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Production of $^{177}$Lu, a Potential Radionuclide for Diagnostic and Therapeutic Applications

Mayeen Uddin Khandakera, Hiromitsu Haba, Hasan Abu Kassima

$^a$Department of Physics, University of Malaya, 50603 Kuala Lumpur, Malaysia
$^b$Nishina Center for Accelerator-Based Science, RIKEN, Wako, Saitama 351-0198, Japan

Abstract. $^{177}$Lu ($T_{1/2}=6.647\text{d}$; $E_{\beta}^{\text{max}}=498.3\text{keV}$, $I_{\beta}^{\text{total}}=100\%$; $E_{\gamma}=112.9498\text{keV}$, $I_{\gamma}=6.17\%$; $E_{\gamma}=208.3662\text{keV}$, $I_{\gamma}=10.36\%$) is widely used in many clinical procedures due to its excellent decay characteristics. Production cross-sections of the $^{\text{nat}}\text{Yb}(d,x)^{177}$Lu reactions have been measured from a 24-MeV deuteron energy down to the threshold by using a stacked-foil activation technique combined with high resolution $\gamma$-ray spectrometry. An overall good agreement is found with some of the earlier measurements, whereas a partial agreement is obtained with the theoretical data extracted from the TENDL-2013 library. Physical thick target yield for the $^{177}$Lu radionuclide was deduced using the measured cross-sections. The deduced yield curves indicate that a low energy (<11 MeV) cyclotron and a highly enriched $^{176}$Yb target could be used to obtain $^{177}$Lu with negligible impurity from $^{177m}$Lu.

Keywords: 24-MeV deuteron, $^{177}$Lu cross-sections, physical yields, TENDL-2013.

PACS: 25.40.-h

INTRODUCTION

Several radiolanthanides such as $^{177}$Lu, $^{172}$Lu, $^{169}$Yb, and $^{175}$Yb, produced via neutron or charged-particles irradiations on natural or enriched ytterbium target find increasing applications in internal radiotherapy and imaging procedures. Among them, $^{177}$Lu ($T_{1/2}=6.647\text{d}$; $E_{\beta}^{\text{max}}=498.3\text{keV}$, $I_{\beta}^{\text{total}}=100\%$; $E_{\gamma}=112.9498\text{keV}$, $I_{\gamma}=6.17\%$; $E_{\gamma}=208.3662\text{keV}$, $I_{\gamma}=10.36\%$), a mixed $\beta$ and $\gamma$-emitter is widely used in many clinical procedures due to its excellent decay characteristics. The emission of $\beta$ particles makes it ideal in targeted radiotherapy applications [1,2], and the emissions of low energy photons facilitate simultaneous scintigraphy and dosimetry studies without posing any extra radiation dose to the patients [3]. Its half-life is long enough to allow sophisticated preparation (e.g., shipping, labelling, purification etc.) for use without any significant loss of activity. $^{177}$Lu can be produced in principle in several ways. Currently, a large scale production of $^{177}$Lu is in practice by using only the high flux nuclear reactor via the direct $^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$ or indirect $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb}\rightarrow^{177}\text{Lu}$ routes followed by a complex separation procedure of $^{177}$Lu from the Yb isotopes [4]. On the other hand, the carrier-free $^{177}$Lu is available in the charged-particle irradiations on various targets, though its activity is relatively lower than those in the reactor productions [5-7, 8-10]. However, it may be possible to overcome this deficiency with recent high-power accelerator technologies, which enable large scale and on-site productions of $^{177}$Lu leading to its various practical applications.

A general survey of the literature reveals that only three earlier investigations [6-8] were carried out for the production of $^{177}$Lu via deuteron irradiations on ytterbium targets, but discrepancies are found among the reported data. Therefore, further experimental data are required to reduce the discrepancies and also to complement the data needed to optimize the production of $^{177}$Lu. Production cross-sections of $^{\text{nat}}\text{Yb}(d,x)^{177}$Lu reactions is therefore measured in the energy range of 2-24 MeV using the AVF cyclotron of the RIKEN RI Beam Factory, Wako, Japan.

