^{155}Tb from natural targets: Reaction modeling of ^{nat}Tb(p, x) and ^{nat}Gd(α, x)

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Abstract. Four terbium radionuclides (^{149}Tb, ^{152}Tb, ^{155}Tb and ^{161}Tb) are promising key players in the field of radiopharmaceutical production: in particular ^{155}Tb emits Auger-electrons and γ rays suitable respectively for therapy and for SPECT imaging. In this work we investigate and compare two ^{155}Tb generators by considering reactions of protons on ^{nat}Tb and of alpha particles on ^{nat}Gd for energies E<70 MeV. Both routes can be studied using intermediate energy cyclotrons for the production of ^{155}Dy, the precursor of ^{155}Tb. The two production routes are analyzed with the nuclear reaction code TALYS by varying the parameters of the models to improve the agreement between the calculated cross sections and the available experimental data. Realistic theoretical simulations for the production of ^{155}Tb are performed by optimizing the activity and the purity of the final product, with a full simulation of the radiochemical separation procedure.

1 Introduction

Among all the chemical elements, terbium appears as a very promising and versatile candidate for medical applications and it is referred to as the *"Swiss Army knife"* for nuclear medicine [1]: it has four isotopes (^{149}Tb, ^{152}Tb, ^{155}Tb, ^{161}Tb) that emit radiation useful for PET (Positron Emission Tomography), SPECT (Single Photon Emission Computed Tomography), Auger electrons and $\alpha-$ and $\beta-$particle therapy [2–4]. A first *in-vivo* study has been performed by Müller et al. [2] confirming the potential use of these radionuclides in Nuclear Medicine, alone or combined in matched pairs for theranostic applications, and suggesting further studies on these radionuclides and on new tumor-targeting molecules. In particular for ^{155}Tb other studies, that open the way for the use of terbium nuclides in clinics (as for SPECT imaging and for Auger electron therapy [5]), have been performed. As for other nuclides, investigations of innovative nuclear reaction routes to achieve high yield and purity are required, both with new measurements and with a thorough validation of the existing theoretical models.
In this work we explore two generator-based reactions using natural targets (natural terbium is monoisotopic and is made 100% of ^{159}Tb):

$$p + {}^{159}\mathrm{Tb} \rightarrow {}^{155}\mathrm{Dy} + 5n \rightarrow {}^{155}\mathrm{Tb}, \quad (1)$$

$$\alpha + {}^{nat}\mathrm{Gd} \rightarrow {}^{155}\mathrm{Dy} + xx \rightarrow {}^{155}\mathrm{Tb}. \quad (2)$$

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They consist in a two step reaction chain: the production of ^{155}Dy (the generator with $T_{1/2} \simeq$ 9.9 h) which decays 100% by electron capture in ^{155}Tb. Generators have been widely developed and still contribute to the production of some of the most used radionuclides, as ^{99m}Tc from ^{99}Mo/^{99m}Tc generator, since they can provide a continuous source of the radionuclide of interest far away from the production site.
A study of the generator system ^{155}Dy/^{155}Tb was performed experimentally by Steyn et al. [6] and by Moiseeva et al. [7] for the reactions with protons and α particles respectively, providing a first estimation of activities and purities. Nevertheless, new investigations are necessary to identify the optimal conditions for the production of ^{155}Tb with high purity: a better description of the cross sections has to be achieved and the number of produced nuclides have to be carefully evaluated, taking into account the radioactive decay chains and also optimizing the timings for the two radiochemical separations.

