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ACTIVATION RATES AND CHEMICAL RECOVERY OF ^{67}Cu PRODUCED WITH LOW ENERGY PROTON IRRADIATION OF ENRICHED ^{70}Zn TARGETS

D. J. JAMRISKA SR, W. A. TAYLOR, M. A. OTT, R. C. HEATON,
D. R. PHILLIPS, M. M. FOWLER

Los Alamos National Laboratory, P.O. Box 1663, MS J514, Los Alamos, NM 87545 USA

Copper-67 is a radioisotope with significant potential for diagnostic and therapeutic applications in nuclear medicine. Despite its promise, ^{67}Cu has failed to make an impact in clinical nuclear medicine, primarily because it is available sporadically, and in limited quantities. Common methods of production rely on high energy proton irradiation of natural zinc targets or on induced reactions using high energy neutrons at nuclear reactors. We have evaluated alternative production methods that could provide year-round adequate supply of this isotope. Using a low energy accelerator, we have studied the production of ^{67}Cu by proton reactions on enriched ^{70}Zn. Our results indicate that it is possible to produce useful quantities of ^{67}Cu from the irradiation of enriched ^{70}Zn with protons that have energies of less than 20 MeV. Production rates are higher than currently used methods at high energy accelerators or reactors. This isotope can be made available throughout the year as a result of this research.

Copper-67 is a radioisotope with significant potential for diagnostic and theraputic applications in nuclear medicine. As it decays to stable ^{67}Zn, with a 2.6 day half-life, it emits beta particles with energy maxima ranging from about 0.4 MeV to about 0.6 MeV[1]. It also emits a gamma photon of 185 keV. Research has shown that the beta particles are effective in treating various tumor types when the radioisotope is delivered to the disease site[2]. The gamma emission is well-suited for imaging applications using the conventional Anger Gamma Camera technology so that ^{67}Cu localized in a tumor can be imaged using equipment typically available in a nuclear medicine facility. Primarily because the isotope is available only in a sporadic and limited quantities, ^{67}Cu has failed to make significant impact in clinical nuclear medicine. Current methods of production rely on either high energy proton interactions with natural zinc targets at large accelerators operating only part of the year or on (n,p) reactions using enriched ^{67}Zn targets and high energy neutrons from nuclear reactors.

Cole, et al.[3,4], the development of techniques for labeling porphyrins with metal ions by Mercer-Smith, et al.[5,6], and research into therapy using ^{67}Cu labeled monoclonal antibodies by de Nardo, et al.[7] have generated increased interest in the availability of ^{67}Cu on a more consistent basis. Currently these interests have been restricted as a result of the inconsistent

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supply of the ^{67}Cu used for preparation of the porphyrins/monoclonal antibodies. At present, accelerator produced ^{67}Cu is only available in quantity from Los Alamos National Laboratory and Brookhaven National Laboratory for 6-8 months of the year. Reactor production via the $^{67}Zn(n,p)^{67}Cu$ reaction is possible but production rates are too low to be financially feasible for long range treatment protocols.[8]

We have examined a number of possible methods of production using the Los Alamos National Laboratory Van de Graaff accelerator. Our initial research centered on the use of the epithermal/fast neutrons produced by proton reactions on Ge and W targets to simulate reactor production methods. Although measurable amounts of ^{67}Cu were produced, expensive (>10 gram) enriched ^{67}Zn targets would have been required to produce the desired quantities. Investigations into other possible production methods at LAMPF indicated that some of our total ^{67}Cu production may be resulting from high energy (p,α) reactions on the ^{70}Zn fraction of our natural zinc targets. Theoretical calculations using the ALICE computer code[9] and our experimental results indicated that a useful cross section for ^{67}Cu production at proton energies less than 25 MeV does exist. Thus, it should be possible to produce ^{67}Cu at any suitable low energy (<30 MeV) proton accelerator throughout the year.

Experimental

Targets and Irradiations: Irradiations were performed using the tandem Van de Graaff accelerator at the Ion Beam Facility at the Los Alamos National Laboratory. This accelerator has a maximum energy of 20.4 MeV for protons and can provide up to 17 μA of current on target for isotope production. Actual beam intensity varied from 2 to 6 μA and proton energies ranged from 19.6 MeV to 18.1 MeV at the face of the target material. Targets, 0.95 cm in diameter, were prepared from both natural zinc and enriched ^{70}Zn. The targets were fabricated from compressed oxide, electrodeposited zinc metal, or stacked zinc metal foils. Four of the six targets were covered with 0.05 mm thick copper monitor foils to measure beam intensity. Table 1 lists the target compositions. Table 2 lists the parameters for each irradiation. Figure 1 is a diagram of the target geometry used for these experiments.

