Theoretical study of ^{47}Sc production for theranostic applications using proton beams on enriched titanium targets

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Abstract. Recently, scandium-47 has attracted attention in the scientific community thanks to its promising features, making it suitable for targeted radiotherapy and theranostic applications, also in combination with the β^+ emitters ^{43}Sc/^{44}Sc. However, in view of possible pre-clinical and clinical studies, finding efficient production routes is still a current research topic. In this work we investigate ^{47}Sc cyclotron production using proton beams on enriched titanium targets. The analysis of the cross sections and yields of both ^{47}Sc ($T_{1/2}$ = 3.35 d) and its main contaminant ^{46}Sc ($T_{1/2}$ = 83.79 d) has been performed with the nuclear reaction code Talys (v.1.95). The experimental data (scarce and relatively old) are compared with model calculations and some discrepancies emerge even after the tuning of parameters defining the nuclear level densities, involved in the compound nucleus formation. The ^{49}Ti case allows a more precise cross sections reproduction, conversely the ^{50}Ti case requires further theoretical investigations. Preliminary yields analysis has been carried out for both ^{47}Sc and ^{46}Sc.

1 Introduction

Radionuclide ^{47}Sc ($T_{1/2}$ = 3.35 d) represents a promising constituent for innovative radiopharmaceutical compounds for theranostics. Its potential stems from its favorable $\beta-$ decay properties accompanied by the emission of γ-rays of an ideal energy for SPECT imaging. Moreover, it may be easily combined with positron emitters ^{43}Sc ($T_{1/2}$ = 3.9 h) and ^{44}Sc ($T_{1/2}$ = 4.0 h) for production of PET/$\beta-$ theranostics [1].

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Indeed, chemically identical radiopharmaceuticals with the same pharmacokinetics are optimal tools in advanced nuclear medicine. Currently preclinical studies have revealed tumor growth delay and an increased survival time of mice treated with the novel ^{47}Sc DOTA-folate conjugate (cm10), demonstrating the therapeutic potential of this radionuclide. For all these reasons ^{47}Sc is a promising new candidate and a potential competitor of ^{177}Lu for targeted radionuclide therapy [2]. However an efficient and convenient production route has still to be identified and the research is devoted to find a reliable production route which guarantees a sufficient quantity and purity of the radionuclide.

In this work we investigate the cyclotron proton-beam production of ^{47}Sc using ^{49}Ti (5.41%) and ^{50}Ti (5.18%) targets, the only two titanium isotopes that could provide an efficient ^{47}Sc production. Since no measurements for ^{49}Ti targets are available and the sole data for ^{50}Ti are quite old [3], theoretical studies are essential to identify the best irradiation parameters for maximizing ^{47}Sc production on both targets, while limiting the co-production of the ^{46}Sc contaminant ($T_{1/2}$ = 83.79 d) that could affect the purity of the final product. This study is developed within the REMIX (Research on Emerging Medical radIonuclides from X-sections) project, a collaboration among INFN (Istituto Nazionale Fisica Nucleare) Laboratori Nazionali Legnaro, INFN Padova, INFN Pavia, INFN Milano, INFN Ferrara, University of Padova, University of Pavia, University of Ferrara, Istituto Oncologico Veneto, Arronax Nantes France, and Sacro Cuore Don Calabria Hospital Negrar.

2 Production cross sections

The simulation of the relevant cross sections and preliminary yields has been carried out mainly with the nuclear reaction code Talys (v.1.95) [4]. Talys describes the nuclear reaction mechanisms with a variety of models, in particular with 4 pre-equilibrium models (PE) and 6 level density models (LD), for a total of 24 possible combinations of models. Commonly in literature Talys default (PE2-LD1) and Talys adjusted (PE3-LD5) are reference options, but they are not always the most representative ones. For this reason, instead of selecting a specific combination of models we describe the results statistically, taking into account the large variety of models that can be selected with this tool. We refer to 18 combinations of models (PE 1-3 and LD 1-6). We excluded the PE4 model because, in this mass region, its results turned out to be not stable and not physical. In the figure shown in this work the maximum and the minimum of the selected Talys models are represented by dashed lines and the interquartile band, defined as the difference between the upper (Q3) and lower (Q1) quartile by a grey band. It exhibits graphically the dispersion introduced by the variety of models. We denote as the most representative value the BTE "Best Theoretical Evaluation", the median of this interquartile band, depicted as a solid black line. For a comprehensive explanation of this statistical approach, we refer to [5].