2 Cross section analysis

We investigate the two reactions by means of the nuclear code TALYS [8, 9], which is a software for the simulation of nuclear reactions that includes many state-of-the-art nuclear models to cover most of the reaction mechanisms. TALYS can be used to generate nuclear reaction data libraries, as TENDL (TALYS-based evaluated nuclear data library) [10], that represents a theoretical reference for a comparison with experimental data or for a preliminary analysis of nuclear reactions when data are not available. This library is based both on default and adjusted calculations, however, in some cases, it does not provide an adequate description of particular reactions and specific refinements have to be performed.
In this work we have used the special version of the code, TALYS v.1.95G [11], in which also the Geometry Dependent Hybrid model is implemented for the description of the pre-equilibrium process [12]. The best results have been obtained by performing considerations both from the numerical and physical points of view, with the goal of reaching a deeper comprehension of the underlying physics and going beyond the mere execution of the code.
We have chosen a linear binning for the treatment of the transitions from the continuum down to the ground states in the de-excitation of the compound nucleus. Moreover, we have enabled automatic coupled-channels calculations since the involved nuclei, that lay in the mass number range $150 < A < 190$, are known to be deformed. The default options for the optical potential are selected, namely the Koning-Delaroche [13] for the reaction with protons and the Avrigeanu model for the one with α particles [14]. Usually the coupled-channels calculations are constructed upon rotational optical potential, while the Koning-Delaroche is known to be spherical. In this case the code performs the calculations by subtracting 15% from the imaginary surface potential overall parameter, to take into account that in rotational models the radius differs from its usual expression $R_i = r_i A^{1/3}$ [8].
Regarding the pre-equilibrium process, the exciton model is considered with the variation of the parameters of the matrix element in the description of the transition rates: this choice allows to reduce the cross section tail at high energy and to increase the magnitude of the cross sections. Moreover other mechanisms are considered, as for example the stripping process for the reaction with protons and the knockout process for the one with α particles, by varying the parameters from their default values.
For the compound nucleus mechanism, minor changes on the level density are also made to locally adjust the cross sections of specific nuclides, while maintaining the global description. Among the different models provided by the code, only the three microscopic ones are considered due to their higher flexibility and modernity. Specifically they allow to rescale the theoretical level density by varying two parameters for specific nuclides as described in Refs.[15–17]. Furthermore also the possibility to consider, in a single run, different level

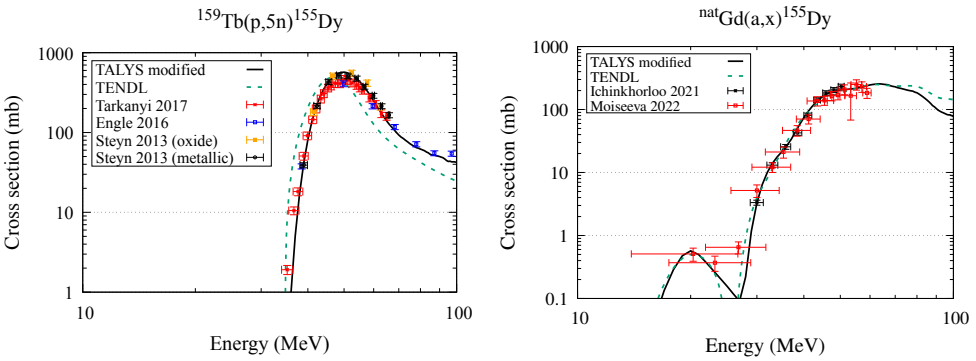

Figure 1. Cross section of ^{155}Dy for the reaction with protons (a) and α particles (b). The solid black line is obtained in this study while the dotted line is the standard TENDL calculation.

