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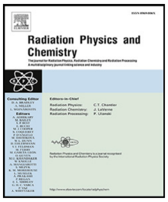

Study of the production of radioisotopes at IFMIF-DONES: ^{177}Lu with deuterons

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ABSTRACT

The production of radioisotopes for nuclear medicine is boosted by different international agencies. The International Fusion Materials Irradiation Facility - Demo Oriented NEutron Source (IFMIF-DONES) will be a infrastructure for testing under high neutron flux the materials to be used in future DEMO fusion reactor. IFMIF-DONES will generate neutrons by means of the impact of a high-power deuteron beam onto a lithium-jet target. There is an important effort to take advantage of the outstanding characteristics of the facility in terms of neutrons and deuterons. Thus, a complementary program is being developed, where the production of radioisotopes for medicine is one of the main applications. Here, we discuss the production of ^{177}Lu with deuterons at IFMIF-DONES.

1. Introduction

International agencies recommend the study of new routes and the use of new facilities for the production of radioisotopes for medical applications as a complementary option to the conventional ones based on nuclear reactors or dedicated cyclotrons (NuPECC, 2014, 2017; EURATOM, 2021). These new facilities can provide several radioisotopes of interest in nuclear medicine. MEDICIS (2020) at Isolde (CERN) is an excellent example of this new framework.

IFMIF-DONES will be a facility for irradiating materials with neutrons to construct key parts of the future fusion reactors (Królas et al., 2021). IFMIF will consist of two accelerators delivering deuterons on the same neutron production target (lithium jet). In a first phase, DONES will consist of a single accelerator delivering deuterons on the lithium jet target. Granada (Spain) was selected as European city host of IFMIF-DONES (ESFRI, 2018). Currently, the project is in the construction phase (CORDIS, 2020).

The high-current deuteron beam (40 MeV at 125 mA) will strike the liquid lithium circulating at 15 m/s for neutron production (Knaster et al., 2016) producing a high neutron flux of 10^{18} m^{-2} s^{-1} (Qiu et al., 2018). IFMIF-DONES characteristics allow developing complementary applications for fundamental and applied physics with a minimum impact of the normal functioning of the facility (Maj et al., 2016; Praena et al., 2020a,b). Some upgrades of the accelerator design are under consideration for such complementary applications. In particular, the deflection of part of the deuteron beam to another experimental hall would be possible (between 0.1-1%). Therefore, 40 MeV deuteron beam at 1.25 mA current would be available for other applications. Here, we describe the production of ^{177}Lu with a realistic device as backing and cooling system for the sample.

^{177}Lu ($T_{1/2}$ = 6.65 d) is an important radioisotope and its use is constantly increasing (Kendi et al., 2019; Kratochwil et al., 2019). The average electron emission energy is 134 keV making it suitable for therapeutic use and the gamma radiation makes it detectable with imaging techniques. Thus, ^{177}Lu is used for theranostics (therapy and diagnosis). As a β-emitter, ^{177}Lu-DOTATATE is used to treat neuroendocrine tumours (Kratochwil et al., 2019). Recently, ^{177}Lu-PSMA has been included in clinical trials for the treatment of castration-resistant metastatic prostate cancer (Camargo-Miranda et al., 2021). ^{177}Lu-Anti HER2 seems to be a potential theranostics agent for breast cancer (Ku et al., 2021). In addition, ^{177}Lu chemical properties allow it to bind to antibodies (Pillai et al., 2003), opening up new possibilities on radiopharmaceuticals (Yeh et al., 2020). Currently, ^{177}Lu is produced by neutron-capture on ^{176}Lu, or carrier added route (c.a), and on ^{176}Yb, or non-carrier added route (n.c.a), at nuclear reactors (Pillai et al., 2003). Nowadays, the n.c.a is preferable used because it has a higher specific activity after purification and therefore higher radiolabelling

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efficiency than ^{177}Lu c.a. (ANM, 2023). In addition and contrary to the c.a, the n.c.a does not produce ^{177m}Lu ($T_{1/2}$ = 160.45 d) which delivers an unwanted dose to the patient.

Several authors have investigated the ^{177}Lu production using deuterons and ^{176}Yb targets (Hermanne et al., 2006; Manenti et al., 2011; Tárkányi et al., 2013; Khandaker et al., 2014; Nagai et al., 2022). ^{177}Lu can be produced with deuterons on ^{176}Yb by means of two routes: the direct route, d+^{176}Yb→n+$^{177(m+g)}$Lu; and the indirect route, d+^{176}Yb→p+^{177}Yb→^{177g}Lu. In the direct route, the production of the metastable state is negligible (Hermanne et al., 2006; Manenti et al., 2011; Tárkányi et al., 2013; Khandaker et al., 2014).