EXPERIMENTAL DETAILS

The irradiation technique, radioactivity determination, and data deduction procedures were similar to our previous works [11-15]. A well-established stacked-foil activation technique combined with HPGe $\gamma$-ray spectrometry was employed to determine the production cross-sections of interest. Ytterbium foils (Yb) (99.9\% purity; 23-µm thickness; Rare Metallic Co. Ltd., Japan) having the natural isotopic composition [16] was used as the target material. Several foils of natural titanium (26-µm thickness, Goodfellow, UK) and aluminium (>99\% purity; 100-µm thickness; Nilaco Corp., Japan) were inserted in between any two consecutive Yb foils throughout the
whole stack. The stacked-foils were irradiated for 2.0 h with a 24-MeV deuteron beam from the AVF cyclotron with an average beam current of 210 nA. The activity measurements of the irradiated samples were started about a cooling time of 1 h after the end of bombardment (EOB) and repeated several times to remove the possible interfering nuclides. The IAEA recommended $^{88}$Ti($d,x^{48}$V ($E_d=23.56$ MeV, $\sigma=222.6$ mb) [17] monitor reaction was used to determine the beam intensity. The deuteron energy degradation along the stacked foils was calculated by using SRIM-2003 [18]. The cross-sections were determined using a well-known activation formula [19-22]. The estimated uncertainty in the deuteron energy for each representing point in the stack ranges from ±0.4 MeV to ±0.8 MeV, whereas the estimated uncertainties in the cross-sections are in the range of 6.6-12.8%.

RESULTS AND DISCUSSION

Cumulative Production Cross-Sections of $^{177g}$Lu

$^{177}$Lu has two states, a long-lived meta-stable state $^{177m}$Lu ($T_{1/2}=160.44$ d) and a relatively short-lived ground state $^{177}$Lu ($T_{1/2}=6.647$ d). In principle, the formation of $^{177}$Lu is contributed by several pathways: the direct $^{176}$Yb($d,n$)$^{177g}$Lu reaction ($E_{th}=0.0$ MeV), $\beta^-$ decay ($b_{\beta^-}=100\%$) of the short-lived parent $^{177}$Yb ($T_{1/2}=1.911$ h) produced via the $^{176}$Yb($d,p$)$^{177}$Yb reaction, and an IT decay ($b_{IT}=21.4\%$) of its long-lived isomeric state $^{177m}$Lu within our investigated energy region. Therefore, the measured cross-section of $^{177}$Lu is cumulative cross-sections. $^{177}$Lu decays to the stable $^{177}$Hf via an emission of $\beta^-$ particles ($b_{\beta^-}=100\%$) followed by the emission of 112.9498-keV ($I_{\gamma}=6.17\%$) and 208.3662-keV ($I_{\gamma}=10.36\%$) $\gamma$-lines. The relatively intense 208-keV $\gamma$-line is also a characteristic $\gamma$-line of its isomer $^{177m}$Lu. By the following reasons, however, we concluded that this line is not contaminated by $^{177}$Lu. In this experiment, the formation of the meta-stable state $^{177m}$Lu was not identified via its characteristic and interference-free 418.5188-keV $\gamma$-line ($I_{\gamma}=21.3\%$). Additionally, none of the highly intense and characteristic 112.95 keV ($I_{\gamma}=21.9\%$), 208.36 keV ($I_{\gamma}=57.4\%$), 228.48 keV ($I_{\gamma}=37.1\%$) or 378.50 keV ($I_{\gamma}=29.9\%$) $\gamma$-lines of $^{177m}$Lu was detected in the $\gamma$-ray spectra acquired after a long cooling time of ~600 days.

![Figure 1](image_url)

**FIGURE 1.** Excitation function for the $^{176}$Yb($d,x$)$^{177g}$Lu nuclear reactions (cumulative).

Actually, $^{177m}$Lu makes no or only an insignificant contribution via an IT process ($b_{IT}=21.4\%$) to the formation of $^{177g}$Lu, and this fact was also confirmed by the data extracted from the TENDL-2013 library (see Figure 1). The
The 208-keV peak also has the possibility to be contaminated by the characteristic 207.8-keV γ-line of $^{167}$Tm ($T_{1/2}=9.25$ d) formed via the $^{168}$Yb($d,2pn$) reaction ($E_{th}=8.5$ MeV). Note that the isotopic abundance of the target $^{168}$Yb is only 0.13%, therefore the contamination by $^{167}$Tm in the 208-keV peak was considered to be negligible. We also confirmed the negligible contribution of $^{167}$Tm by the decay curve analysis on the 208-keV γ-line.

