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Article

Production, quality control, biodistribution assessment and preliminary dose evaluation of [^{177}Lu]-tetra phenyl porphyrin complex as a possible therapeutic agent

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Due to interesting therapeutic properties of ^{177}Lu and tumor avidity of tetraphenyl porphyrins (TPPs), ^{177}Lu-tetraphenyl porphyrin was developed as a possible therapeutic compound. ^{177}Lu of 2.6-3 GBq/mg specific activity was obtained by irradiation of natural Lu_2O_3 sample with thermal neutron flux of 4×10^{13} n.cm^{-2}.s^{-1}. Tetraphenyl porphyrin was synthetized and labeled with ^{177}Lu. Radiochemical purity of the complex was studied using Instant thin layer chromatography (ITLC) method. Stability of the complex was checked in final formulation and human serum for 48 h. The biodistribution of the labeled compound in vital organs of wild-type rats was studied up to 7 d. The absorbed dose of each human organ was calculated by medical internal radiation dose (MIRD) method. A detailed comparative pharmacokinetic study was performed for ^{177}Lu cation and [^{177}Lu]-TPP. The complex was prepared with a radiochemical purity: >97±1% and specific activity: 970-1000 MBq/mmol. Biodistribution data and dosimetric results showed that all tissues receive approximately an insignificant absorbed dose due to rapid excretion of the complex through the urinary tract. [^{177}Lu]-TPP can be an interesting tumor targeting agent due to low liver uptake and very low absorbed dose of approximately 0.036 to the total body of human.

Uniterms: Radiopharmaceuticals/internal dosimetry. Lutetium-177. ^{177}Lu-tetraphenyl porphyrin/ biodistribution. Porphyrins/biodistribution. Medical internal radiation dose. MIRD.

Devido às propriedades interessantes do ^{177}Lu e da avidez tumoral das tetrafenil porfirinas (TPP), desenvolveu-se a ^{177}Lu-tetrafenil porfirina como composto terapêutico potencial. ^{177}Lu de atividade específica de 2,6-3 GBq/mg foi obtido por irradiação de amostra de Lu_2O_3 com fluxo térmico de nêutrons de 4×10^{13} n.cm^{-2}.s^{-1} . Sintetizou-se a tetrafenil porfirina e marcou-se com ^{177}Lu. A pureza radioquímica do complexo foi estudada usando método de Cromatografia Instantânea de Camada Delgada (ITLC). A estabilidade do complexo foi checada na formulação final e no ser humano por 48 h. A biodistribuição do composto marcado em órgãos vitais de ratos do tipo selvagem foi estudada por mais de 7 dias. A dose absorvida para cada órgão humano foi calculada pelo método da Dose Médica de Radiação Interna (MIRD). Estudo farmacocinético comparativo detalhado foi efetuado para o cátion ^{177}Lu e para o [^{177}Lu]-TPP. O complexo foi preparado com pureza radioquímica >97±1% e atividade específica de 970-1000 MBq/mmol. Os dados de biodistribuição e os resultados dosimétricos mostraram que todos os tecidos receberam uma dose absorvida aproximadamente insignificante devido à rápida excreção do complexo pelo trato urinário. O [^{177}Lu]-TPP pode ser um agente interessante de direcionamento do tumor devido à baixa captação pelo fígado e pela dose bem baixa absorvida, de, aproximadamente, 0,036 do corpo humano total.

Unitermos: Radiofármacos/dosimetria interna. Lutécio-177. ^{177}Lu-tetrafenil porfirina/biodistribuição. Porfirinas/biodistribuição. Dose Médica de Radiação Interna.

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INTRODUCTION

Nowadays, radiopharmaceuticals are widely used for diagnostic and therapeutic purposes. An ideal radiopharmaceutical should lead to substantially greater accumulation rate in the target organ while the accumulation in other organ should be as low as possible. Therefore, scientists have paid attention to new ligands to differentiate between malignant and normal cells (Sanderson *et al.*, 1972).

Porphyrin is a heterocyclic macrocycle derived from four pyrrole-like subunits that plays an important role in biological transfer systems. Various porphyrin complexes have shown interesting tumor-avid activity *in vitro* and *in vivo* (Subbarayan *et al.*, 2001; Das *et al.*, 2008; Bonnett, 1995; Jori, 1996).

Radiolabeled porphyrins have been developed for the therapeutic purposes such as, ^{109}Pd-protoporphyrins (Fawwaz *et al.*, 1974), ^{109}Pd-porphyrins (Fawwaz, Hemphill, Winchell, 1971), ^{109}Pd-derivitized porphyrins (Chakraborty *et al.*, 2007), ^{188}Re-porphyrins (Jia, Deng, Pu, 2007; Sarma *et al.*, 2010), ^{123}I-Porphyrins (Jae Hak *et al.*, 2007). Various radiolabeled porphyrin complexes such as ^{57}Co-porphyrins (Hambright *et al.*, 1976), ^{99m}Tc-porphyrin (Murugesan *et al.*, 2001; Wang, Lin, Lin, 2010), and ^{111}In-porphyrin (Fazaeli *et al.*, 2012) have also been introduced for imaging.