In the present work, we will determine the expected production of ^{177}Lu at IFMIF-DONES with the d+^{176}Yb reaction at 40 MeV and 1.25 mA deuteron beam. Since the high-power delivered by the deuteron beam will be an issue, we will study a realistic device used as cooling system for ^{176}Yb sample by means of SolidWorks simulations (Matsson, 2023). The production will be based on the characteristics of the cooling device for sustaining the delivered power.

2. Materials and methods

The production of ^{177}Lu with the direct route is obtained from the differential equation:

$$\frac{dN_{Lu}}{dt} = R_{Lu} - N_{Lu}\lambda_{Lu} \tag{1}$$

where N_{Lu} is the number of nuclei produced of ^{177}Lu, R_{Lu} is the production rate of ^{177}Lu and λ_{Lu} is its decay constant. The number of nuclei produced by the direct route is given by:

$$N_{Lu}(t) = \frac{I(1-e^{-\lambda_{Lu}t})}{q\lambda_{Lu}} \int_{E_i}^{E_f} \frac{\sigma_{dir}(E)}{S^d_{Yb}(E)} dE \tag{2}$$

where $\sigma_{dir}(E)$ is the reaction cross-section; $S^d_{Yb}(E)$ is the stopping power of deuterons in Yb; I is the intensity of the deuteron beam and q is the charge of deuterium.

For the indirect route, the differential equation is,

$$\frac{dN_{Lu}}{dt} = R_{Yb}(1-e^{-\lambda_{Yb}t}) - N_{Lu}\lambda_{Lu} \tag{3}$$

where R_{Yb} is the production rate of ^{177}Yb and λ_{Yb} is its decay constant. Therefore, the number of nuclei produced at the end of bombardment (EOB) can be determined using the following equation:

$$N_{Lu}(t) = \frac{I}{q}\left(\frac{1-e^{-\lambda_{Lu}t}}{\lambda_{Lu}} + \frac{e^{-\lambda_{Yb}t}-e^{-\lambda_{Lu}t}}{\lambda_{Yb}-\lambda_{Lu}}\right) \int_{E_i}^{E_f} \frac{\sigma_{ind}(E)}{S^d_{Yb}(E)} dE \tag{4}$$

where t is the irradiation time. The stopping power is given by the semi-empirical expression developed by Andersen and Ziegler (1985). Here, we will use (SRIM, 2013) code for determining the stopping power. Regarding the cross-sections, the measurements of Hermanne et al. (2006), Manenti et al. (2011), Khandaker et al. (2014) and Nagai et al. (2022) reached up to 20–25 MeV and Tárkányi et al. (2013) measured between 13–40 MeV with a good agreement with the previous ones except between 20–25 MeV, where (Tárkányi et al., 2013) obtained lower values. Here, to obtain the most conservative values of the ^{177}Lu production, we will use (Tárkányi et al., 2013) cross-section above 13 MeV.

For all measurements, the direct route cross section was obtained as the difference between the cumulative cross section and the indirect route. Thus, we will fit the cumulative and indirect experimental cross sections and the direct cross section is obtained as the difference between them. For the fits, we follow the procedure based on Arias de Saavedra et al. (2018). The results of the fits of indirect and direct routes are:

$$\sigma(E) = \begin{cases} a_1 e^{-a_2(E-a_3)^2} & , \quad E < E_{sw} \\ \frac{b_1}{E-b_2} & , \quad E > E_{sw} \end{cases} \tag{5}$$

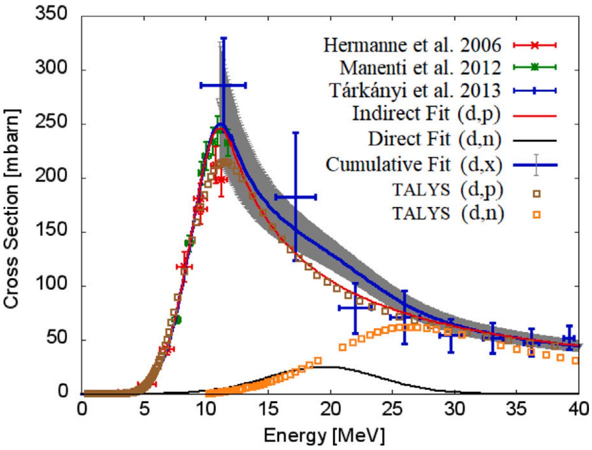

Fig. 1. Fits of the indirect, direct and cumulative cross-sections (mbarn). Statistical error of the cumulative is included. Others statistical errors are negligible.

where E_{sw} is the switching energy connected to the two functional types (12 MeV). Fits are shown in Fig. 1 and fitting parameters are given in Table 1.

