KIT PREPARATION OF $^{153}$Sm–EDTMP AND FACTORS AFFECTING RADIOCHEMICAL PURITY AND STABILITY

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A fast kit method was developed for the production of $^{153}$Sm–EDTMP in two steps avoiding the use of nitric acid, evaporation and sterilization of the final solution by autoclave. Methods of analysis for the determination of chemical and radiochemical purity in the radiopharmaceutical solution were established. Factors affecting radiochemical purity and stability of the complex as the molar ratio of EDTMP/Sm, concentration of phosphate buffer and neutralization of EDTMP prior kit preparation were also analyzed. The use of this radiopharmaceutical in rabbits and patients showed selective skeletal uptake.

Today there is a new interest in radionuclides and radiopharmaceuticals for the use with therapeutic purpose primarily due to the emergence of sophisticated molecular carriers as for example monoclonal antibodies, receptors, biodegradable particles and colloids. Pain palliation of bone metastases is a field which concentrates great expectation. Bone seeking molecules in combination with medium energy $\beta$-emitter radionuclides seem to be ideal for the treatment of bone pain caused by metastatic lesions.

$^{153}$Sm-ethylenediaminetetramethylene phosphonate (EDTMP) has proven to be an effective radiotherapeutic agent in the treatment of metastatic bone cancer pain due to its selective skeletal uptake high lesion affinity and low toxicity.1–3 In most of protocols for production of $^{153}$Sm–EDTMP, $^{152}$Sm$_2$O$_3$ is dissolved in a solution of nitric acid and then sealed into a quartz glass ampoule. After irradiation, the vial is placed into a heating block with 80 °C and the liquid is evaporated under nitrogen flow to total dryness followed by addition of 0.1N chloride acid, chelation to EDTMP, addition of phosphate buffer and sterilization in an autoclave.4,5

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In this report we present a two step fast kit method, for the production of $^{153}$Sm-EDTMP avoiding the use of nitric acid, evaporation and sterilization of the final solution by autoclave. We also analyzed the factors affecting radiochemical purity and stability of the complex as the molar ratio of EDTMP/Sm, concentration of phosphate buffer and neutralization of EDTMP prior kit preparation.

**Experimental**

*Preparation of EDTMP kit:* A solution for the theoretical number of kits utilizing 100 mg EDTMP (from ICN-Biochemicals and neutralized prior kit preparation using 1.0 ml of 1N NaOH), 2 ml phosphate buffer 0.5M pH 7.4, 1.2 ml sodium hydroxide 1.0N and 2 ml injectable water per kit was prepared in laminar flow hood (under aseptic conditions). The mixture was sterilized by membrane filtration (Millipore, 0.22 µm), then dispensed into presterilized and free pyrogen serum vials and stoppered under vacuum. The same procedure was repeated but using different concentration of the components applying a factorial experimental design (SAS, Statistic Analysis System Software, see Table 1) to determine the influence of the molar ratio of EDTMP/Sm and phosphate buffer concentration on the complex yield and its stability.

*Table 1*

<table>
<thead>
<tr>
<th>Class</th>
<th>Levels</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molar ratio of EDTMP/Sm</td>
<td>6</td>
<td>1.05, 1.75, 3.5, 7, 10.5, 21</td>
</tr>
<tr>
<td>Concentration of phosphate buffer, ml added</td>
<td>4</td>
<td>0.5, 1, 2, 4</td>
</tr>
<tr>
<td>Time, h, stability</td>
<td>2</td>
<td>2, 72</td>
</tr>
</tbody>
</table>

*Dependent variable: radiochemical purity.

Also, in two experiments, we did not neutralize EDTMP prior the kit preparation by adding only 1 ml 0.5M, pH 7.4 phosphate buffer and 1.2 ml of 1N NaOH.

*Preparation of $^{153}$SmCl$_{3}$ solution:* Samarium-153 chloride was obtained by neutron irradiation of 10 mg of enriched Sm$_{2}$O$_{3}$ ($^{152}$Sm, 99.4%, from ISOTEC Inc.) in Triga Mark III reactor at a flux in the central thimble of $3 \cdot 10^{13}$ n · cm$^{-2}$ · s$^{-1}$ for 15 hours.