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GAMMA-RAY IMPURITIES OF ^{111}In, ^{201}Tl, ^{177}Lu AND ^{99m}Tc DETERMINED BY MEANS OF A HPGE SPECTROMETER

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ABSTRACT

This work aims to present the radioactive impurities gamma rays emitters detected in some radiopharmaceuticals widely applied to diagnosis and therapy purposes, supplied to nuclear medicine services in Brazil by the Radiopharmaceutical Center(CR) of Nuclear and Energy Research Institute, IPEN, in São Paulo. The analysis was undertaken by means of an HPGe gamma spectrometer. The radiopharceuticals analyzed were: ^{111}In, ^{201}Tl, ^{177}Lu and ^{99m}Tc.

1. INTRODUCTION

In order to be properly used, the radiopharmaceuticals applied to diagnosis and therapy purposes should have their quality evaluated in accordance with the procedures established by quality control agencies, such as “General Requirements for the Competence of Testing and Calibration Laboratories”, ISO/IEC 17025:2005 [1] and the “Good Laboratory Practice” (GLP) [2]. In Brazil, ANVISA (National Agency Health Surveillance) is the agency that controls radiopharmaceutical quality, requiring a confirmation of the values of impurities related on the certificates supplied by the manufacturers.

To attend this requirement, the Nuclear Metrology Laboratory (LMN) of Nuclear and Energy Research Institute, IPEN, in São Paulo, have quantified by means of an HPGe gamma spectrometer the gamma-ray impurities present in some radiopharmaceuticals supplied by the Radiopharmaceutical Center of IPEN to nuclear medicine services in Brazil.

In this work, the concentration of radioactive impurities gamma emitters, detected in the ^{111}In, ^{201}Tl, ^{177}Lu and ^{99m}Tc radiopharmaceuticals is presented. The determined activities were compared with those presented in the manufactures certificates or with the values established by the European Pharmacopeia [3].

2. METHODOLOGY

2.1. Source Preparation

The samples of the investigated radiopharmaceuticals were prepared in flame-sealed ampoules with 1 mL each, similar to the standard sources used to calibrate the spectrometer. The variation in the height of the solutions was estimated and the geometry and attenuation correction factors were calculated. The variations in these factors were included in the overall uncertainty. The sources mass were accurately determined by the pycnometer technique using a XP56 Mettler balance.

Two distinct source-detector distances, called geometry 1 (G1) and geometry 2 (G2) respectively, were used depending on the samples activities in order to minimize the very high sum coincidence effect at low source-detector distances.

2.2. HPGe Spectrometer

The gamma-ray spectrometer system used to determine the activity of the solutions consists of a REGe Canberra detector model GR1520 with 500 μm thick Be window, yielding 1.79 keV FWHM at 1332.5 keV.

For the 17.9 cm source-detector distance (G1), the gamma-ray full efficiency peak curve was determined in the range between 80 keV and 1408 keV using flamed-sealed ampoules of ^{133}Ba, ^{60}Co, ^{152}Eu and ^{137}Cs standardized at the LMN in the 4πβ-γ coincidence system.

The REGe calibration curve was obtained by a forth degree polynomial in log-log scale, applying least square fitting and considering the covariance methodology for determining all uncertainties.

For the source-detector distance of 1.7 cm (G2), the full energy absorption peak efficiency curve, from 20 keV to 1408 keV, was calculated by a Monte Carlo simulation, by means of the MCNP5 radiation transport code [4] instead of using the standard ampoules, because at this distance the coincidence-summing effect is very high, making the measurement of standard calibration ampoules difficult. A few experimental points were used in order to validate the calculations.

The area under the peak was evaluated by code Alpino, developed at the LMN [5], which applies the method of numeric peak integration. Dead time and pile-up corrections were applied by measuring a reference pulser peak near the upper edge of the gamma spectrum simultaneously with the sources [6]. This method was applied for standards sources, radiophamaceuticals under investigation and for all identified radionuclide impurities, with suitable cascade summing corrections.

For gamma emitter impurities, which did not appeared in the spectra, the decision threshold and the minimum detectable activity were calculated from the background counting rate in the expected peak region by means of the Eq. 1 [7].

$$L_D(E) = \frac{2 \times 1.65}{p(E_\gamma)\,\varepsilon(E_\gamma)\,T}\sqrt{2Bg} \qquad (1)$$

Where:

$p(E_\gamma)$ is the gama-ray emission probability with energy E;
$\varepsilon(E_\gamma)$ is the gama-ray efficiency with energy E, obtained by the efficiency curve;
Bg is the background counting rate in the expected peak region
T is the counting time

2.3. Monte Carlo Simulation

The HPGe total energy absorption peak efficiency for 1.7 cm source-detector distance was calculated by the Monte Carlo code MCNP5 [4]. This code makes use of detailed system geometry, comprising: detector dimensions, beryllium window, aluminum end cap, dead layer and internal hole dimensions, as specified by the manufacturer, Canberra. The radioactive source characteristics were: sealed ampoule with 1 mL, housed in a PPMA (poly(methyl methacrylate)) holder. Therefore, all detection geometry characteristics of the gamma spectrometer were simulated, predicting the behavior of the efficiency curve by Monte Carlo technique with good accuracy. Figure 1 shows the geometry considered in the simulation obtained by means of VISED code, included in the MCNP5 package. All components of the system were considered, indicated by different colors.