Then, the specific activity of ^{177}Lu is calculated from the activity and produced mass,

$$SA_{Lu}(t) = \frac{A_{Lu}(t)}{m_{Lu}(t)} = \frac{\lambda_{Lu}(t)N_{Lu}(t)}{m_{Lu}(t)} \tag{6}$$

where $N_{Lu}(t)$ is the number of nuclei generated of ^{177}Lu in the direct and indirect routes and $m_{Lu}(t) = N_{Lu}(t) \cdot M_{atLu}/N_A$.

The power sustained by the Yb sample constrains the ^{177}Lu production. A cooling device for the sample is studied in this work. It is made on copper and it was already constructed and tested for neutron production (Mastinu et al., 2012). Fig. 2 shows the sketch of the final configuration with 7 mm thick and 45 mm width and height. It is composed of 30 “millichannels” of 1 mm diameter with 1.5 mm of separation between them. There is one inlet and one outlet for the cooling fluid (water at 12 m/s) with a radius of 2.5 mm. The Yb sample is located between the double cooling system, with 0.5 mm between the sample and the millichannels. The dimensions of the sample are 10 mm radius and 0.25 mm thickness.

The final configuration was obtained with several simulations of the device with different input parameters using SolidWorks in an iterative process. The sample composition is the same that the one we already used at n_TOF-CERN facility for the measurement of the ^{176}Yb(n, γ)^{177}Yb cross section. It consists of $^{176}Yb_2O_3$ with 99.43% enrichment (García-Infantes et al., 2023). The sample has the same characteristics that those use in nuclear reactors for ^{177}Lu production. The thermal contact resistance was introduced when the heat wave propagation reached the $^{176}Yb_2O_3$/Cu interface. We calculate with SolidWorks the critical temperatures for high and low contact resistance values. These resistances were taken between $1 \cdot 10^{-8}$ to $5 \cdot 10^{-7}$ K m^2/W. A value of $4 \cdot 10^{-7}$ K m^2/W for the contact resistance is considered as reported by Orain et al. (2001). With these parameters, we find that the copper sustains a maximum of 1.59 $\cdot 10^8$ W/m^2 and the $^{176}Yb_2O_3$ sample 2.39 $\cdot$ 10^7 W/m^2, both keeping the temperature below their melting points, see Fig. 2. In this configuration, deuterons reached the sample with 18 MeV with 67% of transmission through the millichannels.

3. Results

With the setup previously discussed, the ^{177}Lu production rate is calculated, see Table 2.

Regarding the main isotopic impurities, it should be noted that the production of ^{177m}Lu, according to Manenti et al. (2011), does not

Table 1
Fit parameters of the cross-section the ^{176}Yb(d,p)^{177}Yb or indirect, and ^{176}Yb(d,n)^{177}Lu or direct, nuclear reactions.

	a_1 (mb)	a_2 (MeV)	a_3 (MeV)	b_1 (mb MeV)	b_2 (MeV)	E_{sw} (MeV)
^{176}Yb(d,p)^{177}Yb	246 ± 3	0.097 ± 0.006	11.16 ± 0.06	1540 ± 180	5.4 ± 0.9	12.0
^{176}Yb(d,n)^{177}Lu	25	0.025	19.5	–	–	–

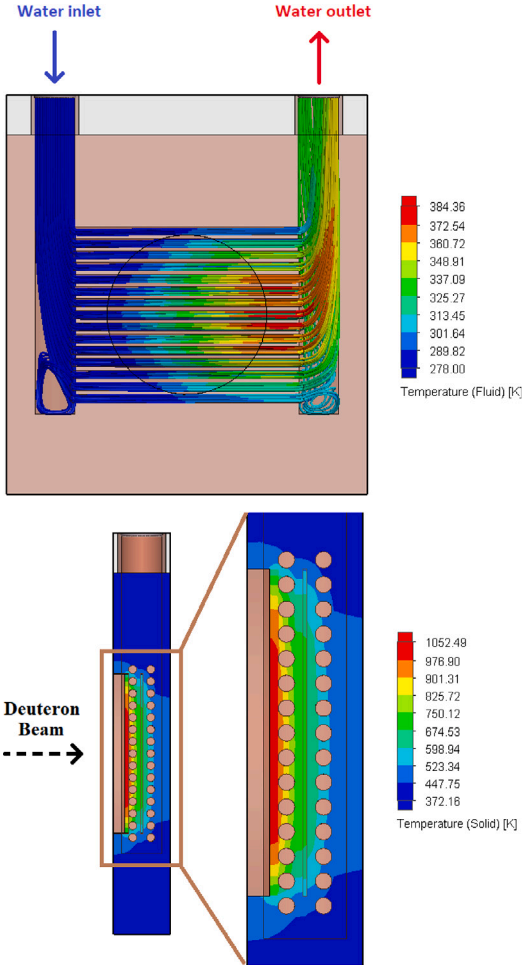

Fig. 2. Fluid temperature distribution in the front face to the deuteron beam (up). Side view of the backing and ytterbium sample temperature distribution (bottom).

