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The 13 MeV cyclotron target for a dual production of ^{89}Zr and ^{32}P

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The production of medical radioisotopes using conventional cyclotrons still faces challenges such as relatively high production costs and limited efficiency when each radionuclide is produced using separate targets. Using multi-material targets offers the chance to produce several radionuclides in a single irradiation process. However, designing an optimal target isn't simple because the interaction between the secondary neutron field and the target geometry can affect the radionuclide yield. To address this problem, this study designed and optimized a 13 MeV cyclotron target system utilizing ^{nat}Y and ^{nat}S for the simultaneous production of ^{89}Zr and ^{32}P. A combined approach of Particle and Heavy Ion Transport Code System (PHITS) simulations and Response Surface Methodology (RSM) was used to evaluate five geometrical factors systematically. These factors included the length (L_Y) and radius (R_Y) of yttrium, the forward (L_S) and backward (B_S) lengths, and the thickness (T_S) of sulfur. The RSM predicted that ^{89}Zr and ^{32}P yields of 52.173 MBq/ μ Ah and 0.014171 MBq/ μ Ah, respectively, for the optimized configuration with: L_Y 0.0254 cm, R_Y 0.3000 cm, L_S 1.9124 cm, B_S 1.9124 cm, and T_S 1.9124 cm. Additional PHITS simulations using that configuration confirmed the RSM prediction of ^{89}Zr and ^{32}P yields, with deviations of 3.91% and 3.60%. These simulation results suggest that the proposed dual-target configuration can improve the production performance of the investigated radioisotopes and warrants further experimental investigation.

Keywords: ^{89}Zr; ^{32}P; Cyclotron target; Simultaneous production; PHITS simulation; Response Surface Methodology

Introduction

The technique of simultaneous multiple radioisotope production is a remarkable method, due to its advantages in terms of cost and efficiency. Initially, this technique utilized a single target material to obtain several radioisotopes through a single irradiation process. In 1990, Mulholland introduced a double-chamber water target design for a 26 MeV proton cyclotron, enabling dual production of two positron-emitting radioisotopes: ^{15}O in combination with ^{13}N or ^{18}F [1]. Then, Lahiri studied the co-production of ^{89}Zr and the isomeric states of ^{90,91m,92m}Nb via alpha-particle irradiation of a Y_2O_3 target [2]. Bonardi also demonstrated the simultaneous production of ^{64}Cu and ^{66,67}Ga through deuteron bombardment of a natural zinc target [3].

Despite its promise, isolating isotopic and isomeric nuclei from a single material target after bombardment presents significant challenges. As a result, radioisotopes other than the primary ones are often considered impurities. Borgna investigated an innovative breakthrough, known as Isotope Separation On Line (ISOL), and attempted to enhance the purity of ^{64}Cu and ^{67}Cu produced from the interaction of the proton beam with a zirconium-germanite target [4]. Within the ISOL, the Accelerator-based Mass Separation (AMS) module separates these isotopes, resulting in a high specific activity. The ISOL, however, is a complex system, making it vulnerable to radioactive contamination along the post-proton-bombardment line, particularly within the ionization and AMS apparatus due to the involvement of radioactive ions. Auditore proposed an alternative approach of dual-material target design for the combined production of ^{18}F and ^{64}Cu, implementing the ^{18}O(p,n)^{18}F reaction on the first target and utilizing the neutron byproduct to activate the second target through the ^{64}Zn(n,p)^{64}Cu reaction. This method is way cleaner than ISOL because it eliminates the need for radioactive ions. The report also noted that the dominant impurities can be chemically removed from the ^{64}Cu, as they are not the copper isotopes [5].

A similar dual-material target system is possible to make a pair of radioisotopes: ^{89}Zr, obtained from ^{89}Y via a (p,n) reaction, and ^{32}P, derived from ^{32}S through an (n,p) reaction. ^{89}Zr is a well-known immuno-PET radioisotope, valued for its sufficiently long half-life of 78.4 hours and low positron mean energy of 395.5 keV [6]. On the other hand, ^{32}P is a beta emitter (E_β 1710 keV) with a half-life of 343 hours (14.3 days), known for radiotherapy [7]. An optimized target design requires careful consideration to maximize the yield of both produced radioisotopes. While Auditore discussed the improvements to the target geometry [5], no statistical methods, such as Response Surface Methodology (RSM), were employed for the optimization. RSM combines mathematical and statistical techniques to model and optimize the output variables or responses influenced by the input variables or factors. Another article indicated that RSM is highly accurate for modelling and optimizing the system of interest while minimizing the number of required data points [8, 9].

