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# Production, quality control, and biodistribution studies of $^{141}$Ce-EDTMP as a potential bone pain palliation agent

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## ABSTRACT

The purpose of the present work was to introduce $^{141}$Ce-EDTMP as a novel potential future pain palliative agent to patients suffering from disseminated skeletal metastases and diagnostic imaging radioisotope as well. Cerium-141 [$T_{1/2}$ = 32.501 days, $E_{\beta}$ (max) = 0.580 (29.8%) and 0.435(70.2%) MeV, $E_{\gamma}$ = 145.44 (48.2%) keV] possesses radionuclidic properties suitable for use in palliative therapy of bone metastases. $^{141}$Ce also has gamma energy of 145.44 keV, which resembles that of $^{99m}$Tc. Therefore, the energy window is adjustable on the Tc-99m energy because of imaging studies. $^{141}$Ce can be produced through a relatively easy route that involves thermal neutron bombardment on natural $CeO_2$ in medium flux research reactors (4–5×$10^{13}$ neutrons/cm$^2$·s). The requirement for an enriched target does not arise. Ethylenediamine (tetramethylene phosphonic acid) (EDTMP) was synthesized and radiolabeled with $^{141}$Ce. The experimental parameters were optimized to achieve maximum yields (>99%). The radiochemical purity of $^{141}$Ce-EDTMP was evaluated by radio-thin layer chromatography. The stability of the prepared formulation was monitored for one week at room temperature, and results showed that the preparation was stable during this period (>99%). Biodistribution studies of the complexes carried out in wild-type rats exhibited significant bone uptake with rapid clearance from blood. The images showed high uptake of complex in bone after 72h and 2 weeks clearly. The percentage injected dose per gram of tissue (%ID/g) for each organ or tissue was calculated. The results show significant bone uptake with rapid clearance from blood. The properties of produced $^{141}$Ce-EDTMP suggest applying a new efficient bone pain palliative therapeutic agent to overcome metastatic bone pains.

Conflicts of Interest: Declared None
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**Keywords**
Cerium-141,
Bone pain palliative,
EDTMP,
Radiopharmaceutical,
Biodistribution

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## INTRODUCTION

Bone metastasis can lead to various complications, including fractures, hypercalcemia, and bone pain, as well as reduced performance and quality of life. Various radiopharmaceuticals are efficient in relieving bone pain, which is secondary to bone metastasis. These radioactive agents that are administered intravenously localize specifically to reactive bone sites and deliver radiation to metastatic sites in a highly focal manner because of the nature of the radioactivity emitted (typically beta/electron emission). Application of radioactive agents has been associated with improved mobility in many patients; reduced dependence on narcotic and non-narcotic analgesics, improved performance and quality of life, and in some studies, improved survival. All of these agents can be used alone or in combination with other forms of treatment [1-4].

Particle-emitting bone-seeking radiopharmaceuticals have attracted the attention of the nuclear medicine community over the last three decades for the treatment of pain resulting from osteoblastic metastases. Published data on clinical trials in humans are available for the eight pharmaceuticals, namely, $^{188}$Re(Sn)HEDP, $^{153}$Sm-ethylenediamine (tetramethylene phosphonic acid) (EDTMP), $^{90}$Y-Citrate, $^{186}$Re(Sn)HEDP, $^{117m}$Sn-DTPA, $^{32}$P-phosphate, $^{89}$Sr-chloride, and $^{85}$Sr-chloride. These pharmaceuticals are reactor-produced and emit a beta particle, except for (Sn)-117 pentetate and strontium-85 (Sr-85), which produce low energy conversion electrons. The major advantage of $^{89}$SrCl2 and $^{153}$Sm-EDTMP is Management of metastatic bone pain that decrease the quality of life. Longer half life of $^{89}SrCl_2$ compare to $^{153}$Sm-EDTMP allow to supply this radiopharmaceutical worldwide. Despite the desirable features of $^{153}$Sm, the relatively short half-life of $^{153}$Sm restricts the usage of it in places far away from the reactors. Many investigators because of the more favorable radionuclidic properties of $^{153}$Sm prefer $^{153}$Sm-EDTMP. However, the relatively short half-life of $^{153}$Sm precludes its use from places other than those in close proximity or well-connected to the production site [5-12]. $^{177}$Lu-EDTMP and other phosphonates are also proposed as alternatives to $^{153}$Sm-EDTMP for their long half-life [13-22].

