Study on preparation technology of 64Cu radionuclide target

Authors: Dr. Haitao Bai, Pan, Mr. Chao, Ms. Furong Li, Cao, Mr. Yifei, Yang, Mr. Feihu, Zhang, Mr. Tao, Du, Dr. Yang, Bai, Dr. Haitao

Date: 2025-02-24T00:00:00+00:00

Abstract

Purpose: The target preparation technology for 64Cu radionuclides, the quality control scheme for isotope target thickness, and the yield of 64Cu radionuclides were systematically investigated. Methods: 1. Based on the principle of nuclear reactions in beam-matter interactions, the nuclear reaction cross-section ratio parameter and the nuclear reaction probability ratio parameter were proposed for evaluating target thickness and isotope yield. 2. A detailed solid target irradiation design was proposed, the Bethe-Bloch formula was employed to derive the detailed calculation method for target thickness, and the target' s mass thickness (mass surface density) was utilized to control its thickness. 3. Based on Faraday' s first and second laws of electrolysis, the electroplating apparatus model was designed and the electroplating process was proposed. Results: 1. SRIM software was employed to calculate in detail the stopping power of targets with different densities, and energy matching was performed according to the theoretical formula. 2. The nuclear reaction cross-section ratio and nuclear reaction probability ratio were calculated for 10.5 MeV protons incident on a 64Ni target and exiting at different energies. The results for the two parameters are similar; however, as the nuclear reaction probability ratio incorporates the stopping power parameter, this parameter is larger and holds greater evaluation significance. 3. SRIM software was employed to calculate the thickness and mass thickness parameters for protons exiting targets of different densities and at different energies. The results demonstrated that when the proton exit energy is 5.5 MeV compared to 0 MeV, the yield efficiency is 91.94% while the required target cost is only 66.39%. 4. The electrochemical equivalent of Ni and electroplating time parameters were calculated according to Faraday' s law of electrolysis, and a 64Ni target was electroplated onto the gold target holder. The electroplated target was irradiated with an 11 MeV proton beam at 48.97 A for 6 hours, yielding a 64Cu radioactivity of 1.34 Ci, with its half-life consistent with expected results. Conclusion: The target preparation technology and elec-

troplating theory for 64Cu radionuclides were systematically investigated. For expensive isotope targets, the nuclear reaction cross-section ratio and nuclear reaction probability ratio were proposed for target thickness evaluation. Using this method, isotope targets can be significantly conserved without severely compromising the yield. This work holds theoretical and practical guiding significance for the design and preparation of isotope targets.

Full Text

Preamble

Study on Preparation Technology of 64Cu Radionuclide Targets

Haitao Bai[1],†, Chao Pan[1], Furong Li[1], Yang Du[1], Yifei Cao[1], Feihu Yang[1], Tao Zhang[1]
(1. Sichuan Longevous BeamTech Co., LTD., Mianyang 621900, China)

Abstract:
Purpose: This study systematically investigated the target preparation technology for 64Cu radionuclides, including quality control schemes for isotopic target thickness and 64Cu radionuclide yield. **Methods:** (1) Based on the nuclear reaction principle of beam-matter interaction, we proposed the nuclear reaction cross-section ratio parameter and nuclear reaction probability ratio parameter to evaluate target thickness and isotope yield. (2) A detailed solid target irradiation design was developed, the Bethe-Bloch formula was employed to derive a detailed calculation method for target thickness, and mass thickness (mass surface density) was used to control target thickness. (3) According to Faraday' s first and second electrolytic laws, an electroplating device model was designed and an electroplating process was proposed. **Results:** (1) SRIM software was used to calculate the stopping power of targets with different densities in detail, and energy matching was performed according to theoretical formulas. (2) The nuclear reaction cross-section ratio and nuclear reaction probability ratio were calculated for 10.5 MeV protons incident on a 64Ni target and exiting with different energies. The results of the two parameters were similar; however, since the stopping power parameter was incorporated into the nuclear reaction probability ratio, this parameter yielded larger values with greater evaluation significance. (3) SRIM software was used to calculate the thickness and mass thickness parameters of protons exiting targets with different densities and energies. The results showed that when the proton exit energy was 5.5 MeV versus 0 MeV, the yield efficiency was 91.94% while the required target cost was only 66.39%. (4) The electrochemical equivalent of Ni and electroplating time parameters were calculated according to Faraday' s electrolysis law, and a 64Ni target was electroplated onto a gold target holder. The electroplated target was irradiated with an 11 MeV proton beam at 48.97 A for 6 hours, producing 64Cu with a radioactivity of 1.34 Ci, and its half-life was consistent with expected results. **Conclusion:** The target preparation technology and electroplating theory for 64Cu radionuclides were systematically studied. For expensive isotope targets,

we propose using the nuclear reaction cross-section ratio and nuclear reaction probability ratio to evaluate target thickness. This approach can significantly conserve isotopic targets without seriously affecting yield. This paper provides theoretical and practical guidance for the design and preparation of isotope targets.

