

On the preparation of a therapeutic dose of ^{177}Lu -labeled DOTA–TATE using indigenously produced ^{177}Lu in medium flux reactor

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Abstract

^{177}Lu could be produced with a specific activity of $\sim 23,000$ mCi/mg (850 GBq/mg) by neutron activation using enriched ^{176}Lu (64.3%) target when irradiation was carried out at a thermal neutron flux of 1×10^{14} n/cm²/s for 21 d. ^{177}Lu –DOTA–TATE could be prepared in high radiochemical yield ($\sim 99\%$) and adequate stability using the ^{177}Lu produced indigenously. The average level of radionuclidic impurity burden in ^{177}Lu due to $^{177\text{m}}\text{Lu}$ was found to be 250 nCi of $^{177\text{m}}\text{Lu}$ /1 mCi of ^{177}Lu (9.25 kBq/37 MBq) at the end of bombardment, which corresponds to 0.025% of the total activity produced. The maximum specific activity achievable via careful optimization of the irradiation parameters was found to be adequate for the preparation of a therapeutic dose of the radiopharmaceutical. The in-house preparation of this agent using 25 μg (17.41 nmole) of DOTA–TATE and indigenously produced ^{177}Lu (0.8 μg , 4.52 nmole), corresponding to peptide/Lu ratio of 3.85 yielded 98.7% complexation. Allowing possibility of decay due to transportation to users, it has been possible to demonstrate that at our end, a single patient dose of 150–200 mCi (5.55–7.40 GBq) can be prepared by using 250–333 μg of DOTA–TATE conjugate. This amount compares well with ^{177}Lu –DOTA–TATE prepared for a typical peptide receptor radionuclide therapy (PRRT) procedure which makes use of 100 μg of the DOTA–TATE conjugate, which incorporates 50 mCi (1.85 GBq) of ^{177}Lu activity, thereby implying that in order to achieve a single patient dose of 150–200 mCi (5.55–7.40 GBq), 300–400 μg of the conjugate needs to be used.

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1. Introduction

Radiometallated peptides which exhibit high specificity for cognate receptors over-expressed on cancerous lesions, offer important potential as site-directed diagnostic and therapeutic radiopharmaceuticals (Boerman et al., 2000; Breeman et al., 2001; Britton, 1997; Eckelman and Gibson, 1993). The highly specific biochemical and physiologic binding capabilities of the receptor-avid peptides can be exploited for using these agents as a vehicle to target the delivery of the radioactivity to the cells over-expressing similar type of receptors after radiolabeling the peptides with the radionuclide of interest. Such peptide analogs

when labeled with therapeutic radionuclides are being actively investigated as agents for use in peptide receptor radionuclide therapy (PRRT) (Kwekkeboom et al., 2000, 2003a, 2005; de Jong et al., 2005).

Among the several classes of radiolabeled peptides, radiolabeled somatostatin analogs have been proved to be the most promising. Octreotide, a metabolically stable analog of native somatostatin (Pauwels et al., 1998), has been radiolabeled with ^{111}In using a bifunctional chelating agent and the resultant radiolabeled peptide, ^{111}In –DTPA–Octreotide (commonly known as OctreoScan[®]) has been successfully employed in clinical diagnosis of somatostatin receptor positive tumors (Pauwels et al., 1998; Krenning et al. 1992, 1993). Efforts are being made to develop suitable therapeutic analogs having the potential to eradicate the cancerous lesions over-expressing somatostatin receptors.

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Recently started clinical trials with ($^{177}\text{Lu-DOTA-Tyr}^3$)-Octreotide (known as $^{177}\text{Lu-DOTA-TOC}$) and ($^{177}\text{Lu-DOTA-Tyr}^3$)-Octreotate (known as $^{177}\text{Lu-DOTA-TATE}$) have shown very encouraging results in terms of tumor regression in patients suffering from different types of neuroendocrine tumors, which are known to over-express somatostatin receptors (Kwekkeboom et al., 2003a,b, 2005; Forrer et al. 2005). However, it is reported that [DOTA-Tyr³]-Octreotate has a ninefold higher affinity for the somatostatin receptor subtype 2 as compared with [DOTA-Tyr³]-Octreotide and therefore, the later agent is expected to be more potent for carrying out PRRT in patients suffering from neuroendocrine tumors (Kwekkeboom et al., 2003a; Reubi et al. 2000).

