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THEORETICAL INVESTIGATION OF ^{64}Cu PRODUCTION IN A p-INDUCED REACTION: MEDICAL AND INDUSTRIAL PERSPECTIVES*

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Copper-64 (^{64}Cu) is a promising theranostic radionuclide owing to its dual decay modes (β^+: 17.4%, β^-: 38.5%, e^- capture: 44.1%) and 12.7 h half-life, enabling both PET imaging and targeted radiotherapy. This work presents a theoretical study of ^{64}Cu production via the $^{64}\mathrm{Ni}(p,n)^{64}\mathrm{Cu}$ reaction using PACE4, EMPIRE-3.2.2, and TALYS-1.96 codes. Reaction mechanisms, excitation functions, and yield predictions were analyzed to identify optimal conditions for medical cyclotron production. The simulations indicate an optimal proton energy range of 10–15 MeV, which maximizes the ^{64}Cu yield while minimizing contaminants. Calculated excitation functions and thick-target yields show good agreement with experimental data, confirming model reliability for the reaction. The results provide theoretical guidance for efficient ^{64}Cu production and target design. Given its established clinical utility in radiopharmaceuticals such as ^{64}Cu-DOTATATE and ^{64}Cu-ATSM, and its industrial role as a radiotracer, ^{64}Cu continues to emerge as a key radionuclide bridging nuclear physics, radiochemistry, and applied science.

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1. Introduction

Copper-64 (^{64}Cu) has attracted considerable attention in recent years as a versatile theranostic radionuclide, owing to its unique combination of nuclear and chemical properties. With a half-life of 12.7 h [1] and a mixed decay scheme comprising β^+ (17.4%) [1], β^- (38.5%) [1], and electron capture (44.1%) [1] transitions, ^{64}Cu enables both positron emission tomography (PET) imaging and targeted radiotherapy using a single isotope. This dual

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functionality makes it highly suitable for personalized medicine, where diagnostic imaging and therapeutic treatment can be performed within the same radiopharmaceutical framework. Among the various production routes, the ^{64}Ni$(p, n)^{64}$Cu [2, 3] reaction on enriched nickel targets is widely regarded as the most efficient method for generating high-purity ^{64}Cu in cyclotron-based production. Accurate modeling of this reaction is crucial for optimizing beam energy, maximizing yield, and minimizing the co-production of impurities, which may compromise radionuclidic purity and dosimetric accuracy.

In this study, three well-established nuclear reaction simulation codes — PACE4, EMPIRE-3.2.2, and TALYS-1.96 were employed to perform a comprehensive theoretical evaluation of proton-induced reactions on ^{64}Ni. Each code incorporates different physical models and computational frameworks. EMPIRE-3.2.2 [4, 5] integrates optical, pre-equilibrium, and Hauser–Feshbach statistical models with width fluctuation corrections; TALYS-1.96 [6] employs a modular structure based on the Hauser–Feshbach formalism for predicting excitation functions and yields; and PACE4 [7, 8] applies a Monte Carlo approach to simulate compound nucleus formation and de-excitation dynamics.

The objective of this work is to determine the optimal proton energy window for maximizing ^{64}Cu production, while minimizing unwanted by-products and to validate the predictive reliability of the theoretical models through comparison with experimental data. Such analysis not only enhances understanding of nuclear reaction mechanisms but also provides a theoretical foundation for improving medical cyclotron operation, target design, and radiochemical recovery. Beyond nuclear medicine, ^{64}Cu has also

