J. Chem. Chem. Eng. 10 (2016) 238-240
doi: 10.17265/1934-7375/2016.05.007

^{177}Hf as a Competitor in the Synthesis of ^{177}Lu-DOTAtate

José de Souza Caldeira Filho

Centro de Tecnologia das Radiações. Instituto de Pesquisas Energéticas e Nucleares - IPEN/CNEN/SP. Av.

Abstract: This study reveals the interference of ^{177}Hf, a decay product of ^{177}Lu, in the synthesis of ^{177}Lu-DOTAtate. In the experiments we followed three ^{177}Lu $t_{1/2}$. The molar ratio Lu: DOTAtate used was calculated for each decay, in two situations: 1) without considering the influence of ^{177}Hf; 2) considering the influence of ^{177}Hf. The results compare both the calculated molar ratio and the radionuclide incorporation yields (%) in these situations. The yields increase when ^{177}Hf influence is considered. This suggests that ^{177}Hf is an important competitor for DOTAtate binding site. These data are relevant in the synthesis of the radiopharmaceutical ^{177}Lu-DOTAtate with high specific activity.

Key words: Hafnium, ^{177}Lu-DOTAtate, molar ratio, radiopharmaceutical.

1. Introduction

In the last two decades, an increasing interest for the ^{177}Lu (Lutetium) radioisotope has been observed in Nuclear Medicine for the development of the radiopharmaceutical somatostatin peptide analogs [1, 2]. These radiopharmaceuticals have been used for diagnosis, but mainly for therapeutic use [3-5] in neuroendocrine tumors.

The ^{177}Lu is prepared by bombarding a target of enriched ^{176}Lu with neutrons. At the end of bombardment a typical lot of Lu contains ~6% ^{177}Hf (Hafnium), ~23% ^{177}Lu, and ~70% ^{176}Lu [6]. These numbers will vary somewhat according to the specific activity of the radioisotope and the radioactive decay. The half-life ($t_{1/2}$) of ^{177}Lu is 6.7 days, and it decays to ^{177}Hf.

Under the conditions normally used for the synthesis of radiopharmaceuticals from DOTA-peptides, the literature has reported that ^{177}Hf does not interfere with the ^{177}Lu labeling [7, 8]. Also, it was reported that the presence of "free" ^{177}Hf in radiolabeling solutions does not compete for ligands during the preparation of ^{177}Lu-AMBA [6], which is another radiopharmaceutical.

This paper presents a study that suggests a competition of ^{177}Hf with ^{177} Lu for the binding site in DOTA, in the synthesis of the radiopharmaceutical ^{177}Lu-DOTAtate.

2. Experimental Section

The peptide DOTAtate (ANASPEC, USA), was diluted in a sodium acetate buffer 0.4 M pH 4.5 (1 μg/mL).

The ^{177}Lu radioisotope (53 Ci/mg) was from the Oak Ridge National Laboratory (ORNL, USA) in the form of $^{177}LuCl_3$ in HCl 0.1 M.

The molar ratio Lu:DOTAtate used in the radiopharmaceutical synthesis was calculated for each decay in two different situations: 1) without considering the influence of ^{177}Hf as a competitor; 2) considering the influence of ^{177}Hf as a competitor in the synthesis.

The synthesis of the radiopharmaceutical ^{177}Lu-DOTAtate was carried out in an ammonium acetate buffer 0.5 M, pH 7.0, temperature 95 °C, 350 rpm for 30 minutes.

The experiments related to the synthesis of ^{177}Lu-DOTAtate were performed 11, 18 and 27 days after the production of ^{177}Lu, respectively, 1.64 $t_{1/2}$, 2.68 $t_{1/2}$ and 4.03 $t_{1/2}$.

Corresponding author: José de Souza Caldeira Filho, Ph.D., research field: new radiopharmaceuticals study, the use of nuclear technology in agriculture-seed germination and management-power and organizational culture.

Table 1 Comparison between the calculated molar ratio Lu: DOTAtate and ^{177}Lu-DOTAtate radionuclide incorporation yields (%) in two situations: 1) without considering the influence of ^{177}Hf; 2) considering the influence of ^{177}Hf.

Half-life ($t_{1/2}$)	1		2	
	Without considering the influence of ^{177}Hf		Considering the influence of ^{177}Hf	
	Molar ratio (*) Lu:DOTAtate	Radionuclide incorporation yields (%)	Molar ratio (*) Lu:DOTAtate	Radionuclide incorporation yields (%)
1.64	1:4.4	5.2 ± 1.5	1:6.7	88 ± 9
2.68	1:8.1	38.1 ± 0.9	1:13.5	98.2 ± 0.7
4.03	1:19	14.4 ± 2.2	1:34.3	69.0 ± 2.1

(*) For details regarding the calculations of molar ratios [9].

All the solutions used were prepared with Milli-Q water, previously treated with chelex 100 (Biorad) chelating resin.

The reaction yield, evaluated as radionuclide incorporation yields (%), was studied in room temperature by ascending chromatography in ITLC-SG, with sodium acetate buffer 0.1 M, pH 5.0 as a mobile phase.

