Half-life measurement of the medical radioisotope ^{177}Lu produced from the ^{176}Yb(n,γ) reaction

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Abstract. ^{177}Lu is a medium energy beta-emitter commonly used in Nuclear Medicine for radiotherapeutic applications. In this work, the half-life of ^{177}Lu has been measured using a re-entrant ionisation chamber over a period of 82 days (approximately 12 half-lives). Unlike the majority of previous studies, the material used in this work was produced via the ^{176}Yb(n,γ)^{177}Yb reaction followed by the β-decay to ^{177}Lu, producing insignificant quantities of ^{177m}Lu. This has resulted in the most precise half-life measurement of ^{177}Lu to date. A half-life of 6.6430 (11) days has been determined. This value is in statistical agreement with the currently recommended half-life of 6.6463 (15) days (z-score = 1.8).

1. Introduction

Lutetium-177 is commonly used in the radiotherapeutic treatment of neuroendocrine tumours and relapsed non-Hodgkin Lymphoma [1,2]. Lutetium-177 decays by the emission of medium energy β particles with a maximum β energy of 498.3 (8) keV to excited and ground states of the stable ^{177}Hf nucleus [3]. These β particles have a maximum tissue penetration of approximately 1–2 mm [4]. The excited states (life-times $<$ 1 ns) of ^{177}Hf decay via characteristic γ-ray emissions to the ground state, with the most abundant γ rays being from the 9/2$^+$ level (112.9 keV) and 9/2$^-$ level (208.4 keV) (see Fig. 1) [3]. These γ-ray emissions provide ^{177}Lu with the benefits of both radiotherapeutic treatment and imaging capability [4].

There are two methods used for the production of medically suitable ^{177}Lu; 1) via the ^{176}Lu(n,γ)^{177}Lu reaction, which results in the production of significant quantity of ^{177m}Lu ($T_{1/2} \sim 160$ days) as an impurity or 2) produced via the ^{176}Yb(n,γ)^{177}Yb reaction followed by β^- decay to ^{177}Lu, which produces no carrier added (n.c.a) ^{177}Lu. This second production mode is claimed to produce significantly smaller activity ratios of the ^{177m}Lu impurity to the desired ^{177}Lu product [5].

There have been 14 previous publications reporting half-life measurements of ^{177}Lu [6–19], which are summarised in Table 1. Of these only the measurement reported by Dryak et al. [18] has used ^{177}Lu from production method 2) and therefore not required corrections for the ^{177m}Lu impurity. In a recent evaluation, Kellett [20] identified that the presence of ^{177m}Lu has had a significant influence on the half-life determinations, while Pommé et al. [14] observed that the omission of the impurity subtraction led to a 0.5% error in their determined half-life after only 7.6 days in their measurement campaign. A recent investigation at IFIN-HH [19] has highlighted the difficulty in determining an accurate activity ratio between the ^{177}Lu and ^{177m}Lu. Therefore, for an accurate half-life determination it would be beneficial that insignificant levels of ^{177m}Lu were present to cause interferences in the measured exponential decay of the ^{177}Lu activity.

The work reported here has used ^{177}Lu generated from the ^{176}Yb(n,γ)^{177}Yb reaction to determine a precise half-life value. The associated uncertainty budget is presented. Throughout this article, uncertainties are stated as standard uncertainties or combined standard uncertainties as defined in the Guide to the Expression of Uncertainty in Measurement (GUM) [21].

2. Experimental conditions

2.1. Source preparation

An aqueous solution of ^{177}Lu n.c.a was received from Isotope Technologies Garching GmbH (ITG) and diluted at the National Physical Laboratory (NPL) using an aqueous solution of 0.04 M HCl containing stable lutetium at a concentration of 10 μg g^{-1}. A nominal mass of 10 g of this solution was gravimetrically dispensed to a 10 mL flame sealed glass ampoule [22] with a total activity of 200 MBq at the start of the measurement campaign. A 1 g aliquot was dispensed to a 2 mL ISO ampoule for impurity assay by high purity germanium (HPGe) γ-ray spectrometry.