$^{141}$Ce decays to stable $^{141}$Pr by emission of β-particles with the maximum energy of 0.58 MeV. The β-energy of $^{141}$Ce is significantly lower than that of $^{89}$Sr; hence, the bone marrow dose is expected to be much lower. The presence of accompanying gamma photons, which can be imaged using widely available gamma camera systems, is advantageous in carrying out simultaneous dosimetry and scintigraphy studies. $^{141}$Ce can be produced through a relatively easy route that involves thermal neutron bombardment on natural Cerium oxide in medium flux research reactors [23,29]. The requirement for an enriched target does not arise, and radionuclidic impurities are not formed by radiative capture during neutron activation [30]. $^{141}$Ce-ethylenediaminetetra-methylinephosphonic acid agent has been introduced for the effective palliative treatment of skeletal metastases [31]. This type of phosphonate complexes concentrate in the skeleton in proportion to osteoblastic activity [9]. This paper reports the preparation, quality control, and biodistribution studies of $^{141}$Ce-EDTMP complex following imaging to prepare the entry of a new therapeutic radiopharmaceutical in clinical applications in the country.

## MATERIALS AND METHODS

### *Material*

Cerium oxide (spectroscopic grade N99.99% pure) was obtained from E. Merck (Darmstadt, Germany). EDTMP was synthesized and characterized in-house as per reported procedure. All other chemicals were of analytical grade and purchased from established manufacturers. A Whatman 3 MM chromatography paper (UK) was used as the stationary phase. The radiochemical purity of gamma-spectroscopy on the base of 145.44 keV peak was carried out using the HPGe detector. All chemicals were purchased from Sigma-Aldrich Chemical Co. UK. Radio-chromatography was performed by counting Whatman 3 MM using a thin layer chromatography scanner (Bioscan AR2000; Paris, France). Animal studies were performed in accordance with the United Kingdom Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations, 2$^{nd}$ edn.

### *Synthesis of EDTMP*

EDTMP was synthesized by following a Mannich-type reaction [24] using orthophosphorus acid, 1,2-ethylenediamine, and formaldehyde in strongly acidic medium. In a typical reaction, 1,2-ethylenediamine (5 g, 0.08 mol) was added slowly to a solution of anhydrous orthophosphorus acid (33.66 g, 0.34 mol) in concentrated HCl (33.44 g, 0.92 mol), and the mixture was allowed to reflux. Formaldehyde 37% (10 g, 0.01 mol) was added dropwise for 15 min to the fluxing mixture. Refluxing was continued for another 2 h, and the mixture was then cooled to room temperature overnight. The resultant was added to ethanol, and EDTMP was precipitated in ethanol. The precipitate was filtered under vacuum and was dried in an oven at 60 °C. The precipitate was then purified after recrystallization from water/methanol m.p. 214–215 °C. IR (KBr, ν $cm^{-1}$): 3308, 2633, 2311, 1668, 1436, 1356. $^{1}$H-NMR ($D_2O$, δ ppm): 3.53 (d, J = 12.3 Hz, 8H,-N-$CH_2$-P = O), 3.85 (s, 4H, -N-$CH_2$-). $^{13}$C NMR ($D_2O$, δ ppm): 51.63, 52.73. $^{31}$P NMR ($D_2O$, δ ppm): 10.52 [21,22,31,232].

### *Production of $^{141}$Ce*

$^{141}$Ce was produced by thermal neutron bombardment on natural $CeO_2$ at the Tehran Research Reactor (TRR) for a period of 7 d at a flux of 4–5 × $10^{13}$ neutrons/$cm^2$.s. In a typical procedure, 50 mg of $CeO_2$ was sealed and irradiated in the reactor after placing it inside an aluminum can. The irradiated powder was cooled for two days and then dissolved in 2 ml of a 1:1 mixture of 30% $H_2O_2$ and 6 M nitric acid heated at 90 °C until all the powder was completely dissolved. The resultant activity was equal to 20 mCi. Heat was then used to take the target to dryness. HCl (2 ml, 0.05 M) was added once the solution was close to dryness. This process was repeated three times to ensure the removal of all nitric acid. The final dissolution was performed with 500 µl of 0.05 M HCl [20]. This