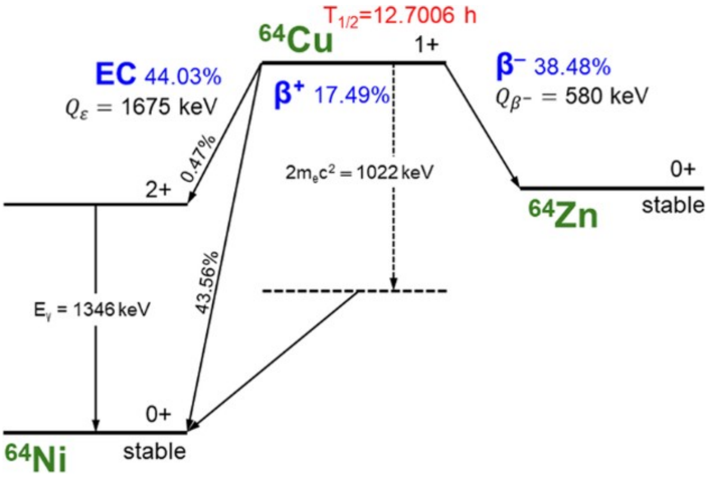

Fig. 1. Decay scheme of ^{64}Cu [10] showing major decay radiations of diagnostic interest.

demonstrated value in industrial applications [9], including metallurgical process tracing, corrosion studies, and fluid dynamic monitoring, due to its favorable half-life and detectability. The interdisciplinary relevance of ^{64}Cu thus underscores the importance of accurate theoretical modeling to support its expanding role in both healthcare and applied nuclear science. In Fig. 1, the decay scheme of ^{64}Cu [10] is displayed, which shows the decay radiations of diagnostic interest.

2. Theoretical model frameworks

2.1. EMPIRE-3.2.2

EMPIRE-3.2.2 [4, 5] is a comprehensive modular code system developed under the International Atomic Energy Agency (IAEA) framework. It integrates several nuclear reaction models, including the optical model, pre-equilibrium exciton model, and Hauser–Feshbach statistical model with width fluctuation corrections. EMPIRE combines experimentally validated nuclear data with theoretical inputs, enabling the calculation of excitation functions, reaction cross sections, and residual nuclei over a wide energy range. Its flexibility and detail, well-suited to competing reaction channels, make it well-suited for investigating reactions such as $^{64}\mathrm{Ni}(p,n)^{64}\mathrm{Cu}$ and potential contaminant production pathways.

2.2. TALYS-1.96

TALYS-1.96 [6] is a versatile nuclear reaction code designed to provide a unified description of nuclear interactions induced by neutrons, photons, protons, deuterons, and alpha particles in the 1 keV–200 MeV energy range. It is based on the Hauser–Feshbach statistical model with pre-equilibrium and direct reaction options, allowing for accurate computation of excitation functions, total and partial cross sections, and thick-target yields. TALYS also incorporates global optical model potentials, nuclear level densities, and γ-strength functions, making it a powerful tool for predicting reaction observables when experimental data are limited.

2.3. PACE4

PACE4 [7, 8] is a Monte Carlo-based statistical model code developed for simulating the decay of an excited compound nucleus formed in heavy-ion and light-particle reactions. It employs the Hauser–Feshbach formalism [4] for compound nucleus de-excitation, incorporating angular momentum coupling, level density parametrization, and γ-ray competition. PACE4 provides an effective means of estimating residual nucleus formation and fragment distributions in the energy range relevant to medical cyclotron applications.

3. Results and discussion

The production of ^{64}Cu through the proton-induced ^{64}Ni$(p,n)^{64}$Cu reaction was studied using three nuclear reaction codes — PACE4, EMPIRE-3.2.2, and TALYS-1.96. These simulations were performed to analyze excitation functions, reaction cross sections, and theoretical thick-target yields, providing a comprehensive understanding of the reaction mechanism and predictive accuracy of each model.