Additionally, 233 days after the start of the measurement campaign ($\sim$ 35 half-lives of ^{177}Lu), the solution from the 10 mL ampoule was transferred to a 20 mL plastic vial, for assay by HPGe γ-ray spectrometry for the presence of ^{177m}Lu in the absence of ^{177}Lu.

2.2. HPGe γ-ray spectrometer

The 2 mL ISO ampoule was assayed at the start of the campaign using a 20% relative efficiency coaxial n-type HPGe γ-ray spectrometer to check for the presence of any γ-ray emitting radionuclides in the solution. No γ-ray emitting radionuclide impurities were detected. The 10 mL aliquot used for the half-life measurement was assayed 233 days after the start of the campaign using a

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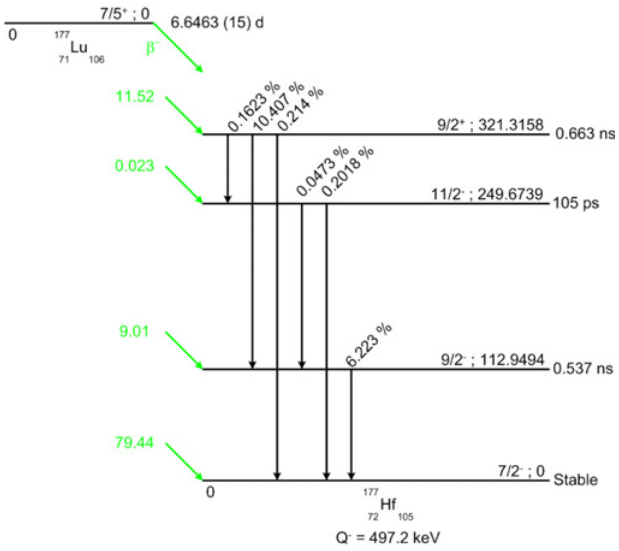

Figure 1. Decay scheme of ^{177}Lu [3].

Table 1. Summary of published half-lives of ^{177}Lu.

Reference	$T_{1/2}$	$\sigma(T_{1/2})$
	/d	/d
Betts *et al.* (1958) [6]	6.75	0.05
Schmid and Stinson (1960) [7]	6.74	0.04
Emery *et al.* (1972) [8]	6.71	0.01
Lagoutine and Legrand (1982) [9]	6.645	0.030
Abzouzi *et al.* (1990) [10]	6.7479	0.0007
Schötzig *et al.* (2001) [11]	6.646	0.005
Zimmerman et al. (2001) [12]	6.65	0.01
Schrader (2004) [13]	6.6475	0.0020
Pommé *et al.* (2011) [14]	6.6465	0.0050
Kossert *et al.* (2012) [15]	6.639	0.009
Fitzgerald (2012) [16]	6.640	0.010
Rezende *et al.* (2012) [17]	6.681	0.006
Dryak *et al.* (2015) [18]	6.645	0.003
Luca *et al.* (2015) [19]	6.645	0.017
Recommended value [20]	6.6463	0.0015
This work	6.6430	0.0011

50% relative efficiency semi-planar p-type HPGe γ-ray spectrometer. The presence of ^{177m}Lu was identified at this stage, and an activity per unit mass of 0.793 (23) Bq g^{-1} at the start of the campaign was determined. This equates to a ^{177m}Lu/^{177}Lu activity ratio of 1.1 $\times$ 10^{-7}% at the start of the campaign.

Both γ-ray spectrometers had been previously calibrated for their full-energy peak detection efficiency using radionuclide standard solutions, in matching geometries, traceable to national standards.