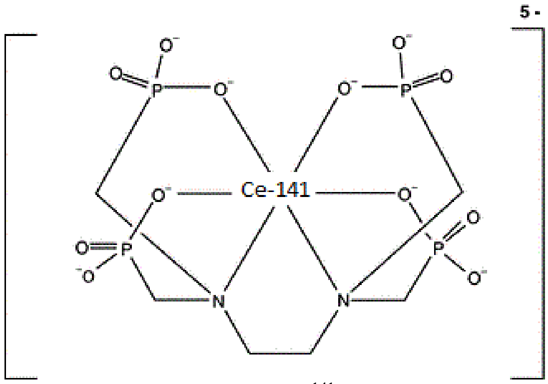

Figure 1. Chemical structure of $^{141}$Ce-EDTMP

radiochemical form was used for the subsequent studies. The radionuclidic purity of the solution was tested for the presence of other radionuclides using HPGe spectroscopy to detect various interfering beta- and gamma-emitting radionuclides.

### *Preparation of $^{141}$Ce-EDTMP complex*

A stock solution of EDTMP was prepared by dissolving EDTMP (250 mg) in $NaHCO_3$ buffer (5 ml, pH .9). A portion of this solution (1.5 ml of 250 mg/ml EDTMP) was used for the complexation of $^{141}$Ce. The pH of the reaction mixture was adjusted to 7, and the mixture was incubated at room temperature for 15 min to facilitate complexation (Fig.1).

The radiochemical purity of the preparation was determined by paper chromatography using two systems. Ammonia/methanol/water (2:20:40 v/v) and Whatman 3 MM were used as eluting solvent and stationary phase for paper chromatography, respectively.

### *Stability of $^{141}$Ce-EDTMP in final formulation*

The final formulation was stored at 25 °C for seven days to determine the stability. The radiochemical purity of the complex was investigated by frequent ITLC analyses using the aforementioned system.

### *Stability of $^{141}$Ce-EDTMP in the presence of human serum*

To determine the stability of the final formulation in human serum, we incubated 50 µCi–60 µCi (100 µl) of complex ($^{141}$Ce-EDTMP) in the freshly prepared human serum (500 µl) at 37 °C. The stability was determined by performing frequent ITLC analyses using the aforementioned system.

### *Biodistribution studies in rats*

Biodistribution studies of the $^{141}$Ce-EDTMP complex were carried out in wild-type rats weighing 190 g–250 g. A volume of 100 µl containing 100 µCi of radioactivity was injected via the lateral tail vein. The animals were sacrificed at 2 h, 4 h, 48 h, 1 week, and 1 month post-injection (pi). The tissue and organs were excised, and the activity associated with each organ/tissue was measured in a flat-type NaI (Tl) scintillation counter. The uptake in different organs/tissues was calculated from these data and expressed as % injected dose (% ID/gram).

### *Scintigraphic studies in rats*

The distribution pattern of $^{141}$Ce-EDTMP complex was determined by carrying out scintigraphic imaging studies in wild type Wistar rats weighing 190 g–250 g. Complex solution (100 µl, 100 µCi) and free $^{141}$Ce were injected via the tail vein. Scintigraphic images were recorded at 72 h pi for the $^{141}$Ce-EDTMP injected into the rats by a single-head SPECT system (Siemens) based on 145.44 keV peak. The rat-to-septa distance was 12 cm.

## RESULT

### *Production and quality control of $^{141}$Ce*

Irradiation of natural $CeO_2$ was performed at a thermal neutron flux of 4–5 × $10^{13}$ neutrons/cm$^2$.s for 7 d at TRR, and the radionuclide was prepared according to regular methods with a specific activity of 11.1-14.8 MBq/mg (0.3–0.4 mCi/mg) for radiolabeling use. The gamma ray spectrum of the appropriately diluted $^{141}CeCl_3$ solution showed a major peak at 145.44 keV, which is the photo-peak of $^{141}$Ce, and a minor peak at 293 keV, which is the photo-peak associated with the $^{143}$Ce decay (Fig. 2). The radioisotope was dissolved in acidic media as a starting sample, further diluted and evaporated to obtain the desired pH and volume,