The large discrepancies between models and experimental data that emerges from the plots, in particular Fig. 1 and Fig. 4, and the practical aim of the project oriented to medical applications compelled us to improve the model description. Indeed, a better reproduction of the relevant cross sections would allow to achieve a higher accuracy in the predicted yields, purities, and in the assessment of the absorbed dose to the patients' organs. The new analysis approach refers to the microscopic theory of the nuclear reactions where the thermalisation processes use the nuclear level density based on the Hartree-Fock (HF) method. The original HF microscopic level densities can be rescaled by tuning two parameters, c and p, responsible for a normalization change and an energy

shift of the level density curves, respectively. A detailed description of the method is presented in [6].

Predictions for the cross sections of the reactions ^{49}Ti(p,x)^{47}Sc and ^{49}Ti(p,x)^{46}Sc are presented in Figs 1 and 2. In particular, these figures show the comparison between the statistical approach (BTE curve) and the results of the optimization performed by tuning the c and p parameters trying to reproduce the experimental data available only for the contaminant ^{46}Sc [7]. The best agreement has been achieved with the values $c = 0.11$ and $p = -0.17$ (red line) for the LD4 model and considering the default option for preequilibrium (PE2). The good agreement obtained for the ^{46}Sc case and the lack of ^{47}Sc data from ^{49}Ti targets led us to consider the selected set of parameters for ^{46}Sc to be reliable also for the ^{47}Sc cross section. Starting from the cross sections we identified the optimal energy window that maximizes the yield of ^{47}Sc while minimizing the co-production of ^{46}Sc. Comparing both curves it is evident that the energy range $32 - 40$ MeV could optimize the production with ^{49}Ti targets.
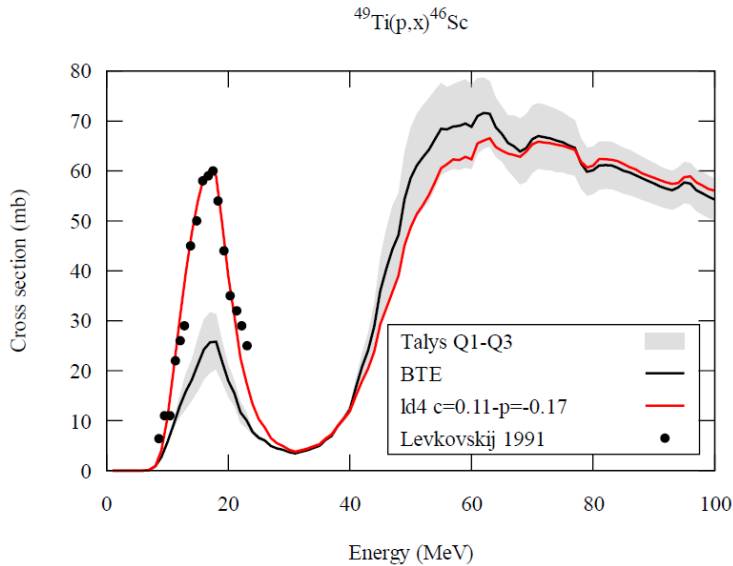