2.3. Ionisation chamber

The half-life of ^{177}Lu was measured using the NPL secondary standard re-entrant ionisation chamber (IC) [23]. The system is comprised of two identical TPA Mk II ionisation chambers [23], filled with argon gas at a pressure of 2 MPa, connected in a "back-to-back" formation as previously described by Fenwick *et al.* [24]. Each IC is surrounded by an inner 5 cm thick lead shield and an outer 10 cm thick lead shield. The "back-to-back" formation and the dual lead shield reduces the background noise and consequently the effect of the background in low current measurements. The background was measured daily before starting the ^{177}Lu measurements (see Fig. 2a).

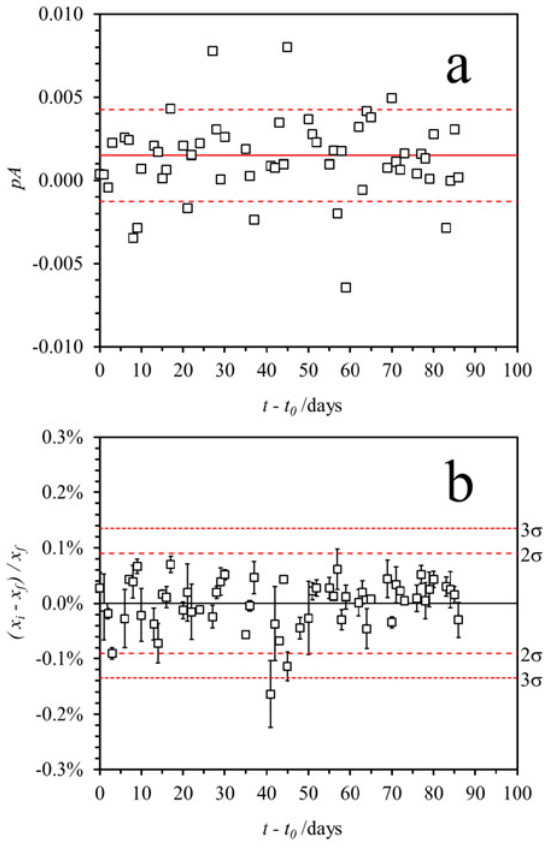

Figure 2. a) Background measurements and b) residuals of the stability checks measurements using a ^{226}Ra check source. The uncertainties in the graph correspond to the standard error of the mean of 2 measurements of 6 cycles each.

The mean background over the course of the campaign was 1.2 (23) $\times$ 10^{-6} pA. The ratio of the mean background/^{177}Lu current was 0.0003% at the start of the measurement campaign, 0.02% after 38 days and 1.2% at the end of the measurement campaign (82 days). A ^{226}Ra check source was measured prior to the ^{177}Lu measurements to check the stability of the system (see Fig. 2b). The variations of the ^{226}Ra were attributed to the check source geometrical reproducibility in the well of the IC and statistical variations. For the ^{177}Lu measurements, the 10 ml ampoule was placed in a dedicated plastic holder for reproducible positioning in the well of the ionisation chamber.

3. Measurement results

A total of 11370 individual measurements were acquired over a period of 82 days ($\sim$ 12 half-lives), shown in Fig. 3a. The measurements were grouped in sets of ten