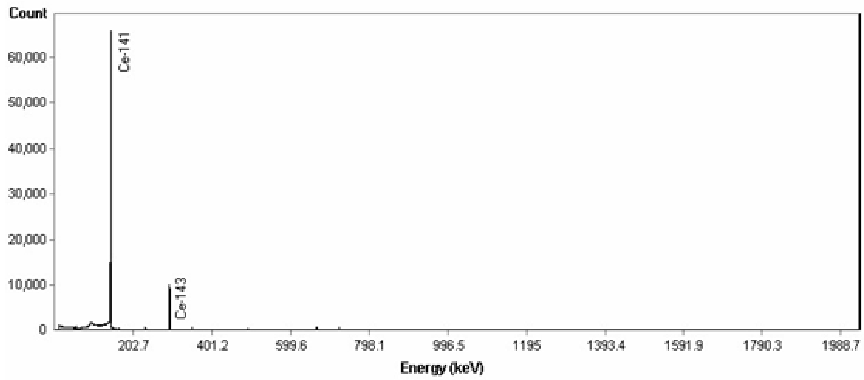

Figure 2. γ-ray spectra for $^{141}$Ce chloride solution

and sterile filtered. Ce-143 was produced as a radionuclidic impurity formed by radiative capture during neutron activation of natural target. The ratio of Ce-143 to Ce-141 can be decreased to an acceptable value by increasing the irradiating time to one month and cooling time to one week. Consequently, the absence of any other photo-peaks in the gamma ray spectrum indicated that the $^{141}Ce$ was produced with a radio-nuclidic purity of >90% [23]. The radiochemical purity of the $^{141}Ce$ solution was evaluated in a solvent system using ammonia/methanol/water (2:20:40 v/v) as solvent and Whatman 3MM as stationary phase. The results showed that $^{141}Ce$-EDTMP was in lipophilic form and migrated to high $R_f$. Figs. 2a and b show ITL chromatography.

### *Preparation of $^{141}Ce$-EDTMP complex*

Various parameters, such as ligand concentration, temperature, pH of reaction, and time, were varied to reach the maximum complexation.

Complexation gradually increased with the increase in ligand concentration and reached ~100% at a ligand to metal ratio of ~20:1. On the variation of reaction pH from 4 to 10, a maximum complexation yield of >99% was achieved at a pH range of 7 to 9. *In vitro* stability studies were performed by incubating the complex at room temperature and showed that the radiochemical purity of the complex remained >96% up to 1 week after preparation. In paper chromatography using ammonia/methanol/water (2:20:40 v/v) as solvent and Whatman 3MM as stationary phase, the $^{141}Ce$-EDTMP complex moved toward the solvent front ($R_f$ = 0.9–1) and the uncomplexed $^{141}Ce$ remained at the point of spotting ($R_f$ = 0) under identical conditions (Figs. 3a and 3b). The stability of $^{141}Ce$-EDTMP complex was monitored up to one week after preparation. The complex was stable in the final sample and its radiochemical purity was above 99% even up to 4 weeks after preparation using Whatman 3MM eluted with ammonia/methanol/water (2:20:40 v/v). Stability test was developed for the complex in the presence of human serum at 37 °C using ITLC as aforementioned (Fig. 4).

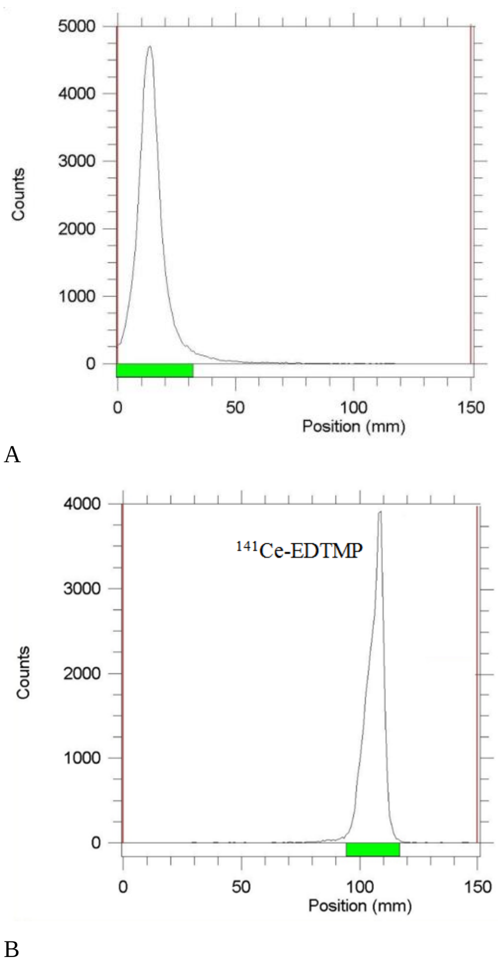


Figure 3. TLC-chromatogram of (a) $^{141}CeCl_3$ and (b) $^{141}Ce$-EDTMP solutions in $NH_4OH/MeOH/H_2O$:2/20/40, Whatman 3 MM.