density models for each nuclide involved in a given channel is explored, in order to vary as less as possible the parameters of all the models in the description of a nuclear reaction.
The attention is focused initially both on ^{155}Dy and on its isotopes because, after the irradiation, they are extracted from the target and by decay produce the nuclide of interest (^{155}Tb) and all its contaminants. In particular, among all the different dysprosium nuclides produced in the reactions, only four radionuclides are relevant for this study: ^{153}Dy, ^{155}Dy, ^{157}Dy and ^{159}Dy, for which experimental data are available (with the exception of ^{153}Dy in the reaction with α-particles). Many nuclides are stable (^{156}Dy, ^{158}Dy, ^{160}Dy, ^{161}Dy, ^{162}Dy, ^{163}Dy and ^{164}Dy), one (^{154}Dy) has a very long half-life ($T_{1/2} \simeq 3$ My) and all the others are produced only for E > 70 MeV.
We present here only the cross section of ^{155}Dy, but the analysis has involved all the nuclides for which experimental data are available. The curve obtained in this work is referred to as "TALYS modified" and is represented in Fig.1 both for the reaction with protons and α particles, in comparison with the standard TENDL calculations and with the experimental data [6], [7], [18–20].
In the first case a better global description is obtained: the new curve reproduces well the rise and the tail of the cross section. In particular, it appears shifted to the right as a result of the performed optimization. For the reaction with α particles the TALYS modified curve and the TENDL one are in good agreement with each other and describe quite well the trend of the experimental data: in general however the curve obtained in this work is better for all the other considered dysprosium radionuclides, while TENDL underestimates the cross section of ^{159}Dy and ^{157}Dy and overestimates the one of ^{153}Dy. The found solution is unique and indeed many other parameters can be considered, before finding the optimal adjustments in terms both of the number of parameters and of the deviation from the default values. The values used in this work are reported in Tab. 1.
The current calculations represent the starting point to compute activities and purities and to compare the two routes.

3 Optimization of ^{155}Tb production

In the study of the production of a medical radionuclide, the cross section analysis is extremely useful to select an energy window that maximizes the production of the nuclide of

Table 1. TALYS parameters adjustment used in this work to reproduce the experimental data of the two considered reactions: ^{159}Tb(p, 5n) on the left, and ^{nat}Gd(α, x) on the right.

^{159}Tb(p, 5n) reaction	
Parameter	Value
equidistant	y
bins	0
rotational	n p d a
autorot	y
preeqmode	3
M2constant	1.4
Cstrip	d 4.2
preeqspin	n
mpreeqmode	1
phmodel	2
ldmodel	6
colenhance	y
strength	8
ctable	66 153 –0.4
ptable	66 153 –0.6

^{nat}Gd(α, x) reaction			
Parameter	Value	Parameter	Value
equidistant	y	ldmodel	6 65 161
rotational	n p d a	ctable	66 153 –0.4
autorot	y	ptable	66 153 –0.6
M2constant	0.9	ptable	65 161 –0.2
M2shift	1.4		
Cstrip	t 2.0		
Cknock	a 0		
ldmodel	5		
colenhance	y		
ldmodel	6 66 153		
ldmodel	6 66 155		
ldmodel	6 65 153		
ldmodel	6 65 155		
ldmodel	6 65 156		
ldmodel	6 65 160		

interest and minimizes the co-production of contaminants. The study of the ratio of the cross section of ^{155}Dy and the ones of all the produced dysprosium nuclides suggests promising energy windows to explore: 35–60 MeV for the reaction with protons and 20–70 MeV for the one with α particles. Moreover, since we are considering generator-reactions, also the timings of the chemical separations have to be carefully examined for the calculations of activities and the isotopic (IP) and radionuclidic (RNP) purities:

$$A_{^{155}Tb}(t) = \lambda_{^{155}Tb} N_{^{155}Tb}(t), \qquad IP(t) = \frac{N_{^{155}Tb}(t)}{\sum_j N_{j^{Tb}}(t)}, \qquad RNP(t) = \frac{A_{^{155}Tb}(t)}{\sum_j A_{j^{Tb}}(t)}. \tag{3}$$

The activity is the number of disintegrations per second, while the isotopic purity is the number of ^{155}Tb nuclides available in the final product with respect to all the other Tb isotopes produced by the decay of their Dy progenitors. The radionuclidic purity is similarly defined by means of the activity. In particular, the European Pharmacopoeia suggests to consider and use a final product with RNP≥99% in order to reduce as much as possible the effect of the contaminants.

