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Production and quality control of ^{65}Zn radionuclide

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Abstract Zinc-65 was produced in the Nuclear Research Center for Agriculture and Medicine (NRCAM) by the bombardment of natural copper targets with 30 MeV protons *via* the $^{65}Cu(p,n)^{65}Zn$ nuclear reaction. Natural copper was used instead of enriched ^{65}Cu because of the quick decay of undesired radioisotopes. It was also more desirable for cost effectiveness. Cross-section calculations were performed by ALICE nuclear code and the results were compared with the experimental data given in the literature, which showed good agreement. A 160 μm copper layer target was bombarded with a 150 μA current of 30 MeV protons for 20 min, which resulted in 170 MBq activity of ^{65}Zn product. The yield was 3.4 MBq/μAh. The concentration of the product was 6.8 MBq/ml. Radiochemical separation was carried out by anion exchange chromatography with the yield of about 98%. Quality control of the final product showed a radionuclide purity of more than 98% and no traces of possible impurities (copper) were detected by a colorimetric method with a 1 ppm detection limit using dithizone as the reagent. The materials used for targetry and chemical separation were quite cost-effective.

Key words zinc-65 • production • cyclotron • radiochemical separation • quality control

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Introduction

The zinc-65 radioisotope is widely used in medical, biomedical and agricultural research. It is also used for industrial and metrological purposes. A variety of research data on ^{65}Zn have been published, and the most important of them are: zinc metabolism research in humans [48] and mice [27], zinc absorption research in normal and tumoral tissues in humans [15, 16, 18, 41] and rats [4, 56], zinc biodistribution studies in humans [50] and animals [5, 11, 31, 46], study of human tumors [24] and rat tumors [58–60], study of rat brain [36, 55, 57], agricultural research [2, 7, 8, 26], and finally, its use as a standard source for the calibration of X and gamma-ray detectors [45, 53, 61].

The idea of ^{65}Zn production arose due to its wide range of applications. Regarding previous projects in our research group in the NRCAM on the cyclotron production of neutron-deficient isotopes in the country, we were interested in the production of high quality ^{65}Zn in the chloride form for research purposes. Important nuclear characteristics of ^{65}Zn radioisotope are as follows: $T_{1/2}$ = 244.26 d, decay mode: E.C. (98.3%), β^+ (1.7%, $E_{\beta+}$ = 300 keV), gamma energies: 1115.5 (50.6%), 511 (β^+) keV [17].

It can be seen that ^{65}Zn can be considered as a desirable Auger electron emitter and can be used for therapeutic purposes [24].

Experimental

Materials

High purity chemicals were purchased from Merck (Darmstadt, Germany). Production of ^{65}Zn was performed in the NRCAM 30 MeV cyclotron (IBA, Cyclone-30) using natural copper (purity > 99%) as the target material. Gamma spectroscopy was carried out by a high purity germanium (HPGe) detector (model GC1020-7500SL) coupled with a Canberra™ multichannel analyzer. Radionuclide purity was checked by the same detector. Calculations were based on the 1115.5 keV peak from ^{65}Zn and 283 keV peak from ^{61}Cu.

Methods

Selection of the best nuclear reaction

The main nuclear reactions that lead to the production of ^{65}Zn radioisotope are specified below: ^{65}Cu(p,n)^{65}Zn, ^{66}Zn(p,d)^{65}Zn, ^{65}Cu(d,2n)^{65}Zn, ^{66}Zn(d,t)^{65}Zn, ^{64}Zn(d,p)^{65}Zn, ^{66}Zn(^{3}He,α)^{65}Zn and ^{64}Zn(n,γ)^{65}Zn [17, 35].

The reactions which use deuteron or ^{3}He beams were discarded, since high energy and high intensity deuteron beams are not yet available and we have no facilities in the country for ^{3}He acceleration. For the ^{66}Zn(p,d)^{65}Zn and ^{64}Zn(n,γ)^{65}Zn reactions (the latter performed in nuclear reactors), chemical separation processes are difficult, expensive and time-consuming, due to the identical chemical properties of the product and the target material and low specific activity of the final product. Our best choice for the production of ^{65}Zn radioisotope was the ^{65}Cu(p,n)^{65}Zn reaction.