^{177}Lu is presently being considered as a potential radionuclide for use in in vivo therapy, because of its favorable decay characteristics. ^{177}Lu decays with a half-life of 6.73 d by emission of β^- particles with maximum energies of 497 keV (78.6%), 384 keV (9.1%), and 176 keV (12.2%) to stable ^{177}Hf (Firestone, 1996). The emission of suitable energy γ photons of 113 keV (6.4%) and 208 keV (11%) (Firestone, 1996) with relatively low abundances provides the opportunity to carry out simultaneous scintigraphic studies, which helps to monitor the proper in vivo localization of the injected radiopharmaceutical as well as to perform dosimetric evaluations. An important aspect for the countries with limited reactor facility is the comparatively long half-life of ^{177}Lu which provides logistic advantage towards facilitating supply to locations far away from the reactors (Das et al., 2002). Besides this, the high thermal neutron capture cross-section ($\sigma = 2100b$) of ($^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$) reaction (Firestone, 1996) ensures that ^{177}Lu can be produced with sufficiently high specific activity using the moderate flux reactors. In fact, the cross-section is the highest encountered among all (n,γ) produced radionuclides presently used for therapy. These favorable nuclear parameters ensure that there will be no constraints with respect to large-scale isotope production.

In connection with our ongoing research on the development of novel agents for radiotherapy of tumors (Banerjee et al., 2004; Das et al., 2004), production of ^{177}Lu , identified as the ideal radioisotope is being extensively optimized with an aim to achieving the maximum specific activity via a cost-effective route. This is an essential requirement for designing agents for PRRT since the primary criterion is to deliver sufficient number of radionuclides to the receptors over-expressed on the targeted tumor site without saturating the target (Mausner and Srivastava, 1993; Volkert and Hoffman, 1999; Breeman et al., 2003).

^{177}Lu can be produced by two different routes, namely, by irradiation of Lu target and by irradiation of Yb target followed by radiochemical separation of ^{177}Lu from Yb isotopes. Though the latter method enables production of no-carrier-added (NCA) ^{177}Lu , the radiochemical separation of ^{177}Lu activity from irradiated Yb target is a difficult

adjacent members of the lanthanide series. Presence of Yb in substantial amounts, attributable to its low cross-section, besides reducing the effective specific activity of the product, will also compete with ^{177}Lu in the complexation procedure unless effectively eliminated from the irradiated target. This is one of the major impediment in the ready production of NCA ^{177}Lu via $^{176}\text{Yb}(n,\gamma,\beta^-)^{177}\text{Lu}$ route. Moreover, use of enriched targets with low activation cross-section ($\sigma = 2.4b$ for $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb}$) (Firestone, 1996) is not economical for isotope production, as a significant part of the target remains unutilized. Though, ^{176}Yb recovery is theoretically feasible, the aforementioned practical problems associated with the cumbersome separation still remains.

Our experiences in the production of ^{177}Lu have provided an insight towards envisaging $^{177}\text{Lu-DOTA-TATE}$ as a radiopharmaceutical, which can be indigenously produced and supplied to local users as an agent for PRRT. The primary aim in the designing of this agent attempts to maximize the specific activity of the resultant radiolabeled preparation. Towards this, ^{177}Lu production is envisaged via (n,γ) using an enriched Lu_2O_3 target and efforts are directed to obtain ^{177}Lu with maximum possible specific activity utilizing the moderate flux reactor available in our country. However, careful optimization of the irradiation parameters is required for obtaining ^{177}Lu in adequate specific activity for PRRT applications, particularly when production is envisaged at high flux positions owing to the high thermal neutron capture cross-section of ^{176}Lu which eventually leads to considerable target burn up. The present paper describes optimization of ^{177}Lu production with sufficiently high specific activity using a moderate flux reactor and successful preparation of patient dose of $^{177}\text{Lu-DOTA-TATE}$ using the ^{177}Lu indigenously produced at our end.