While the masive accumulation of ^{109}Pd-porphyrins was indicated in fibrosarcoma tumours (Chakraborty *et al.*, 2007), I-123-labeled porphyrin demonstrated high focal accumulation in the B16-F10 melanoma tumor (Jae Hak *et al.*, 2007). (^{188})Re-labeled 5,10,15,20-tetrakis[3,4-*bis*(carboxymethyleneoxy)phenyl]porphyrin has also shown specific affinity toward the fibrosarcoma and thymic lymphoma tumors in mice (Sarma *et al.*, 2010).

Accumulation of the radiolabeled prophyrins in tumour is dependent on various parameters such as porphyrin structure, choice of radioisotope, pH, the presence of inflammation and many other factors. However, the balance between hydrophilicity and lipophilicity is also recognized as an important factor in tumour accumulation. Whereas, lipophilicity of the agent plays an important role in tumor accumulation, hydrophilicity is a significant key in the clearance of the agent from the non-target organs. Therefore, a_balance between these two properties is necessary for developing a suitable agent and for contributing to the challenge in designing suitable derivatives of porphyrin (Das *et al.*, 2010).

^{177}Lu decays with a half life of 6.73 d by emission β^-particles with maximum energy of 497 keV (78.6%) and γ-photons of 112 keV (6.4%) and 208 keV (11%) to stable ^{177}Hf (TOI, 1993). Due to these good physical characteristics as well as the feasibility of large-scale production in adequate specific activity and radionuclidic purity using a moderate flux reactor, ^{177}Lu has been considered as a promising radionuclide for developing therapeutic radiopharmaceuticals due to its suitable half-life.

^{177}Lu-radiopharmaceuticals have been developed and used in the therapy of various diseases and malignancies, such as somatostatin receptor radiotherapy (Bodei *et al.*, 2009), radioimmunotherapy (Michel *et al.*, 2005), bone palliation therapy (Chakraborty *et al.*, 2008a) and radiosynovectomy (Chakraborty *et al.*, 2006; Chakraborty *et al.*, 2008b). ^{177}Lu-5,10,15,20-tetrakis[4-carboxymethyleneoxyphenyl] porphyrin have recently been developed and have shown active tumor uptake in mice bearing fibrosarcoma tumors (Das *et al.*, 2010).

According to the interesting pharmacological properties of porphyrins such as solubility in serum, rapid wash-out, tumor avidity and feasible complexation with various bi/tri-valent metals (Falk, 1975), the idea of developing a possible tumor targeting agent by incorporating ^{177}Lu into a suitable porphyrin ligand, *i.e.* $TPPH_2$ was investigated (Figure 1).

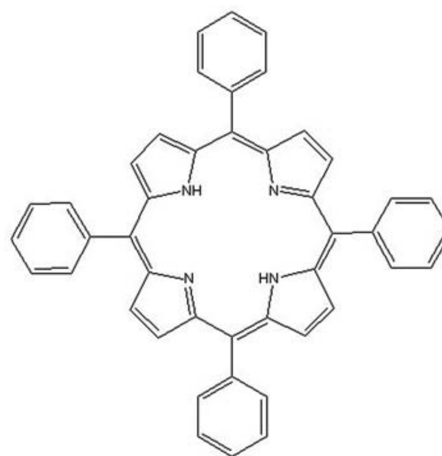

FIGURE 1 - Structure of $TPPH_2$.

As for the amount of energy uptake in any organs by ionizing radiation, the absorbed dose, plays an important role in evaluating the risks associated with the administration of radiopharmaceuticals and thus the maximum amount of activity that should be undertaken (Stabin *et al.*, 1999). In nuclear medicine, the most commonly used method for calculation of the internal dose estimates is the one developed by the medical internal radiation dose (MIRD) committee (Stabin, 1996)

summarized in MIRD primer (Loevinger, Budinger, Watson, 1988).

In this work, we endeavour to report, synthesis, radiolabeling, quality control and biodistribution studies of ^{177}Lu-TPP in wild-type rats. The time/decay diagrams for the labeled compound in vital organs were plotted compared to lutetium cation. Also the partition coefficient of the complex was calculated and the absorbed dose to each organ of human was evaluated by biodistribution studies in rats by MIRD method.

