Original Article

Production, biodistribution, and dosimetry of ^{47}Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid as a bone-seeking radiopharmaceutical

Fatemeh Fathi, Leila Moghaddam-Banaem[1], Mojtaba Shamsaei, Ali Samani[1], Mohammad G. Maragheh[1]

Faculty of Nuclear Engineering and Physics, Amirkabir University of Technology, [1]Radiopharmaceutical Research and Development Lab (RRDL), Nuclear Science and Technology Research Institute (NSTRI), Postal Code: 14155-1339, Tehran, Iran

Received on: 12-08-2014 **Review completed on: 27-04-2015** **Accepted on: 28-04-2015**

ABSTRACT

In this study 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (DOTMP) was used as the polyaminophosphonic acid carrier ligand and the therapeutic potential of the bone seeking radiopharmaceutical ^{47}Sc-DOTMP was assessed by measuring its dosage–dependent skeletal uptake and then the absorbed radiation dose of human organs was estimated. Because of limited availability of ^{47}Sc we performed some preliminary studies using ^{46}Sc. ^{46}Sc was produced with a specific activity of 116.58 MBq/mg (3.15 mCi/mg) and radionuclide purity of 98%. ^{46}Sc-DOTMP was prepared and an activity of 1.258 MBq (34 μCi) at a chelant-to-metal ratio of 60:1 was administered to five groups of mice with each group containing 3 mice that were euthanized at 4, 24, 48, 96 and 192 h post administration. The heart, lungs, liver, spleen, kidneys, intestine, skin, muscle, and a femur were excised, weighed, and counted. The data were analyzed to determine skeletal uptake and source organ residence times and cumulated activities for ^{47}Sc-DOTMP. ^{46}Sc-DOTMP complex was prepared in radiochemical purity about 93%. *In vitro* stability of complex was evaluated at room temperature for 48 h. Biodistribution studies of complex in mice were studied for 7 days. The data were analyzed to estimate skeletal uptake and absorbed radiation dose of human organs using biodistribution data from mice. By considering the results, ^{47}Sc-DOTMP is a possible therapeutic agent for using in palliation of bone pain due to metastatic skeletal lesions from several types of primary cancers in prostate, breast, etc.

Key words: $^{47/46}$Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid, biodistribution, dosimetry, radiopharmaceuticals

Introduction

A large percentage of cancer patients suffer from bone pain caused by bone metastases in the advanced stage of their diseases.[1-4] One of the methods for therapy in these patients is systematic palliative therapy that uses suitable radionuclides linked to bone seeking ligands. This method has emerged the most effective treatment modality compared with other conventional methods such as the use of pain relieving drugs or radiotherapy with external sources for these patients, because this model has the most noticeable effect and minimal side-effects.[3-6] The important factor in designing effective radiopharmaceuticals for palliative

Address for correspondence:
Dr. Leila Moghaddam-Banaem,
Radiopharmaceutical Research and Development Lab,
Nuclear Science and Technology
Research Institute, 14155-1339 Tehran, Iran.
E-mail: Lmoghaddam@aut.ac.ir

Access this article online	
Quick Response Code:	Website: www.jmp.org.in
	DOI: 10.4103/0971-6203.165078

How to cite this article: Fathi F, Moghaddam-Banaem L, Shamsaei M, Samani A, Maragheh MG. Production, biodistribution, and dosimetry of ^{47}Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid as a bone-seeking radiopharmaceutical. J Med Phys 2015;40:156-64.

treatment of bone pain is to deliver sufficient radiation dose to bone lesions at skeletal surface and meanwhile minimize the radiation dose to the red bone marrow and normal tissues. Hence, an ideal radiopharmaceutical for palliative treatment should be selectively absorbed by the bone and concentrate in skeletal lesions, thereby delivering adequate dose at these lesion sites while minimizing radiation dose to the red bone marrow.[1,3,5] Researchers' results indicate that the radionuclides emit moderate or low energy β^- or conversion electron, are suitable candidates for attachment to bone seeking ligands and delivering effective absorbed dose to bones.[1,3,6]

^{47}Sc is one of these suitable radioisotopes which has ability to link to bone-seeking ligands with short half-life of 3.47 days and has attracted attention for using in nuclear medicine in recent years.[2,7-12] ^{47}Sc is a low β^- emitter ($E_{\beta 1Max}$ = 0.600 MeV [32%], $E_{\beta 2\ Max}$ = 0.439 MeV [68%]) which emits a γ-ray at 0.159 MeV, therefore images could be obtained to assess bone target, document disease status, and predict therapeutic efficacy at the time of administering the therapeutic agent.[13] There are different nuclear reactions such as ^{47}Ti(n, p)^{47}Sc and ^{46}Ca (n, γ) ^{47}Ca→^{47}Sc for production of ^{47}Sc in a reactor. The first reaction requires E_n > 1 MeV and an enriched target, but the second reaction uses thermal neutrons. The disadvantage of the latter reaction is the requirement of an enriched target while presently ^{46}Ca is available with only 30% enrichment and at a very high price.[10,14,15] Due to limited access to ^{47}Sc, in this study and preliminary experiments, ^{46}Sc radionuclide, which has similar chemical properties, was used.[2,7-9,11,12] ^{46}Sc with a long half-life (83.8 days) and one medium energy β^- and two γ-rays ($E_{\beta Max}$ = 0.3 MeV, E_γ = 1.12 MeV (100%), E_γ = 0.88) MeV (100%) can be produced simply by direct thermal neutron irradiation of natural ^{45}Sc and it is an ideal radionuclide for assessing the chemistry, stability, and biodistribution of scandium-labeled compounds. However, its long half-life and emission characteristics are unsuitable for clinical studies.[9,13] Similar chemical properties have also resulted in similar activity bio-distribution and hence for dose calculations replacing the nuclear physical characteristics of ^{47}Sc with those of ^{46}Sc can be considered equivalent to ^{47}Sc dosimetry.