Natural copper is comprised of only two stable isotopes: ^{65}Cu (31%) and ^{63}Cu (69%). The possibility of replacing natural copper with ^{65}Cu isotope as the target material was also investigated in this research.

Cross-section calculations for proton reactions with copper

Characterization of excitation function is an important step for the determination of optimal energy of the incident beam. Excitation function can be predicted by computer codes (e.g. ALICE nuclear code [6]) or determined by experimental methods.

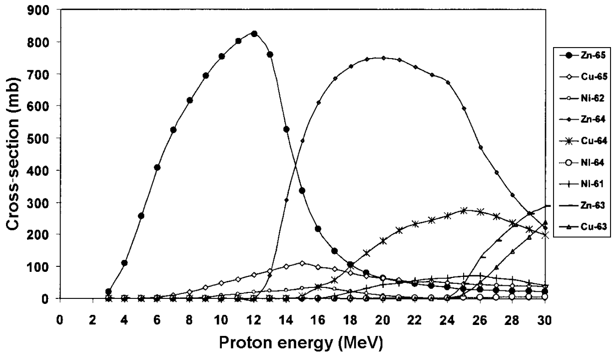

Fig. 1. Results of ALICE code for ^{65}Cu reactions with protons.

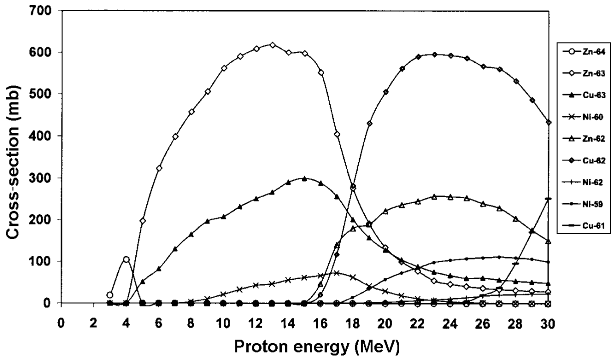

Fig. 2. Results of ALICE code for ^{63}Cu reactions with proton.

In the present research, performed in the cyclotron department of Atomic Energy Organization of Iran, cross-sections were calculated for different possible nuclear reactions of copper (for both ^{65}Cu and ^{63}Cu) with 3–30 MeV protons using ALICE nuclear code. The upper limit for energy range was determined according to the limitations of our system for proton acceleration. Results of cross-section calculations for ^{65}Cu and ^{63}Cu are given in Figs. 1 and 2, respectively.

Predictions of ALICE code for the products of ^{63}Cu and ^{65}Cu nuclear reactions with a proton beam are listed in Table 1.

Table 1 shows that ^{65}Zn has a longer half-life than all the other products. As a result, the presence of ^{63}Cu in the target makes no interference in the process, and natural copper can replace ^{65}Cu as the target material for the production of ^{65}Zn in a cyclotron. Seven days after the bombardment of natural copper, undesired radioisotopes will decay, and the final product will be left with high radionuclide purity.

Table 1. Products of ^{63}Cu and ^{65}Cu nuclear reactions with a proton beam, predicted by ALICE code

Nickel isotopes	Half-life	Copper isotopes	Half-life	Zinc isotopes	Half-life
^{59}Ni	stable	^{61}Cu	3.4 h	^{63}Zn	38.1 min
^{60}Ni	stable	^{62}Cu	9.7 min	^{64}Zn	stable
^{61}Ni	stable	^{63}Cu	stable	^{65}Zn	244.2 d
^{62}Ni	stable	^{64}Cu	12.7 h		
^{64}Ni	stable	^{65}Cu	stable		

Selection of the proton beam energy

Figure 1 shows that the probability of $^{65}Cu(p,n)^{65}Zn$ reaction begins at the proton beam energy of about 3 MeV ($Q_{reaction}$ = –2.6 MeV) and reaches its maximum (824 mb) at about 12 MeV, then it gradually decreases to 23 mb at 30 MeV.