MATERIAL AND METHODS

^{177}Lu was produced at Tehran Research Reactor. Chemicals were purchased from the Aldrich Chemical Co. (Gemany). NMR spectra were obtained on a FT-80 Varian instrument (80 MHz) with tetramethylsilane as an internal standard. Infrared spectrum was measured on a Perkin-Elmer 781 spectrometer by means of a KBr disc. Mass spectrum was recorded by a Finnigan Mat TSQ-70 Spectrometer. Thin layer chromatography (TLC) for cold compounds was performed on polymer-backed silica gel (F 1500/LS 254, 20 × 20 cm, TLC Ready Foil, Schleicher & Schuell®, Germany). Normal saline and sodium acetate used for labeling were of high purity and had been filtered through 0.22 µm Cativex filters. Instant thin layer chromatography (ITLC) was performed by counting Whatman No. 2 papers using a thin layer chromatography scanner, Bioscan AR2000, Bioscan Europe Ltd. (France). Biodistribution data were obtained by counting normal saline washed tissues after weighing on a Canberra™ high purity germanium (HPGe) detector (model GC1020-7500SL). Radionuclidic purity was checked with the same detector. For activity measurement of the samples a CRC Capintech Radiometer (NJ, USA) was utilized. All calculations as well as tissue count were based on the 112 keV peak of ^{177}Lu. Animal studies were performed in accordance with the United Kingdom Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations, 2nd ed.

Production and quality control of $^{177}LuCl_3$ solution

^{177}Lu was produced by irradiation of natural Lu_2O_3 target (1 mg) at a thermal neutron flux of approximately 4×10^{13} n/cm^2.s for 5 days at Tehran Research Reactor (TRR) according to the reported procedures (Yousefnia *et al.*, 2011). The irradiated target was dissolved in 200 µL of 1.0 M HCl, to prepare $^{177}LuCl_3$ and diluted to the appropriate volume with ultra pure water, to produce a stock solution of final volume of 5 mL with approximately 2.8 GBq. The mixture was filtered through a 0.22 µm biological filter and sent for use in the radiolableing stage in the process. For radionuclidic purity determination, the sample was checked by gamma-ray spectroscopy on an HPGe detector for 5 h based on two major photons of ^{177}Lu (6.4% of 0.112 MeV and 11% of 0.208 MeV). The radiochemical purity of the $^{177}LuCl_3$ was checked using 2 solvent systems for ITLC (A: 10 mM DTPA pH.4 and B: ammonium acetate 10%:methanol (1:1)).

Preparation of Tetraphenyl Porphyrin ($TPPH_2$)

This compound was prepared according to the reported method using freshly distilled benzaldehyde, pyrrole and propionic acid followed by oxidation (Adler *et al.*, 1967). Yield; 20%, m.p.> 248-250 °C. ^{1}H NMR ($CDCl_3$) δ (ppm) –2.8 (2 H, NH), 7.71-7.82 (12 H), 8.14-8.27 (8 H), 8.85 (8 H). ^{13}C-NMR (CDCl3) δ (ppm) 120.20 (C), 126.74 (CH), 127.76 (CH), 131.16 (CH), 134.62 (CH), 142.22 (C), 145.6 (C).UV (toluene) λ_{max} (ε) = 418 nm (413200), 514 (19060), 549 (8080), 594 (5380), 648 (3870). IR (KBr) 3320, 3055, 3025, 1595.

Preparation of [^{177}Lu]-TPP

0.2 ml of $^{177}LuCl_3$ with 111 MBq radioactivity was transferred to a 5 mL-borosilicate vial and heated to dryness by using a flow of N_2 gas at 50-60 °C, followed by the addition of fifty microliters of TPP in absolute ethanol (1 mg/mL ≈ 81 nmoles) and 450 microliters of acetate buffer pH 5 (0.1 M). The mixture vortexed at 25 °C for 4 h. The final solution was then passed through a 0.22 µm filter and the radiochemical purity was checked by ITLC. For this purpose, 5 µL of the final solution was spotted on a chromatography Whatman No. 2 paper, and developed in two mobile phase mixtures, A: water:acetonitrile (3:1) and B: water:acetonitrile (1:3).

Determination of partition coefficient

Partition coefficient (log P) of [177Lu]-TPP was calculated. A mixture of 1 mLof 1-octanol and 1 mL of isotonic acetate-buffered saline (pH 7) containing approximately 3.7 MBq of the radiolabeled complex at 37 °C was vortexed 1 min and left 5 min. Following centrifugation at >1200 g for 5 min, the octanol and aqueous phases were sampled and counted in an automatic well-type counter. A 500 µL sample of the octanol phase from this experiment was shaken again thrice with fresh buffer samples. The reported log P values are the average

of the second and third extractions from three to four independent measurements.

Stability tests

The stability of the complex was checked according to the conventional ITLC method. A sample of [^{177}Lu]-TPP (37 MBq) was kept at room temperature for 2 days while being checked by ITLC at time intervals in order to check stability in final product using above chromatography system. For serum stability studies, to 36.1 MBq of [^{177}Lu]-TPP was added 500 µL of freshly collected human serum and the resulting mixture was incubated at 37 °C for 5 h; Aliquots (5 µL) were analyzed by ITLC.

