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

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Abstract: This study reveals the interference of 177Hf, a decay product of 177Lu, in the synthesis of 177Lu-DOTAtate. In the experiments we followed three 177Lu t1/2. The molar ratio Lu: DOTAtate used was calculated for each decay, in two situations: 1) without considering the influence of 177Hf; 2) considering the influence of 177Hf. The results compare both the calculated molar ratio and the radionuclide incorporation yields (%) in these situations. The yields increase when 177Hf influence is considered. This suggests that 177Hf is an important competitor for DOTAtate binding site. These data are relevant in the synthesis of the radiopharmaceutical 177Lu-DOTAtate with high specific activity.

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

1. Introduction

In the last two decades, an increasing interest for the 177Lu (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 177Lu is prepared by bombarding a target of enriched 176Lu with neutrons. At the end of bombardment a typical lot of Lu contains ~6% 177Hf (Hafnium), ~23% 177Lu, and ~70% 176Lu [6]. These numbers will vary somewhat according to the specific activity of the radioisotope and the radioactive decay. The half-life (t1/2) of 177Lu is 6.7 days, and it decays to 177Hf.

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

This paper presents a study that suggests a competition of 177Hf with 177Lu for the binding site in DOTA, in the synthesis of the radiopharmaceutical 177Lu-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 177Lu radioisotope (53 Ci/mg) was from the Oak Ridge National Laboratory (ORNL, USA) in the form of 177LuCl3 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 177Hf as a competitor; 2) considering the influence of 177Hf as a competitor in the synthesis.

The synthesis of the radiopharmaceutical 177Lu-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 177Lu-DOTAtate were performed 11, 18 and 27 days after the production of 177Lu, respectively, 1.64 t1/2, 2.68 t1/2 and 4.03 t1/2.

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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.

<table>
<thead>
<tr>
<th>Half-life ($t_{1/2}$)</th>
<th>Without considering the influence of $^{177}$Hf</th>
<th>Considering the influence of $^{177}$Hf</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Molar ratio (*) Lu:DOTAtate</td>
<td>Radionuclide incorporation yields (%)</td>
</tr>
<tr>
<td>1.64</td>
<td>1:4.4</td>
<td>5.2 ± 1.5</td>
</tr>
<tr>
<td>2.68</td>
<td>1:8.1</td>
<td>38.1 ± 0.9</td>
</tr>
<tr>
<td>4.03</td>
<td>1:19</td>
<td>14.4 ± 2.2</td>
</tr>
</tbody>
</table>

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

All the solutions used were prepared with Milli-Q water, previously treated with chelax 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.

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References


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