2. Materials and methods

Lutetium oxide (64.3% enriched in ^{176}Lu , spectroscopic grade, >99.99% pure) was obtained from Isoflex, Russia. DOTA-TATE was obtained from PiChem, Finland, through International Atomic Energy Agency (IAEA) as a part of a coordinated research project (CRP). All chemicals and solvents used in the experiments were of AR grade and supplied by reputed chemical manufacturers. Radionuclidic purity of ^{177}Lu was ascertained by high resolution γ -ray spectrometry using an HPGe detector (EGG Ortec/Canberra detector) coupled to a 4K multi-channel analyzer (MCA) system after radiochemical processing. ^{152}Eu reference source used for energy and efficiency calibration of the detector was obtained from Amersham Inc., USA. All other radioactivity measurements were carried out using a well type NaI (TI) scintillation counter after adjusting the 150 keV baseline and keeping a window of 100 keV, thereby utilizing the 208 keV γ photon of ^{177}Lu . Whatman 3 mm chromato-

studies. The high performance liquid chromatography (HPLC) system used was obtained from JASCO (PU 1580), Japan, equipped with a PU 1575 UV/VIS detector. A well-type NaI (TI) scintillation detector was coupled to the system for radioactivity measurements in the eluate. All the solvents used for HPLC analyses were of HPLC grade and purchased from reputed local manufacturers, degassed and filtered prior to use.

2.1. Production and radiochemical processing of ^{177}Lu

^{177}Lu was produced by thermal neutron bombardment on isotopically enriched (64.3% in ^{176}Lu) Lu_2O_3 target. A stock solution of enriched target was prepared by dissolving enriched Lu_2O_3 powder in 0.1 M HCl (1 mg/mL concentration). A known aliquot of this solution was taken in a quartz ampoule and carefully evaporated to dryness. The ampoule was subsequently flame sealed and irradiated after placing inside an aluminum can. Irradiations were carried out at different available flux positions (1.4×10^{13} – 1.0×10^{14} n/cm²/s) for different durations (7–21 d) in order to optimize the irradiation conditions towards achieving maximum specific activity of ^{177}Lu . The irradiated target was dissolved in 1 M HCl by gentle warming inside a lead-shielded plant. The resultant solution was evaporated to near dryness and reconstituted in de-ionized water. The pH of the $^{177}\text{LuCl}_3$ solution thereby obtained was adjusted to ~4 prior to complexation studies. A known aliquot was drawn for assay of radioactivity and determination of radionuclidic purity.

Radioactivity assay was carried out by measuring the ionization current obtained when an aliquot of the batch was placed inside a pre-calibrated well-type ion-chamber. Radionuclidic purity was determined by recording γ -ray spectra of the appropriately diluted solution of the irradiated target using an HPGe detector connected to a 4K MCA system. Energy as well as efficiency calibration of the detector were carried out using a ^{152}Eu reference source prior to the recording of γ -ray spectra. Several spectra were recorded for each batch at regular time intervals. Samples measured initially for the assay of ^{177}Lu were preserved for complete decay of ^{177}Lu (8–10 $T_{1/2}$ of ^{177}Lu , i.e. for a period of 50–70 d) and re-assayed to determine the activity of long-lived $^{177\text{m}}\text{Lu}$ ($T_{1/2} = 160.5$ d). Appropriately diluted sample solutions were counted for 1 h.

2.2. Preparation of ^{177}Lu -DOTA-TATE complex

For the preparation of ^{177}Lu -labeled DOTA-TATE complex, a stock solution of the DOTA-TATE was prepared by dissolving DOTA-TATE conjugate in HPLC grade water with a concentration of 1 mg/mL. To a 25 μL aliquot of this stock solution, 25 μL of $^{177}\text{LuCl}_3$ solution was added and the volume was made upto 200 μL using the 0.1 M ammonium acetate buffer of pH 5. The reaction mixture was incubated at 80 °C for 1 h after adjusting the pH to 4.5–5. Various

and temperature were varied extensively in order to arrive at the protocol for maximum complexation.

2.3. Quality control techniques

The characterization of the ^{177}Lu -labeled DOTA-TATE conjugate as well as the determination of the complexation yield was carried out by paper chromatography (PC) as well as by HPLC techniques.

2.3.1. Paper chromatography (PC)

5 μL portions of the test solutions were applied at 1.5 cm from the lower end of the chromatography paper strips. The strips were developed in 50% aqueous acetonitrile, dried, cut into segments of 1 cm each and the radioactivity associated with each segment was measured in a NaI (TI) detector.