In designing suitable radiolabeled agents for palliative bone pain, multidentate- polyamino-phosphonic acids such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (DOTMP) are found to be the most promising candidates as carrier ligands owing to their high bone affinity, selective localization in skeletal lesions and ability to form metal chelates with high *in vivo* stability [Figure 1].[3,5] Based on the well-documented phenomenon DOTMP is a macrocyclic chelator that form thermo-dynamically more stable and kinetically more inert complexes with lanthanides and metals, compared to its acyclic analogs such as EDTMP.[1,3,6]

In the present paper, preparation of ^{46}Sc-DOTMP complex and its preliminary biological studies in animal models were studied.

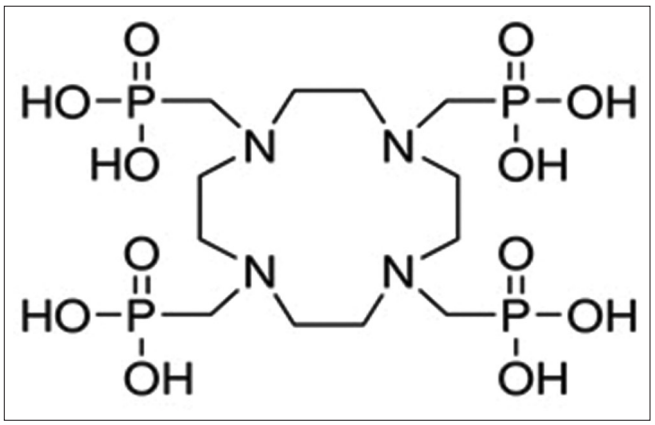

Figure 1: Structure of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid

Then we evaluated the potential of ^{47}Sc-DOTMP to deliver ^{47}Sc to the skeletal surfaces of human by using MIRD formalism and considering to ^{46}Sc-DOTMP biodistribution data from mice. In nuclear medicine, MIRD formalism is the most commonly used method for the calculation and estimation of internal dose.[16]

Experimental

Materials and methods

^{46}Sc was produced with a specific activity of approximately 116.58 MBq/mg (3.15 mCi/mg) and radionuclide purity of >98% by irradiation of natural Sc_2O_3 target (0.73 mg) at a thermal neutron flux of approximately $3.5\times10^{13}\ \frac{n}{cm^2.s}$ for 3 days at Tehran Research Reactor (TRR). DOTMP was purchased from Fluka Co. (Switzerland). Whatman No.1 paper was obtained from Whatman (Maidstone, UK) for instant thin layer chromatography (ITLC). All other chemical reagents were purchased from Merck (Darmstadt, Germany). 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.[17] This study was performed using five groups of healthy male mice, each group containing 3 mice, with nominal weight of between 25 and 35 g which were purchased from Pasteur Institute, Tehran, Iran.

The radiopharmaceutical was injected into the tail vein of the mice. Following administration and at certain times, animals were sacrificed. The heart, lungs, liver, spleen, kidneys, intestine, urinary bladder, femur and the muscles surrounding the femur were dissected, weighed, and counted. A high purity germanium (HPGe) detector coupled with a Canberra™ (model GC1020-7500 SL) multichannel analyzer and a dose calibrator ISOMED 1010 (Dresden, Germany) were used for counting distributed activity in mice organs.

Production and radiochemical processing of ^{46}Sc

^{46}Sc was produced by irradiation of natural Sc_2O_3 target at a thermal neutron flux of $3.5\times10^{13}\ \frac{n}{cm^2.s}$ for a period

of 48 h at the TRR. Following irradiation, the target was cooled for 8 days and subsequently dissolved in 3M HCl by gentle warming to prepare $^{46}ScCl_3$. The resultant solution was diluted to the appropriate volume with ultra-pure water, to produce a stock solution of final volume of 10 ml. The radionuclide purity of the solution and assay of the total activity produced was carried out by using HPGe spectroscopy. The total activity was obtained ~85.1 MBq (~2.3 mCi). The radiochemical purity of $^{46}ScCl_3$ was evaluated by employing ITLC using (a) %10 ammonium acetate:methanol (1:1) mixture and (b) 10 mM/l diethylenetriaminepenta-acetic acid (DTPA).