3.1. Excitation functions and reaction cross sections

The calculated excitation functions from all three codes exhibit similar overall trends as displayed in Fig. 2, with the reaction cross section increasing rapidly with proton energy, reaching a pronounced maximum between 11–13 MeV, followed by a decrease beyond 15 MeV due to the onset of competing reaction channels, notably ^{64}Ni$(p,2n)^{63}$Cu and ^{64}Ni$(p,\alpha)^{61}$Co. The cross-section predictions from EMPIRE-3.2.2 and TALYS-1.96 showed close agreement in both magnitude and peak energy, while PACE4 produced a slightly broader distribution, reflecting its Monte Carlo-based treatment of compound nucleus de-excitation. These model results are consistent with the available experimental datasets reported by Kim *et al.* [9] and Jensen *et al.* [11], validating the accuracy of the theoretical approach for a proton beam with a few tens of MeV in the medium-mass target region. The agree-

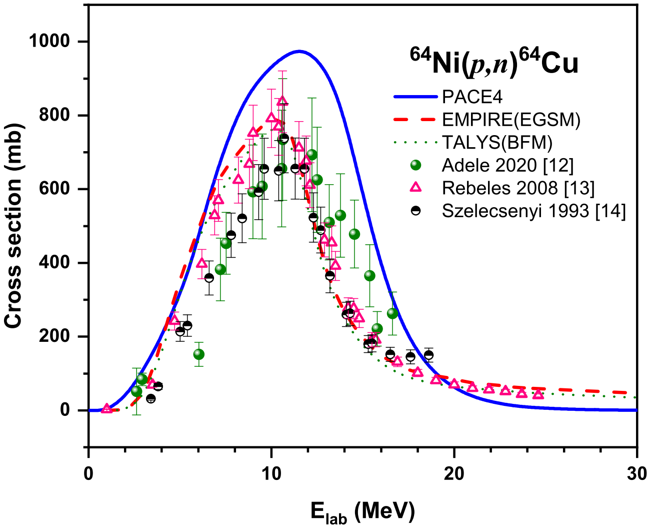

Fig. 2. Experimental excitation functions (EFs) of ^{64}Cu and predictions by PACE4, EMPIRE-3.2.2, and TALYS-1.96 for p-induced reaction with medium-mass target ^{64}Ni.

ment confirms that the Hauser–Feshbach statistical model, combined with pre-equilibrium and optical model components, effectively reproduces the experimental excitation behavior of the ^{64}Ni$(p, n)^{64}$Cu reaction.

3.2. Theoretical yield estimation and optimal energy window

Integration of the excitation functions allowed for the calculation of the theoretical thick-target yield of ^{64}Cu. The maximum yield was observed in the 4–14 MeV proton energy range as shown in Fig. 3, corresponding to the optimal production window for high-purity ^{64}Cu using medical cyclotrons. Below 10 MeV, the yield drops significantly due to reduced reaction probability, while beyond 15 MeV, competing $(p, 2n)$ and (p, α) channels produce contaminant isotopes ^{63}Cu (stable) and ^{61}Co, where ^{61}Co ($T_{1/2} = 1.65$ h) decays to ^{60}Ni (stable), lowering radionuclidic purity. Any radionuclide formed at beam energy E is generally estimated using its formation cross section and a set of experimental variables given in Eq. (1)

$$Y(E) = \frac{N_{\mathrm{tg}}\sigma(E)\phi\left(1 - e^{-\lambda t_r}\right)}{\text{Integral charge}} . \tag{1}$$

Here, N_{tg} is the number of target atoms per unit area, $\sigma(E)$ [mb] is the formation cross section of the residue at beam energy E [MeV], and ϕ is the beam flux, which is the electrical current of the beam$/(Z_p\, e)$. Z_p is the beam's charge state, while e is the electronic charge. λ is the decay constant of the residue, and t_r is the duration of irradiation. Among the three codes, EMPIRE-3.2.2 and TALYS-1.96 produced closely matching yield estimates,

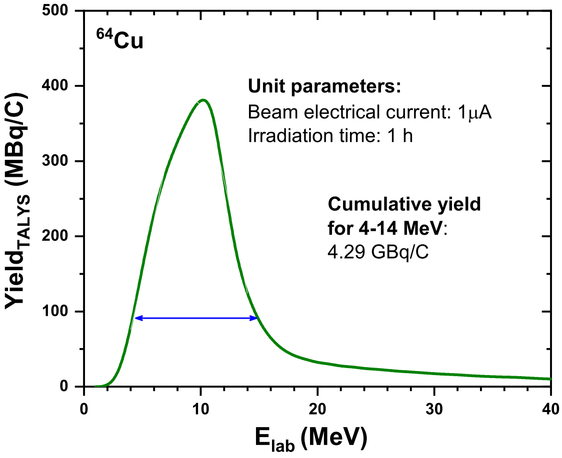

Fig. 3. TALYS-BFM predicted yield of ^{64}Cu from $p + {}^{64}$Ni reaction from Eq. (1) assuming the conditions of a unit beam electrical current and irradiation time.

