tissue paper to dry for an hour. Radio electrophoretograms were accomplished by placing the filter paper strip on the 2π -scanner. Paper electrophoresis was carried out with the Delux electrophoresis chamber coupled with the power supply (Gelman Instrument Company USA).

Results

After elution, the dried Whatman 3 MM paper strips were subjected to 2π -scanner. The scanner generated radiochromatograms [Figure 2a-2c] which depicted the labeling of ^{177}Lu -PYP, ^{177}Lu -MDP and ^{177}Lu -EDTMP to be 99.689%, 99.379% and 99.698%, respectively. All

the complexes moved towards solvent front while free $^{177}\text{LuCl}_3$ remained at the origin. Radiochemical purity and labeling efficiency was found to be >99%. While the radiochromatogram [Figure 2d] showed peak at RT = 1.14 (98.021%) indicating $^{177}\text{Lu-HA}$ and shoulders at RT = 5.52 indicating $^{177}\text{Lu-EDTA}$.

Labeling yield at different time intervals 1 h, 6 h, 18 h and 24 h after the initiation of reaction came out to be 99.99 ± 0.01 , 99.34 ± 0.89 , 98.74 ± 0.74 , and 98.14 ± 0.67 for $^{177}\text{Lu-PYP}$ complex while 99.14 ± 0.25 , 99.31 ± 0.20 , 99.19 ± 0.10 , 99.35 for $^{177}\text{Lu-MDP}$, and 99.11 ± 0.21 , 99.04 ± 0.29 , 98.44 ± 0.14 , and 98.05 ± 0.37 for $^{177}\text{Lu-EDTMP}$ and 99.88 ± 0.52 , 99.74 ± 0.49 , 99.44 ± 0.34 and 98.55 ± 0.47 for $^{177}\text{Lu-HA}$. The complexes retained >98% labeling efficiency even after 24 h hence all the 4 complexes could be considered quite stable. Graphic representation of this result is depicted in Figure 3.

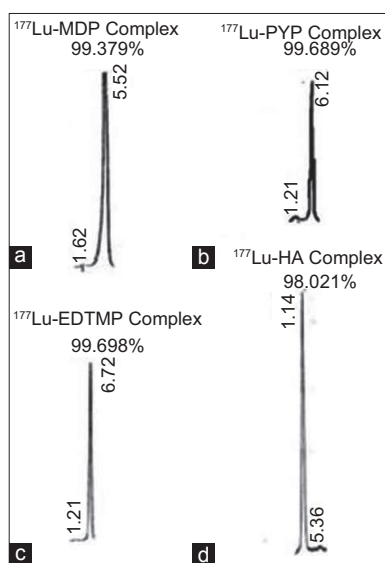


Figure 2: Peaks of actigrams (a-c) representing ^{177}Lu -pyrophosphate complex, ^{177}Lu -Methylene diphosphonate complex and ^{177}Lu -ethylenediaminetetramethylene phosphonic acid complex respectively and actigram (d) representing ^{177}Lu -Hydroxyapatite (% radiochemical purity is depicted as shown by the Printout of 2π -scanner)

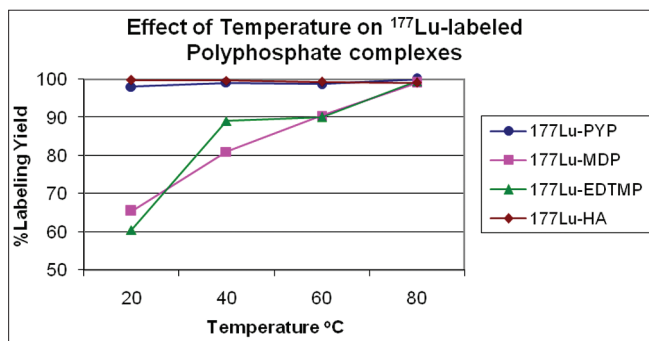


Figure 4: Labeling yield at various temperatures

The labeling yield for $^{177}\text{Lu-PYP}$ at various temperatures 20, 40, 60 and 80°C was determined to be 98.09 ± 0.13 , 99.13 ± 0.10 , 99.76 ± 0.14 and 100.00 ± 0.00 respectively. The labeling yield for $^{177}\text{Lu-MDP}$ was 65.43 ± 5.05 , 81.03 ± 1.29 , 90.42 ± 0.61 , 99.11 ± 0.21 and was 60.53 ± 4.25 , 89.05 ± 1.18 , 90.12 ± 0.43 , 99.41 ± 0.31 for $^{177}\text{Lu-EDTMP}$ and 99.79 ± 0.15 , 99.63 ± 0.19 , 99.26 ± 0.24 , 99.06 ± 0.04 for $^{177}\text{Lu-HA}$. The results as depicted in Figure 4 showed that the stability of the complexes remained intact at temperatures higher than room temperature.