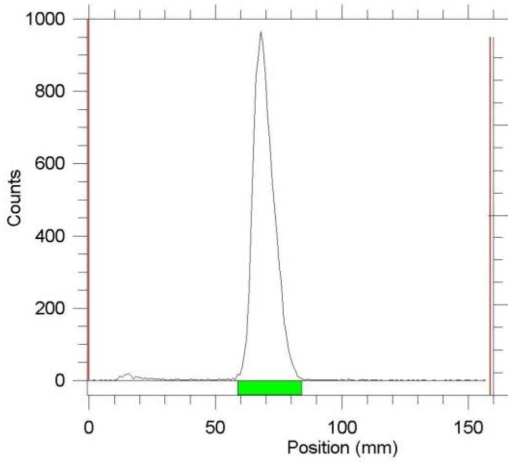


Figure 4. TLC-chromatogram of $^{141}Ce$-EDTMP in the presence of human serum at 37 °C using $NH_4OH/MeOH/H_2O$:2/20/40, Whatman 3 MM

### *Biodistribution studies in rats*

The animals were sacrificed by $CO_2$ asphyxiation at 2 h, 4 h, 48 h, 1 week, and 1 month pi. Dissection began by drawing blood from the aorta, followed by removing the heart, spleen, bone, kidneys, liver, intestine, and stomach and lungs. The tissue uptakes were calculated as the percent of area under the curve of the related photo peak per gram of tissue (% ID/g).

The biodistribution of $^{141}Ce$ cation was determined in wild-type animals for 2 h–48 h and 1 week pi (Fig. 5).

The liver uptake of the cation was comparable to many other radio-lanthanides mimicking calcium cation accumulation. The blood content was low at all-time intervals, indicating the rapid removal of activity in the circulation. The lung did not demonstrate significant uptake, but was in accordance with other cation accumulation rates. Bone uptake for the cation increased up to 1.1% up to 4 h and then decreased to 0.7% in one week. The spleen exhibited relatively significant uptake, which was possibly related to reticuloendothelial uptake. $Ce^{3+}$ is a water soluble

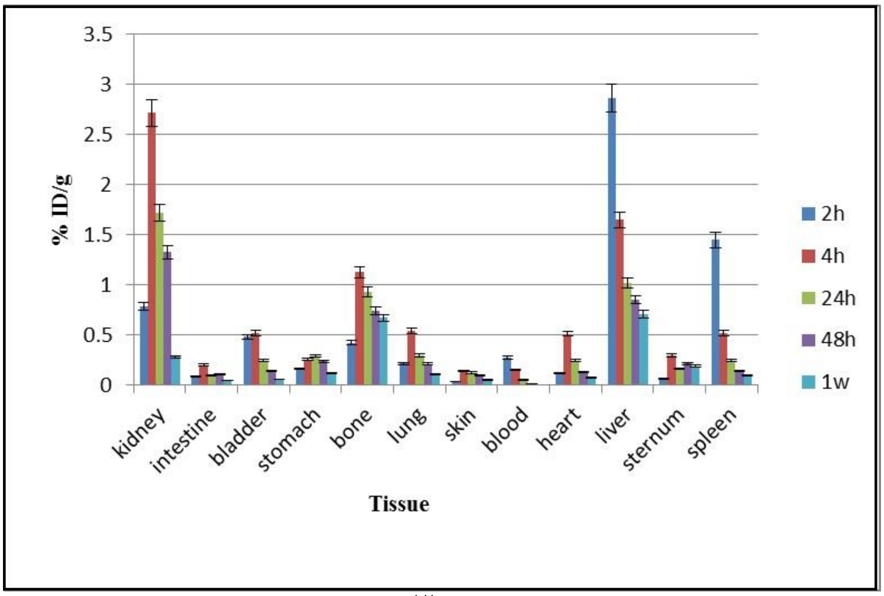


Figure 5. Percentage of injected dose per gram (ID/g %) of free $^{141}$Ce in wild-type rat tissues at 2 h, 4 h, 24 h, 48 h and 1 week post-injection

cation; therefore, kidney possesses an important role in excretion via urine.