Biodistribution in wild-type rats

The distribution of ^{177}Lucl$_3$ and the radiolabeled complex among tissues were determined for wild-type rats. 50–100 µL of ^{177}Lu-TPP or ^{177}LuCl$_3$ solutions with 1.85 MBq radioactivity were injected intravenously via their tail veins. The total amount of radioactivity injected into each rat was measured by counting the 1 mL syringe before and after injection in a dose calibrator with fixed geometry. The animals were sacrificed by CO_2 asphyxiation at selected times after injection (2, 4, 24, 48, 120 and 168 h). The tissues (blood, heart, lung, brain, intestine, feces, skin, stomach, kidneys, liver, muscle and bone) were weighed and rinsed with normal saline and their specific activities were determined with an HPGe detector equipped with a sample holder device as percent of injected dose per gram of tissues.

Dosimetric studies

The absorbed dose of each human organ was calculated by MIRD method based on biodistribution data in wild-type rats. The accumulated activity in animals was extrapolated to the accumulated activity in humans by the proposed method of Sparks *et al.* (eq. 1) (Sparks, Aydogan, 1996).

$$\tilde{A}_{\text{human organ}} = \tilde{A}_{\text{animal organ}} \frac{\text{OrganMass}_{\text{human}} / \text{BodyMass}_{\text{human}}}{\text{OrganMass}_{\text{animal}} / \text{BodyMass}_{\text{animal}}} \quad (1)$$

where $\tilde{A}$ is the accumulated activity in the source organs and can be calculated by the equation 2.

$$\tilde{A} = \int_{t_1}^{\infty} A(t)\, dt \quad (2)$$

It should be noticed that A (t) is the activity of each organ at time t.

The accumulated source activity for each organ of animals was calculated by plotting the percentage-injected dose versus time for each organ and computing the area under the curves. For this purpose, the data points which represent the percentage-injected dose were created. The curves were extrapolated to infinity by fitting the tail of each curve to a monoexponential curve with the exponential coefficient equal to physical decay constant of ^{177}Lu. Then the area under the curve was calculated. In order to extrapolate this accumulated activity to human, the mean weights of each organ for standard human were used (Table I).

TABLE I - The mean weights of organs for human with standard weight (ICRP 89, 2001)

Organ	Weight (g)
Bone	5500
Heart	330
Stomach	150
Kidneys	310
Small intestine	650
Spleen	150
Muscle	29000
Liver	1800
Lung	500
Total body	73000

The radiation absorbed dose was calculated by MIRD formulation (Henrichs, Kaul, Roedler, 1982):

$$D(r_k) = \sum_h \tilde{A}_h \times S(r_k \longleftarrow r_h) \quad (3)$$

where $D(r_k)$ is the absorbed dose of the target organ, and $S(r_k \longleftarrow r_h)$ called S factor which is defined as the mean absorbed dose to the target region r_k per unit accumulated activity in the source region r_h. S factor represents the physical decay characteristics of the radionuclide, the range of the emitted radiations, and the organ size and configuration (Bevelacqua, 2005) expressed in mGy/MBq.s. The S factors have been taken from the OLINDA software (OLINDA, 2007).

RESULTS AND DISCUSSION

Radionuclide production

The radionuclide was prepared in a research reactor according to the regular methods with a range of specific

activity 2.6-3 GBq/mg for radiolabeling use. The obtained radionuclidic purity was 99.98% (Figure 2). Furthermore, half-life of the ^{177}Lu was also studied by counting the sample at different time intervals. The decay scheme for the radionuclide is shown in Figure 3.

The radioisotope was dissolved in acidic media as a starting sample and was further diluted and evaporated for obtaining the desired pH and volume followed by sterile filtering. The radiochemical purity of the ^{177}Lu solution was checked in two solvent systems: in 10 mM DTPA, free Lu^{3+} cation as a complex in more lipophilic LuDTPA form migrates to higher R_f, while small radioactive fraction remains in its origin which could be related to other Lu ionic species, not forming LuDTPA complex, such as $LuCl_4^-$, etc. and/or colloids.

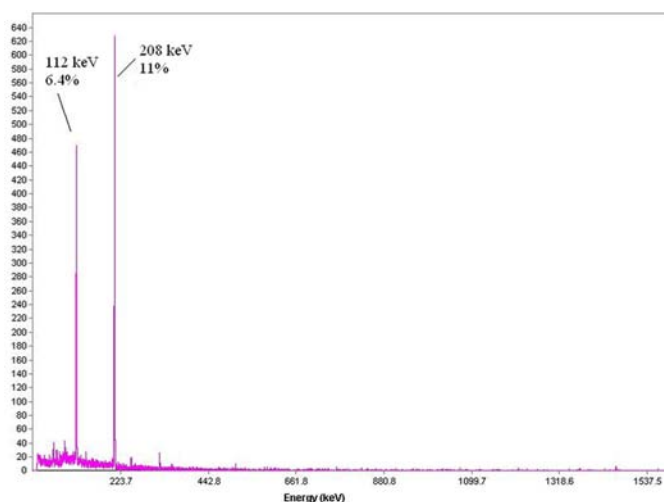

FIGURE 2 - Gamma-ray spectrum for $^{177}LuCl_3$ solution used in this study.