†Corresponding author: Haitao Bai, Ph.D., Cyclotron target design, binary113@163.com

Keywords: 64Ni target design; 64Cu radionuclides; Isotope yield; Target plating

The half-life of 64Cu is 12.7 h, with primary decay modes of β^+ (0.65308 MeV, 17.4%), β^- (0.5789 MeV, 39%), and EC (43%). Consequently, 64Cu can serve as both a PET/CT diagnostic nuclide and a cancer therapeutic nuclide [1][2][3]. The role of copper in human cancer cell metabolism has been extensively studied over the past two decades, demonstrating a close relationship between copper and cancer progression. In 2013, Laura Evangelista and Italian colleagues discussed differences in copper content between cancer and normal cells, and copper' s involvement in tumor angiogenesis and non-neoplastic diseases such as neurodegenerative disorders [4]. In 2016, Paola Panichelli et al. applied $64CuCl_2$ to diagnose brain astroglioma in 19 patients, showing good agreement between PET/CT and MRI results [5]. In 2020, Kristoffer Kjærgaard et al. in Denmark studied hepatic removal kinetics, biodistribution, and radiation dosimetry of 64Cu in six healthy patients via intravenous and oral administration, finding that both 50 MBq doses were sufficient for continuous PET/CT studies in humans [6]. In 2022, Gabriela Capriotti et al. from Italy clarified that copper ions play important roles in many biological processes, serving as cofactors for enzymatic reactions, structural components of various proteins, and key regulators of cell proliferation and growth, with copper being highly accumulated in numerous tumors in its simple ionic form. $64CuCl_2$ has been successfully applied in PET imaging of prostate cancer, bladder cancer, glioblastoma multiforme, and non-small cell lung cancer, and $64CuCl_2$ shows promise as a therapeutic nuclide [7].

Furthermore, drug labeling with 64Cu has advanced to the forefront of nuclear medicine. In 2019, Marc Pretze et al. in Germany conducted a 64Cu-Nodagaaunps labeling study [8]. In 2020, Garima Singh et al. reported synthesis of novel BFCs based on hexadentate bis(amine)tetrakis(pyridine) bispidine-9-ol [9]. In 2021, James H. McMahon et al. performed a clinical study on non-invasive imaging of HIV-infected individuals and uninfected controls using anti-HIV antibodies labeled with 64Cu [10]. In 2022, Daniel F. Earley et al. successfully demonstrated the feasibility of photochemically induced conjugation methods for developing copper-based radiotracers for diagnostic PET imaging and targeted radionuclide therapy [11]. In 2023, Olga O. Krasnovskaya et al. in Russia systematically studied copper labeling drugs, including [64Cu]Cu-DOTA-TOC, [64Cu]Cu-DOTA-TATE, [64Cu]Cu-PSMA-ALB-89, [64Cu]Cu-RSP-085, etc. [12].

Currently, the main nuclear reaction principles for 64Cu production are: 64Ni(p,n)64Cu, 64Ni(d,2n)64Cu, thermal neutron capture 63Cu(n,γ)64Cu, and fast neutron reaction 64Zn(n,p)64Cu. To meet the demands of 64Cu for scientific research and clinical applications, it is necessary to address corresponding issues of 64Ni target supply, accelerator target design, 64Cu nuclide separation and purification, and to establish strict quality control standards in all aspects to ensure stable 64Cu supply. In 1991, Guoji Xu et al. proposed a nuclear target thickness uniformity measurement scheme including balance weighing methods (direct, destructive, twice), quartz crystal measurement, equivalent air alpha particle measurement, ion beam backscattering, optical absorption, etc. [13]. In 1995, Guoji Xu continued to propose research on isotope target preparation technologies, including vacuum evaporation, focused heavy ion beam sputtering, rolling, electroplating, centrifugal precipitation, etc. [14]. In 1997, Deborah W. McCarthy et al. used a CS-15 cyclotron to produce 15.5 MeV and 11.4 MeV protons to irradiate 64Ni targets, obtaining about 600 mCi of 64Cu with a yield of 5.0 mCi/(Ah) [15]. In 2003, Atsushi Obata et al. used a 12 MeV proton cyclotron for 64Cu targeting research, obtaining an average 64Cu yield of 1.983 mCi/(Ah) [16]. In 2009, Jung Young Kim et al. in South Korea used a 50 MeV cyclotron to study target preparation, producing an actual beam of 18 MeV at 30–50 A for 1 hour, achieving a yield of about 20 mCi/h. With a calculated beam current of 40 A, the yield was 0.5 mCi/(Ah) [17]. In 2016, Xilin Sun et al. used a cyclotron to produce 16.5 MeV protons for target preparation, electroplating, purification, and related work [18]. In 2017, Qinghua Xie et al. used an accelerator to generate 20 MeV protons, obtaining about 200 mCi of 64Cu through the 64Ni(p,n)64Cu reaction [19]. In 2021, Maite Jauregui-Osoro et al. in London, UK, used a cyclotron to generate 11 MeV protons at 30 A to bombard a 64Ni target for 8 hours, obtaining 3.67 GBq (99 mCi) of 64Cu, with a converted yield of 0.41 mCi/(Ah) [20]. In 2023, Ivanna Hrynchak et al. from Portugal studied 64Cu solutions for solid and liquid targets, obtaining yields of 13.5 GBq and 2.8 GBq, respectively. According to the paper' s data, the converted yields were 2.4 mCi/(Ah) and 0.34 mCi/(Ah), respectively [21].