Preparation and characterization of ^{46}Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid

2.2 ml of $^{46}ScCl_3$ solution (18.5 MBq of ^{46}Sc activity) was evaporated to near-dryness by slight warming 2 times. The ^{46}Sc-DOTMP complex was prepared by adding 2.2 ml of $^{46}ScCl_3$ solution to 80 mg of DOTMP and then dissolved in 1 ml of 0.5M NaOH buffer (metal to ligand ratio of 1:60). The pH of solution was adjusted to ~8 by adding another 2.2 ml of 0.5 M NaOH buffer. The mixture was gently heated for 10 min and then stirred in water bath with a temperature of 90° for 1 h. The radiochemical purity of ^{46}Sc-DOTMP complex formed was determined by employing TLC using %10 ammonium acetate:methanol (1:1) mixture as the eluting solvents to discriminate free scandium from radiolabeled compound. For optimization of the labeling yield, experiments were carried out to determine the complexation yields of ^{46}Sc-DOTMP at different ligand to metal ratios ranging between 20:1 and 60:1 by varying the ligand amount, while keeping the amount of ^{46}Sc fixed at 0.35 mg.

In vitro stability studies

The *in vitro* stability of the ^{46}Sc-DOTMP was studied by incubating the complex (prepared using 80 mg of DOTMP and 0.35 mg of ^{46}Sc) in pH ~8 at room temperature for a period of 48 h after preparation. The radiochemical purity of the complex was determined at regular time intervals by employing paper chromatography using %10 ammonium acetate:methanol (1:1) mixture and 10 mM/L DTPA as the eluting solvents and using standard quality control techniques.

Biodistribution studies in mice

Biodistribution study of ^{46}Sc-DOTMP complex was carried out in five groups of mice weighing between 25 and 35 g. Three ml (with 6.29 MBq/ml activity) of the complex solution were injected through the tail veins and the animals were sacrificed by suffocating in CO_2 room at different intervals (4, 24, 48, 96 and 192 h) postinjection. From each group, one mouse was sacrificed at each time point. The tissues and the organs were excised and the activity associated with each organ/tissue was measured in gamma spectrometer with an HPGe detector. Distribution of the activity in different organs was calculated as decay corrected percentage of injected activity per gram (%ID/g). The skeletal and blood uptakes were calculated by assuming skeletal and blood weights to be 10% and 8% of the total body weight, respectively.[5,18]

Estimated human dosimetry

The dose calculation and estimation was done for a certain group of organs of human following the MIRD technique, in which the absorbed dose, D, to a target organ (r_k) is given in equation (1). In this equation, $\tilde{A}_h$ is the cumulated activity in the source region r_k, S ($r_k \leftarrow r_h$) is the so-called S-value, which gives the dose in region r_k per unit cumulated activity in source region r_h, k is some proportionality constant which in MIRD formalism is 2.13, ϕ_i ($r_k \leftarrow r_h$) is fraction of energy emitted from source region r_h that is absorbed in the target region r_k, y_i is number of radiation with energy E_i emitted per nuclear transition, E_i is energy per radiation and m_{r_k} is mass of target region.[19,20]

$$\begin{cases} D_{r_k} = \sum_h \tilde{A}_h S(r_k \leftarrow r_h) \\ S(r_k \leftarrow r_h) = \dfrac{k \sum_i y_i E_i \phi_i (r_k \leftarrow r_h)}{m_{r_k}} \end{cases} \quad (1)$$

As shown in equation (1), the S-values depend only on physical factor such as decay data of radioisotope and masses of the target regions, while $\tilde{A}_h$ depends only on biodistribution and retention of radiopharmaceutical in the body (f: Uptake fraction and Te: Effective half-life of radiopharmaceutical) and can be calculated in each organ according to equation (2) where $\tilde{A}_h$ is activity in source organ at time t and A_0 is the activity administered to the body at time $t = 0$, and $f_s(t)$ is the fraction of administered activity present within the source region at time t and (τ) is residence time.[20-22]

$$\tilde{A}_h = \int_0^\infty A_h(t)dt = A_0 \int_0^\infty f_s(t)dt = A_0 \times \tau \quad (2)$$

Since the chemical behavior of an element is dictated by its atomic number and all isotopes of the same element have identical behavior, biological systems fail to recognize the difference between atomic weights and treat all isotopes in the same fashion.[23] Therefore, in calculating the cumulated activities for ^{47}Sc the biodistribution data of ^{46}Sc were used while considering the physical half-time of ^{47}Sc.

Before calculating the cumulated activity in source organs, a mass correction method (kg/g method) was used to extrapolate biokinetic data from the animal model to human. In this method, the %ID/g in a certain human organ is equal to the %ID/g in the same mouse organ multiplied by the ratio of the body mass of human and mouse as equation (3).[20] The required mass data for the standard adult male of 73 kg were taken from ICRP89.[24]

$$(\%ID)_{\text{human}} = \left[\left(\frac{\%ID}{g}\right)_{\text{animal}} \times (kg_{\text{TBweight}})_{\text{animal}} \right] \times \left(\frac{g_{\text{organ}}}{kg_{\text{TBweight}}}\right)_{\text{human}} \quad (3)$$