When no interfering radionuclides are produced, it is preferable to use the highest possible beam energies in order to achieve the highest activity of the product. Therefore, 30 MeV proton beams were used for the bombardment of thick copper targets; although a 12 MeV beam seemed to be the best choice. Interfering radionuclides decayed in seven days.

It should be noted that the target had to be thick enough to decrease the incident proton beam energy at least to 3 MeV, according to the calculated value for the threshold energy (2.6 MeV), in order to achieve a high production yield.

Targetry

SRIM nuclear code was used for the determination of optimum target thickness [64]. Results of SRIM nuclear program for variation of proton range with the beam energy in a copper target are illustrated in Fig. 3.

Figure 3 shows that 1590 μ of copper is required to totally stop the 30 MeV protons. It should be noted that in IBA-Mark II cyclotrons, solid targets are fixed on special shuttles and sent to the solid target room by a rabbit system. The shuttles are designed to place the targets at an angle of 6° against the proton beam. This enables a 160 μ target to stop the 30 MeV protons and produce ^{65}Zn with higher efficiency. The efficiency increases since higher currents can be used for these targets due to the larger focal area and better heat transfer. In this project, there was no need for any special targetry because the targets were made of the same material used for solid target backings in IBA Mark II cyclotrons (natural copper). The 2 mm thick copper backings were used as the target material. The targets were cooled by a flow of 18°C distilled water with a rate of 50 l/min in the backing grooves.

Chemistry

The process of ^{65}Zn radiochemical separation from the copper target was performed using anion exchange chromatography on a BioRad AG 1 × 8 column (15 cm height, and 1 cm diameter) [9, 12, 32, 42, 51, 54].

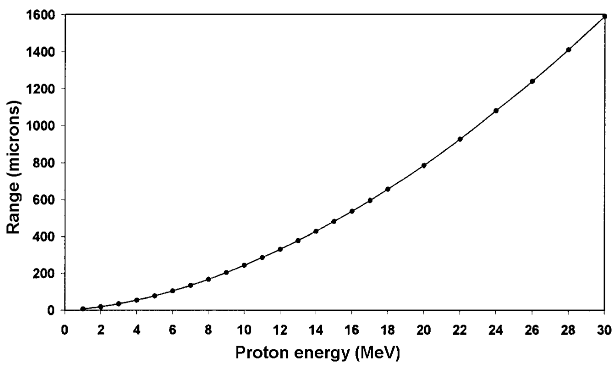

Fig. 3. Variation of proton range in a copper target.

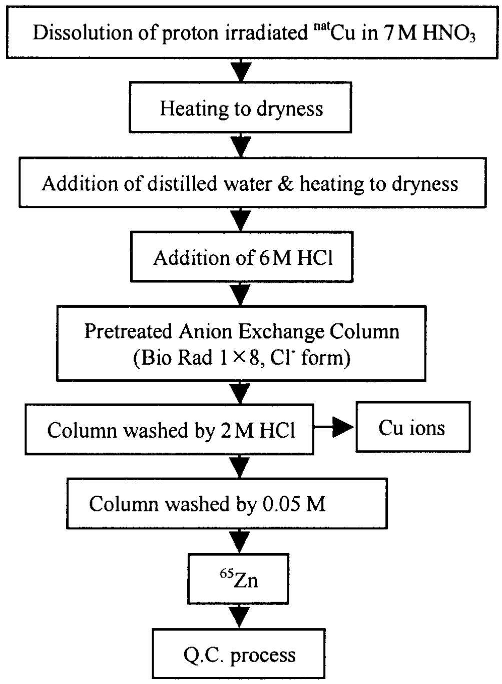

Fig. 4. Flow chart for ^{65}Zn radiochemical separation.

The copper target was dissolved in 25 ml of 7 M nitric acid. This solution was heated to dryness. Then 10 ml of distilled water was added and it was again heated to dryness. The residue was dissolved in 75 ml of 6 M hydrochloric acid and the solution was passed over a chromatography resin (BioRad AG 1 × 8, Cl^- form) previously treated with 6 M hydrochloric acid. Then, 50 ml of 2 M hydrochloric acid was passed over the resin with the elution rate of 1 ml/min to separate all copper ions. Finally, 150 ml of 0.05 M hydrochloric acid was used with the elution rate of 1 ml/min to separate ^{65}Zn ions.