From the perspective of 64Cu target preparation schemes, the main existing problems are: (1) Targets obtained through different preparation processes exhibit varying degrees of compactness—some loose, some dense—requiring a unified method to determine target thickness. (2) Non-destructive thickness testing methods are difficult to find: the EDXRF method is limited by the relationship between X-ray energy and thickness, while alpha-step meter testing requires sample destruction. This paper investigates the preparation technology of radioisotope 64Cu targets based on the LB-11MTS proton cyclotron at Sichuan Longevous BeamTech Co., LTD. The accelerator primarily provides an 11 MeV proton beam with a target current intensity of about 100 A. The main research contents of this paper include systematic study of the influencing factors on plating thickness, proposal of target plating equipment and plating thickness quality control schemes, and detailed calculation of factors affecting 64Cu yield.

The nuclear reaction cross-section ratio and reaction probability ratio were used to calculate energy deposition on the target. A target electroplating device was proposed for the LB-11MTS proton cyclotron, and the electroplated target was tested for 64Cu production.

Materials and Methods

1.1 Calculation of the Nuclear Reaction Cross-Section Ratio and Nuclear Reaction Probability Ratio

The nuclear reaction cross-section for 64Ni(p,n)64Cu is shown in [Figure 1: see original paper] [2][22]. The nuclear reaction threshold energy is 2.6 MeV, with a maximum cross-section of about 659.5 mb at a proton beam energy of 11 MeV. At proton beam energies of 4 MeV, 4.5 MeV, and 5 MeV, the nuclear reaction cross-sections are 82.4 mb, 131.5 mb, and 193.6 mb, respectively [23]. At low beam energies, the nuclear reaction cross-section is much smaller than the maximum cross-section corresponding to 11 MeV beam energy. Therefore, to conserve 64Ni materials and reduce 64Ni target thickness, the cutoff energy of the beam on the target can be considered as 4–5 MeV. The specific evaluation scheme employs both the nuclear reaction cross-section ratio and the nuclear reaction probability ratio, with the evaluation process shown in [Figure 2: see original paper].

In [Figure 2: see original paper], it is necessary to calculate the nuclear reaction cross-section ratio and the nuclear reaction probability ratio. The specific calculation principle is based on the thick target nuclear reaction formula [24]:

..... (1)

Where: is the number of target nuclei per unit volume, is the material density, is the target density, is the relative atomic mass, is Avogadro' s constant, is the initial energy of the proton beam, is the target thickness, and is the cross-section for a beam with energy to undergo a nuclear reaction in the target.

The beam energy is transformed with the depth of the beam in the target:

..... (2)

Where: is the stopping power of the target to the beam, which depends on the target type and beam energy. The energy loss formula for interactions between heavy charged particles such as protons and alpha particles with matter is expressed as [24]:

..... (3)

By introducing formula (3) into formula (2), the nuclide yield is not correlated with the atomic density . Substituting into the above equation yields:

..... (4)

Therefore, the energy loss (or stopping power) generated by the interaction of heavy charged particles such as protons and alpha particles with matter is related to the atomic number of the target, the relative atomic mass , the charge number of the charged particle, and the density of the target. The stopping power is proportional to the target density , and because , the stopping power is inversely proportional to the beam energy. In formula (4), is the rest mass of the electron, is the laboratory reference frame velocity of the beam particle, is the relativistic velocity of the beam particle, and is the average excited energy level of the atom when eV is the unit.

The formula for saturation yield and particle number of nuclear reaction (Particles/s) are as follows:

..... (5)

..... (6)

Where is the number of charges of the beam, i.e., the coulomb number corresponding to a single charge for protons and alpha particles, namely: . Thus, the yield at any time can be obtained as follows:

Where: ..... (7)

is the nuclear reaction constant.

In [Figure 2: see original paper], is the cross-section proportion of the selected nuclear reaction energy interval in the entire energy interval, and is the corresponding probability proportion of the nuclear reaction. The two formulas are as follows:

..... (8)

..... (9)

In the evaluation of formula (9), although the stopping power of the target for heavy charged particles is proportional to the target density according to formula (4), and the density of the target prepared by actual electroplating is unknown, the upper and lower limits of the integral in the formula represent the sum of the integral of the stopping power during the interaction between the beam and the target. Therefore, the sum of beam energy attenuation is fixed according to formulas (1) and (2), so even if the target density is not precisely known, if the upper and lower limits of beam energy attenuation in the target are determined, formula (9) has clear evaluation significance.

1.2.1 Solid Target Design

The diagram of solid target bombardment is shown in [Figure 3: see original paper]. The beam bombards the tilted target from right to left, and it is assumed that the beam energy is completely deposited after passing through path in the target. The inclination angle of the target is evaluated by the formed by the beam and the target plane . According to the triangular relationship:

, so the corresponding target thickness when the beam penetration thickness is . When the beam injection energy is fixed, corresponds to a fixed beam penetration depth. Therefore, the more inclined the target, the smaller the thickness required to deposit all the energy.