The results are expressed as mean ± SD, n ≥ 3.

3. Results and Discussion

The molar ratios Lu:DOTAtate calculated for the experimental design followed by the ^{177}Lu radionuclide incorporation yield (%) obtained experimentally are presented in Table 1, in two situations: without considering and considering the influence of ^{177}Hf.

Experiments conducted using the molar ratio Lu:DOTAtate calculated without the presence of ^{177}Hf result in low incorporation of radioisotope in the radiopharmaceutical. When the experiments are conducted considering the presence of ^{177}Hf in the calculations, the incorporation of the radioisotope in the radiopharmaceutical is relatively higher. This becomes more evident when the elapsed time in ^{177}Lu half-life is greater, for example in 4.03 $t_{1/2.}$

A radioisotope incorporation greater than 95%, which is suitable for clinical use of the radiopharmaceutical ^{177}Lu-DOTAtate, was not always achieved, since we dealt with limit molar ratios. Thus, small increases in the amount of DOTAtate beyond the limit calculated with the presence of ^{177}Hf would lead to incorporations greater than 95%.

4. Conclusion

The results indicate that ^{177}Hf, a decay product of ^{177}Lu, competes for the DOTA binding site. This discovery was possible due to the schematization with molar ratios (shown in Table 1), which was developed along the research. This procedure is not common in the literature, which typically uses a notation of the radioisotope activity (mCi) in relation to the mass of DOTAtate (μg).

These data will be relevant in the synthesis of the radiopharmaceutical ^{177}Lu-DOTAtate with high specific activity, to be used in peptide receptor radionuclide therapy.

Acknowledgment

The author wishes to thank the colleague from Universidade Federal do ABC, Prof. Dr. Alexander de Freitas, for stimulating discussions.

References

[1] Krenning, E. P., Valkema, R., Kwekkeboom, D. J., De Herder, W. W., Van Eijck, C. H., De Jong, M., Pawels, S., and Reubi, J. C. 2005. "Molecular Imaging as *In Vivo* Molecular Phatology for Gastroenteropancreatic Neuroendocrine Tumours: Implications for Follow-up after Therapy." *Journal of Nuclear Medicine* 46: 76S-82S.

[2] Reubi, J. C., Macke, H. R., and Krenning, E. P. 2005. "Candidates for Peptide Receptor Radiotherapy Today and in Future." *Journal of Nuclear Medicine* 46 (1): 67S-75S.

[3] Schmitt, A., Bernhardt, P., Nilsson, O., Ahlman, H., Kolby, H. R., Maecke, H. R., and Forssel, A. 2004.

"Radiation Therapy of Small Cell Lung Cancer with ^{177}Lu-DOTA-Tyr^{3}-octreotate in an Animal Model." *Journal of Nuclear Medicine* 45: 1542-8.

[4] Teunissen, J. J. M., Kwekkeboom, D. J., and Krenning, E. P. 2004. "Quality of Life in Patients with Gastroenteropancreatic Tumors Treated with [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate." *Journal of Clinical Oncology* 13: 2724-9.

[5] Forrer, F., Usijarvi, H., Storch, D., Maecke, H. R., and Mueller, B. 2005. "Treatment with ^{177}Lu-DOTATOC of Patients with Relapse of Neurondocrine Tumors after Treatment with ^{90}Y-DOTATOC." *Journal of Nuclear Medicine* 46: 1310-6.

[6] Aldo, C., Nicola, d'A., Edmundo, M., Hanh, D. N., Silvio, A., Rolf, E. S., and Karen, E. L. 2009. "Isolation of a Complex Formed by β-Decay of a 177Lu-Labeled Radiotherapeutic Compound and NMR Structural Elucidation of the Ligand and Its Lu and Hf Complexes." *Inorganic Chemistry* 48: 3114-24.

[7] Breeman, W. A. P., De Jong, M., Visser, T. J., Erion, J. L., and Krenning, E. P. 2003. "Optimising Conditions for Radiolabelling of DOTA-peptides with ^{90}Y, ^{111}In and ^{177}Lu at High Specific Activities." *European Journal of Nuclear Medicine and Molecular Imaging* 30: 917-20.

[8] Breeman, W. A. P. 2012. "Practical Aspects of Labeling DTPA-and DOTA-Peptides with ^{90}Y, ^{111}In, ^{177}Lu, and ^{68}Ga for Peptide-Receptor Scintigraphy and Peptice-Receptor Radionuclide Therapy in Preclinical and Clinical Applications." UNM College of Pharmacy, v. 16, lesson 5.

[9] Caldeira, Filho, J. S. 2009. "Síntese, Análise, Purificação e Biodistribuição em Modelo Animal do Radiofármaco ^{177}Lu^{3+}-DOTATATO Para uso DiagnóStico e Terapêutico em Tumores Neuroendócrinos." Ph.D. Thesis, Instituto de Pesquisas Energéticas e Nucleares, Universidade de São Paulo, São Paulo. Recuperado em 2014-08-23, de http://www.teses.usp.br/teses/disponiveis/85/85131/tde-02062009-160531/pt-br.php.