ABSTRACT

LNMRI has sought to develop a methodology for the identification and accurate detection of impurities emitting gamma radiation at the metrological level, aiming to meet the recommendations not only of the international pharmacopoeia, but also of CNEN and ANVISA regarding quality control that can ensure patients that the doses received by the practices are as low as practicable. As an initial goal, it was possible to obtain an efficiency curve with uncertainty around 1% necessary to start future measurements of interest applied to nuclear medicine and to begin the development of the impurities analysis technique.

Keywords: Radiopharmaceuticals, Radionuclide Impurities, Radionuclide Metrology.
1. INTRODUCTION

Radiopharmaceuticals are preparations consisting of one or more radionuclides and a pharmacological moiety. The use of these radiopharmaceuticals in nuclear medicine facilitates the diagnosis and therapy of patients [1]. In the country, the largest quantity of radiopharmaceuticals is due to $^{99m}$Tc, which presents several useful properties to the patient as a gamma-ray tracer radionuclide [2]. There are thirty-one (31) fully listed radiopharmaceuticals for imaging studies of important organs such as the brain, myocardium, thyroid, lung, liver, bladder, kidneys, skeletal, blood and follow-up as well as tumor treatment. Of the 31 existing ones the main ones used in Brazil are: $^{67}$Ga, $^{123}$I, $^{131}$I, $^{210}$Tl, $^{18}$F and $^{223}$Ra, where all of them can present impurities are emitting gamma radiation (generally according to the production process).

It is important to note that, according to the pharmacopoeia; these impurities must not only be identified but also quantified with a certain level of precision. A standardized radioactive source must always be accompanied by a statement of the presence of all possible and measurable radioactive impurities. It is also important that purity checks be continued over time for the entire working life of a reference source or even a radiopharmaceutical administered to the patient, since the impurities of long half-lives have a longer life and their Percentage of the radionuclides with short half-lives, as is the case with radiopharmaceuticals. Furthermore, it should not be forgotten that the sample radioactive purities deteriorate continuously because of the radioactive decay itself and due to radiation damage around the active material, especially labeled compounds. This problem becomes more pronounced when it comes to the case of radiopharmaceutical applications in patients [1].

The radiopharmaceutical is characterized by a short half-life, but in this mode of production the presence of radionuclide impurities, usually of larger half-lives in relation to the main one, is common. For most purposes of the user of radioactive materials it is necessary to know their specific activities or concentrations of activity and purity, their decay constants and the nature of their radiations, including the energy of each.

Rarely, however, would it be a secondary standardization laboratory that would be assigned to measure or verify more than activity and impurity, and would normally be measured with calibrated equipment using activity standards provided by national laboratories via gamma spectrometry meth-
ods; Purity (chemical and radionuclide) should be the responsibility of the producing center and nuclear data are generally produced by specialized national metrology laboratories with their decay parameters related to radionuclides published in updated tables of nuclear data. Thinking in this light, the LNMRI has sought to develop a methodology for analyzing these impurities in order to have as an end product an internal document where concepts for approaching the subject are well delineated.

Some recent work brings us analyzes related to the control of impurities that can be seen in the work of Ferreira et. Al. [2]. Where, for example, $^{99}$Mo appears as an impurity of the $^{99m}$Tc, with a half-life of 6 h while the impurity has a half-life of 66 h, both emitting gamma radiation. The US pharmacopoeia stipulates an impurity limit with respect to the major radionuclide of 0.15 mCi / mCi (15%) of $^{99}$Mo / $^{99m}$Tc at the reference date.

On the other hand, the gamma spectrometry technique not only identifies how it quantifies radionuclides emitting gamma radiation since it allows distinguishing peaks of very close energies due to their high resolution power. Therefore, it is necessary to develop a procedure using gamma spectrometry techniques to ensure that these limits set by the pharmacopoeia are not exceeded [4..10]

2. OBJECTIVES

The initial objective of this work was to obtain a good efficiency curve with low associated uncertainties (around 1%) as a starting point for the establishment of a methodology for the analysis of radionuclide impurities. With this, it is expected to be able to make feasible the determination of the activity quantity, aiming at the quantification, qualification and determination of nuclear parameters using techniques of gamma spectrometry to ensure that the limits established by the pharmacopoeia are not exceeded.

3. THEORY

3.1 Production of Radiopharmaceuticals and Nuclear Medicine
In Nuclear Medicine, ionizing radiations are emitted from within the patients from incorporated radionuclides and detected externally for imaging. Radiopharmaceuticals are used in well established procedures, based on their selective incorporation by the organs within the human body [3]. In order to succeed in the exam it is necessary that the value of the applied activity be well determined. A lower value may compromise the diagnosis and, therefore, the determination of the activity of the radiopharmaceuticals administered to the patients should have good accuracy. To measure it, the Nuclear Medicine Services use activity meters (activimeters). Basically, this equipment does not distinguish the energies and consists of a well-type detector and a system of processing the signals or the current generated. In the reentrant part of the meter the radiopharmaceutical is placed and may be packed in ampoules, vials or syringes [2]. To detect the activity from the radionuclide of interest it is necessary to make use of another suitable detector with resolution so that it can be identified by the energy; therefore, the germanium detector (HPGe) was used here.