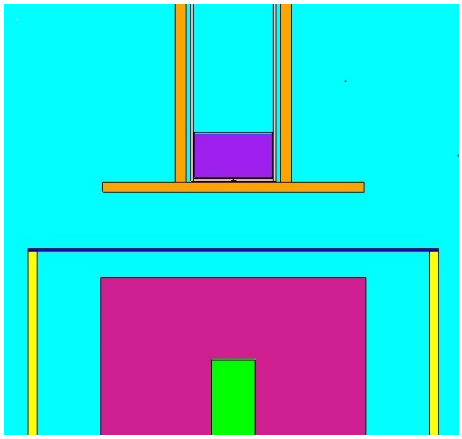

Figure 1. Geometry of the experimental setup. The HPGe detector is shown in pink and hole in light green. The purple color represents the ampoule with radioactive solution in the middle, the orange part represent the PPMA holder. The rectangle that involves the detector is shown in yellow and the end cap in dark blue.

3. RESULTS

Fig. 2. shows the efficiency curve for 17.9 cm source detector distance (G1) fitted by least squares method using LOGFIT code [8], in comparison with the experimental data points; the reduced Chi-square value was 0.91, indicating a satisfactory fit.

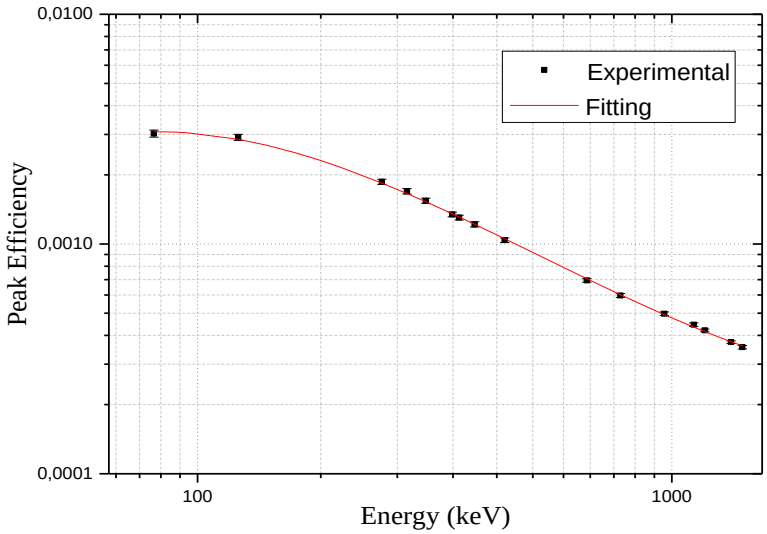

Figure 2: Full energy peak efficiency of the REGe coaxial detector. The black marks correspond to experimental points and the continuous line to fitting.

Fig. 3 shows the efficiency curve for 1.7 cm source detector distance (G2) calculated by means of Monte Carlo simulation.

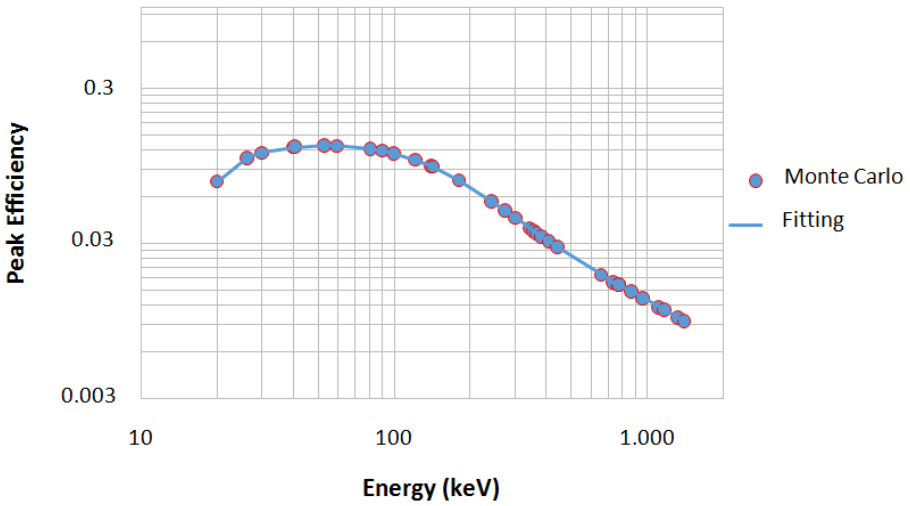

Figure 3: Full peak efficiency curve calculated by Monte Carlo simulation.

All values were calculated with the reference to the date calibration. The radiopharmaceuticals samples were measured at G1 geometry, due to the high level of the activity, while to identify and measure the impurities, the G2 geometry was used.