1.2.2 Target Thickness Calculation

The energy lost after inelastic collisions between protons, alpha particles, and extranuclear electrons through a unit path is the stopping power ( ). When the charged particle beam deposits energy through the target, ionization and excitation effects are the main forms of energy loss in formula (2), expressed by the Bethe-Bloch formula [25]:

·····.. (10)

·····. (11)

In the formula: represents the atomic number of the target, represents the number of charges carried by a single beam particle, is the rest mass of the electron, is the speed of light, is the relativistic velocity of the beam particle, is the laboratory reference speed of the beam particle, is the rest energy of the electron (0.511 MeV), is the relative atomic or molar mass of the target, is the average excitation energy of atoms in the matter ( ), is the shell correction term, is the density-dependent correction term, and is Avogadro' s constant.

Formula (10) corresponds to formula (4). In electrochemical target preparation, different electroplating processes produce targets of different densities and thicknesses, and the coating thickness must be calculated according to actual conditions. In practice, it is difficult to obtain the density and thickness of the target without destroying it, so theoretical methods are needed to evaluate target thickness.

In formula (10), the square brackets contain dimensionless parameters, so substituting the expression for into the Bethe-Bloch formula yields:

·····. (12)

The relationship between kinetic energy and velocity of heavy charged particles at low velocity is , where is the mass of the heavy charged particle, hence:

Thus, the penetration depth is obtained:

·····.. (13)

·····.. (14)

·····. (15)

It can be seen from formula (15) that the beam penetration depth is related to the density of the prepared target, the atomic number of the target, the relative atomic mass of the target, the charge number carried by a single beam particle, the mass of the beam particle, and the beam velocity (beam energy

). It is difficult to evaluate the thickness of targets with different densities due to varying electroplating processes. Transforming formula (15) yields the mass thickness of the electroplating target:

..... (16)

It can be seen from formula (16) that the plating mass thickness of the target is not related to the plating density of the target, but only depends on the atomic number of the target, the relative atomic mass of the target, the charge number carried by a single beam particle, the beam particle mass , and the beam velocity (beam energy). In general, the mass thickness required for the beam to penetrate the target is only related to target and beam parameters, and has nothing to do with the target density.

The design of the solid target is shown in [Figure 4: see original paper], which includes: 1. Solid target plate; 2. Water cooling inlet; 3. Water cooling channel; 4. Water cooling outlet. To reduce the amount of 64Ni used during irradiation, a 30° tilt design is adopted. The beam energy of the LB-11MTS is about 11 MeV, and after passing through the vacuum window film, helium cooling chamber, and target film, the beam energy entering the target is about 10.5 MeV. The solid 64Ni target is designed with a 30° tilt to calculate the required thickness of the 64Ni target.

To verify the above theory, the penetration depth of 10.5 MeV protons was simulated using the Monte Carlo program SRIM [26], and the corresponding mass thickness was obtained.

1.3 Electroplating Device Design

The electroplating device design primarily references Faraday' s laws of electrolysis. Faraday' s first law of electrolysis states that in an electrochemical process, the mass of substance reduced at the electric cathode is proportional to the amount of charge passed through the electrochemical circuit. The expression is as follows [27]:

..... (17)

Faraday' s second law of electrolysis states that in an electrochemical reaction, the mass of substance precipitated at the cathode is proportional to its electrochemical equivalent for the same total amount of charge:

..... (18)

In the above two formulas, represents the mass of material precipitated at the electric cathode, represents the amount of charge equal to the accumulation of current over time, represents the molar mass of the substance (g/mol), represents the valence of the substance in the electroplating solution, is Faraday' s constant, representing the amount of charge carried by 1 mol of charge. is the electrochemical equivalent, representing the mass deposited per unit charge at the cathode, in g/C. Conversion of Faraday' s constant:

C/mol] [8.26 , the electrochemical equivalent can be expressed as: 8.26× [g/(A · h)]····· (19)

The diagram of the electroplating device is shown in [Figure 5: see original paper], including: 1. Electric cathode; 2. Electroplating target film; 3. Main body of electroplating device; 4. Electric anode. After the electroplating solution is loaded into the main body of the electroplating device, the anode and cathode are installed. Cations in the electroplating solution move toward the electroplating target under the action of electric field force, obtain electrons on the electroplating target to form 64Ni atoms, and finally deposit continuously on the target.

In actual electroplating, the actual mass of precipitated material at the electric cathode differs from the theoretical calculation , so electroplating efficiency is defined as:

····· (20)

According to the electrolytic law, electrochemical equivalent, and current efficiency formula, the formula for coating thickness can be derived as follows:

····· (21)

In the above formula, is the volume of the plating layer, is the area of the plating region, and is the density of the plating layer. However, in practice, the plating layer density varies due to different plating processes such as plating solution concentration and electroplating current power supply mode. According to formula (16), in practice we only need the mass thickness of the coating, so the coating can be used for irradiation as long as it meets the irradiation conditions.

1.4 Solid Target Electroplating Process

The target process of electroplating is shown in [Figure 6: see original paper]. The solid target plating process is primarily illustrated in [Figure 6: see original paper], which mainly includes target holder cleaning and drying, plating solution preparation, plating operation, and completion of plating target drying, weighing, and quality inspection. The main cleaning process includes degreasing with 0.1 mol/L nitric acid, ultrasonic shock cleaning with pure water, etc. After cleaning, the target plate is dried and weighed, and the initial mass of the target plate before electroplating is recorded. After electroplating, the target plate is dried and weighed again, the mass after electroplating is recorded, and the mass thickness of the electroplated target plate can be calculated according to the electroplating area . Based on formula (16), whether the mass thickness of the electroplated target plate meets requirements can be determined. Plating solution preparation mainly includes Ni material weighing, adding 18 M sulfuric acid to Ni, heating dissolution, etc. After dissolution, to match the electroplating environment, the solution must be neutralized and diluted with ammonia and pure water, and the pH of the electroplating solution adjusted to 9.5–10.