3.1. Radiopharmaceuticals

These are preparations containing one or more radionuclides which, in addition to meeting pharmacopeia specifications, have their production, supply, and storage use and disposal regulated by relevant governmental regulations. Radionuclide emissions of choice should be easily identified and perceived by nuclear detectors so that the dose of radiation to the patient is required for performing the process. About 95% of radiopharmaceuticals are used for diagnosis, while the remaining 5% are used for treatments [2].

4. MATERIALS AND METHODS

The experimental data were obtained through measurements performed at the National Laboratory of Metrology of Ionizing Radiation - LNMRI at the Institute of Radioprotection and Dosimetry. It is the first laboratory stage for the development of the work: the preparation of the measurement system through its calibration. A gamma spectrometry system was used, consisting of a hyperpure
germanium detector (GMX) that allows the identification of radiation with energy of 10 keV to 10 MeV.

4.1 The Efficiency Curve Method

The Efficiency Curve method consists of a methodology to obtain the photoperiod efficiency of a gamma or X spectrometry system. The efficiency of photopeak is defined as the ratio between the rate of radiation detected by the system and the rate emitted by the source [6]. With the use of calibrated standard sources of known energies and intensities, using the same detection system and the same counting geometry, an energy efficiency curve is obtained through the relation:

\[ \varepsilon = \frac{S}{T \cdot A \cdot K \cdot P_r} \] (1)
Where $S$ is energy photopeak area of a standard source at $(s^{-1})$, $T$ is the count time $(s)$, $A$ is activity of standard source at $(s^{-1})$, $K$ is decay factor of the radionuclide standard source, $P_{\gamma}$ is a probability of emission of the gamma radiation of photopeak in $(s^{-1})$ [10].

With the above data we obtain the efficiency curve that will be given by means of an adjustment of experimental points by the LABFIT® that will provide a mathematical adjustment for each type of curve. The format of the mathematical adjustment of the efficiency curve used is given arbitrarily by those who use the program. Some criteria of choice are taken into account such as: physical behavior of the quantities or parameters involved and the mathematical expression in which the value of the correlation factor ($r^2$) of the adjustment should be as close as possible to 1.

5. EXPERIMENTAL PROCEDURES

In order to make the efficiency curve, the AKIRA detector of HPGe model Gem-45P4 (detector with 40% relative efficiency for 1.33MeV of $^{60}$Co), series: 47-JP12399A, positive operating voltage was used. Radionuclide patterns in the puntual geometry of $^{166m}$Ho, $^{152}$Eu, $^{133}$Ba, $^{137}$Cs, $^{134}$Cs, $^{241}$Am, $^{54}$Mn and $^{22}$Na were also used to determine the Energy versus Efficiency points.

Table 1. Some energies of radionuclidic standards

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>Principal energies</th>
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<tbody>
<tr>
<td>$^{166m}$Ho</td>
<td>184.4 keV</td>
</tr>
<tr>
<td></td>
<td>711.7 keV</td>
</tr>
<tr>
<td>$^{152}$Eu</td>
<td>121.78 keV</td>
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<td></td>
<td>244.69 keV</td>
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<tr>
<td></td>
<td>344.28 keV</td>
</tr>
<tr>
<td>$^{133}$Ba</td>
<td>81.00 keV</td>
</tr>
<tr>
<td></td>
<td>356.01 keV</td>
</tr>
<tr>
<td>$^{137}$Cs</td>
<td>661.66 keV</td>
</tr>
<tr>
<td>$^{134}$Cs</td>
<td>604.70 keV</td>
</tr>
<tr>
<td></td>
<td>795.85 keV</td>
</tr>
<tr>
<td>$^{241}$Am</td>
<td>59.54 keV</td>
</tr>
<tr>
<td>$^{54}$Mn</td>
<td>1022.21 keV</td>
</tr>
<tr>
<td></td>
<td>1115.87 keV</td>
</tr>
<tr>
<td>$^{22}$Na</td>
<td>511 keV</td>
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<td></td>
<td>1274 keV</td>
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</tbody>
</table>

The respective standards were selected in the LNMRI, each one in the point sources geometry. The sources were positioned at a distance $d = 20$ cm from the top of the detector and a geometry fixture
was used to ensure reproducibility of the measurements. The data acquisition was performed considering MAESTRO® software associated to a multichannel of 16000 channels. Counts were obtained by considering a 24 hours measurement time interval for each standard. The spectrum obtained gives the counts for each peak of interest with good accuracy in addition to providing data such as live time and real-time counting and dead time.

6. RESULTS AND DISCUSSION

In this first preliminary step, the patterns in the point geometry were measured during a 1-day average time interval at a fixed source-detector distance of 20 cm. It is important to emphasize that when performing long measurements, we are improving the counting rate and decreasing some of the associated uncertainties since the dead time is very low (less number of pulse stacks) [1]. With the measured energy it was possible to construct an efficiency curve that presented uncertainties of the order of 1% for the calculated efficiencies. Figure 2 represents the efficiency curve for the AKIRA detector that will be used in the next.

![Efficiency curve](image)

**Figure 2:** Efficiency curve obtained for the spectrometry system using patterns in dot-geometry.
7. CONCLUSIONS

In this first step we were able to first establish an overview of the bibliographies that carried out studies for the quantification and/or analysis of radionuclide impurities each with a particular criterion. Here, it was possible to establish an efficiency curve that will be needed to start future measurements of radiopharmaceuticals of interest in nuclear medicine. In initial criterion, this stage was important because it will act as mediator of the next steps of the development of said methodology of analysis of radionuclide impurities.

REFERENCES

1. Journal


