Primary activity standardization of $^{177}$Lu for calibrating commercial dose calibrator

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Abstract. Primary activity standardization of $^{177}$Lu has been conducted at the Center for Technology of Radiation Safety and Metrology–National Nuclear Energy Agency (PTKMR-BATAN) to establish a national reference standard for $^{177}$Lu measurements. The standardization was performed using a 4πβ(LS)-γ coincidence counting system with digital coincidence counting (DCC) technique. The activity standardization of $^{177}$Lu gave a result of 148 kBq/g ± 1.78 kBq/g at a reference time with uncertainty value evaluated at $k = 2$. The result was then used to establish a secondary standard by calibrating the reference ionization chamber using the ‘dialing-in’ method. A dial setting value of 024 was obtained on the standard reference IC. The new dial setting will be used in the routine calibration services of commercial dose calibrator to ensure all measurements of $^{177}$Lu are traceable to the national standards.

1. Introduction

Lutetium-177 ($^{177}$Lu) is one of the rare-earth radionuclides that became very important recently due to its application in radiotherapy. The $^{177}$Lu decays by beta-emission to the ground state and to three excited levels of $^{177}$Hf with a half-life of $T_{1/2} = 6.647$ (4) days [1]. These physical decays provide at least two advantages for the use of $^{177}$Lu in radiotherapy. First, the maximum beta energy of 498 keV make it suitable for the treatment of small-size cancer and also will result in less damage to the healthy tissue around the cancer cells being irradiated. The second advantage is due to the gamma-emissions with energies 113 keV (6.2%) and 208 keV (10.4%) which can be used for imaging purposes [2]. A simplified decay scheme of $^{177}$Lu is shown in Fig.1.

As a radiopharmaceutical, the use of $^{177}$Lu is classified as high pharmaceutical risk products. Therefore, it must be very carefully characterized in terms of three main parameters: physicochemical, metrological, and biological [3]. The metrological parameter, in particular, precise and accurate measurements of activity, is crucial as it determines directly the effective dose given to the patient. The only way to ensure that the measurements of activity are being made accurately and consistently is for them to be traceable to the national or international standards [4]. The traceability can be obtained through a calibrated sources or calibration service provided by the National Metrology Institute (NMI) or Designated Institute (DI) [5]. Therefore, as a DI, it is necessary for the Center for Technology of Radiation Safety and Metrology–National Nuclear Energy Agency (PTKMR-BATAN) to conduct a
primary activity standardization of this radionuclide to provide a standard to be used as a reference in
the activity measurement of $^{177}$Lu in hospitals and industries.

Due to its short half-life, the standard reference of $^{177}$Lu was established in terms of the calibration
factor of the reference ionization chamber (IC). This calibration factor provides a critical repository for
the results of activity standardization. In this way, standardization that performs at a different time can
be compared by appeal to the reference ionization chamber [6]. The calibration factor was determined
based on the results of the primary activity standardization of $^{177}$Lu using the $4\pi\beta-\gamma$ coincidence counting
method. In the case of IC and other commercial dose calibrators, the calibration factor is commonly
obtained by determining the appropriate dial setting of the instrument for $^{177}$Lu measurement.

![Fig. 1. Simplified decay scheme of $^{177}$Lu.]

2. Methodology

2.1. $^{177}$Lu Sample preparation

Source solution of $^{177}$Lu used in this experiment was provided by the Center for Radioisotope and
Radiopharmaceuticals Technology –National Nuclear Energy Agency (PTRR–BATAN) in the form of
$^{177}$LuCl$_3$. The radioactive $^{177}$Lu was produced at the Multi-Purpose GA Siwabessy Reactor-BATAN by
neutron irradiation of isotopically enriched $^{176}$Lu$_2$O$_3$ target, which was then dissolved in 2 mL of 6M
HCl and 2 mL of H$_2$O$_2$. The mixture was then heated to dryness and re-dissolved with 3 mL of 0.5 M
HCl [2].