Then the activity versus time curves for the source organs including: lung, stomach, intestine, liver, spleen, kidney, bone, muscle, skin, and remainder of the body in human were plotted. The residence times in the source organs are calculated by fitting a multi-component exponential function to these activity-time curves using Matlab software (The Mathworks Inc. R2013.) The program returned the values of f_i and λ_i for the equation (4).

$$f_s(t) = f_1 e^{-(\lambda_1+\lambda_p)t} + f_2 e^{-(\lambda_2+\lambda_p)t} + \ldots \quad (4)$$

Where f_i is the amount of activity associated with the component i of source region, and λ_i is the biologic elimination constants for the component i $\lambda_i = 0.693/T_i\ (\text{hr}^{-1})$, where T_i is the biological half-time for component i(hr) and λ_p represents the physical decay constant for the radionuclide of interest.[16,22] The residence times (τ) in the source organs were obtained by integration of respective fit functions, from $t = 0$ to $t =$ infinity, after accounting for the physical decay of the ^{47}Sc.[25] These values were calculated using the same method as described in the MIRDOSE3 code.[16] Then the cumulated activities in the source organs for a 3.7 MBq (100 μCi) injected activity, in MBq-s, were calculated as equation (2).

One of the parameters for dose calculation is S-factor. The S-factor for each radiation type can be written by equation (5):

$$s(t,s) = D\frac{f(t,s)}{m} \quad (5)$$

In equation (5), D is a measure of the total energy associated with the particular radiation type and is a physical entity known from the radioisotope's decay scheme, $f(t, s)$ is the absorbed fraction for the particular radiation emitted in the source organ, s, and absorbed by the target organ, t, and m is the mass of the target organ.

The absorbed fraction represents the fraction of the total energy emitted by radiation of a particular type that is absorbed in the target organ. For beta particles, which have a short range in tissue, it can be assumed that all the energy will be deposited in the source organ and other target organs will not be irradiated. That is:

$$f(t,s) = 0 \quad (6)$$

Unless $t = s$, in which case:

$$f(t,s) = 1 \quad (7)$$

So as the S-factor is relevant to the particle energy that is emitted by radionuclide and the particle energies of ^{46}Sc is different from ^{47}Sc, for dose calculation the S-factor of ^{47}Sc is used.

Tables of S for many target and source organs and for many radioisotopes were published in MIRD pamphlet No. 11. In this study, the S-factors for ^{47}Sc were used from this pamphlet.[26] The S-factor for the remainder of the body, RB, were calculated by equation (8) according to MIRDOSE III computer software recommendation.[16,25,27] In equation (5), $S(r_k \leftarrow \text{RB})$ is the S-factor for remainder of body irradiating target region r_k, $S(r_k \leftarrow \text{TB})$ is the S-factor for total body irradiating target region r_k, $S(r_k \leftarrow r_h)$ is the S-factor for source region r_h irradiating target region r_k, m_{TB} is the mass of the total body, m_{RB} is the mass of the remainder of the body, and m_h is the mass of source region r_h.

$$S(r_k \leftarrow RB) = S(r_k \leftarrow TB) \times \frac{m_{TB}}{m_{RB}} - \sum_h S(r_k \leftarrow r_h) \times \frac{m_h}{m_{RB}} \quad (8)$$

The radiation absorbed dose to red marrow was also estimated according to MIRD recommendation[25,28] and calculated by equation (9).

$$D_{rm} = 0.5 \times \tilde{A}_{bone} \times S(rm \leftarrow cortB) + 0.5 \times \tilde{A}_{bone} \times S(rm \leftarrow traB) + \tilde{A}_{Total\ body} \times S(rm \leftarrow TB) + \tilde{A}_{Bladder} \times S(rm \leftarrow Bladder) \quad (9)$$

The dynamic bladder model and the gastrointestinal tract model were not used.

The equivalent dose calculated as equation (10) where $D_{T,R}$ is the dose delivered by radiation type R averaged over a tissue or organ T, and w_R is the radiation weighting factor for radiation type R. The current values recommended by the ICRP60 in which for photons and electrons, numerical values of the absorbed dose in gray and equivalent dose in sievert are equal. Then effective dose calculated as the product of the individual tissue equivalent doses (H_T) and the tissue-weighting factors (w_T) according to ICRP 103 and equation (11).[20,25]

$$H_T = w_R \times D_{T,R} \quad (10)$$

$$E = \sum_T H_T \times w_T \quad (11)$$

Results and Discussion

Production of ^{46}Sc

Irradiation of natural Sc_2O_3 target at a thermal neutron flux of $3.5 \times 10^{13}\ \frac{n}{\text{cm}^2.\text{s}}$ for a period of 48h and 8 days after the end of bombardment yielded ^{46}Sc with a specific activity of ~116.58 MBq/mg (~3.15 mCi/mg). Scandium is

mono-isotopic with the atomic mass of 45 and usually, besides ^{46}Sc, formation of any other scandium radionuclide such as ^{47}Sc is not expected. However, ^{45}Ca may be formed via the (n, p) reaction. ^{45}Ca is a pure beta emitter and thus difficult to detect. On the other hand considering the cross-sections of (n, γ) and (n, p) reactions on ^{45}Sc as well as the half-lives of ^{46}Sc and ^{45}Ca, it is estimated that the ^{45}Ca impurity, if at all, was <0.1%.[9] Therefore the radionuclide purity of ^{46}Sc produced was >98%. The radiochemical purity of ^{46}Sc was evaluated employing ITLC using two solvent system: (a) In %10 ammonium acetate:methanol (1:1), free Sc^{3+} cation was remained at the point of spotting, (b) in 10 mM/L DTPA, free Sc^{3+} cation was complexed into more Sc-DTPA form and moved from solvent front while almost no radioactive fraction was remained at the point of spotting. In both chromatographic systems no other radiochemical species was detected [Figures 2 and 3].