Therefore, the present work intended to design and optimize the 13 MeV cyclotron target for pair production of ^{89}Zr and ^{32}P. The method was a combination of RSM analysis and the PHITS simulation. The result would be valuable for the medical and scientific community, suggesting an efficient production route for both ^{89}Zr and ^{32}P radioisotopes.

Materials and methods

The target system model was a cylinder composed of metallic yttrium (Y) as the primary target and sulfur (S) as the secondary target. Both were encased within an aluminum alloy 6061 (Al-6061), equipped with a fast neutron reflector made of tungsten, as illustrated in Figure 1. A 13 MeV proton beam with a radius of 0.3 cm and a normalized current of 1 μA was directed from left to right, initially impinging on the Y target. The S target was positioned downstream of the Y target to interact with neutrons generated by the proton–yttrium interaction.

The Design of Experiment (DoE), based on the Central Composite Design (CCD), was arranged using five factors within a specific range as detailed in Table 1. In the current study, the selected optimization parameters were the radioactivity yields of both ^{89}Zr and ^{32}P. To provide the response data required by the DoE, particle transport simulations were conducted using the Particle and Heavy Ion Transport code System (PHITS) version 3.35 [10].

DCHAIN-PHITS module calculated radioactivity data for the produced ^{89}Zr, ^{32}P, and their impurities after one hour of irradiation. In the PHITS simulation, the TALYS Evaluated Nuclear Data Library - 2021 (TENDL-2021) [11] served as the default data library, while Liege Intranuclear Cascade (INCL) [12] and KUROTAMA [13] models provided complementary data. Each simulation incorporated 1×10^8 particle histories to achieve statistically reliable outcomes. RSM then generated the model equation using simulation data and predicted the optimal value of each factor that maximized the yield of both ^{89}Zr and ^{32}P. The model equation was verified using PHITS by applying those values to obtain the corresponding radioactivity data for the produced ^{89}Zr and ^{32}P at the End of Irradiation (EoI).

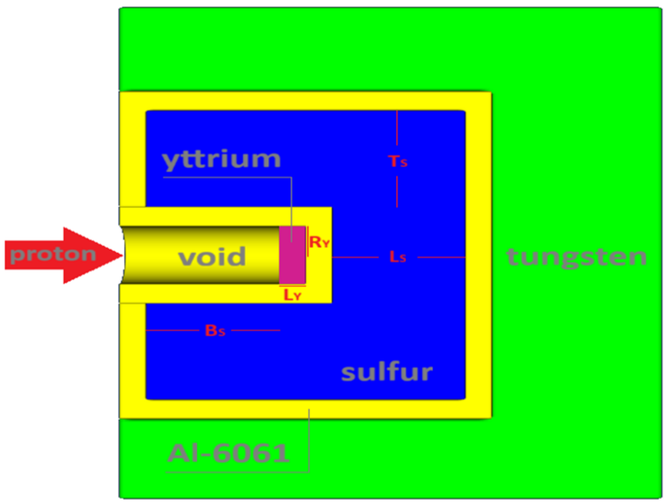

Figure 1. Basic geometry of the target system.

Table 1.
List of factors and the corresponding range for DoE.

Factor	Symbol	Lowest value (cm)	Highest value (cm)
Thickness of yttrium	L_Y	0.01000	0.10512
Radius of yttrium	R_Y	0.30000	0.39512
Forward length of sulfur	L_S	0.01000	1.91240
Backward length of sulfur	B_S	0.01000	1.91240
Radial thickness of sulfur	T_S	0.01000	1.91240

Results and discussion

Predicted activity of the ^{89}Zr radioisotope

RSM successfully generates a model equation for predicting the radioactivity yield (Bq/ μ Ah) of ^{89}Zr at the EoI, as presented in Eq. (1). It is important to note that the obtained ^{89}Zr activity includes contributions from ^{89}Zr and ^{89m}Zr, since both are products of the ^{89}Y(p,n)^{89}Zr reaction with a difference in their energy state. The ^{89m}Zr will decay into its ground state of ^{89}Zr, with a probability of 93.77% and a half-life of 4.16 minutes, via Isomeric Transition (IT).