2.3.2. High performance liquid chromatography (HPLC)

HPLC of the ^{177}Lu -labeled conjugate was carried out using a dual pump HPLC unit with a C-18 reversed phase HiQ-Sil (5 μm , 25 \times 0.46 cm) column. The elution was monitored both by detecting UV signals at 270 nm as well as by radioactivity signal using NaI (TI) detector. Water (A), and acetonitrile (B) mixtures with 0.1% trifluoroacetic acid were used as the mobile phase and the following gradient elution technique was adopted for the separation (0–4 min 95% A, 4–15 min 95% A to 5% A, 15–20 min 5% A, 20–25 min 5% A to 95% A, 25–30 min 95% A). Flow rate was maintained at 1 mL/min.

2.4. Maximization of specific activity of ^{177}Lu -DOTA-TATE complex

In order to obtain ^{177}Lu -labeled DOTA-TATE conjugate in highest possible specific activity, experiments were carried out to achieve maximum complexation yield of ^{177}Lu -DOTA-TATE at the minimum possible $[L]/[M]$ ratio. For this, 25 μg of the peptide (already optimized ligand amount) was allowed to react with different amounts of Lu ranging from 0.2 to 1.6 μg under the same reaction conditions described earlier.

2.5. Stability of ^{177}Lu -DOTA-TATE

The in vitro stability of the ^{177}Lu -labeled conjugate was ascertained by storing the radiolabeled product at room temperature and determining the radiochemical purity at different time intervals post-preparation employing the standard quality control techniques described earlier.

3. Results and discussions

3.1. Production of ^{177}Lu

^{177}Lu was produced by thermal neutron bombardment

Dhruva reactor at our Institute. The radionuclidic purity of ^{177}Lu produced was determined by analyzing the γ -ray spectrum and found to be 99.975%. A typical γ -ray spectrum recorded after the radiochemical processing of the irradiated target exhibited major γ photopeaks at 72, 113, 208, 250, and 321 keV. All of these photopeaks correspond to that of ^{177}Lu (Firestone, 1996). This was further confirmed from the decay as followed by monitoring peak area cps values at those peaks according to the half-life of ^{177}Lu . It is well documented in the literature that there is a possibility of formation of $^{177\text{m}}\text{Lu}$ ($T_{1/2} = 160.5\text{ d}$) on thermal neutron bombardment of Lu target (Neves et al., 2002; Pillai et al., 2003; Nir-El, 2004). However, γ -ray spectrum of the irradiated Lu target after chemical processing did not show any significant peak corresponding to the photopeaks of $^{177\text{m}}\text{Lu}$ (128, 153, 228, 378, 414, 418 keV) (Firestone, 1996). This can be explained from the fact that the radioactivity due to $^{177\text{m}}\text{Lu}$ produced will be insignificant compared to that of ^{177}Lu , owing to its long half-life and comparatively low cross-section ($\sigma = 7$ barns) (Firestone, 1996) for its formation. The trace level of $^{177\text{m}}\text{Lu}$ produced was determined by recording the γ -ray spectrum of a sample aliquot, initially having high radioactive concentration, after complete decay of ^{177}Lu activity (8–10 $T_{1/2}$ of ^{177}Lu , i.e. for a period of 50–70 d). The average level of radionuclidic impurity burden in ^{177}Lu due to $^{177\text{m}}\text{Lu}$ determined by this technique was found to be 250 nCi of $^{177\text{m}}\text{Lu}$ /1 mCi of ^{177}Lu (9.25 kBq/37 MBq) at EOB, which corresponds to 0.025% of the total activity produced.

In order to produce ^{177}Lu with maximum possible specific activity using the moderate flux reactor available at our end, Lu_2O_3 target was irradiated at different available flux positions for different periods of time. Four different flux positions with thermal neutron flux ranging between 1.4×10^{13} and 1.0×10^{14} n/cm²/s were available for irradiation. Since the normal irradiation schedule of this multi-facility reactor allowed irradiation of the target only in

multiples of 7 d, irradiations were carried out for 7, 14, and 21 d. The specific activity of the ^{177}Lu obtained on irradiation of enriched target for varied time durations and at different thermal neutron flux positions are tabulated in Table 1. A maximum specific activity of ~ 23000 mCi/mg (850 GBq/mg) was achieved when irradiation was carried out at a thermal neutron flux of 1×10^{14} n/cm²/s for 21 d, which corresponds to $\sim 21\%$ of the maximum achievable specific activity. It is evident from Table 1 that the specific activities of ^{177}Lu obtained were significantly higher compared to the theoretically calculated values accounting for only thermal neutron capture. A possible reason for practically obtaining an activity higher than theoretically calculated values could be attributed to the contribution from epithermal neutrons (resonance integral = 1087b), which is not accounted for in theoretical calculations (Pillai et al., 2003; Nir-El, 2004; Knapp et al., 1995). However, the contribution from epithermal neutron alone could not provide a satisfactory explanation for obtaining 2.5–2.8 times higher specific activity of ^{177}Lu than that of theoretically calculated values.