On the other hand, 10% ammonium acetate:methanol mixture was also used for the determination of radiochemical purity. In this solvent system, the fast eluting species were possibly Lu-177 cations, other than Lu^{3+} and the remaining fraction at R_f.0 was a possible mixture of Lu^{3+} and/or colloids. The difference in values of impurity in two solvent systems is possibly due to the presence of colloidal impurity in the sample (Figure 4).

Preparation of [^{177}Lu]- TPP

The synthetic scheme for radiolabeling of TPP with $^{177}LuCl_3$ is demonstrated in Figure 5. Because of the engagement of NH polar functional groups in its structure, labeling of TPPH2 with lutetium cation affects its chromatographic properties and the final complex is more lipophilic. Two different chromatographic systems were used. Using water/acetonitrile (1:3) mixture, free lutetium remains in its origin of the paper as a single peak,

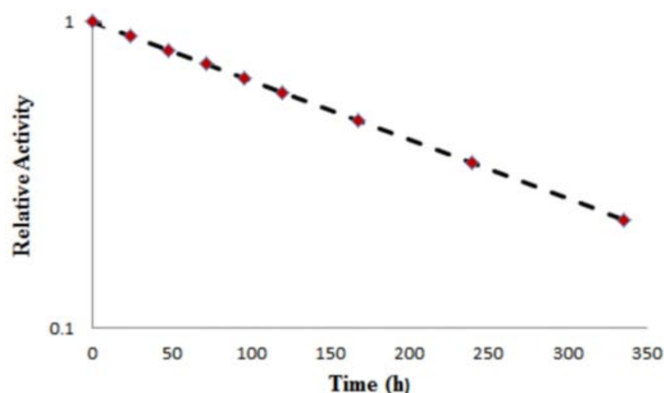

FIGURE 3- Decay scheme for ^{177}Lu used in this study.

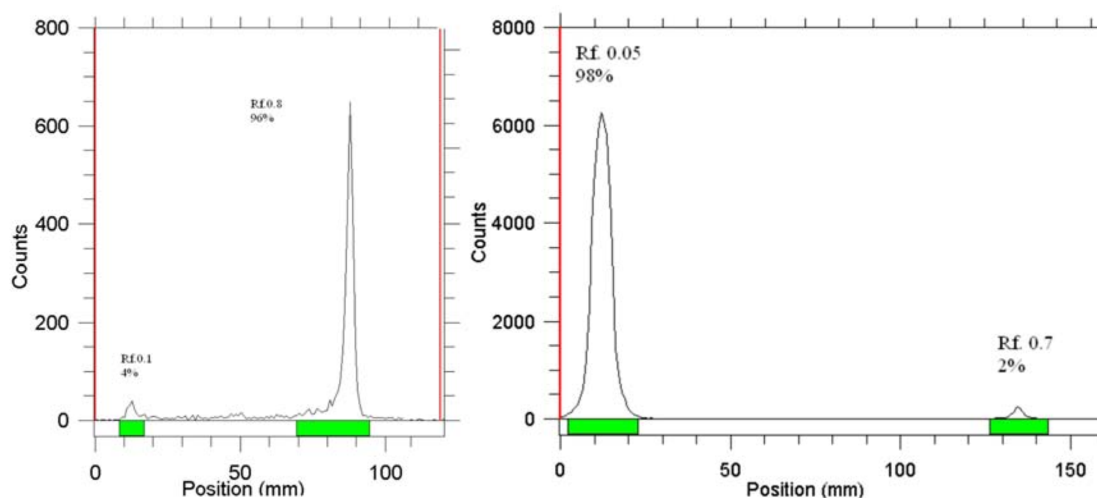

FIGURE 4 - ITLC chromatograms of $^{177}LuCl_3$ solution in DTPA solution (pH. 4) (left) and 10% ammonium acetate:methanol (1:1) solution (right) using Whatman No. 2.

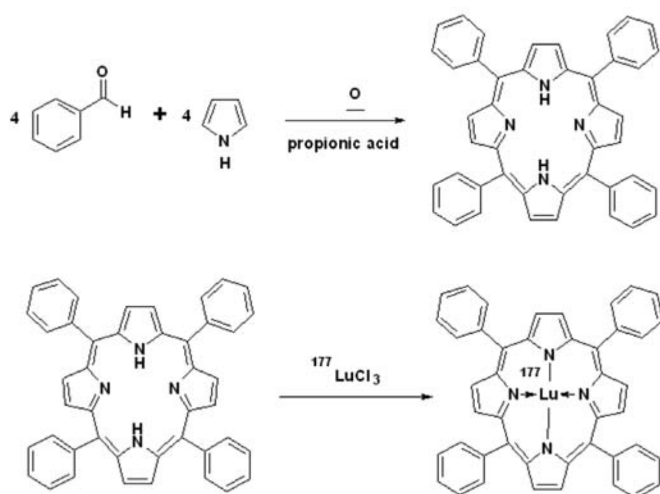

FIGURE 5 - Synthetic scheme for radiolabeling of TPP with $^{177}LuCl_3$.

while the radiolabeled compound migrates to higher R_f. Using a more polar mobile phase, acetonitrile:water (1:3), free lutetium cation migrated to a higher R_f, while the radiolabeled compound remained at the origin (Figure 6).