Fig. 1. Experimental and theoretical cross sections for the reaction ^{49}Ti(p,x)^{46}Sc. The red curve corresponds to the choice of the c and p parameters given in the legend. The grey area is the interquartile band (Q3-Q1) and the black line (BTE) its most representative value.
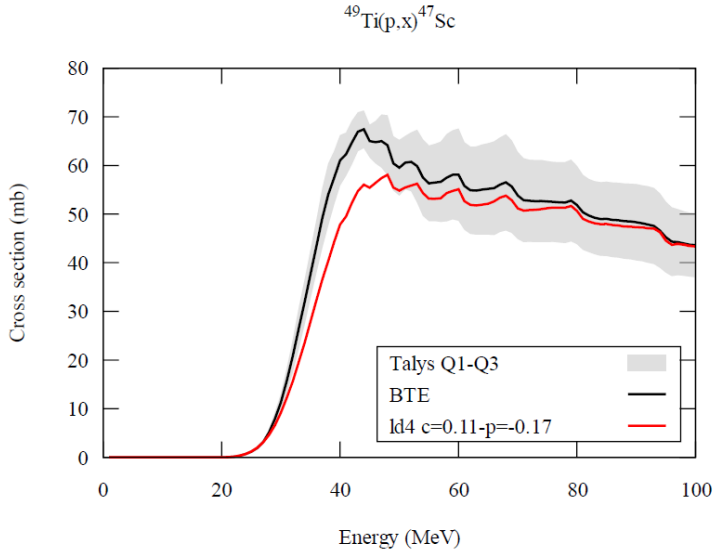
Fig. 2. Calculated cross sections for the reaction ^{49}Ti(p,x)^{47}Sc. No data are available, and the choice of the c and p parameters is based on the tuning performed to reproduce ^{46}Sc data (Fig. 1).
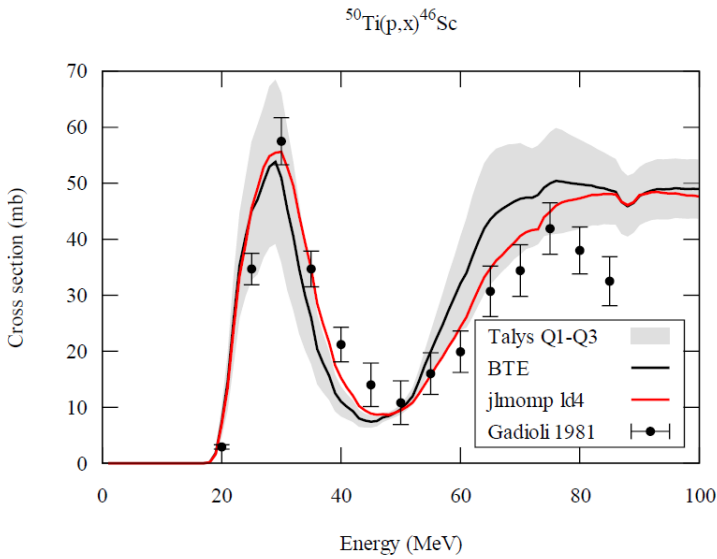

Fig. 3. Experimental and theoretical cross sections for the reaction ^{50}Ti(p,x)^{46}Sc. The Talys modified curve (red line) refers to the ld4 option combined with semi microscopic optical potential JLM. The interquartile band and the BTE curve (black line) refer to a statistical analysis of the standard Talys models.
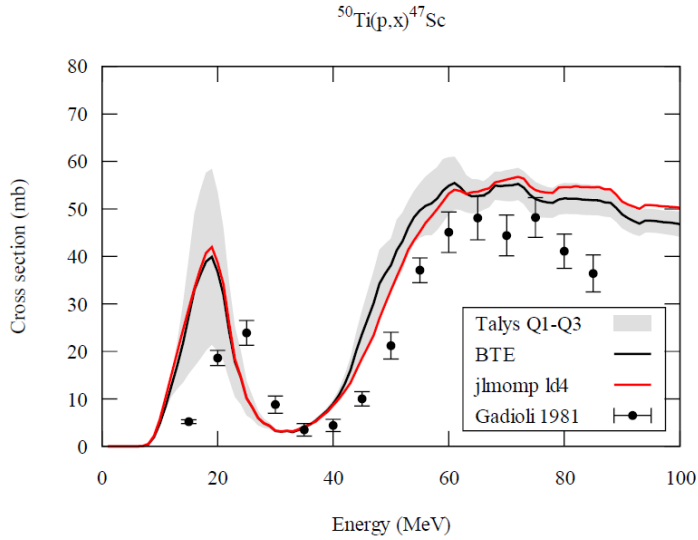
Fig. 4. Experimental and theoretical cross sections for the reaction ^{50}Ti(p,x)^{47}Sc. Notations and legend same as Fig 3.