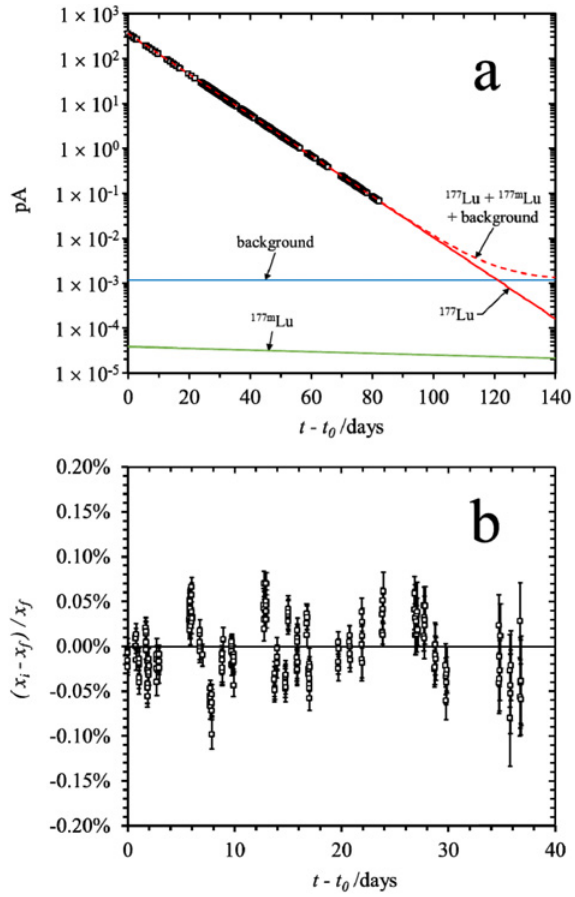

Figure 3. The ionisation chamber current response to the ^{177}Lu source as a function of time (hollow squares) is shown in a). The mean background current, fitted exponential decay curves of ^{177}Lu and ^{177}mLu and the sum of these components are shown. The residuals of the least squares fit to the selected measurements in the initial 36.8 days are shown in b), the uncertainty bars represent the standard deviation of the mean of the ten measurements.

and the standard uncertainty for each data point was determined from the standard deviation of the mean of the ten measurements. In the course of the measurement campaign the source was repositioned a total of 37 times over the 82 days. The number of measurements made for each repositioning were not equal, therefore to remove possible biases due to any repositioning, the same number of measurements were used for each positioning. The half-life was determined from the least squares fit of:

$$A_t = a_0 k_a e^{-\lambda_1 t} + b_0 k_b e^{-\lambda_2 t} + C \qquad (1)$$

where A_t is the IC response at time t, a_0 and b_0 are the respective responses to ^{177}Lu and ^{177m}Lu at $t = 0$, C is the background response, λ_1 and λ_2 are the decay constants of ^{177}Lu and ^{177m}Lu respectively. As the measurement times varied over the campaign period an additional correction factor $[k = (1 - e^{-\lambda \Delta t})/\lambda \Delta t]$ was incorporated to account for decay during the measurement, where Δt is the measurement time.

Using fixed values for b_0, C and λ_2, the half-life of ^{177}Lu was derived by the iterative refinement of parameters a_0 and λ_1, where the sum of squares of the relative deviations between calculated and measured values were minimised. A final ^{177}Lu half-life of 6.6430 (11) days was determined. The relative residuals of the least squares fit to the data are shown in Fig. 3b.

Table 2. Half-life of ^{177}Lu and respective uncertainty.

Component	σ_A/A	n	**factor**	$\sigma_{T_{1/2}}/T_{1/2}$
Standard deviation of residuals	0.034%	230	0.05	0.0016%
Repositioning	0.050%	24	0.15	0.0074%
Stability	0.020%	1	0.52	0.010%
Background	0.018%	1	0.52	0.0090%
Linearity	0.010%	1	0.52	0.0052%
^{177m}Lu Impurity	0.000026%	1	0.52	0.000014%
$T_{1/2}(^{177}\mathrm{Lu})$	6.6430 (11) days			0.0017%

4. Uncertainty

The uncertainty of each component was calculated using the uncertainty propagation formula proposed by Pommé [25] and combined in quadrature to determine the standard uncertainty of the half-life. The uncertainty budget is presented in Table 2.

The main sources of uncertainty are the systematic errors associated with the detector stability and the background subtraction. As the background value C has a high systematic relative uncertainty (see Sect. 2) the uncertainty contribution of the background subtraction increases significantly as the measured current reached low currents. Due to this effect there was no benefit to the accuracy of the measurement in using the entire dataset. Therefore, the initial 36.8 days ($\sim$ 5.5 half-lives) of the measurement campaign were found to provide the optimum balance for the assessment of the uncertainty budget. This provided a total of 230 sets of 10 measurements for the half-life determination.