The HPLC chromatogram of the test solutions clearly showed distinct peaks at different retention times thereby confirming the labeling of ^{177}Lu with PYP, MDP and EDTMP. The HPLC chromatograms are shown in Figure 5. It was observed that the retention time of $^{177}\text{Lu-PYP}$ complex was 1.42 ± 0.01 min, $^{177}\text{Lu-MDP}$ 1.35 ± 0.05 min and $^{177}\text{Lu-EDTMP}$ 1.54 ± 0.01 min while that of the free $^{177}\text{LuCl}_3$ was found to be 2.23 ± 0.02 min. On injecting all the three labeled species simultaneously, 4 distinct peaks appeared as shown in Figure 6. Results shown by HPLC were in close agreement with those shown by TLC.

In paper radio-electrophoresis (0.025 M phosphate buffers pH 6.9), $^{177}\text{LuCl}_3$ did not show any movement from point of spotting. Peaks for $^{177}\text{LuCl}_3$ appeared at 15 cm (point of spotting). Activity peaks of $^{177}\text{Lu-PYP}$ complex appeared far from point of spotting [Table 2]. $^{177}\text{Lu-PYP}$

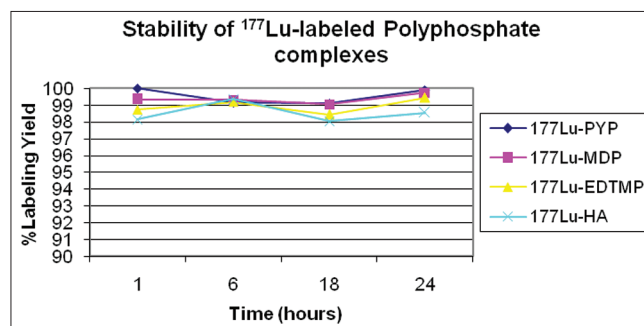


Figure 3: Labeling yield at various time intervals

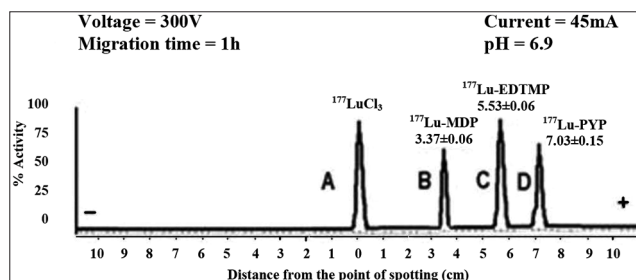


Figure 5: Radio-electrophorotograms (A) free $^{177}\text{LuCl}_3$ (B) ^{177}Lu -pyrophosphate complex (C) ^{177}Lu -methylene diphosphonate complex (D) ^{177}Lu -ethylenediaminetetramethylene phosphonic acid complex

complex showed migration toward anode to the extent of 7.03 ± 0.06 cm, indicating the formation of negatively charged complex. Point of spotting for each experiment was 15.0 cm. Data pertaining to all three radiopharmaceuticals is tabulated in Table 3.

Peaks for ^{177}Lu -MDP and ^{177}Lu -EDTMP appeared at 3.37 ± 0.06 cm and 5.53 ± 0.15 cm respectively. Radio electrophoretograms accomplished by placing the filter paper strip on the 2π -scanner are shown in Figure 5.

Radio-electrophoresis not only confirmed the labeling of ^{177}Lu with PYP, MDP and EDTMP but also confirmed that all three complexes ^{177}Lu -MDP, ^{177}Lu -PYP and ^{177}Lu -EDTMP are negatively charged as they migrated toward positive anode.