Partition coefficient

As expected, the lipophilicity of the [^{177}Lu]-TPP compound is rather high. The measured octanol/water partition coefficient, P, for the complex was found to depend on the pH of the solution. At the pH 7, the log P was 1.63.

Stability

The stability of [^{177}Lu]-TPP prepared complex at room temperature was checked up to 48 hours. The radiochemical purity of the complex remained at 98% for 2 days. Also the stability of the complex was determined at 37 °C for 48 h and the data were almost consistent with the final solution stability.

Biodistribution studies of $^{177}LuCl_3$ and ^{177}Lu-TPP in wild-type rats

The animals were sacrificed by CO_2 asphyxiation at selected times after injection (2, 4, 24, 48 and 168 h). The biodistribution data show that the liver uptake of

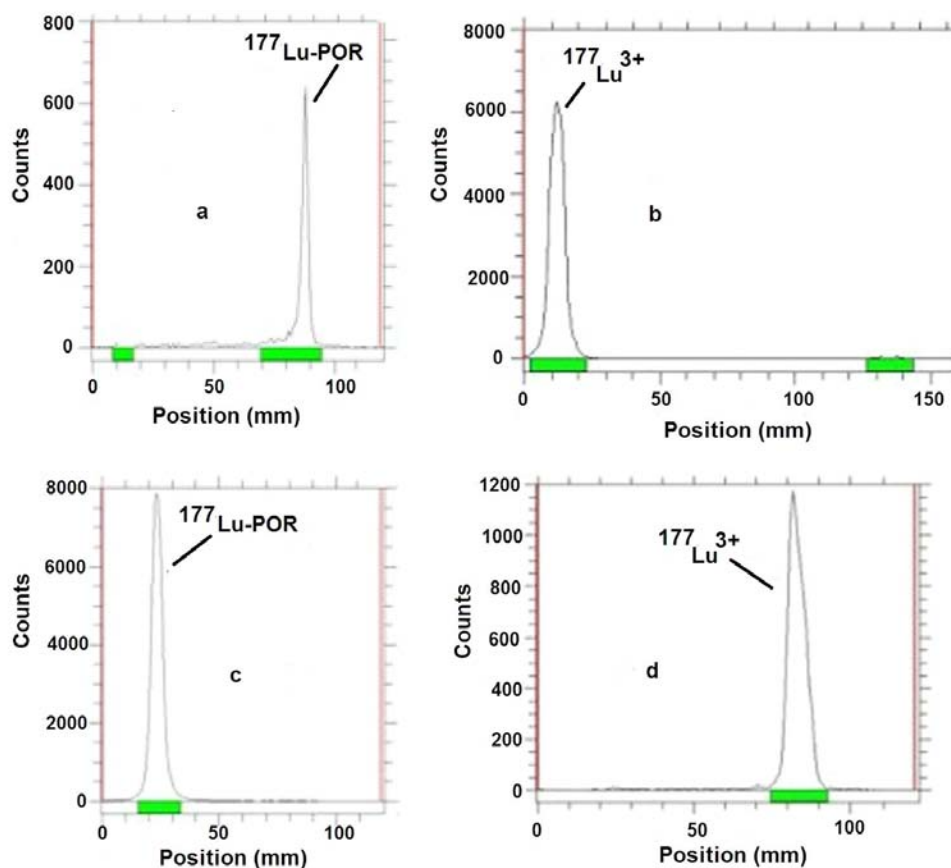

FIGURE 6 - ITLC chromatograms of $^{177}LuCl_3$ and ^{177}Lu-TTP on Whatman No. 2 paper using water:acetonitrile (1:3) [up (a & b)] and acetonitrile:water (1:3) [down (c & d)] mixtures.

the cation is comparable to many other radio-metals mimicking ferric cation accumulation; about 3% of the activity accumulates in the liver after 48 h. Binding of ^{177}Lu by transferrin and transport to the liver appears to be the route of accumulation (Figure 7).

As it can be seen from Figure 5, the blood content is low at all time intervals, which shows the rapid removal of activity in the circulation. The lung, muscle and also skin do not demonstrate significant uptake while it is in accordance with other cations accumulation. A 5% bone uptake is observed for the cation at 168 h. The spleen also has uptake (1%) possibly related to reticuloendothelial uptake. The kidney plays an important role in ^{177}Lu cation excretion especially after 24 h (1%). Biodistribution of ^{177}Lu-TPP in different organs of wild-type rats is shown in Figure 8.