During the plating process, a 20 mA DC power supply is used for plating for 15 hours.

The main chemical reaction formulas for Ni dissolution and electroplating process are shown in formulas (22) and (23), respectively:

Heated ·····. (22)

·····. (23)

Results and Analysis

Stopping Power Calculation Results

The nuclear reaction probability ratio formula requires the energy decay curve, which is calculated by SRIM. According to formula (4), the energy decay curves obtained with different densities are different, and the stopping power curves of targets with different densities are as follows:

The relation between stopping power and beam energy for different density targets is shown in [Figure 7: see original paper]. According to formula (4), the stopping power is proportional to the density of the target and inversely proportional to the energy of the beam. Therefore, inverse energy ratio curve fitting was performed on the simulated target of 9 g/cm^3, and the fitting results are shown in [Figure 8: see original paper] and formula (24):

The inverse ratio of stopping power and energy fitted to:

·····.. (24)

It can be seen from the fitting results of [Figure 8: see original paper] and formula (24) that the simulation experimental results are consistent with theoretical analysis, and the fitting results can be used to analyze the nuclear reaction probability ratio.

The Nuclear Reaction Cross-Section Ratio and the Nuclear Reaction Probability Ratio

In this paper, the 64Ni(p,n)64Cu nuclear reaction was carried out using the LB-11MTS cyclotron to study the preparation technology of 64Cu radionuclide targets. The LB-11MTS cyclotron can produce an 11 MeV proton beam with a maximum beam current above 100 A. After the beam passes through the vacuum window film, helium cooling chamber, and target film, the beam energy entering the target is about 10.5 MeV. Therefore, the maximum beam energy hitting the 64Ni target is calculated as 10.5 MeV. According to formula (8), the proportions of nuclear reaction cross-sections and nuclear reaction probabilities for the beam exiting the target with energies from 2.6 MeV to 7.5 MeV are calculated. The nuclear reaction cross-section data are obtained from the IAEA official website [23]. The calculation for 4 MeV energy exiting the target is shown in equation (25):

..... (25)

According to formula (9), the probability proportion of nuclear reactions ranging from 4 MeV to 10.5 MeV is calculated as follows:

..... (26)

In the calculation, the stopping power is calculated using SRIM results for 9 g/cm^3 target material.

Based on formulas (25) and (26), when a 10.5 MeV proton beam is incident on the target surface and beams exit the target at different energies, the proportions of nuclear reaction cross-sections and nuclear reaction probabilities are shown in :

Table 1. Results of the proportion of nuclear reaction cross-section and the proportion of nuclear reaction probability

Exit Energy (MeV)	Cross Section Integral (mb · MeV)	Cross Section Ratio	Probability Integral	Probability Ratio
2.6	100.00%	99.93%	99.49%	98.23%
4.0	96.54%	93.77%	89.67%	84.65%
4.5	78.14%	71.02%	62.94%	58.73%
5.0	45.32%	38.91%	32.45%	29.18%
5.5	21.67%	17.89%	14.56%	12.87%
6.5	8.87%	7.12%	5.68%	4.95%
7.5	3.24%	2.51%	1.98%	1.71%

According to the calculation results, because the stopping power of the material to the beam is incorporated into the proportion of the nuclear reaction probability, the result of the proportion of the nuclear reaction probability is slightly larger than that of the cross-section proportion. Since the formula for the proportion of the nuclear reaction probability is derived from the yield of the nuclear reaction, the result of the proportion of the nuclear reaction probability has greater reference significance for the thickness design of expensive target materials. Based on the calculation results of the cross-section proportion and the proportion of the nuclear reaction probability, the energy of the beam emitted from the target material is selected to be 5.5 MeV.

The Yield Calculation

From , when a proton beam with an energy of 10.5 MeV is incident on the 64Ni target and exits at 5.5 MeV, the nuclear reaction probability integral is 8.15E-04. Thus, information such as the saturation yield can be obtained. The yield information for incident energy of 10.5 MeV and exit energy of 2.6 MeV is compared as shown in :

Table 2. The yield results of 10.5 MeV proton incident on the target with energies of 2.6 MeV and 5.5 MeV proton exiting the target

Exit Energy (MeV)	Saturation Yield (MBq/ A)	Saturation Yield (mCi/ A)	1h Yield (mCi/ A · h)
2.6	5.53$×10^{3}$	149.5	7.94
5.5	5.09$×10^{3}$	137.5	7.30

From the results in , when the incident proton beam with an energy of 10.5 MeV exits the target material at 5.5 MeV, the yield is approximately 7.3 mCi/ A/h, accounting for 91.94% of the yield when the target material is exited at 2.6 MeV. Therefore, in terms of theoretical yield calculation, it is feasible and effective to evaluate and select the nuclear reaction energy range through the proportion of nuclear reaction cross-section and the proportion of nuclear reaction probability.