Discussion

Large-scale production of ^{177}Lu with excellent radionuclide purity and adequate specific activity due to high thermal neutron capture cross-section of ^{176}Lu using moderate flux reactors makes it a suitable candidate for therapeutic applications. As much interest is being shown currently in the use of ^{177}Lu for various

applications, so pursuing, the evaluation of any of its complexes would be quite reasonable^[14,15]

From the present study, it is clearly evident that ^{177}Lu could be labeled with MDP, PYP and EDTMP with radiochemical purity higher than 99% at 30 min after the start of the reaction. Also, the preparation of complexes ^{177}Lu -MDP, ^{177}Lu -PYP and ^{177}Lu -EDTMP is very simple, and the complexes are quite stable. Lu^{+3} ions are oxygen seekers and phosphonic acid groups (containing oxygen) of MDP, PYP and EDTMP are available for co-ordination with $^{177}\text{Lu}^{+3}$. HA particulates too, could be labeled with ^{177}Lu with high radiochemical yields (>98%). The lanthanides chemically are very similar, and any ligand that makes complex with one could make complexes with all of them.

This study has indicated that numerous radiolanthanide complexes like ^{169}Er -MDP, ^{161}Tb -MDP, ^{143}Pr -MDP, ^{159}Gd -MDP, ^{153}Sm -MDP, ^{149}Pm -MDP, ^{165}Dy -MDP, ^{166}Ho -MDP, ^{142}Pr -MDP, could be developed as well as their analogs with HA, PYP and EDTMP. All these complexes have potentials to be utilized as palliative agents for bone metastasis. Based on the results obtained, hypothetical Structures of the polyphosphate complexes namely ^{177}Lu -PYP, ^{177}Lu -MDP and ^{177}Lu -EDTMP could be designed as mentioned in Figure 7.

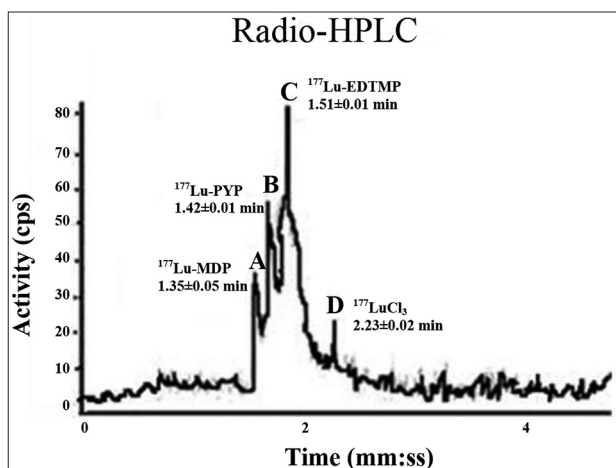


Figure 6: High performance liquid chromatography pattern of (a) Free $^{177}\text{LuCl}_3$ (b) ^{177}Lu -pyrophosphate complex (c) ^{177}Lu -Methylene diphosphonate complex (d) ^{177}Lu -ethylenediaminetetramethylene phosphonic acid complex

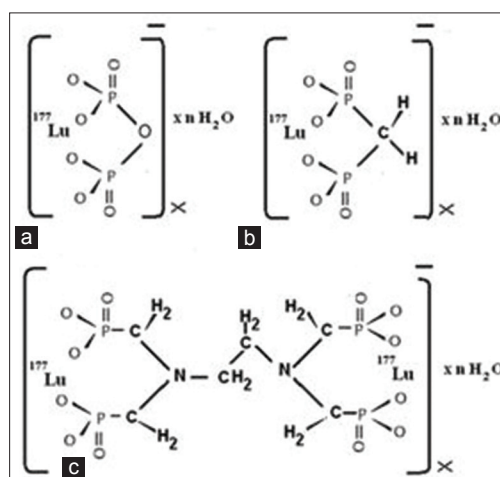


Figure 7: Hypothetical structure of (a) ^{177}Lu -pyrophosphate (b) ^{177}Lu -Methylene diphosphonate and (c) ^{177}Lu -ethylenediaminetetramethylene phosphonic acid complex

Table 2: Labeling yields of ^{177}Lu -PYP ^{177}Lu -MDP and ^{177}Lu -EDTMP complexes for various quantities of Lutetium as a function of fixed quantity of ligands

Vail No	Ratio PYP/Lu	% labeling yield	Ratio MDP/Lu	% labeling yield	Ratio EDTMP/Lu	% labeling yield
1	318.47	99.93±0.03	114.69	99.09±0.04	79.81	99.39±0.24
2	190.83	99.88±0.09	84.11	99.33±0.27	69.68	99.33±0.31
3	60.60	99.24±0.24	53.52	92.21±1.20	50.01	99.39±0.15
4	30.03	45.21±0.97	24.85	86.49±1.23	30.51	99.42±0.75
5	22.99	39.17±0.58	16.98	74.43±2.11	20.09	99.33±0.37
6	10.25	16.33±0.34	7.18	24.67±1.26	10.15	40.57±1.26