Comparison of vital organs uptake for ^{177}Lu-TPP and $^{177}LuCl_3$ demonstrates kinetic pattern difference for both species. ^{177}Lu cation is accumulated in the liver within the first 24 h post injection slightly, while ^{177}Lu-TPP second major excretion route is through the liver and slow uptake of less than 1% is observed in 168 h for the radiolabeled compound (Figure 9).

Intestinal activity increases in $^{177}Lu^{3+}$ after 7 days as a consequence of the liver excretion through GI tract, however, in case of Lu porphyrin, the amount of activity

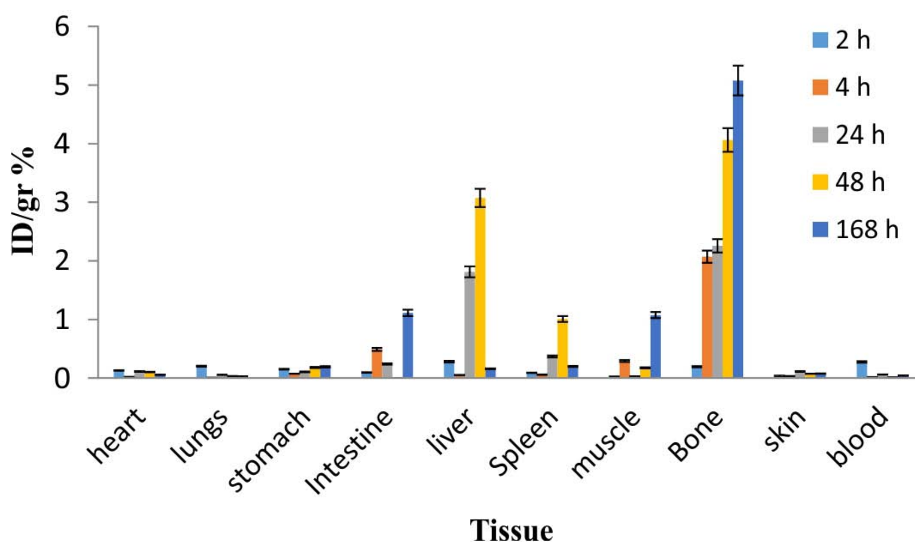

FIGURE 7 - Percentage of injected dose per gram (ID/g%) of $^{177}LuCl_3$ in wild-type rat tissues at 2, 4, 24, 48 and 168 h post injection (ID/g%: percentage of the injected dose per gram of tissue calculated based on the area under curve of 112 keV peak in gamma spectrum) (n=5).

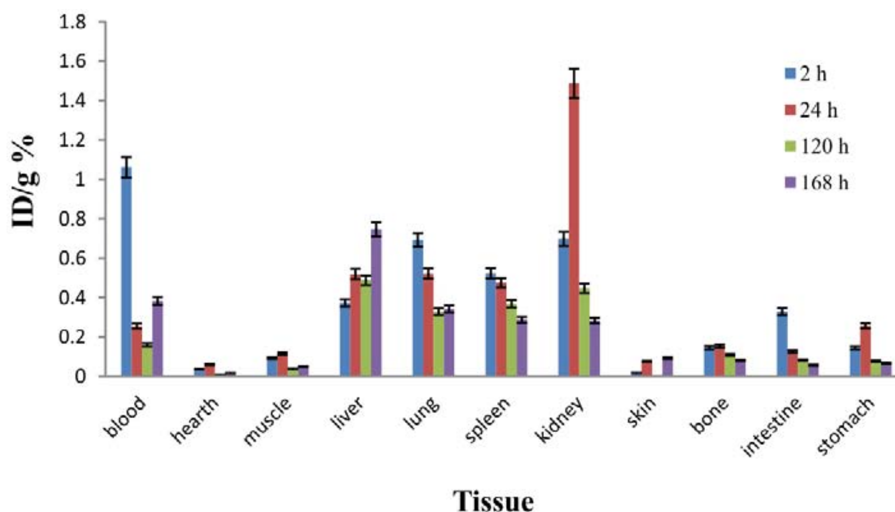

FIGURE 8 - Biodistribution of [^{177}Lu]-TPP (1.85 MBq) in wild type rats 2, 24, 120 and 168 h after iv injection via tail vein (ID/g%: percentage of injected dose per gram of tissue calculated based on the area under curve of 112 keV peak in gamma spectrum) (n=5)