The same analysis has been performed for the production routes ^{50}Ti(p,x)^{47}Sc and ^{50}Ti(p,x)^{46}Sc, Figs 3 and 4. For both cases a dataset is available to guide the optimization procedure of the theoretical curves. A good reproduction of ^{46}Sc data is achieved by the combined effects generated by the semi microscopic optical potential JLM (JeukenneLejeune-Mahaux) and by the selected model LD4 without any tuning of the *c* and *p* parameters. Conversely for ^{47}Sc cross section from ^{50}Ti all Talys models seem not able to reproduce the data peak around 25 MeV. We noticed the persistence of an offset of about 5 MeV between the data by Gadioli *et al.* [3] and the model results. Further investigations are necessary, and the new experimental data planned at ARRONAX within the REMIX project will be fundamental to validate the theoretical models and to optimize the models free parameters.

In the present situation of uncertainty, we consider the theoretical cross sections to set an optimal range of 8-18 MeV, for ^{50}Ti targets. This range will be employed to evaluate yields, purities, and dosimetric assessments.

3 Yields

In this paper we considered the results obtained within the statistical approach, denoted as BTE cross sections. The analysis performed with the optimized cross section are presently in development. As first step we calculated the production rate for both radionuclides of interest. Secondly, we solved numerically the generalized Bateman equations for the decay chains, whose solutions give the time evolution of the number of nuclei of a certain species produced. Then we evaluated the activity produced by radionuclides and the integral yields at the End of Bombardment (EoB), defined as [8]

$$y_{i,EoB} = \frac{A_i(T)}{I_0} \qquad \text{(1)}$$

where i indicates the considered radionuclide, $A_i(T)$ is the activity produced by the radionuclide i at the irradiation time T at *EoB,* and I_0 is the beam current.
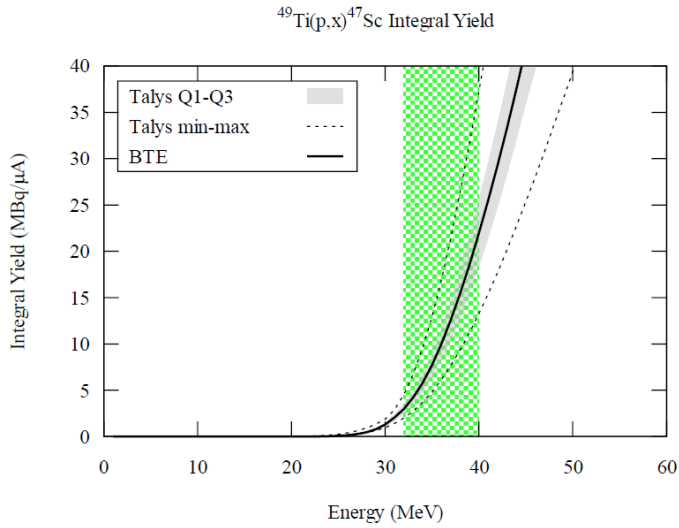

Fig. 5. Predicted yield for ^{47}Sc from ^{49}Ti. The yield has been calculated for a current $I_0 = 1\ \mu A$ and irradiation time T = 1h. The green area highlights the energy window (40-32 MeV) that optimizes the production of ^{47}Sc.
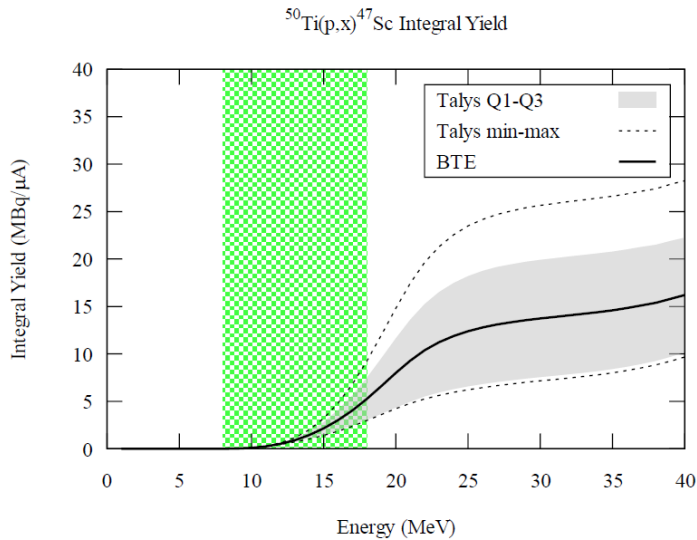

Fig. 6. Predicted yield for ^{47}Sc from ^{50}Ti. The yield has been calculated for a current $I_0 = 1\ \mu A$ and irradiation time T = 1h. The green area highlights the energy window (18-8 MeV) that optimizes the production of ^{47}Sc.