Two type of samples were prepared, liquid scintillation (LS) sample for activity standardization using
the $4\pi\beta$($\text{LS}$)-$\gamma$ coincidence counting system, and liquid samples in glass vials for calibrating the
reference IC. The LS samples were prepared in Ultima Gold™ (UG) and Hionic Fluor (HF) cocktail
solutions. Three samples for each cocktail solution were prepared by gravimetrically adding the aliquots
of $^{177}$Lu solution into 10 mL of cocktail in a 20 mL vial glass. Each samples series comprised one sample
without a $^{177}$Lu solution in order to measure the background counting rate, which was then subtracted.
Source masses on the sample of both series were ranged between 9 mg and 46 mg. For IC calibration,
two samples with a mass around 3.7 mg were prepared in glass vials.

2.2. Measurement

2.2.1. Activity standardization by $4\pi\beta$($\text{LS}$)-$\gamma$ coincidence counting. The $4\pi\beta$$\gamma$ coincidence counting
method is one of the most powerful methods for direct measurement of activity and is applicable to all
radionuclides decaying by two or more coincidence emission [7]. The same method was also used by
Kossert, et al., (2012) and Rezende, et al., (2012) to standardize the $^{177}$Lu using the proportional counter
(PC) as beta detector [8][9]. In this experiment, we use liquid scintillation (LS) cocktail solution as beta
detector instead of using the PC. The LS provides a much easier in sample preparation as well as a better
efficiency for beta detection.
Using this method, the activity of $^{177}$Lu can be determined based on three parameters obtained from measurements, the $N_\beta$, $N_\gamma$, and $N_c$. The experimental extrapolation curve of $N_\beta N_\gamma/N_c$ for $(1-\varepsilon_\beta)/\varepsilon_\beta$ was used to get the activity value which defined in equation (1).

$$\frac{N_\beta N_\gamma}{N_c} = A \left[ 1 + C \left( \frac{1-\varepsilon_\beta}{\varepsilon_\beta} \right) \right]$$  \hspace{1cm} (1)

where $A =$ activity; $\varepsilon_\beta =$ detection efficiency in the beta channel, $N_\beta$, $N_\gamma$, and $N_c =$ counting rates for the beta, gamma, and coincidence channels, respectively; and $C$ is a constant that represents the slope of equation (1). Using the computer discrimination for the variation of $\varepsilon_\beta$ and by applying the least square method, the activity value can be obtained from the extrapolation curve when the $\varepsilon_\beta$ tends to unity.

The activity of $^{177}$Lu was determined based on coincidence events between beta and gamma in gamma windows 112.95 keV and 208.37 keV using a $4\pi$ $\beta$(LS)-$\gamma$ coincidence counting system. The system consists of two NaI(Tl) detectors for gamma detection and liquid scintillation detector with two PMTs for beta detection. A schematic diagram of the system is shown in Fig.2.

![Fig. 2. Schematic diagram of the 4$\pi$ $\beta$(LS)-$\gamma$ coincidence counting system.](image)

The high voltage on both gamma channel was set at 750 V with no window setting is required as data acquisition was performed using a digital sampling technique. The technique was adopted from Lee et al., (2011), which has been proven to give a good result on primary activity standardization of $^{60}$Co [10]. The shaping time for both gamma and beta were set at 3 $\mu$s with the threshold level set at 30 mV and 150 mv for beta and gamma, respectively. A 2600 V high voltage was applied for the beta anode and 700 V for beta dynode channel. We set the beta-beta resolving time at 0.5 $\mu$s and beta-gamma resolving time at 1.0 $\mu$s with the time delay of beta signals to gamma signals set at -1.05 $\mu$s to obtain optimum coincidence counts.

2.2.2. Impurities check by Gamma spectrometry. The impurities of the $^{177}$Lu solution were checked using the NaI(Tl) detector attached to the 4$\pi$ $\beta$(LS)-$\gamma$ coincidence counting system. The spectrum from measurement was analyzed for any impurities using the data from the Table of Radionuclides as the reference of $^{177}$Lu gamma emissions.