Preparation and characterization of ^{46}Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid

Radiochemical purity of ^{46}Sc-DOTMP complex was ascertained by using ITLC. For ITLC %10 ammonium acetate:methanol (1:1) used as the eluting solvent, and it was observed that ^{46}Sc-DOTMP moved toward the solvent front while $^{46}ScCl_3$ under identical conditions remained at the point of spotting. ^{46}Sc-DOTMP complex was obtained with a radiochemical purity of ~93% using 80 mg of DOTMP and 0.35 mg of ^{46}Sc in 3 ml reaction volume (corresponding to a ligand-to-metal ratio of 60:1) within a pH range of 7–8 at room temperature.

Experiments carried out by keeping the amount of ^{46}Sc fixed at 0.35 mg and gradually increasing the amount of DOTMP. The excellent complexation yields (~93%) were achieved at ligand to metal ratio of 60:1. Table 1 shows the complexation yields of ^{46}Sc-DOTMP obtained at various ligands to metal ratios.

In vitro stability studies

^{46}Sc-DOTMP complex exhibited excellent *in vitro* stability at pH ~8 when stored at room temperature. The radiochemical purity of above-mentioned conditions was found to be retained to extend of ~93% after 48 h postpreparation [Figures 4 and 5].

Biodistribution studies in mice

The uptake of ^{46}Sc-DOTMP complex in the different organs/tissue of mice expressed as percentage of injected activities (%ID) per organ/tissue at different postinjection times is shown in Table 2 and Figure 6. The results of the biodistribution studies revealed significant bone uptake within 4 h postinjection. The observed uptake in femur at this time point was 3.7 %ID/g corresponding to a skeletal uptake of 33.11 %ID/g for ^{46}Sc-DOTMP that is similar to the 3.94 %ID/g and 3.72 %ID/g measured by Banerjee *et al*.[1] for ^{153}Sm-DOTMP and ^{153}Sm-EDTMP respectively

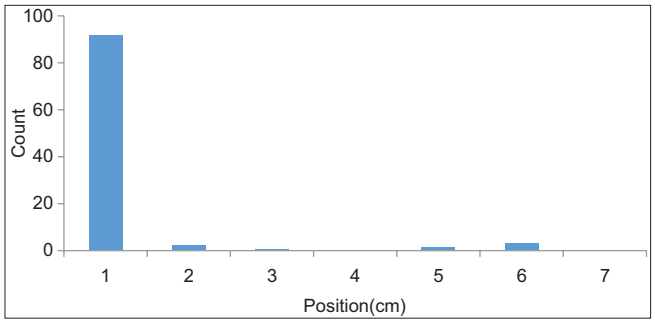

Figure 2: $^{46}ScCl_3$ paper radiochromatogram eluted with 10% ammonium acetate:methanol (1:1)

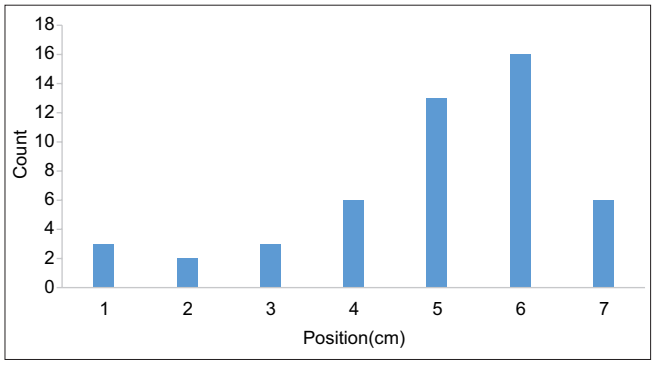

Figure 4: Paper radiochromatogram of "^{46}Sc-DOTMP" complex eluted with 10% ammonium acetate: methanol (1:1)

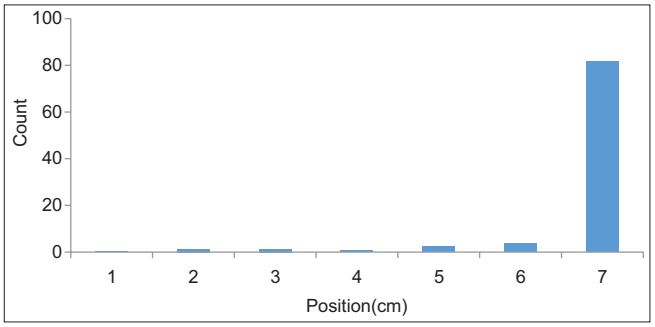

Figure 3: $^{46}ScCl_3$ paper radiochromatogram eluted with diethylenetriaminepenta-acetic acid 10 mM/L