differing by less than 10% in the optimal range, whereas PACE4 provided comparable predictions within its statistical uncertainty. The consistency among these independently developed frameworks enhances confidence in their predictive reliability.

3.3. Model benchmarking and predictive reliability

Benchmarking against experimental excitation data demonstrated that EMPIRE-3.2.2 exhibited the closest agreement with reported measurements due to its inclusion of width fluctuation corrections and a comprehensive nuclear model library. TALYS-1.96 showed strong predictive capability across a broad energy range for the production of ^{64}Cu, confirming its robustness for reaction modeling in medical isotope production. PACE4, although primarily designed for heavy-ion reactions, provided complementary information on compound nucleus formation and residual product distributions.

The convergence of model predictions reinforces the credibility of theoretical evaluations as reliable tools for guiding experimental optimization of target thickness, beam energy, and irradiation time in ^{64}Cu production.

3.4. Medical and industrial applications

From the medical perspective, ^{64}Cu continues to demonstrate high clinical relevance in both diagnostic and therapeutic contexts. Radiopharmaceuticals such as ^{64}Cu-ATSM [9] and ^{64}Cu-DOTATATE [11] are widely investigated for imaging neuroendocrine tumors, hypoxic tissues, and for personalized theranostic protocols. The combination of positron emission for PET imaging and β^- emission for therapeutic use underscores its dual utility.

In industrial and research contexts, ^{64}Cu serves as a reliable radiotracer for metallurgical process monitoring, corrosion analysis, and fluid dynamic modeling. Its moderate half-life and strong γ-emission allow for accurate detection while maintaining operational safety and feasibility in tracer studies.

3.5. Broader implications

The theoretical insights gained from the use of PACE4, EMPIRE-3.2.2, and TALYS-1.96 not only optimize the nuclear reaction parameters for high-yield ^{64}Cu production but also contribute to improving radiochemical recovery, target recycling, and waste management strategies. The integration of nuclear reaction theory with applied radiochemistry thus highlights the interdisciplinary nature of ^{64}Cu research, bridging nuclear physics, medical technology, and industrial innovation.

Overall, the results confirm that the 4–14 MeV energy range is ideal for efficient ^{64}Cu production using medical cyclotrons as shown in Fig. 3, with minimal contamination and maximum yield-producing, both theoretical justification and practical guidance for future experimental and clinical developments.

4. Conclusions

A comprehensive theoretical investigation of ^{64}Cu production through the ^{64}Ni$(p,n)^{64}$Cu reaction has been carried out using the nuclear reaction codes PACE4, EMPIRE-3.2.2, and TALYS-1.96. The comparative analysis of excitation functions, cross sections, and thick-target yields demonstrated strong consistency among the three models and good agreement with available experimental data. The optimal proton energy window of 4–14 MeV was identified as providing the highest ^{64}Cu yield with a cumulative yield of 4.29 GBq/C and minimal co-production of contaminants.

The study validates the predictive capability of modern nuclear reaction codes for optimizing radionuclide production such as ^{64}Cu and provides valuable theoretical guidance for medical cyclotron operations, target design, and yield optimization. Given its dual decay characteristics and favorable half-life, ^{64}Cu remains a cornerstone radionuclide for theranostic radiopharmaceuticals and industrial radiotracing. The integration of theoretical nuclear physics with applied radiochemistry underlines the growing interdisciplinary relevance of ^{64}Cu in advancing both nuclear medicine and applied isotope technologies.

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