The distribution of injected dose in rat organs up to one month pi of $^{141}$Ce-EDTMP (3.7 MBq/100 µl or 100 µCi/100 µl) solution was determined. Based on the results, the major portion of the injected activity was extracted from blood circulation into bones. The results of the biodistribution studies are shown in Fig. 6 and revealed significant uptake in skeleton within less than 4 h pi.

The blood wash-out mechanisms were different for the two compounds. $^{141}$Ce-EDTMP was washed out from the circulation sooner than the free radionuclide. Figures 4 and 5 show that the clearance of the species occurred after 24 h in both cases.

$^{141}$Ce-EDTMP was rapidly taken up into the bones 2 h after administration and retained almost constantly up to 1 month, whereas the free $^{141}$Ce uptake decreased in one week and reached a minimum value less than that of $^{141}$Ce-EDTMP. This result may be attributed to the affinity of the lanthanide ions to the bone because of their similarity to the

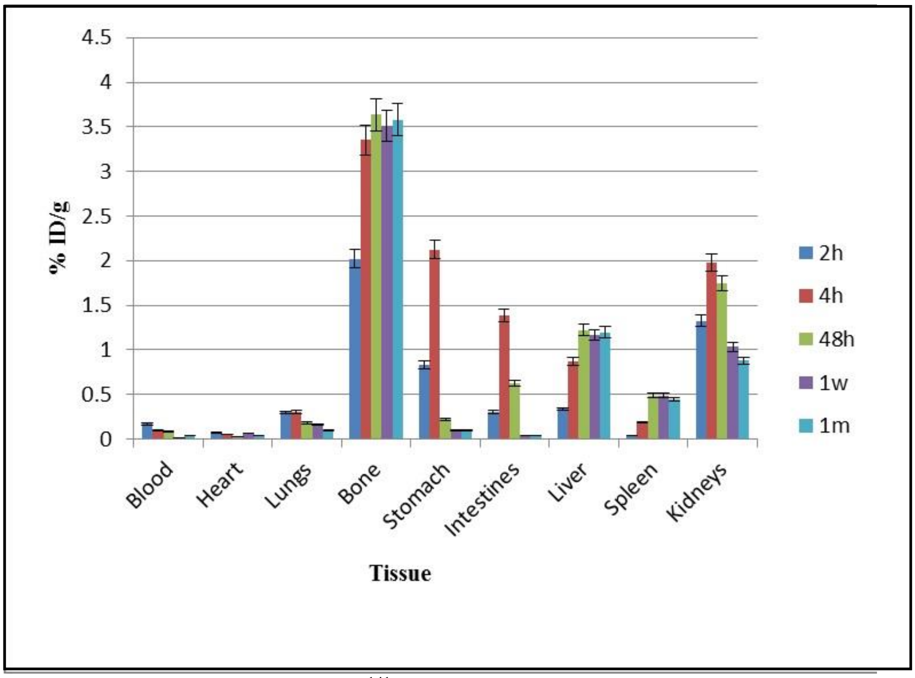


Figure 6. Percentage of injected dose per gram (ID/g %) of $^{141}$Ce-EDTMP in wild-type rat tissues at 2 h, 4 h, 24 h, 48 h, 1 week and 1 month post-injection.

calcium cation. However, the affinity of the phosphonate complex to the bone was more than that of the free ion; therefore, the free cation was released from the bone structure faster than $^{141}$Ce-EDTMP.

As previously mentioned, $^{141}$Ce-EDTMP was rapidly taken up into the bones and the trapping continued until almost no blood circulation activity and kidney excretion could be observed. Fig. 4 shows that the washed-out activity of free cation was higher than that of the complexed isotope.

A major difference in liver uptake was observed for the two species. $^{141}$Ce-EDTMP exhibited almost no significant accumulation in the liver, which is a major advantage as a therapeutic radiopharmaceutical because of the possibility of increasing the maximum injectable dose. By contrast, free $^{141}$Ce accumulated in the liver as a free cation being transferred by serum metalloproteins. A hepatobilliary excretion route may reduce the liver accumulation after 4 h.

A major difference in spleen uptake was also observed for the two species ($^{141}$Ce-EDTMP and free $^{141}$Ce cation). $^{141}$Ce-EDTMP exhibited almost no accumulation in the spleen, which can be a major advantage as a therapeutic radiopharmaceutical because of the possibility of increasing the maximum injectable dose, whereas free $^{141}$Ce accumulated in the spleen during the first 2 h pi.