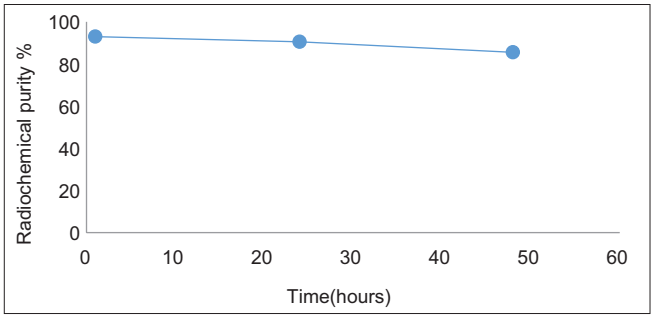

Figure 5: Stability of the ^{46}Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid complex up to 48 h (pH 7–8)

and reasonably close to the 4.37 %ID/g by Banerjee *et al.* for ^{175}Yb-EDTMP. The measured uptake for bone in this study is also close to the 4.23 %ID/g measured by Das *et al.*[5] for ^{177}Lu-DOTMP. A comparison between biodistribution results (%ID) in this study for $^{46/47}$Sc-DOTMP, 4 h postinjection and in Neves *et al.*[11] for $^{46/47}$Sc-IDZBP and $^{46/47}$Sc-Me-IDZBP, 3 h postinjection showed that the former provided significantly better biodistribution profile in animal model because of higher uptake in bone and lower uptake in other major organs [Figure 7].

Table 1: Complexation yields of ^{46}Sc-DOTMP complex at different ligand: Metal ratios

Ligand: Metal	*Percentage of complexation yield*
20:1	68.12
30:1	83.33
40:1	89.65
50:1	89.75
60:1	93

Table 2: Biodistribution pattern of ^{46}Sc-DOTMP complex in mice

Organ	*% ID/g*				
	4 h	*24 h*	*48 h*	*96 h*	*192 h*
Blood	8.51	1.93	0.99	0.60	0.42
Heart	1.49	0.24	0.33	0.55	0.08
Lung	1.22	0.57	0.18	0.39	0.30
Stomach	0.75	0.23	1.06	0.29	0.05
Intestine	0.60	0.46	0.48	0.14	0.08
Liver	0.92	1.75	1.88	1.75	0.99
Spleen	1.06	1.11	1.21	0.61	0.32
Kidney	1.93	1.26	1.21	0.99	0.31
Bone	3.70	2.62	2.48	2.35	1.15
Muscle	0.46	0.92	1.02	0.89	0.16
Skeleton[a]	33.11	21.56	25.18	16.74	16.74

[a]Total uptake in skeleton was calculated considering femur as representative of skeleton and skeletal weight to be 10% of the total body weight. % ID/g: Percentage of injected dose per gram

Dosimetry

The estimated %ID for human using a mass correction method are shown in Figure 8. The results showed the most of activity was accumulated in the bone, blood and muscle. The activity versus time curves for the source organs were plotted [Figure 9]. The residence times in the source organs are calculated by nonlinear regression analysis that was performed by the activity-time curves [Table 3]. Then cumulated activities in the source organs for a 3.7 MBq injected dose, in MBq-s, were calculated.

Table 4 gives the human target organ doses that are estimated by applying MIRD scheme. The human dose estimates indicate that the bone would receive a radiation absorbed dose from ^{47}Sc-DOTMP is more than 2 times that any other target organ. This estimate was 3.27 mSv/MBq that is >0.920 mSv/MBq measured by Breitz *et al.*[29] for ^{166}Ho-DOTMP in patients with multiple myeloma and is almost close to the 3.93 mSv/MBq measured by Simón *et al.*[30] for ^{153}Sm-DOTMP. Because of similar nuclear physical characteristic between ^{153}Sm and ^{47}Sc, it was assumed that the absorbed dose should have been more closer than these values, but the difference between ^{153}Sm and ^{47}Sc could be the result of following factors: 1:different S-values, 2:different formalism for calculating the red marrow accumulated activity that Stabin and *et al.* indicated[28] and, 3:different experimental conditions. The dose to the red marrow estimated here, 0.836 mSv/MBq, is almost close to the 0.517 mSv/MBq measured by Breitz *et al.* and near to the 0.755 mSv/MBq measured by Simón *et al.* The results that obtained in this study are compared with the Breitz *et al.*'s and Simón *et al.*'s results in Figure 10.