Apart from the use of enriched target and choosing the highest available neutron flux position in a reactor, the other factor, which can be optimized for achieving the maximum possible specific activity of a radioisotope produced by neutron activation, is the duration of irradiation. In most cases of radioisotope production using (n,γ) route, irradiation of the target 4–6 times of the half-life of the radioisotope being produced results in maximum specific activity. However, the same does not hold good in case of production of ^{177}Lu by neutron capture, particularly, when the production is being carried out at a comparatively higher neutron flux position, owing to the high thermal neutron capture cross section of ^{177}Lu . In this case, a careful optimization of the time of irradiation needs to be considered in order to obtain the highest specific activity (Pillai et al., 2003). In high flux positions of a

Table 1
Specific activity of ^{177}Lu obtained at different thermal neutron flux for irradiation of different durations

| Neutron flux (n/cm ² /s) | Irradiation time (d) | Activity obtained (mCi/mg) (GBq/mg) | Theoretical activity (mCi/mg) (GBq/mg) | Experimental/theoretical |
|-------------------------------------|----------------------|-------------------------------------|--|--------------------------|
| 1.4×10^{13} | 7 | 2322 ± 102 | 846 | 2.74 |
| | | 85.9 ± 3.8 | 31.3 | |
| 3.0×10^{13} | 7 | 4635 ± 269 | 1814 | 2.56 |
| | | 171.5 ± 9.9 | 67.1 | |
| 3.0×10^{13} | 14 | 7460 ± 253 | 2696 | 2.77 |
| | | 276.0 ± 9.4 | 99.8 | |
| 6.75×10^{13} | 7 | 11000 ± 782 | 4081 | 2.70 |
| | | 407.0 ± 28.9 | 151.0 | |
| 6.75×10^{13} | 14 | 17750 ± 1476 | 6406 | 2.77 |
| | | 656.8 ± 54.6 | 237.0 | |
| 1.0×10^{14} | 21 | 23185 ± 658 | 8622 | 2.69 |

reactor, the target burn up will be considerably higher owing to the high thermal neutron capture cross section of ^{176}Lu and hence, the usual assumption that the number of target atoms remains constant during the period of irradiation will not be valid in this case. Considering the fact that the number of target atoms is not fixed but a function of time, the commonly used differential equation used for the calculation of the activity produced i.e.

$$dN_2/dt = N_1\sigma\phi - N_2\lambda \quad (1)$$

can be modified as

$$dN_2/dt = N^0 e^{-\sigma\phi t} \sigma\phi - N_2\lambda, \quad (2)$$

where N^0 is the number of ^{176}Lu atoms used as target (at $t = 0$), N_1 the number of ^{176}Lu atoms at any time t , N_2 the number of ^{177}Lu atoms at any time t , λ the decay constant of ^{177}Lu , σ the thermal neutron capture cross section of ^{176}Lu , ϕ the thermal neutron flux of the reactor and t the time of irradiation. Solution of the above mentioned modified differential equation leads to the following mathematical expression, which enables calculation of the ^{177}Lu activity (A) produced at EOB, taking into account that the number of the target atoms is also a function of time of irradiation.

$$A = \frac{N^0 \lambda \sigma \phi}{\lambda - \sigma \phi} [e^{-\sigma\phi t} - e^{-\lambda t}] \quad (3)$$

Fig. 1 shows the variation of the theoretically calculated specific activity of ^{177}Lu obtained at EOB with irradiation time at $1 \times 10^{14} \text{ n/cm}^2/\text{s}$ thermal neutron flux. It is evident that the activity of ^{177}Lu produced will be maximum after 21 d irradiation, beyond which, the activity will decrease owing to the high target burn up. Therefore, in order to obtain maximum specific activity of ^{177}Lu using the maximum available flux position in our reactor, the time of irradiation was fixed as 21 d.