Activity was retained in the skeleton until 30 d pi up to which time the biodistribution studies were continued.

### *Imaging studies*

Figure 7 shows the scintigraphic images of the wild-type rats recorded at 72 h pi of $^{141}$Ce-EDTMP. The complex was mostly washed out from the circulation in the first few hours, and the uptake of activity in the skeleton was observed within the first hours of injection. The images show that $^{141}$Ce-EDTMP was trapped in bone tissues, especially in vertebra and thigh bones, and insignificant activity was accumulated in other tissues. The initially accumulated activity in the kidneys had completely cleared, and no uptake was observed in any of the non-target organs. Only skeletal uptake was visible, indicating the complete retention of activity.

## DISCUSSION

Several factors, including the difficulty in transporting short-lived radiopharmaceuticals ($^{153}$Sm-EDTMP, $^{186}$Re-HEDP), higher cost, and limited capacity for producing radionuclide ($^{89}$Sr in $^{89}SrCl_2$), minimize the usage of radiopharmaceutical agents in bone metastasis treatment. Patients with limited skeletal involvement (e.g., those with higher performance status and those with predominant osteoblastic lesions on bone scintigraphy) demonstrate greater pain relief with a longer duration [2]. We focused our effort on developing $^{141}$Ce-labeled agents as a proper alternative to $^{89}SrCl_2$. No extensive radiochemical processing is required to produce $^{141}$Ce in the radionuclidically pure form because the target used is inexpensive and the resultant product has acceptable radionuclidic purity for animal studies.

Irradiation of natural cerium nitrate salt for 7 d produced 0.3–0.4 mCi/mg of $^{141}$Ce with a flux density of $4–5 \times 10^{13}$ neutrons/cm$^2$.s. EDTMP ligand was synthesized in-house, and the structure was determined using authentic spectroscopic methods. $^{141}$Ce-EDTMP and $^{141}CeCl_3$ preparations were administered to normal rats, and related biodistribution data were monitored 2 h to 1 month for the prepared formulation and 1 week for the uncomplexed formulation, which later showed at least 70% accumulation of the drug in the bone tissues. SPECT image was taken 72 h pi from wild-type rats injected with $^{141}$Ce-EDTMP and $^{141}CeCl_3$. The biodistribution data were consistent with the scarification data. A comparative accumulation study for

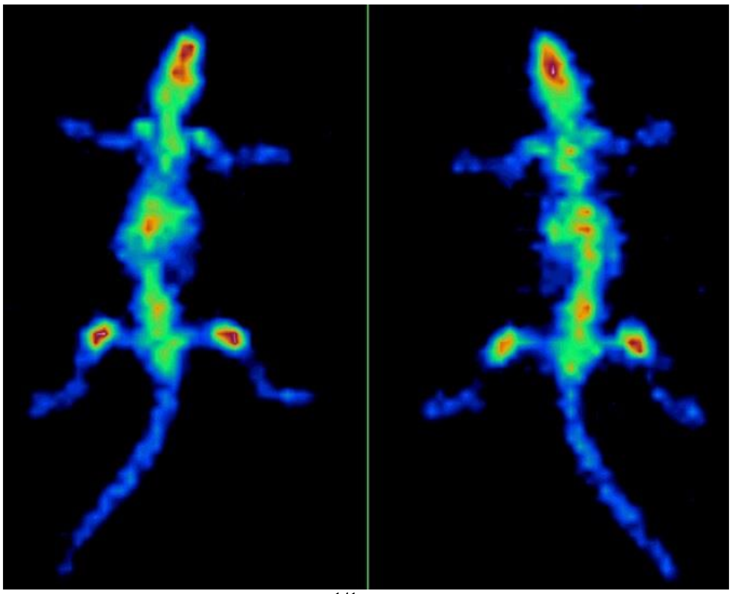

Figure 7. SPECT image of $^{141}$Ce-EDTMP 72 h post-injection

$^{141}$Ce-EDTMP and $^{141}$CeCl$_3$ was performed for vital organs up to one week.

The specific activity achieved by irradiation for 7 d was not very high using longer irradiation times (up to one month) and one week cooling, higher specific activities could be achieved for human uses. Dosimetric studies are necessary before clinical applications because of the relatively long half-life of the radionuclide. These two concerns are not significant in animal experiments presented in this study.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

The authors declare that this research does not have any conflict of interest with anyone or any Institute.

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