Further, we confirmed that $^{172}$Gd formed via the $^{174}$Yb($d,4n$) ($E_{th}=19.6$ MeV) reaction contaminates the peripheral area of the 208.366-keV γ-line by its characteristic 210.28-keV γ-line ($I_{\gamma}=0.088\%$). As $^{174}$Yb is the highest abundant (31.81%) isotope among all of the activated target isotopes of Yb and the $^{nat}$Yb($d,xn$)$^{172}$Lu reactions show a large cross-section above 20 MeV, the contribution of the $^{174}$Yb($d,4n$)$^{172}$Lu channel at the weak 210.28-keV γ-line ($I_{\gamma}=0.088\%$) cannot be neglected. Therefore, the contribution of $^{172}$Gd in the 208.366-keV γ-line was separated following the standard equation available in our earlier publication [19]. Finally, the radioactivity of $^{177}$Lu was assessed by using the 208.3662-keV γ-line. The obtained cross-section was renormalized to the isotopic cross-section for the $^{176}$Yb($d,2n$)$^{177}$Lu reaction since no other target isotope contributes to the formation of $^{177}$Lu.

The present result shows a good agreement (see in FIG. 1) with the earlier measurements by Hermann et al. [6] and Manenti et al. [7], but not with the recent measurement by Tarkanyi et al. [8]. The data from the TENDL-2013 library [23] do not properly reproduce our cumulative $^{177}$Lu cross-sections and found an agreement only up to 8 MeV. At the higher energy, only the shape of the measured excitation function with lower absolute values is reproduced by the TENDL-2013 library, and this underestimation is resolved if we replace the ($d,p$) cross-section in the TENDL-2013 library with the TENDL-2011 library [24] renormalized by Ignatyuk in the FENDL-3.0 library [25]. Therefore, we may expect the indirect $^{176}$Yb($d,p$)$^{177}$Yb$\rightarrow^{177}$Lu route makes the major contribution to the formation of $^{177}$Lu.

### Thick Target Yields

Physical thick target yields were deduced using the measured cross-sections and the electronic stopping power of natural ytterbium over an energy range from threshold to the initial deuteron energy. A detailed explanation about the deduction of the yield is available in our previous publication [19-22]. The deduced yields in MBq/μA-h are shown in Figure 2.

![FIGURE 2. Physical thick target yields for the $^{176m}$Lu and $^{177g+m}$Yb radionuclides.](image-url)
This experiment shows that the deuteron irradiation on the enriched $^{176}$Yb produces $^{174}$Lu, $^{174g}$Lu, $^{176m}$Lu, $^{177m}$Lu, $^{177g}$Lu, $^{175}$Yb, and $^{177}$Yb within our investigated energy region. Among them, the short-lived $^{177}$Yb ($T_{1/2}=1.911$ h) completely decays to the medically important $^{177}$Lu within a period of 19 hours after the EOB. The formation of $^{175}$Yb ($T_{1/2}=4.185$ d) via the $^{176}$Yb($d,p2n$) reaction could only be occurred after a practical threshold of 11 MeV. The formation of the long-lived $^{177}$Lu ($T_{1/2}=160.44$ d) was below the detection limit. The existence of the simultaneously produced short-lived $^{176m}$Lu ($T_{1/2}=3.664$ h) via the $^{176}$Yb($d,2n$) reaction would practically be absent in the irradiated targets after ~30 hours from the EOB due to its decay to the stable $^{176}$Hf. Formation of $^{174m}$Lu and $^{174g}$Lu via the $^{176}$Yb($d,4n$) reaction could only be occurred after a practical threshold of ~18 MeV. Under these situations, the deduced yield curves show that a low amount of no-carrier-added radioactivity of $^{177}$Lu (2.4 MBq/μA-h) could be obtained at the 11-MeV deuteron energy on the enriched $^{176}$Yb target. However, a chemical separation procedure may facilitate a large scale production of $^{177}$Lu in a pure form by removing the simultaneously produced $^{175}$Yb contaminant. An approximate estimation based on the deduced yield curves show that a batch yield of 55 GBq of $^{177}$Lu could be obtained via 72 h irradiations of 18-MeV deuterons having a 100-μA beam current on a 250-μm thick metallic $^{176}$Yb target. It may be pointed out that the use of mA-range beam current from a high intense accelerator could provide a large scale on-site production of $^{177}$Lu leading to its various practical applications.

**CONCLUSIONS**

Deuteron-induced cross-sections of the $^{177}$Lu radionuclides were measured in the energy range of 2-24 MeV using a stacked-foil activation technique with an overall uncertainty of better than 13%. The measured data were critically compared with the available literature data and found an overall good agreement, and partial agreements were obtained with the extracted data from the TENDL-2013 library. The deduced yield curves indicate that a low energy (<11 MeV) cyclotron and a highly enriched $^{176}$Yb target could be used to obtain $^{177}$Lu with no/negligible impurity from $^{177m}$Lu. Therefore, the obtained experimental data are indispensable for the applications in medical radioisotope production.

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