PYP: Pyrophosphate; MDP: Methylene diphosphonate; EDTMP: Ethylenediaminetetramethylene phosphonic acid

Table 3: Electrophoresis data of Lu-phosphate complexes

Specie	Experiment number	Point of appearance of activity (cm)	Distance moved towards positive terminal
Lu-PYP complex	1	22.0	7.0
	2	21.9	7.2
	3	22.2	6.9
Lu-MDP complex	4	18.4	3.4
	5	18.3	3.3
	6	18.4	3.4
Lu-EDTMP complex	7	20.5	5.5
	8	20.5	5.5
	9	20.6	5.6

PYP: Pyrophosphate; MDP: Methylene diphosphonate; EDTMP: Ethylenediaminetetramethylene phosphonic acid

Conclusion

The study demonstrated that MDP, EDTMP and Na-PYP form stable complexes with ^{177}Lu in injectable solution form. HA, particulates too could be labeled with ^{177}Lu with high radiochemical yields (>98%) in suspension form. Former three could be utilized as bone-pain palliation agents for the treatment of bone metastases, and the later could be applied for the treatment of Rheumatoid arthritis of small joints. The study has also indicated the possibility of developing other numerous radiolanthanide analogs with the potentials of possible use in radiation therapy.

References

- Loutfi I, Collier BD, Mohammed AM. Nonosseous abnormalities on bone scans. *J Nucl Med Technol* 2003;31:149-53.
- Subramanian G, McAfee JG, Blair RJ, Kallfelz FA, Thomas FD. Technetium-99m-methylene diphosphonate – A superior agent for skeletal imaging: Comparison with other technetium complexes. *J Nucl Med* 1975;16:744-55.
- Domstad PA, Coupal JJ, Kim EE, Blake JS, DeLand FH. $^{99\text{m}}\text{Tc}$ -hydroxymethane diphosphonate: A new bone imaging agent with a low tin content. *Radiology* 1980;136:209-11.
- Love C, Din AS, Tomas MB, Kalapparambath TP, Palestro CJ. Radionuclide bone imaging: An illustrative review. *Radiographics* 2003;23:341-58.
- Marì C, Catafau A, Carriò I. Bone scintigraphy and metabolic disorders. *Q J Nucl Med* 1999;43:259-67.
- Suzuki Y, Hisada K, Takeda M. Demonstration of myositis ossificans by $^{99\text{m}}\text{Tc}$ pyrophosphate bone scanning. *Radiology* 1974;111:663-4.
- Pandit-Taskar N, Batraki M, Divgi CR. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. *J Nucl Med* 2004;45:1358-65.
- Kampen WU, Brenner W, Czech N, Henze E. Intraarticular application of unsealed beta-emitting radionuclides in the treatment course of inflammatory joint diseases. *Curr Med Chem Anti Inflamm Anti Allergy Agents* 2002;1:77-87.
- Chakraborty S, Das T, Banerjee S, Sarma HD, Venkatesh M. Preparation and preliminary biological evaluation of ^{177}Lu -labelled hydroxyapatite as a promising agent for radiation synovectomy of small joints. *Nucl Med Commun* 2006;27:661-8.
- Chang Y, Jeong J, Lee YS, Kim Y, Lee D, Chung JK, *et al.* Comparison of potential bone pain palliation agents Lu-177-EDTMP and Lu-177-DOTMP. *J Nucl Med* 2008;49:93P.
- Pillai MR, Chakraborty S, Das T, Venkatesh M, Ramamoorthy N. Production logistics of ^{177}Lu for radionuclide therapy. *Appl Radiat Isot* 2003;59:109-18.
- Chakraborty S, Das T, Sarma HD, Venkatesh M, Banerjee S. Preparation and preliminary studies on ^{177}Lu -labeled hydroxyapatite particles for possible use in the therapy of liver cancer. *Nucl Med Biol* 2008;35:589-97.
- Firestone R. In: Shirly VS, editor. *Table of Isotopes*. 8th ed. New York: John Wiley; 1996. p. 2112-4.
- Abbasi IA. Studies on ^{177}Lu -labeled methylene diphosphonate as potential bone-seeking radiopharmaceutical for bone pain palliation *Nucl Med Biol* 2011;38:417-25.
- Abbasi IA. Preliminary studies on ^{177}Lu -labeled sodium pyrophosphate (^{177}Lu -PYP) as a potential bone-seeking radiopharmaceutical for bone pain palliation *Nucl Med Biol* 2012;39:763-9.

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