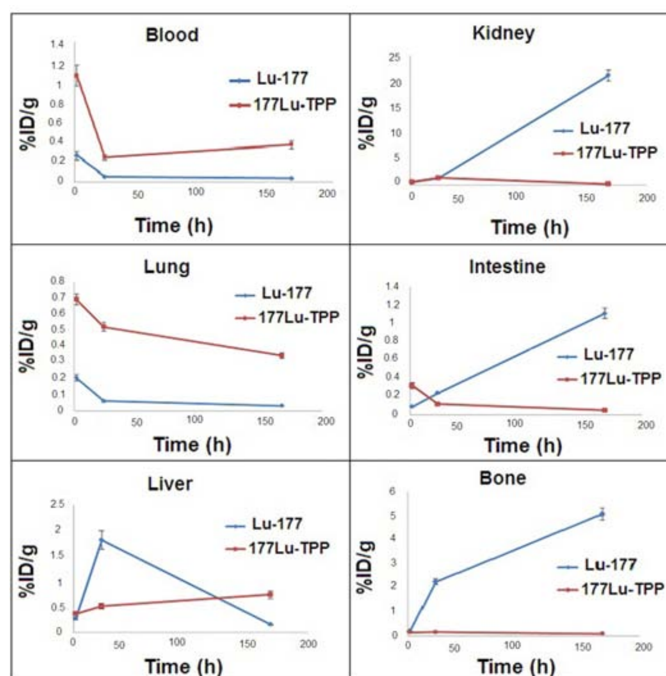

FIGURE 9 - Comparative organ uptake of $^{177}LuCl_3$ and ^{177}Lu-TPP in wild-type rats.

decreases due to the low liver uptake compared with urinary excretion. As shown earlier, ^{177}Lu cation is slightly absorbed in the skeletal system (5%) while the labeled compound almost shows no uptake in the bone.

Since the urinary tract is a major route of excretion of the porphyrins, the amount of the kidney activity is maximum for the labeled compound especially after 24 h, however in 7days major urinary excretion is observed in free cation. The circulation wash-out for the labeled compound is observed while a lesser amount of activity in blood is observed for free Lu cation.

Dosimetric studies

Dosimetric evaluation in human organs was made by MIRD method based on biodistribution in rat organs. The clearance curves from each organ of the rats are shown in Figure 10. The absorbed dose in each organ of human after injection of ^{177}Lu-TPP is given in Table Π.

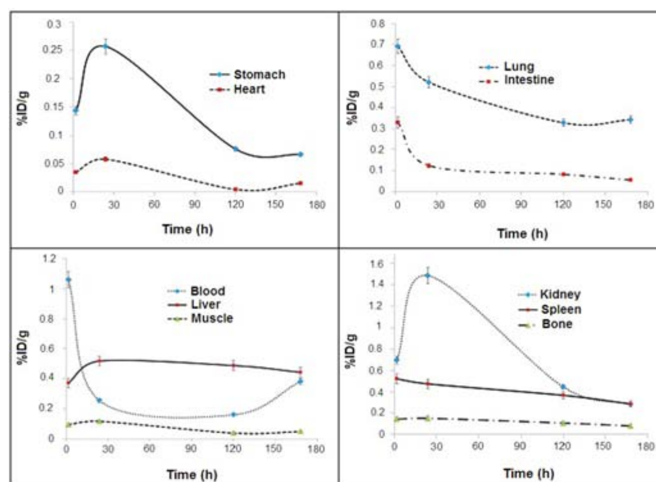

FIGURE 10 - The clearance curves from each organ of the rats.

TABLE Π - Absorbed dose in each organ of human after injection of ^{177}Lu-TPP

Organ	Absorbed Dose (mSv/MBq)	Organ	Absorbed Dose (mSv/MBq)
Adrenals	0.005	Ovaries	0.003
Brain	0.001	Pancreas	0.005
Breasts	0.001	Red Mar.	0.069
GB Cont.	0.006	Cort Bone Sur.	0.081
LLI Cont.	0.101	Trab. Bone Sur.	0.105
SI Cont.	0.003	Cort Bone Vol.	0.039
Stom. Cont.	0.036	Trab. Bone Vol.	0.099
ULI Cont.	0.003	Spleen	0.149
Heart Cont.	0.007	Testes	0.001
Heart Wall	0.015	Thymus	0.002
Kidneys	0.313	Thyroid	0.002
Liver	0.233	UB Cont	0.002
Lungs	0.089	Uterus	0.002
Muscle	0.033	Tot. Body	0.036

CONCLUSION

Total labeling and formulation of [^{177}Lu]-TPP took about 4 h (radiochemical purity: >97 ± 1% ITLC, specific activity, 970-1000 MBq/mmol). The complex was stable in final formulation and human serum at least for 24 h. The biodistribution of the labeled compound in vital organs of wild-type rats was studied up to 7 days post injection. The accumulation of the tracer in other tumor models is under investigation due to the low liver uptake and rapid excertion through the urinary tract. Biodistribution data and dosimetric results showed that all tissues receive virtually insignificant absorbed dose due to rapid excretion of the complex through the urinary tract. [^{177}Lu]-TPP can be an interesting tumor targeting agent due to the low liver uptake and very low absorbed dose of approximately 0.036 mSv/MBq to the total body of human.

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