$$\begin{aligned} Y_{89Zr} = \big((&-80135754 + 1019653810\,L_Y + 394198294\,R_Y + 2663854\,L_S \\ &+ 2663854\,B_S + 2663854\,T_S - 6646209934\,L_Y^2 \\ &- 566868892\,R_Y^2 - 1385692\,L_S^2 - 1385692\,B_S^2 \\ &- 1385692\,T_S^2) \times 1.61785916025799 \times 10^{16} + 1\big)^{(1/3)} \end{aligned} \quad (1)$$

The transformed-response regression model provides an excellent fit to the data, explaining 97.31% of the variability in the response. The adjusted R^2 of 95.57% confirms that the included predictors contribute substantially to the model. With a predicted R^2 of 87.57%, the model also demonstrates strong predictive performance, although the difference between adjusted and predicted R^2 suggests that predictive accuracy on new observations is somewhat lower than the fit observed in the sample data. Overall, the model can be considered reliable for explanation and prediction purposes.

Table 2.
Optimal Geometrical Configuration of the Target System.

Factor	Symbol	Value (cm)
Thickness of yttrium	L_Y	0.025373
Radius of yttrium	R_Y	0.300000
Forward length of sulfur	L_S	1.912400
Backward length of sulfur	B_S	1.912400
Radial thickness of sulfur	T_S	1.912400

Besides the model equation, RSM also predicted the optimal value of each factor, resulting in the maximum yield of both ^{89}Zr and ^{32}P, as shown in Table 2. Several optimized parameters were found at the boundaries of the investigated ranges. These ranges were selected based on practical considerations related to target dimensions, beam coverage, and target-holder constraints. The boundary solutions suggest that the predicted radionuclide yields may continue to improve outside the explored design space. Therefore, a wider optimization range could potentially identify configurations with higher production yields. Nevertheless, any extension of the target dimensions should be evaluated together with considerations of manufacturability, neutron transport efficiency, cooling requirements, and overall system integration. Future studies may investigate a broader parameter space to determine whether additional performance gains can be achieved.

By substituting the optimal values into Eq. (1), RSM estimated an ^{89}Zr yield of 52.173 MBq/μAh. On the other hand, the PHITS simulation indicated 54.214 MBq/μAh under the same configuration. The cross-validated results from the PHITS simulation show that the RSM prediction is highly accurate, with a deviation of 3.91%. Alongside PHITS, the analytical method validated the RSM model using a reaction rate equation with energy decrement and decay factor, as detailed in Eq. (2). Analytical calculations estimated that 13 MeV proton bombardment of the yttrium target would yield an ^{89}Zr activity of 65.878 MBq/μAh by applying the following data: ^{89}Zr decay constant (image) of 8.837×10^{-3} h^{-1}, one-hour duration of irradiation (image), incident particle currents (image) of 6.250×10^{12} protons/s (equivalent to 1 μA), target mass density (image) and molar mass (image) of 4.469 g/cm^3 and 89 g/mol, the Avogadro constant (image) of 6.022×10^{23} mol^{-1}, also energy integration over the ratio of ^{89}Y(p,n)^{89}Zr reaction cross section (image) and stopping power (image) of 3.962×10^{-26} cm^3. The analytical estimation represents the maximum yield achievable, regardless of the geometrical effects of the target system. However, it is still in the same league as the RSM prediction for our model, with a difference of 26.27%.

$$Y = \left(1 - e^{-\lambda t}\right) I \frac{\rho N_A}{M} \int_{E_{th}}^{E_i} \frac{\sigma(E)}{S(E)} dE \tag{2}$$

In comparison with prior studies, our result surpasses Amanuel's design [6] by 27.17%, indicating the benefits of the RSM optimization. For a practical case, irradiating our target system using 10 μA for 6 minutes will be more than enough to meet the required activity of 37 MBq for the ^{89}Zr immuno-PET procedure, as suggested by Dijkers [14]. According to the PHITS simulation result, the obtained ^{89}Zr had an acceptable radiopurity of 91.47%. There were two major contaminants, namely ^{89m}Y (4.936 MBq/ μ Ah) and ^{90m}Zr (0.119 MBq/ μ Ah). While the others, such as ^{90m}Y, ^{90}Y, ^{88}Y, and ^{89}Sr, were only trace amounts. However, both ^{89m}Y and ^{90m}Zr are short-lived radioisotopes, with half-lives of 15.66 s and 0.81 s, respectively, and they decay into stable isotopes. It contributed to a very high ^{89}Zr radiopurity of the final product, which is in agreement with the findings by Amanuel [6].