The low frequency components of uncertainty are not visible in the residuals plot, therefore an attentive analysis needs to be performed. In this paper, a conservative approach was considered for the analysis of the low frequency components, therefore $n = 1$ for the stability, linearity, background and impurity components. The standard deviation of the ^{226}Ra measurements was used to estimate the uncertainty associated with the electrometer stability, all the measurements from day 0 to 82 were included. The standard deviation of the background measurements was also included in the uncertainty associated with the background. The uncertainty associated with the presence of ^{177m}Lu is also reported in table and is shown to be negligible. The system linearity has been tested previously for the DVM range 1 V to 10 V and the uncertainty associated was estimated to be 0.010%.

5. Discussion

Previous publications highlighted the issues of using ^{177}Lu from the ^{176}Lu(n,γ)^{177}Lu reaction, due to the production of the long lived impurity ^{177m}Lu [14, 19, 20]. Several

authors have reported the activity ratio between the activity of ^{177m}Lu and the activity of ^{177}Lu in solution: A(^{177m}Lu)/A(^{177}Lu)= 0.007% [11] A(^{177m}Lu)/A(^{177}Lu)= 0.031% [15], A(^{177m}Lu)/A(^{177}Lu)= 0.035% [17] and A(^{177m}Lu)/A(^{177}Lu)= 0.02% [19].

The first published values (from 1958 and 1990) for the determination of the half-life used ^{177}Lu from the ^{176}Lu(n,γ)^{177}Lu reaction, however no correction was applied for the presence of the ^{177m}Lu impurity, resulting in an overestimation of the half-lives values determined [6–8, 10], with the exception of the value reported by Lagoutine and Legrand (1982) [9].

For this work ^{177}Lu from the ^{176}Yb(n,γ)^{177}Yb reaction was used and showed to be advantageous in determining a more accurate half-life, since no additional correction for the ^{177m}Lu response was required. The low activity of ^{177m}Lu present in the solution was found to have no effect in determining the half-life of ^{177}Lu. Dryak et al. [18], reported a detection limit of 6×10^{-9} for ^{177m}Lu when using ^{177}Lu n.c.a., confirming the results presented in this paper regarding the negligible amount of impurity present in solution for this method of production.

Previous published values showed that the presence of ^{177m}Lu and the effect of background when measuring low currents in the ionisation chamber are the components with the highest impact in the uncertainty budged [13, 14, 19]. The improved uncertainty achieved in this work compared to previous published values is due to a combination of: the negligible amount of ^{177m}Lu present, low background (due to the "back-to-back" formation and the dual lead shield) and the high starting ^{177}Lu activity. These allowed the useful measurement campaign to extend over 36.8 days (over five half-lives), which resulted in an uncertainty propagation factor that allowed the significant reduction of the initial uncertainty component estimates.

The determined value in this work of $T_{1/2}(^{177}\text{Lu}) = 6.6430\ (11)$ days is the most accurate value to date. It was found to be in agreement with the recommended value of 6.6463 (15) days (z-score = 1.8). [20].

6. Conclusion

This work used a n.c.a. ^{177}Lu solution produced by the ^{176}Yb(n,γ)^{177}Yb reaction followed by β decay to ^{177}Lu. This production mode was found to contain negligible ^{177m}Lu activity, with an activity ratio of ^{177m}Lu/^{177}Lu = 1.1×10^{-7}% determined at the start of the measurement campaign.

The half-life of ^{177}Lu was measured using a re-entrant ionisation chamber over a campaign period of 82 days. A total of 11370 measurements were acquired. To obtain a good balance between the campaign length and the standard uncertainty only the first 36.8 days ($\sim$5.5 half-lives) of the measurement campaign were used to determine the half-life.

The value of the ^{177}Lu half-life was determined by a least squares fit of an exponential decay to the measured data. A half-life of 6.6430 (11) days was determined, with a full uncertainty budget presented. This value is the most accurate and precise value to date due in part to the low background of the IC and the negligible ^{177m}Lu content. This value was found to be in good agreement with the current recommended value (z-score = 1.8).

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