The Calculation Results of Target Thickness

When the beam penetrates the target material, the energy attenuation curve along the unit path can be calculated using the stopping power formula. It has been demonstrated above that the stopping power is proportional to the density of the target material and inversely proportional to the beam energy. In actual electroplating, different electroplating target-making processes result in target materials with different densities. Referring to formula (16) and using the SRIM Monte Carlo program, when calculating the 10.5 MeV proton beam incident on 64Ni target materials with different densities, the parameters of required target material thickness and mass thickness when the beam exits the target material at different energies are shown in . In , according to the irradiation scheme design in [Figure 3: see original paper] and [Figure 4: see original paper], the parameters of required target thickness and mass thickness when the beam is incident perpendicularly to the target and at a 30° angle to the target sheet are also obtained.

Table 3. The target thickness and surface density parameters for 0, 2.6, and 5.5 MeV proton emission targets when 10.5 MeV protons are incident on targets with different densities

Density (g/cm^3)	Depth @ 0 MeV (m)	Depth @ 0 MeV, 30° (m)	Mass Thickness @ 0 MeV (mg/cm^2)	Depth @ 2.6 MeV (m)	Depth @ 2.6 MeV, 30° (m)	Mass Thickness @ 2.6 MeV (mg/cm^2)	Depth @ 5.5 MeV (m)	Depth @ 5.5 MeV, 30° (m)	Mass Thickness @ 5.5 MeV (mg/cm^2)
7.0	175	202	122	158	182	110	116	134	81
8.0	153	177	122	138	159	110	102	117	81
9.0	136	157	122	123	142	110	90	104	81

Density (g/cm^3)	Depth @ 0 MeV (m)	Depth @ 0 MeV, 30° (m)	Mass Thickness @ 0 MeV (mg/cm^2)	Depth @ 2.6 MeV (m)	Depth @ 2.6 MeV, 30° (m)	Mass Thickness @ 2.6 MeV (mg/cm^2)	Depth @ 5.5 MeV (m)	Depth @ 5.5 MeV, 30° (m)	Mass Thickness @ 5.5 MeV (mg/cm^2)
10.0	122	141	122	110	127	110	81	93	81

In , "depth"corresponds to the thickness of the target material. When the energy of the beam incident on the target and the energy emitted from the target are constant, the greater the density of the electroplated target, the smaller the required thickness of the target, but the mass thickness remains basically constant. Therefore, in electroplating design, the mass thickness parameter of the target is used as the main quality control parameter for electroplating target fabrication. In the case of 30° beam irradiation of the target, with proton energies of 0, 2.6, and 5.5 MeV for the emitted target, the required target mass thicknesses are approximately 122, 110, and 81 mg/cm^2, respectively.

Referring to the above discussion, when the energy of the proton emitted from the target material is selected as 5.5 MeV, the yield efficiency is 91.94% of that when the beam is emitted at 0 MeV and 2.6 MeV, while the required target material masses correspond to 66.39% and 73.64%, respectively.

The Electroplating Equipment and Electroplating Process

The electroplating equipment is shown in [Figure 9: see original paper]. The equipment used in the electroplating process is the IsotopeX Lab series TPS 1.0 electroplating device independently developed by Sichuan Longevous BeamTech Co., LTD, which can be used for electroplating various metal target sheets. According to the target sheet area of approximately 1.815 cm^2, with a 10.5 MeV proton beam incident on the target sheet, and the required mass thickness of 81 mg/cm^2 for the 5.5 MeV energy outgoing target sheet, the actual required amount of 64Ni can be calculated to be approximately 147 mg. According to formula (18), the electrochemical equivalent of Ni can be calculated to be 0.33161 mg/C. Therefore, according to Faraday' s first law of electrolysis formula (17), the total required charge can be calculated to be 443.29 C. If a 20 mA DC power supply is used, the required electroplating time is approximately 6.2 hours. Actually, based on process debugging methods, using a 20 mA DC power supply for 12 hours of electroplating, the electroplating results are shown in [Figure 10: see original paper]: For different applications, the left side shows the designed elliptical 64Ni target, and the right side shows the designed circular 64Ni target.

Irradiation

The time diagram of Nickel-64 target irradiation is shown in [Figure 11: see original paper]. The electroplated target sheet was irradiated and bombarded

using a cyclotron proton beam. The bombardment time is shown in [Figure 11: see original paper]. The average beam current on the target was approximately 48.97 A, and the irradiation time was 6 hours, obtaining 64Cu radioactive activity of 1.34 Ci. According to the above discussion, the theoretical yield was: 7.3 * 48.97 * 6 = 2.14 Ci. The reason for the low yield was that the mass thickness of this target sheet was 58.6 mg/cm^2, which was relatively lower than the required value of 81 mg/cm^2. Comparing , it can be estimated that the energy of the proton beam exiting the target material was approximately 7 MeV. Combining with , the yield was approximately 74.73% of the total energy deposition. Therefore, for the 7 MeV beam exiting the target material, the yield was approximately: 1.74 Ci. The radioactive activity was monitored, and the results are shown in [Figure 12: see original paper]. In [Figure 12: see original paper], the decay constant obtained by fitting was 0.05731/h, which converts to a half-life of 12.09 hours, basically consistent with the half-life of 64Cu. A gamma energy spectrum test was performed on the target sheet after bombardment, and the test results are shown in [Figure 13: see original paper]. The gamma energy spectrum results show a sharp peak on the Compton scattering platform. The possible reason was that the target sheet contained other radionuclides immediately after bombardment.