The final solution was taken for quality control (QC) processes. The flow chart of the chemical separation process is given in Fig. 4.

Quality control

The following processes were performed for quality control of the final product:

1. Chemical control was performed to ensure the absence of undesired ions. During the ^{65}Zn production process, the only undesired ion was Cu^{2+}. Dithizone is the most sensitive reagent for the determination of Cu^{2+} ions [38]. In an acidic medium containing an excess of dithizone, copper(II) forms the violet dithizonate ($Cu(HDz)_2$). Cu^{2+} was proved to be eliminated, by high precision colorimetry (1 ppm detection limit) using dithizone as reagent.
2. Radionuclide control was performed by investigation of the spectrum from the high purity germanium (HPGe) detector coupled with a Canberra™ multichannel analyzer, seven days after the bombardment. The only observed peaks were 511 keV and 1115.5 keV, both originating from ^{65}Zn.

Results

The results of cross-section calculations performed in this research for ^{65}Cu and ^{63}Cu reactions with an incident proton beam using ALICE nuclear code were compared with the experimental data given in the literature, and are shown in Figs. 5–10.

It can be concluded from Figs. 5–10 that the results of ALICE nuclear code are in good agreement with the experimental data reported in previous research studies.

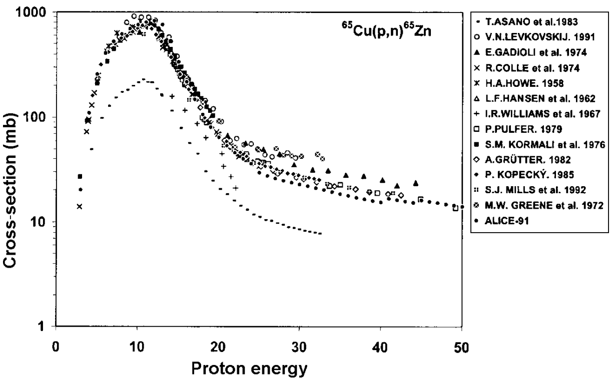

Fig. 5. Comparison of cross-section calculations with the experimental data for ^{65}Cu(p,n)^{65}Zn reaction [3, 10, 19, 21, 23, 25, 30, 33, 34, 37, 40, 49, 63].

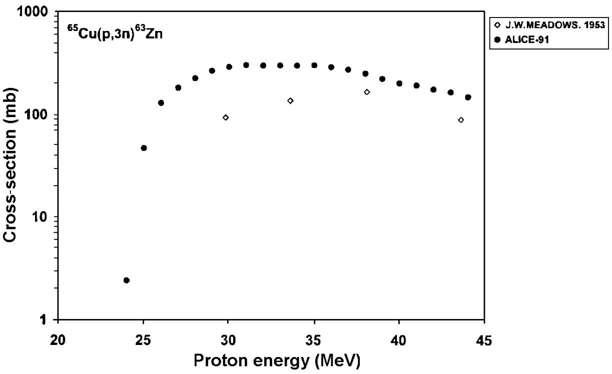

Fig. 6. Comparison of cross-section calculations with the experimental data for ^{65}Cu(p,3n)^{63}Zn reaction [39].

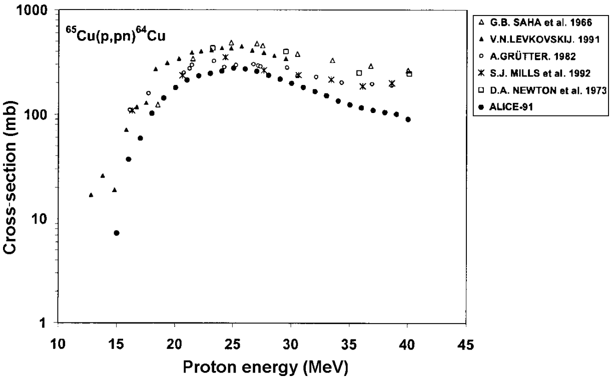

Fig. 7. Comparison of cross-section calculations with the experimental data for ^{65}Cu(p,pn)^{64}Cu reaction [23, 37, 40, 43, 52].