2.2.3. Calibration of the ionization chamber. In this experiment, Capintec CRC 7-BT is used as the secondary standard reference IC. Using the activity value from the standardization of $^{177}$Lu as a reference value, the standard reference IC was calibrated by determining the dial setting using the ‘dialing-in method’ as described by Zimmerman and Cessna (2000) [11]. The setting was then used as the reference in calibrating other commercial dose calibrators. The calibrations were performed using a relative method by comparing the measurement results of standard reference IC with the results from other dose calibrators.
3. Results

The impurities of $^{177}$Lu solution were checked by NaI(Tl) detectors using the same sample used in the activity determination. A typical of gamma spectrum obtained from the measurements is shown in Fig. 3. The result shows that there are no other nuclides detected on the $^{177}$Lu solution. Compared to the works performed by Kossert, et al., (2012) and Rezende, et al., (2012) who use an HPGe type detector, the $^{177m}$Lu was able to be detected by observing its energy at 378.5 keV and 418.5 keV, while our results from NaI(Tl) detector shows that there are no peaks detected other than gamma emissions from the $^{177}$Lu. Another work that use the same method to produce the radioactive $^{177}$Lu was also detected some $^{177m}$Lu impurities at the level of 0.02% [11]. Based on those results, we consider that the reason for $^{177m}$Lu not detected in our results is due to the limitation of our gamma spectrometry system. Therefore, the impurities of $^{177}$Lu were taken into account as type B in our uncertainty analysis.

Fig. 3. shows the typical beta and gamma spectrum from the activity measurement of LS samples by $4\pi$β(LS)-γ coincidence counting system. Three data files are generated for each measurement of LS sample, one for the gamma detection channel, and two for the beta detection channels. A data pre-processing program written in FORTRAN was used to analyze all three data files to extract the time and amplitude of the peaks and to obtain the histograms showing the pulse height distributions and time intervals. From the pre-processed data, the two beta files were merged to obtain the events that only detected on both channels within the resolving time. The final data set containing all the three count rates, their standard uncertainties and the error matrix for each beta discrimination level were generated. The count rates were then plotted into an efficiency curve in terms of $N_{\beta}/N_c$ as a function of $(1-\varepsilon_{\beta})/\varepsilon_{\beta}$.

Fig. 4. shows the efficiency curve with y-axis is the three parameters obtained from the measurements and x-axis is the efficiencies of beta detection. The linear fit was performed using a generalized least squares method to obtain the final activity value at 100% of beta efficiency.

The activity values for both UG and HF samples series as of the reference time are given in Table 1, with uncertainties value evaluated based on GUM - JCGM, (2008) [12]. The uncertainty budget for activity standardization of $^{177}$Lu is given in Table 2. The final value of the $^{177}$Lu activity is $148.64 \pm 1.78$ at the reference time with quoted uncertainty in $k = 2$. 

![Image](image-url)
Fig. 4. Typical of efficiency extrapolation curve from the activity standardization of $^{177}$Lu.

Taking the above result as a reference, a calibration setting value for $^{177}$Lu measurement on the reference IC was determined by changing the dial setting. Using this method, a dial setting of 024 was found to provides an equal activity value with the reference value. This new dial setting represents the calibration factor and will be used in the routine calibration services of commercial dose calibrator to ensure all the measurements of $^{177}$Lu are traceable to the national standards.

Table 1. Activity standardization of $^{177}$Lu.

| Sample ID  | Specific Activity (kBq/g) |
|------------|---------------------------|
| $^{177}$Lu_UG | 149.73 ± 1.79             |
| $^{177}$Lu_HF | 147.55 ± 2.07             |

Table 2. Relative standard uncertainty budget for activity standardization of $^{177}$Lu.

| Parameter              | Type | Relative standard uncertainty (%) |
|------------------------|------|-----------------------------------|
| SD of counting         | A    | 0.40                              |
| Weighing               | B    | 0.25                              |
| Half-life of $^{177}$Lu| B    | 0.02                              |
| Impurities of $^{177}$Lu| B   | 0.02                              |
| Eff. Extrapolation     | B    | 0.30                              |
| $\beta-\beta$ resolving time | B  | 0.22                              |
| Combined standard uncertainty |   | 0.60                              |
| Expanded uncertainty   |      | 1.20                              |

4. Conclusion

A new measurement standard for $^{177}$Lu has been established by the Center for Technology of Radiation Safety and Metrology-National Nuclear Energy Agency. The final value of the $^{177}$Lu activity is $148.64 \pm 1.78$ at the reference time with expanded uncertainty $1.20\%$ at $k = 2$. A dial setting value of 024 was obtained on the standard reference IC. The new dial setting will be used in the routine calibration services of commercial dose calibrator to ensure all measurements of $^{177}$Lu are traceable to the national standards.
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