Discussion

For elemental targets, referring to formulas (2), (3), and (4), the probability of nuclear reaction occurring when a beam of a certain energy is incident on the target is related to the upper and lower limits of the deposited energy of the beam, the charge number of the charged beam, and the atomic number of the target. It is not related to the atomic density of the target, the relative atomic mass , or the density of the target. For nuclides such as 124I and 44Sc, the target needs to be powder-pressed and sintered, and the target is a compound or mixture of multiple compounds. If the average excitation energy of atoms remains unchanged, for compound or mixture targets, the formula for the probability of nuclear reaction between the beam and the target is as follows:

…….. (27)

In formula (27), represents the element content of a certain element in the entire target material, represents the effective atomic number of the compound or mixture target material [28], and represents the element density of a certain element in the target material. The nuclear reaction probability of the beam with the compound or mixture target material is related to the upper and lower energy limits of the beam, the charge number of the charged beam, the effective atomic number of the target material, and is positively correlated with the element content . The specific value of is related to the type of the acting beam current.

The main factors affecting radionuclide purity and radiochemical purity include the purity of the target material, the energy related to the incident and exit

of the beam on the target material, and the subsequent chemical purification process. To produce 64Cu using 64Ni target material, the 64Ni(p,2n)63Cu reaction will occur when the beam energy is greater than 11 MeV, and 63Cu is a stable nuclide. When the proton beam energy is 17 MeV, the nuclear reaction cross-section for producing 63Cu is 768.75 mb, which is comparable to that for producing 64Cu. 64Cu and 63Cu are difficult to separate by chemical purification. If the incident beam energy is too high, the prepared Cu nuclides will affect the radiochemical purity and labeling efficiency of the drug.

The nuclear reaction of 197Au(p,n)197Hg is shown in [Figure 14: see original paper]. After the beam is emitted and hits the target material, the outgoing beam will deposit its remaining energy on the target holder. If the energy hitting the target holder exceeds the threshold energy for nuclear reaction between the beam and the target holder, it will cause radioactive contamination of the target holder. In the preparation of the 64Cu isotope, a gold target holder is used. Querying the EXFOR data reveals that when protons with energy greater than 3.13 MeV are incident on the gold target holder, the 197Au(p,n)197Hg nuclear reaction occurs as shown in [Figure 14: see original paper], causing radioactive contamination of the target holder. 197Hg undergoes EC decay with a half-life of 64.14 hours. The assessment of radioactive nuclear reactions of the target holder can be studied by referring to the methods of nuclear reaction cross-section proportion and nuclear reaction probability proportion described in this article.

Conclusion

This paper systematically discussed the nuclear reaction principle of proton beams with 64Ni target material, theoretically demonstrated the mass thickness parameters of 64Ni target sheets, and calculated the stopping power. For expensive target materials, methods of nuclear reaction cross-section ratio and nuclear reaction probability ratio were proposed for evaluation. The conclusion was drawn that when a 10.5 MeV proton beam is incident on the target material and a 5.5 MeV proton beam is emitted from the target material, the cost of the target material is 66.39% of that for total energy deposition, but the yield is 91.94% of that for total energy deposition. Moreover, an electroplating device was designed based on electroplating principles, and 64Ni target sheets were successfully electroplated. The target was bombarded with an average current intensity of 48.97 A for 6 hours, and the obtained 64Cu radioactive activity was 1.338 Ci.

References

[1] Boschi A, Martini P, Janevik-Ivanovska E, et al. The emerging role of copper-64 radiopharmaceuticals as cancer theranostics[J]. Drug Discovery Today, 2018, 23(8): 1489-1501.
[2] REPO A L S, TS N. Cyclotron Produced Radionuclides: Emerging Positron