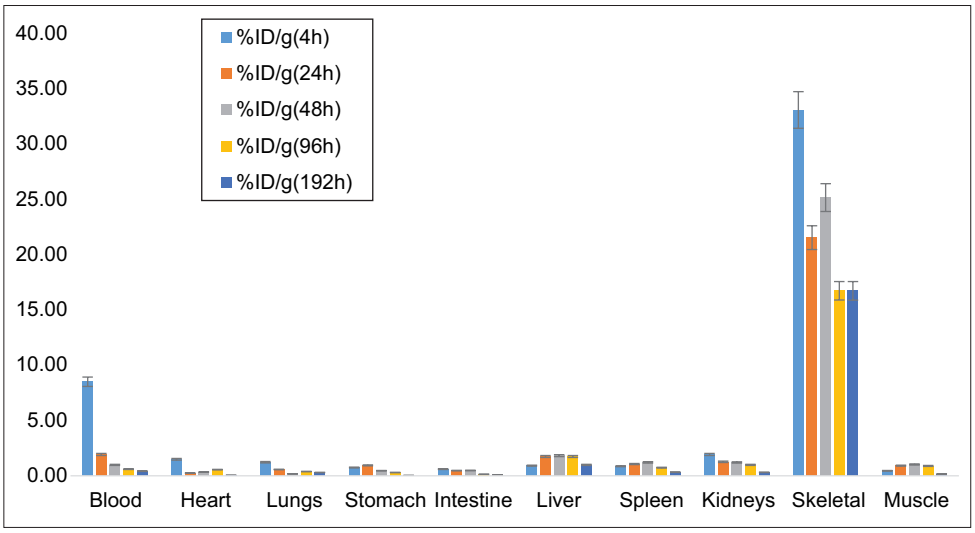

Figure 6: Percentage of injected dose per gram of ^{46}Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid in mice tissues at 4, 24, 48, 96 and 192 h postinjection

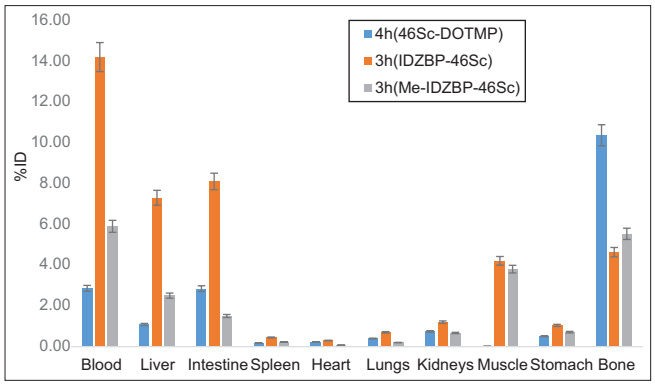

Figure 7: Comparison between biodistribution results (percentage of injected activities) in this study for $^{46/47}$Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid and in Neves *et al.* for $^{46/47}$Sc-IDZBP and $^{46/47}$Sc-Me-IDZBP

Table 3: The residence times in the source organs

Organ	*Residence time (h)*
Blood	2.95
Heart	0.19
Lung	0.05
Stomach	0.07
Intestine	0.08
Liver	2.41
Spleen	0.11
Kidney	0.22
Bone	81.38
Muscle	12.84
Skin	2.19
Remain body	26.95

Table 4: The human absorbed dose estimation

Target organ	*Dose (mSv/MBq)*
Small intestine	0.133
Large intestine	0.273
Stomach	0.066
Kidneys	0.109
Liver	0.168
Lungs	0.078
Muscle	0.081
Spleen	0.113
Bone surfaces	3.27
Red marrow	0.836
Skin	0.112
Total body	0.254
Effective dose	0.195

Conclusion

^{46}Sc-DOTMP complex was prepared in high yield and excellent radiochemical purity (~93%) using ^{46}Sc produced by thermal neutron irradiation of natural Sc_2O_3 target and DOTMP. The complex exhibited excellent *in vitro* stability (~90% radiochemical purity) at room temperature up to 48 h postpreparation. Radiochemical studies showed that the complex could be prepared in high yield at a ligand-to-metal ratio of 60:1. Biodistribution studies in mice showed rapid selective skeletal uptake of injected activity (3.7 %ID/g in femur at 4 h postinjection) with fast clearance from blood and small uptake in any of the major organs/tissue [Table 2].

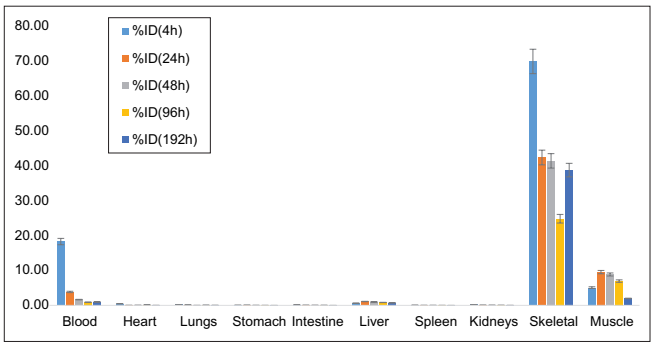

Figure 8: Extrapolation of percentage of injected activity of ^{46}Sc-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid in mice to human