Spectrum of the induced neutron

PHITS calculations using the [T-Product] tally on the yttrium target and the [T-Track] tally on the sulfur target provided detailed insights into the induced neutron spectrum, as shown in Figure 2. The red dotted curve corresponds to the neutron yield from the proton-irradiated yttrium target. On the other hand, the blue dash-dot curve depicts the ambient neutron flux within the sulfur target. The total neutron strength emitted from the proton-irradiated yttrium target was 1.783×10^8 n/s, with the spectrum extending up to 8.75 MeV. The highest value recorded was 4.611×10^6 n/s, which occurred at an energy of 600 keV. Similarly, the neutron spectrum inside the sulfur target also spans up to 8.75 MeV, with a total neutron flux being 4.768×10^7 n/cm^{2}s. Two pronounced peaks appear in the spectrum at 700 keV with 1.373×10^6 n/cm^{2}s, and 2.85 MeV with 6.506×10^5 n/cm^{2}s. However, the first peak and the rest of the neutron flux below the threshold energy of 1.2 MeV were unusable for the ^{32}S(n,p)^{32}P reaction, as shown by the green square-dot curve.

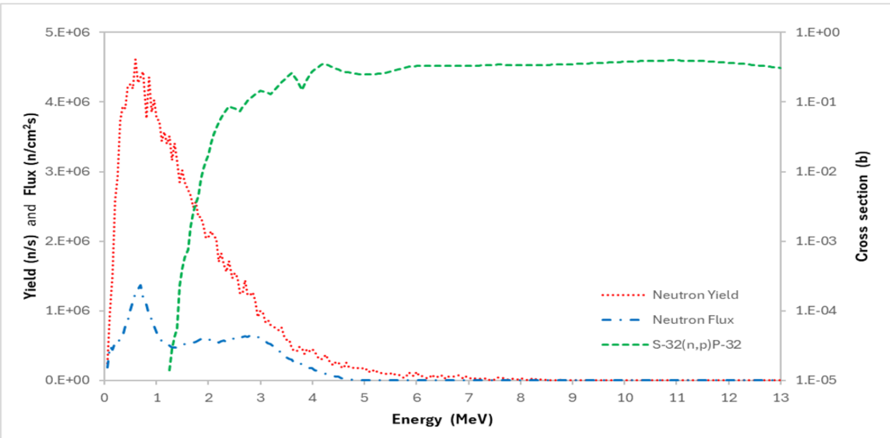

Figure 2. Neutron spectrum for 1 μ A of the incident proton and the cross section of the ^{32}S(n,p)^{32}P reaction.

Predicted activity of the ^{32}P radioisotope

A predictive model equation for the radioactivity yield (Bq/ μ Ah) of ^{32}P at the end of irradiation (EoI) was generated by the RSM, as given in Eq. (3). Integrating the optimal values from Table 2 into Eq. (3) yields an expected radioactivity of ^{32}P equal to 0.014171 MBq/ μ Ah. This value is 3.60% lower than the cross-validated results using the PHITS simulation (0.014681 MBq/ μ Ah).

$$
\begin{aligned}
Y_{32P} = \big(&24 - 165.8\,L_Y - 86.3\,R_Y + 0.52\,L_S - 0.08\,B_S + 1.47\,T_S \\
&+ 1168.7\,L_Y^2 + 124.3\,R_Y^2 + 0.024\,L_S^2 + 0.14\,B_S^2 \\
&- 0.275\,T_S^2 - 3\,L_Y R_Y - 5.39\,L_Y L_S + 0.05\,L_Y B_S - 3.85\,L_Y T_S \\
&+ 0.37\,R_Y L_S + 0.01\,R_Y B_S - 0.41\,R_Y T_S - 0.066\,L_S B_S \\
&+ 0.131\,L_S T_S + 0.136\,B_S T_S\big)^{0.23337}
\end{aligned}
\tag{3}
$$

The transformed-response regression model provides an excellent fit to the observed data, explaining 96.14% of the variability in the response variable. The adjusted R^2 value of 93.66% confirms that the predictors contribute meaningfully to the model. However, the predicted R^2 of 82.20% is substantially lower than the adjusted R^2, suggesting that the model's predictive performance on new observations may be somewhat weaker.