Emitters for Medical Applications: 64Cu and 124I[J].
[3] Alves F, Alves V H P, Do Carmo S J C, et al. Production of copper-64 and gallium-68 with a medical cyclotron using liquid targets[J]. Modern Physics Letters A, 2017, 32(17): 1740013.
[4] Evangelista L, Luigi M, Lucio Cascini G. New issues for copper-64: from precursor to innovative PET tracers in clinical oncology[J]. Current Radiopharmaceuticals, 2013, 6(3): 117-123.
[5] Panichelli P, Villano C, Cistaro A, et al. Imaging of brain tumors with copper-64 chloride: early experience and results[J]. Cancer Biotherapy and Radiopharmaceuticals, 2016, 31(5): 159-167.
[6] Kjærgaard K, Sandahl T D, Frisch K, et al. Intravenous and oral copper kinetics, biodistribution and dosimetry in healthy humans studied by [64 Cu] copper PET/CT[J]. EJNMMI Radiopharmacy and Chemistry, 2020, 5: 1-12.
[7] Capriotti G, Piccardo A, Giovannelli E, et al. Targeting copper in cancer imaging and therapy: a new theragnostic agent[J]. Journal of Clinical Medicine, 2022, 12(1): 223.
[8] Pretze M, van der Meulen N P, Wängler C, et al. Targeted 64Cu - labeled gold nanoparticles for dual imaging with positron emission tomography and optical imaging[J]. Journal of Labelled Compounds and Radiopharmaceuticals, 2019, 62(8): 471-482.
[9] Singh G, Zarschler K, Hunoldt S, et al. Versatile Bispidine -Based Bifunctional Chelators for 64CuII-Labelling of Biomolecules[J]. Chemistry–A European Journal, 2020, 26(9): 1989-2001.
[10] McMahon J H, Zerbato J M, Lau J S Y, et al. A clinical trial of non-invasive imaging with an anti-HIV antibody labelled with copper-64 in people living with HIV and uninfected controls[J]. EBioMedicine, 2021, 65.
[11] Earley D F, Flores J E, Guillou A, et al. Photoactivatable bis (thiosemicarbazone) derivatives for copper-64 radiotracer synthesis[J]. Dalton Transactions, 2022, 51(13): 5041-5052.
[12] Krasnovskaya O O, Abramchuck D, Erofeev A, et al. Recent advances in 64Cu/67Cu-based radiopharmaceuticals[J]. International Journal of Molecular Sciences, 2023, 24(11): 9154.
[13] 许国基, 孟祥金, 罗兴华等. 核靶厚度和均匀性测量 [J]. 原子能科学技术,1991,25(3):34-39.
Xu Guoji, Meng Xiangjin, Luo Xinghua et al. Measurement of thickness and uniformity of nuclear target [J]. Atomic Energy Science and Technology,1991,25(3):34-39. (in Chinese)
[14] 许国基, 关守仁, 罗兴华等. 同位素靶制备技术的研究 [J]. 原子能科学技术,1995,29(1):68-74.
XU Guoji, Guan Shouren, Luo Xinghua et al. Study on preparation technology of isotope target [J]. Atomic Energy Science and Technology,1995,29(1):68-74. (in Chinese)
[15] McCarthy D W, Shefer R E, Klinkowstein R E, et al. Efficient production of high specific activity 64Cu using a biomedical cyclotron[J]. Nuclear medicine and biology, 1997, 24(1): 35-43.
[16] Obata A, Kasamatsu S, McCarthy D W, et al. Production of therapeutic

quantities of 64Cu using a 12 MeV cyclotron[J]. Nuclear medicine and biology, 2003, 30(5): 535-539.
[17] Kim J Y, Park H, Lee J C, et al. A simple Cu-64 production and its application of Cu-64 ATSM[J]. Applied Radiation and Isotopes, 2009, 67(7-8): 1190-1194.
[18] 孙夕林, 王凯, 林艳红, 等. 医用回旋加速器的 64 Cu 高效制备 [J]. Progress in Modern Biomedicine, 2016, 16(19).
Sun Xilin, Wang Kai, Lin Yan-Hong, et al. Efficient preparation of 64 Cu by medical cyclotron [J]. Progress in Modern Biomedicine, 2016, 16(19). (in Chinese)
[19] Xie Q, Zhu H, Wang F, et al. Establishing reliable Cu-64 production process: from target plating to molecular specific tumor micro-PET imaging[J]. Molecules, 2017, 22(4): 641.
[20] Jauregui-Osoro M, De Robertis S, Halsted P, et al. Production of copper-64 using a hospital cyclotron: targetry, purification and quality analysis[J]. Nuclear Medicine Communications, 2021, 42(9): 1024-1038.
[21] Hrynchak I, Cocioabă D, Fonseca A I, et al. Antibody and Nanobody Radiolabeling with Copper-64: Solid vs. Liquid Target Approach[J]. Molecules, 2023, 28(12): 4670.
[22] INTERNATIONAL ATOMIC ENERGY AGENCY, Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods, Technical Report Series No. 468, IAEA, Vienna, (2009)
[23] https://www-nds.iaea.org/medical/nip64cu0.html
[24] 卢希庭主编. 原子核物理修订版 [M]. 北京：原子能出版社,2000.
Lu Xiting (Ed.). Nuclear Physics Revision [M]. Beijing: Atomic Energy Press,2000.(in Chinese)
[25] 祥云, 刘元方. 核化学与放射化学 [M]. 北京大学出版社,2007.
Xiang Yun, Liu Yuanfang. Nuclear Chemistry and Radiochemistry [M]. Peking University Press,2007. (in Chinese)
[26] http://www.srim.org/
[27] 徐致远, 戴洁琼, 吴波等. 法拉第电解定律表述的辨析 [J]. 凯里学院学报,2015,33(3):175-176.
Xu Zhiyuan, Dai Jieqiong, Wu Bo et al. Analysis of Faraday' s Law of Electrolysis [J]. Journal of Kaili College,2015,33(3):175-176.
[28] 张伟军. 化合物或混合物的有效原子序数研究 [J]. 核电子学与探测技术,2013,33(1):120-126.
Zhang Weijun. Study on effective atomic number of Compounds or mixtures [J]. Nuclear Electronics and Detection Technology,2013,33(1):120-126. (in Chinese)

Note: Figure translations are in progress. See original paper for figures.