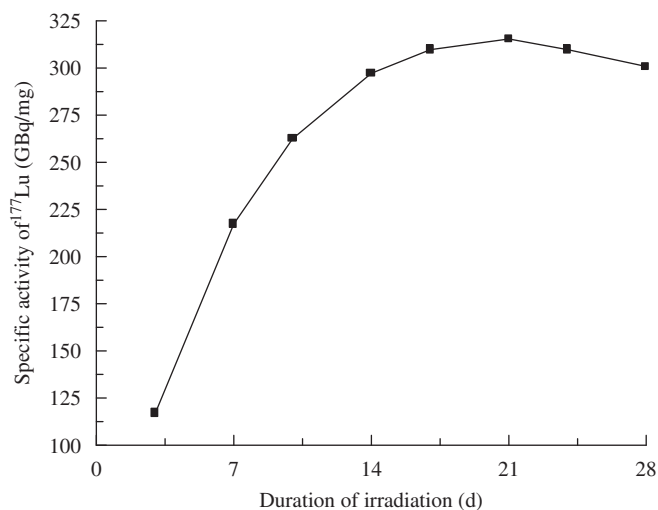


Fig. 1. Variation of theoretically calculated specific activity of ^{177}Lu obtained at EOB with time of irradiation at thermal neutron flux of

3.2. Characterization of ^{177}Lu -DOTA-TATE

In PC using 50% aqueous acetonitrile, the activity corresponding to ^{177}Lu -DOTA-TATE complex moved towards the solvent front with $R_f = 0.8-0.9$, while uncomplexed ^{177}Lu remained at the point of spotting ($R_f = 0$) under identical conditions. The PC patterns of $^{177}\text{LuCl}_3$ and ^{177}Lu -DOTA-TATE complex are shown in Fig. 2.

The ^{177}Lu -labeled DOTA-TATE complex was also characterized by HPLC studies. Fig. 3(a) shows the typical HPLC pattern of ^{177}Lu -labeled DOTA-TATE conjugate prepared under optimized conditions. Fig. 3(b) shows the HPLC pattern of $^{177}\text{LuCl}_3$ under identical conditions. The actual extent of complexation achieved was also determined from the HPLC studies.

3.3. Optimization of complexation yield of ^{177}Lu -DOTA-TATE

Various parameters such as, conjugate concentration, pH of the reaction mixture, reaction time and temperature were varied extensively in order to achieve maximum complexation yield. Keeping the reaction volume as 200 μL , the amount of DOTA-TATE was varied from 5 to 100 μg in order to determine the optimum ligand concentration required for obtaining maximum complexation. It was observed that a minimum of 25 μg DOTA-TATE was required to obtain a complexation yield of 99%. The reaction was carried out by incubating the reaction mixture at three different temperatures (room temperature, 50 and 80 $^\circ\text{C}$) for different time periods (5 min, 15 min, 30 min, 1 h, and 2 h) in order to determine optimum reaction time and temperature. It was observed that, maximum complexation was achieved when the reaction mixture was incubated at 80 $^\circ\text{C}$ for a period of 1 h. It is well documented in the literature that the

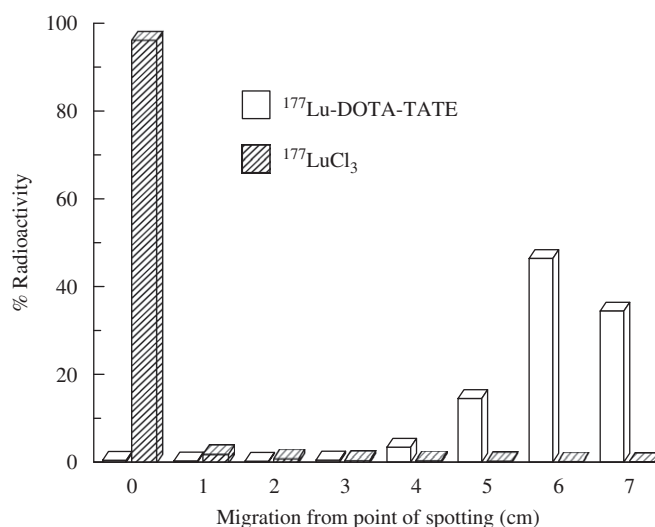


Fig. 2. Paper chromatography patterns of $^{177}\text{LuCl}_3$ and ^{177}Lu -DOTA-TATE.

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