The results of activities of the radionuclides, the activity of the impurities detected, the impurity ratio to radiopharmaceutical and the manufacture certificate value or the values established by the European Pharmacopeia, for ^{111}In, ^{201}Tl and ^{177}Lu are shown in Table 1, 2, 3, respectively.

Values of activity and/or ratio impurity calculated by means of the decision threshold equation (equation 1) are presented preceded with the less than sign.

Table 1: Activities of the radionuclides; activity of the impurities detected, impurity ratio to radiopharmaceutical and the manufacture certificate value or the values established by the European Pharmacopeia (EP), for ^{111}In.

Radionuclide	Activity* MBq	Impurity	Activity* Bq	Ratio* %	Certificate/ EP %
^{111}In	0.1387 (3)	^{114}In	107 (2)	7.75 (20) x 10^{-2}	0.25
		^{110m}Ag	0.276 (3)	2.00 (22) x 10^{-4}	-

* Absolute uncertainty is given in brackets.

The impurities found in the ^{111}In were ^{114}In, which is in agreement with the specification of the European pharmacopoeia. The presence of ^{110m}Ag was identified by means of the gamma-ray energy of 657.76 keV similar to the gamma energy of ^{110m}In, which was disregarded because of a short half life of 4.9 hours.

Table 2: Activities of the radionuclides; activity of the impurities detected, ratio impurity to radiopharmaceutical and the manufacture certificate value or the values established by the European Pharmacopeia (EP), for ^{201}Tl.

Radionuclide	Activity* MBq	Impurity	Activity* Bq	Ratio* kBq/MBq	Certificate kBq/MBq
^{201}Tl	95.5 (1)	^{200}Tl	<5.93 x 10^{-4}	<1.99 x 10^{-12}	3.1
		^{202}Tl		4.6 (1) x 10^{-6}	2.9

* Absolute uncertainty is given in brackets.

^{201}Tl showed impurities of ^{200}Tl and ^{202}Tl, according described on the certificate and specified by pharmacopoeias.

Table 3: Activities of the radionuclides; activity of the impurities detected, impurity ratio to radiopharmaceutical and the manufacture certificate value or the values established by the European Pharmacopeia (EP), for ^{177}Lu.

Radionuclide	Activity* MBq	Impurity	Activity* Bq	Ratio* %	Certificate %
^{177}Lu	37.07 (4)	^{177m}Lu	9.57 (43) x 10^{3}	0.026 (1)	< 0.05

* Absolute uncertainty is given in brackets.

The main impurity detected in ^{177}Lu was its ^{177m}Lu isomer, and the value found is in agreement with that specified in the manufacturer's certificate of analysis and the specification of the European pharmacopoeia.

The results obtained for the ^{99m}Tc are presented in Table 4. Three samples from distinct manufactures (A, B and C) were investigated.

Table 4: Activities of the radionuclides; activity of the impurities detected, ratio impurity to radiopharmaceutical and the manufacture certificate value or the values established by the European Pharmacopeia (EP), for three samples of ^{99m}Tc.

Radionuclide/ Manufactor	Activity* GBq	Impurity	Activity* Bq	Ratio* %	Certificate/ EP %
^{99m}Tc/ A	1.025 (22)	^{99}Mo	2.638(58) x10^{3}	2.57(9) x10^{-4}	<0.1
		^{103}Ru	<1.09 x 10^{-5}	<1.06 x 10^{-12}	<5x10^{-3}
		^{106}Ru	<1.13 x 10^{-5}	<1.10 x 10^{-12}	
		^{137}Cs	0.22 (7)	2.2 (7) x10^{-8}	
^{99m}Tc/ B	0.3319 (73)	^{99}Mo	54.06 (26)	1.63 (9) x 10^{-5}	<0.1
		^{103}Ru	<7.57 x10^{-6}	<7.39 x 10^{-13}	<5x10^{-3}
		^{106}Ru	<2.62 x10^{-5}	<2.56 x 10^{--12}	-
		^{137}Cs	0.43 (5)	1.28 (2) x10^{-7}	-
^{99m}Tc/ C	4.914 (108)	^{99}Mo	739.18 (30)	1.50(7) x10^{-5}	<0.1
		^{103}Ru	0.323 (6)	3.15(1) x10^{-8}	<5x10^{-3}
		^{106}Ru	<9.27 x 10^{-5}	<9.04 x 10^{-12}	-
		^{137}Cs	0.223 (5)	2.2 (5) x10^{-8}	-

* Absolute uncertainty is given in brackets.

For the ^{99m}Tc samples the main impurity identified was ^{99}Mo and ^{103}Ru as predicted, both within the expected concentrations.

4. CONCLUSION

As proposed, the main gamma-ray impurities present in the radiopharmaceuticals ^{99m}Tc, ^{111}In, ^{177}Lu and ^{201}Tl produced by the IPEN Radiopharmacy Center were identified and quantified.

The results for the emitter gamma impurities analyzed in this work present in the radiopharmaceuticals produced by the CR, are in compliance with the specifications of the adopted pharmacopoeias and the calibration certificates, showing that the outcome are reliable.

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