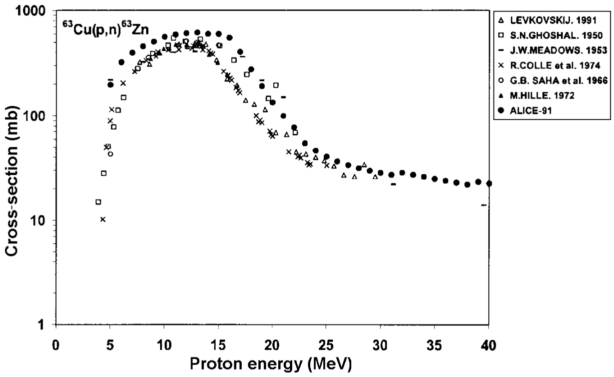

Fig. 8. Comparison of cross-section calculations with the experimental data for ^{63}Cu(p,n)^{63}Zn reaction [10, 20, 29, 37, 39, 52].

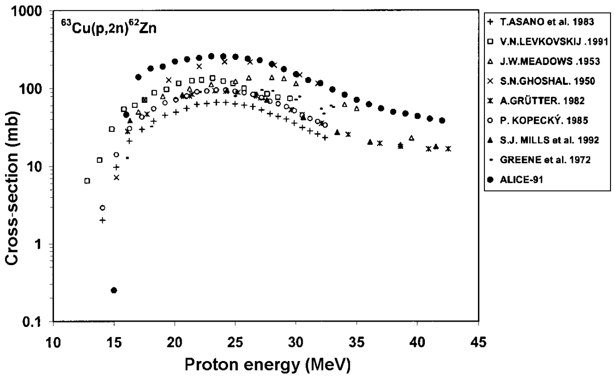

Fig. 9. Comparison of cross-section calculations with the experimental data for ^{63}Cu(p,2n)^{62}Zn reaction [3, 20, 21, 23, 33, 37, 39, 40].

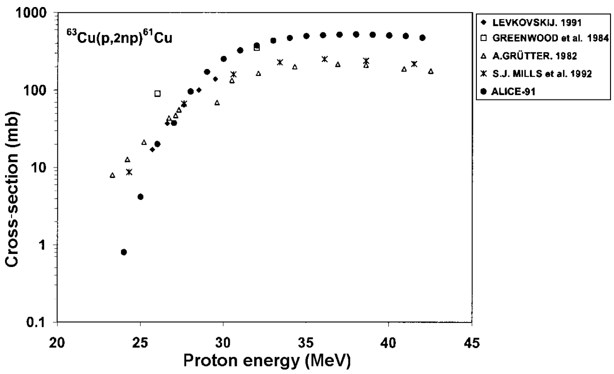

Fig. 10. Comparison of cross-section calculations with the experimental data for ^{63}Cu(p,2np)^{61}Cu reaction [22, 23, 37, 40].

After the bombardment of natural copper targets with a 150 μA current of 30 MeV protons for 20 minutes, ^{65}Zn was produced with an activity of 170 MBq which corresponds to the yield of 3.4 MBq/μAh. The concentration of the product was 6.8 MBq/ml with a high radionuclide purity (>98%).

The thick target yield obtained in this research is much higher than in the previous works reported in the literature (Table 2). This may be attributed to the lower proton energies used by other researchers for the bombardment in earlier experiments.

Table 2. Comparison of the thick target yield obtained in this research with previous studies [1, 13, 14]

Researchers	Proton energy (MeV)	Thick target yield (MBq/μAh)
Dmitriev and Molin (1981)	22	0.59
Dmitriev (1983)	22	1.92
Abe *et al.* (1984)	15.6	0.196
This research	30	3.4 ± 0.2

The chemical separation method used in this research was quite cost effective [62], due to the use of a rather inexpensive resin [28, 44, 47].