To treat this complex picture, we have adopted the strategy used in the analysis to solve multi-objective optimization problems [21, 22]. Indeed, the goal is to perform a simultaneous maximization of the activity and of the purities, while respecting the limit on RNP. In this type of problems, a single and unique solution can not be identified, but a set of optimal and equally good solutions can be considered. We have created a database with the activities and purities calculated by exploring all the combinations of different possible values for the incoming and outgoing energy (i.e. the thickness of the target) and the timings of the irradiation and of the chemical separations. More specifically for the energies we have explored the selected energy range with a 1 MeV step, while for the irradiation time we have considered the range from 0.5 hours to 10 hours with a step of 0.5 hours. For the first separation time (of the dysprosium nuclides from the target) we have carried out the calculations from 0.5 hours

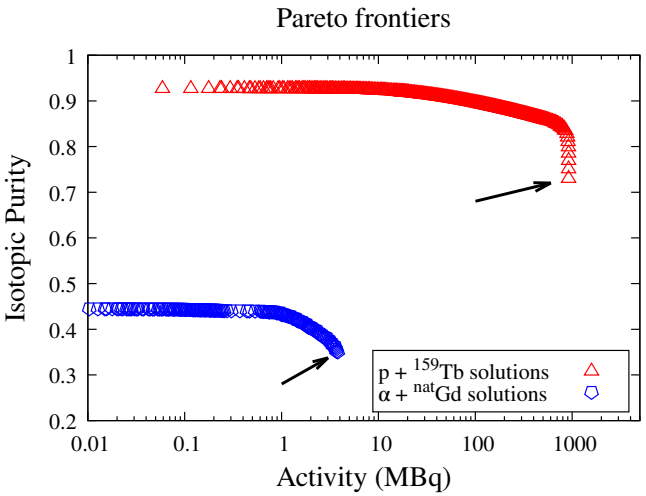

Figure 2. Pareto frontiers for the two reactions analyzed: the one with protons at the top of the plot, the one with α particles at the bottom. The solutions maximize both activity and isotopic purity. The arrows indicate the case of maximum activity for the two reactions: the values are reported in Tab. 2.

Table 2. Values of the variables and of the activities and purities for the case of maximum activity for the two reactions.

	E_{in}–E_{out} (MeV)	t_{irrad} (h)	Δt_1 (h)	A (MBq)	IP	RNP	Δx (mm)
p	60–35	10	0.5	919	0.73	0.9962	4.6
α	52–43	10	8	3.8	0.35	0.99	0.16

to 100 hours with a 0.5 hours step. Regarding the second chemical process (of terbium from dysprosium), this study confirms the result found in the literature [6, 7]: the optimal time is a constant that depends only on the half-lives of ^{155}Dy and ^{155}Tb. Its value is 39.6 hours, and in our analysis for simplicity it is rounded to 39.5 hours to fit in our time steps.
Among all the solutions, only the ones that fulfill the constraint RNP>99% are considered and thereafter the optimal solutions are found. They are represented in the A–IP plane, as shown in Fig. 2 for both reactions for all the different irradiation and cooling configurations examined. In particular, the solutions indicated by arrows represent the best cases for the activity for the two reactions. The corresponding value of the activity and the purities, as well as the values of the used variable are reported in Tab. 2. It is evident that the reaction with protons allows to obtain higher values of activity and isotopic purity with respect to the one with α particles. However, the corresponding time for the first chemical separation (Δt_1) is probably too short and may not represent a realistic scenario. However, many other valuable solutions can be selected in the frontier, always respecting the condition RNP≥0.99.

4 Conclusions

In this work we have investigated two generator-reactions to produce the innovative medical radionuclide ^{155}Tb. With the use of the TALYS code, new cross section curves have been obtained that perform better than standard calculations with TENDL. In the analysis, the problem of the optimization of the production of a radionuclide has been solved with the Pareto frontier, that maximizes simultaneously the activity and the purity of the final product. Using this general approach, from the comparison of the two considered routes, the one with

protons is the most promising one: the high values of activity and purities make this route suitable for the production of ^{155}Tb and for its use in clinics.

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