The integral yields have been calculated for a current $I_0 = 1$ μA and $T = 1$ h, with an energy range from E_{max} to 0, namely, assuming full beam energy loss inside the target. Preliminary results of the [47]Sc integral yields for both [49]Ti and [50]Ti cases are plotted in Figs 5 and 6, with the same notation adopted for the other figures (BTE, interquartile band and min/max). We added a green area highlighting the optimal energy window maximizing [47]Sc production. From the integral yields plots we obtained the yield for these two specific irradiation energy windows by selecting the values at the corresponding energies E_{in} and E_{out}. The difference $y(E_{in}) - y(E_{out})$ provides the yield for a target of given thickness. In Table 1 we summarize the preliminary yield results for [47]Sc and [46]Sc from both production routes. The optimized energy windows correspond to a thickness of 1.6 mm for [49]Ti target and of 0.93 mm for [50]Ti target.

Table 1. [47]Sc and [46]Sc yields for both [49]Ti and [50]Ti targets. The irradiation parameters correspond to 1 μA current and 1 h irradiation time.

	$E_{in} - E_{out}$ (MeV)	[47]Sc Yield (MBq/μA)	[46]Sc Yield (MBq/μA)
[49]Ti(p,x)	40 – 32	19.00	0.13
[50]Ti(p,x)	18 – 8	5.26	1.08E-4

4 Outlook on dosimetric studies

In view of possible clinical applications of scandium radionuclides, it is important to consider the impact of the radiocompounds to the patients' health. Indeed, to ensure the safety of a radiopharmaceutical and verify the compliance of the European Pharmacopoeia requirements, biodistribution studies and dosimetric calculations are fundamental to assess the impact of the produced radionuclide and main contaminants in terms of dose released to the patient's organs. Contamination is of primary importance, since a radiopharmaceutical must satisfy a minimal purity to be adequate for clinical applications. Nevertheless, it is not sufficient to verify only the percentage of radionuclidic impurities, but it is fundamental to quantify also the dose increase due to the presence of these impurities.

In the near future we plan to develop our study using the CoKiMo (Compartmental Kinetic Model) software [9], that models the human body in compartments connected one to each other and describes the phase of accumulation of the radiopharmaceutical as well as both the fast and slow elimination phases. The approach allows to determine the absorbed dose to a target tissue with the OLINDA (Organ Level Internal Dose Assessment) software, based on the RADAR (RAdiation Dose Assessment Resource) method for internal dose estimation [10]. Finally, combining the OLINDA output with the information of the activity obtained with the irradiation conditions we evaluate the efficacy and quality of the selected radiopharmaceutical.

5 Conclusions

The therapeutic potential of [47]Sc has been demonstrated in preclinical trials. However, finding reliable production routes (in terms of quantity and purity) for clinical trials is still an issue that needs to be solved. In this work we report on preliminary results

concerning the [47]Sc cyclotron production using proton beams on enriched titanium targets, [49]Ti and [50]Ti. Cross section results, for both [47]Sc and its main contaminant [46]Sc, have been obtained with the nuclear reaction code Talys. We have explored the capacity of Talys predefined models to reproduce the data and applied a tuning procedure for the nuclear level densities to improve the cross-section reproduction. We have found that the level density tuning significantly improves the [46]Sc production cross section in the case [49]Ti targets while no data are available for [47]Sc. In the [50]Ti case, the [46]Sc production cross section is well reproduced by all calculations while for [47]Sc the offset of the low-energy peak could not be resolved. New measurements, in progress within the REMIX experiment, will be useful to better clarify the situation with that cross sections.

We calculated preliminarily the BTE yields of both radionuclides for both enriched targets. The results show a higher yield in the case of [49]Ti targets, however with [50]Ti targets the contamination due to [46]Sc is significantly lower. In addition, in this last case, the lower energy range makes the production suitable for typical hospital cyclotrons. These conclusions need to be validated by the planned measurements.

It is expected to complete this study with the evaluation of the dose absorbed in the patients' organs. In fact, in the assessment of the production route, particular attention to contaminants must be paid in order to determine their contribution to the final dose, in line with the European Pharmacopeia requirements.

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