Although the principles of inter-species dose extrapolation are poorly understood and applied[31] earlier studies have shown the usefulness of using animal biodistribution as a model for absorbed dose estimations in humans.[32,33] Therefore, the amount of radiation absorbed doses to human were estimated using MIRD scheme by multiplying the cumulated activities in the source organs that were calculated by estimating %ID for human (using a mass correction method from mice biodistribution data) and using Matlab software, to S-values of ^{47}Sc from MIRD pamphlet No. 11 and are shown in Table 4. The highest absorbed doses were estimated for the bone (3.27 mSv/MBq), red marrow (0.836 mSv/MBq) and large intestine (0.273 mSv/MBq). The absorbed dose for the bone that was estimated in this study is similar to the Simón *et al.*'s result for ^{153}Sm-DOTMP[30] [Figure 10]. This result was expected due to almost identical range of beta rays in bone (0.32 mm for ^{153}Sm and 0.20 mm for ^{47}Sc[11]). The preclinical results reported here indicated that ^{47}Sc-DOTMP showed promising features in animal models that warrant further investigation in higher animals to become useful in treating patients with skeletal metastasis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

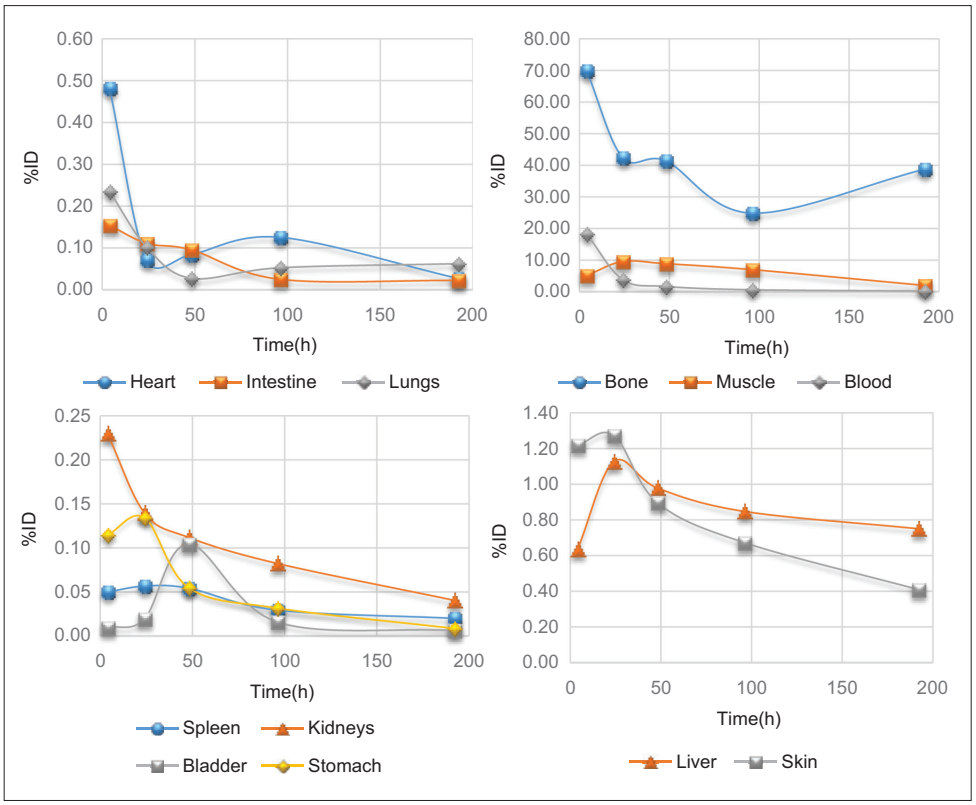

Figure 9: Estimated time-activity curves for organs of human as percentage of injected dose per gram

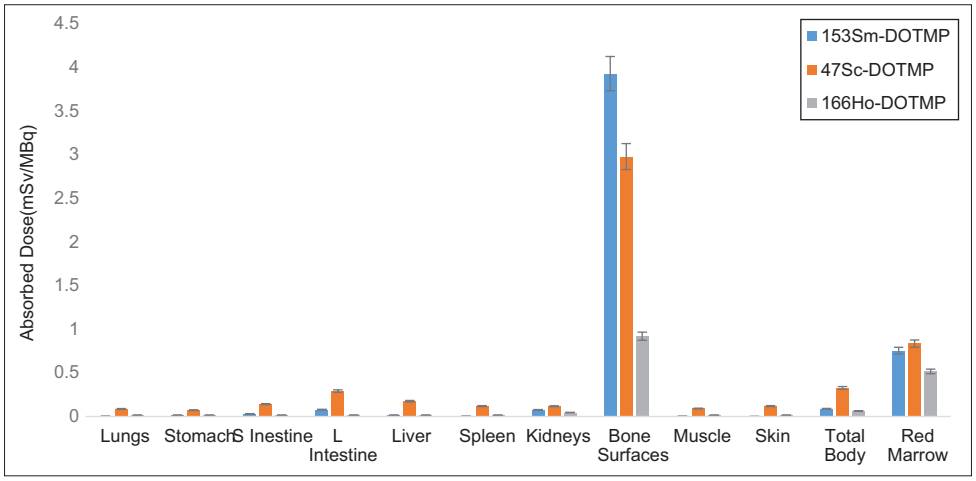

Figure 10: Comparison of data that obtained in this study with the Breitz *et al.*'s and Simón *et al.*'s results for ^{153}Sm-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid (DOTMP) and ^{166}Ho-DOTMP

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