Table 2
Production rate of ^{177}Lu with 99.43% sample enrichment.

	Route	R_{Lu} (mg/s)
$^{176}Yb_2O_3$	Indirect, ^{176}Yb(d,p)	$3.58 \cdot 10^{-7}$
	Direct, ^{176}Yb(d,n)	$3.28 \cdot 10^{-8}$

exceed 0.0045% and according to Tárkányi et al. (2013), it is less than 1/100 of ^{177}Lu production. Therefore, the contamination of the final product by this metastable isotope is negligible. Concerning other isotopic impurities, such as ^{176m}Lu, ^{174g}Lu or ^{174m}Lu, their abundance is lower than 0.0001% 2.5 days after the EOB (Nagai et al., 2022).

Table 3 shows a comparison between nuclear reactors (upper part) and DONES (lower part). At nuclear reactors, before the purification of the sample, the specific activity obtained by c.a. route is 738 GBq/mg, and 1.11 GBq/mg by the n.c.a., for eight and seven days of neutron irradiation, respectively (Henkelmann et al., 2013). The specific activity is obtained dividing by the Yb mass of the corresponding sample. After seven days of deuteron irradiation, the sum of the specific activity for both routes is equivalent to n.c.a route in nuclear reactors. Calculations of the production calculations have been also carried out with TALYS's cross-sections. The ^{177}Lu production is approximately 8.5% lower than our estimated theoretical fits of the cross-sections.

Table 3
Comparison between the activity and specific activity at nuclear reactors and at IFMIF-DONES at EOB. First row is the c.a. and second row is the n.c.a in nuclear reactors (Henkelmann et al., 2013; Henkelmann, 2021). Third and fourth rows correspond to the indirect and direct routes at DONES without transmission effects.

Reaction		Time (d)	Activity (GBq)	Specific activity (GBq/mg)
^{176}Lu(n, γ)		8	251	738
^{176}Yb(n, γ)		7	590	1.11
^{176}Yb	(d,p)	7.3	643	1.02
	(d,n)		60	0.09

Conclusions

We have studied the production at DONES of ^{177}Lu with 40 MeV deuteron beam at 1.25 mA on a sample of $^{176}Yb_2O_3$ with the same characteristics that those use in nuclear reactors. A realistic device has been optimized with SolidWorks simulations keeping the copper and sample temperature below melting points. According to the results shown in Table 3, the perspectives are promising because the production at DONES could be similar (470 GBq or 0.7 GBq/mg) to the n.c.a. at nuclear reactors. At present, there is a tendency to use the ^{177}Lu produced by the n.c.a route because of the advantage that, once the produced lutetium is separated from the ytterbium sample, the product consists only of useful ^{177}Lu with a high specific activity (Vogel et al., 2021). This is not the case of the c.a. where unreacted stable ^{176}Lu remains in the by-product and cannot be chemically separated, reducing the final specific activity. In addition, the same activity of ^{177}Lu provides poorer diagnosis images of the same tumour in case of c.a. production. Identically occurs with the therapy, approximately the double of dose is provided to the tumour with the same ^{177}Lu activity produced with the n.c.a. (Henkelmann et al., 2013; Van Noorden, 2015). On the other hand, the n.c.a prevents the presence of the undesirable ^{177m}Lu. All these positive characteristics are fulfilled by the production with deuterons at DONES.

^{177}Lu has been identified as "an indispensable isotope" (Vogel et al., 2021) and "an important candidate isotope that may not be produced in sufficient quantities in the near future, in case of insufficient availability of high-flux neutron irradiation facilities" (Van Noorden, 2015). For instance, therasnostics of neuroendocrine tumours has recently experienced a breakthrough thanks to ^{177}Lu-DOTATATE (Kendi et al., 2019). This treatment requires four doses of 7.4 GBq per dose. Thus, DONES could produce almost seventy doses which means around twenty treatments per week. The incidence of this disease in Spain is 2–5 cases per 100,000 inhabitants per year (Novoa et al., 2014). Considering three cases, it is straightforward that DONES could almost cover the needs for treatment in Spain.

CRediT authorship contribution statement

E. López-Melero: Investigation, Methodology, Writing – original draft. **F. García-Infantes:** Investigation, Methodology. **F. Arias de Saavedra:** Conceptualization, Investigation, Methodology. **L. Fernández-Maza:** Conceptualization. **I. Porras:** Conceptualization. **A. Roldán:** Investigation, Methodology. **J. Praena:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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