Variation of copper and zinc ion elution percentage with the effluent volumes are given in Figs. 11 and 12. The results are based on the ^{61}Cu and ^{65}Zn tracers for copper and zinc, respectively.

Figures 11 and 12 show that the simple chemical separation method used in this research is quite efficient and has a considerable yield of about 98%.

Two percent of the ^{65}Zn activity remained in the resin and column wall. By optimization of the radiochemical separation process based on the detection of ^{65}Zn and ^{61}Cu (as radiotracers), it was found that about 95% of the copper was separated using just 25 ml of 2 M HCl, and 90 ml of 0.05 M HCl was enough for the separation of almost 95% of the zinc.

No Cu^{2+} ions were detected as a result of chemical control process with a sensitivity of 1 ppm, which is below the USP limits (5 ppm).

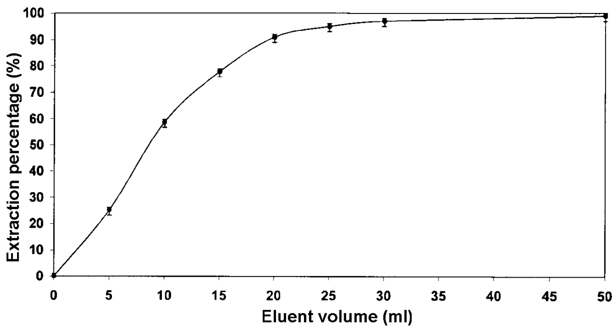

Fig. 11. Variation of copper ion elution percentage with the effluent volume (2 M HCl) based on the ^{61}Cu tracer, $n = 5$, SE < 3%.

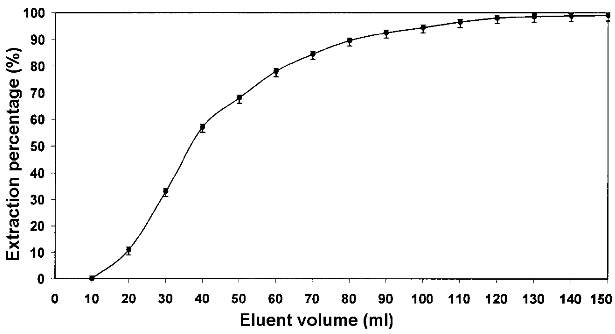

Fig. 12. Variation of zinc ion elution percentage with the effluent volume (0.05 M HCl) based on the ^{65}Zn tracer, $n = 5$, SE < 3%.

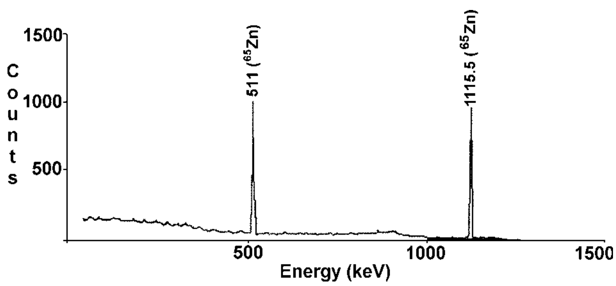

Fig. 13. Gamma spectrum of the final product in HPGe detector.

Gamma spectroscopy of the product seven days after the end of bombardment (Fig. 13) confirmed the high radionuclide purity of the product (> 98%). ^{64}Cu was the only detected impurity.

Conclusion

The method used in this research for the production of ^{65}Zn, was quite cost effective and ^{65}Zn was produced with high activity, high production yield and high radionuclide purity (> 98%).

The thick target yield obtained in this research was much higher than in previous reports given in the literature, and the radiochemical separation yield was more than 98%, while chemical and radionuclide quality control processes using colorimetry and gamma spectroscopy gave satisfactory results for the purity of the final product.

According to the wide range of applications for ^{65}Zn in different fields of study, the process introduced in this research can be considered as an efficient method for its better production in large amounts. The radionuclide produced in this research is presently being used for a research project on zinc absorption in wheat in the Nuclear Agriculture Department of NRCAM.

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