An analytical calculation utilizing Eq. (4) estimated the ^{32}P activity of 0.015409 MBq/μAh by substituting the following data: ^{32}P decay constant (image) of 2.025×10^{-3} h^{-1}, one-hour duration of irradiation (image), target mass (image) and molar mass (image) of 149.8 g and 32 g/mol, the Avogadro constant (image) of 6.022×10^{23} mol^{-1}, also energy integration over the multiplication product of ^{32}S(n,p)^{32}P reaction cross section (image) and neutron flux (image) of 2.702×10^{-18} s^{-1}. The analytical estimation is similar to the prediction of RSM, with a deviation of 8.74%. Once again, it indicates the accuracy of the RSM.

$$
Y = \left(1 - e^{-\lambda t}\right) \frac{mN_A}{M} \sum_{E_{th}}^{E_i} \sigma(E)\Phi(E) \tag{4}
$$

The ^{32}P yield of 0.0261 MBq/μAh reported by Prastha [15] is higher than our result. The difference is attributable to the choice of primary targets, which influences the induced neutron intensity and spectrum correlated to the ^{32}S(n,p)^{32}P cross section. Specifically, the $H_2^{18}O$ target employed by Prastha produces more neutrons of 10^{10} n/s than our yttrium target of 10^8 n/s. However, our neutron flux spectrum inside the sulfur target is more favorable, with a peak at 2.85 MeV, than Prastha's at around 1 MeV, which has a far lower cross-section of 10^{-5} barns than 10^{-1} barns at 2.85 MeV. This compensation makes the difference in the ^{32}P yield between our target design and Prastha negligible.

To produce sufficient activity for clinical application in bone metastasis treatment, which requires a minimum of 3.45 MBq as described by Zhai [16], our target needs to be irradiated using 50 μA protons for 5 hours. The calculated beam power density is approximately 2.30 kW/cm^2 at a proton beam current of 50 μA and an energy of 13 MeV. Such a relatively high power density warrants further thermo-mechanical analysis to assess heat deposition, temperature distribution, thermal stresses, and the adequacy of the cooling system during irradiation. These analyses are beyond the scope of the present study and should be addressed in future work to further evaluate the practical feasibility of the proposed target design.

The radiopurity of ^{32}P obtained from our target system at the EoB was 97.44% with four major contaminants: ^{31}Si (1.34%), ^{34}P (0.78%), ^{33}P (0.42%), and ^{37}S (0.02%). ^{31}Si will decay into stable ^{31}P through beta decay with a half-life of 2.62 h. Prompt removal of ^{31}S after bombardment is essential to achieve high specific activity ^{32}P in the final product. ^{34}P is a short-lived radioisotope with a half-life of 12 s and decays into ^{34}S, which can be removed through a post-irradiation process (along with ^{37}S and its decay product). The problem is ^{33}P, which has a long half-life (25 days) and is difficult to eliminate because it is similar to ^{32}P. Thus, it will stay in the final product as an impurity.

Conclusion

The 13 MeV cyclotron target system was designed and optimized for the simultaneous production of ^{89}Zr and ^{32}P radioisotopes using a combination of RSM and PHITS simulations. The optimized configuration was predicted to yield 52.173 MBq/μAh of ^{89}Zr and 0.014171 MBq/μAh of ^{32}P, with high calculated radiopurity for both products. The RSM prediction proved to be highly accurate, with a deviation of less than 4% compared to the cross-validated PHITS simulation and in agreement with analytical calculation. RSM optimization also demonstrated its benefits by yielding higher product activity of up to 27.17% compared to the previous study. However, these values represent the production potential estimated from computational modeling and have not yet been experimentally validated. While the simulation results demonstrate the promise of the proposed dual-target concept, practical implementation will require additional thermo-mechanical and cooling analyses, target fabrication, and irradiation experiments to verify target performance under realistic operating conditions. Therefore, the present work should be regarded as a design and feasibility assessment based on numerical simulations that provide a foundation for future experimental development.

Acknowledgments

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