Calculations using ALICE[9] generated cross section curves indicate a maximum cross section for the (p,α) reaction at ~ 17 MeV. Recently acquired data from Levkovskii,[11] place the maximum at 14.8 MeV and with a cross section more than twice that estimated from ALICE calculations. Data from Barbier also indicate that (p,α) reactions on Zn are possible[12]. Figure 2 shows the comparision between the data of Levkovskii and ALICE.

Activity Measurements: The radioisotopes of interest and their major decay properties are listed in Table 3. All radioassays were made using a HPGE detector coupled to a 4000 channel pulse height analyzer which had been calibrated using NIST traceable standards to determine the detector efficiency curve. Data was processed using the computer codes Specanl and Raygun.

Table 1.

Description Of Targets

No.	Weight	Enrichment	Thickness	Composition	Window
1A	10.2 mg	99.72%	0.015 mm	comp. ZnO	0.15 mm Al
1B	10.2 mg	99.72%	0.015 mm	comp. ZnO	0.15 mm Al
1C	10.2 mg	99.72%	0.015 mm	comp. ZnO	0.15 mm Al plus 0.05 mm Cu
5	10.7 mg	71.80%	0.015 mm	comp. ZnO	0.15 mm Al plus 0.05 mm Cu
3	10.8 mg	natural	0.015 mm	electroplated Zinc	0.15 mm Al plus 0.05 mm Cu
0	283.5 mg	natural	0.5 mm	stacked foils	0.15 mm Al plus 0.05 mm Cu

Table 2.

Irradiation Parameters

Target No.	Incident Energy	Exit Energy[a]	Average Beam Current[b]	Irradiation Time
1A	18.1 MeV	17.8 MeV	2.0 μA	20 min.
1B	18.1 MeV	17.8 MeV	5.0 μA	20 min.
1C	18.8 MeV	18.5 MeV	4.0 μA	50 min.
5	18.8 MeV	18.5 MeV	5.1 μA	60 min.
3	18.8 MeV	18.5 MeV	5.7 μA	60 min.
0	18.8 MeV	11.4 MeV	5.3 μA	60 min.

a) Calculated values using Ziegler, et al.[10]

b) See text for derivation

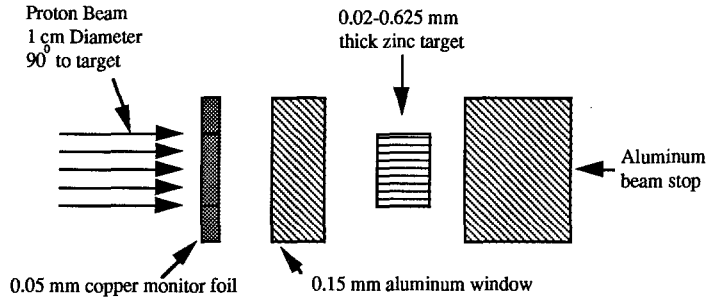

Fig. 1 Target assembly

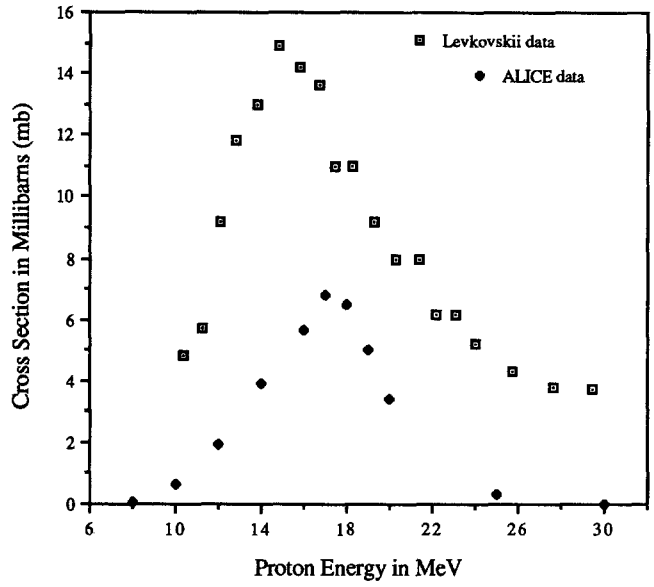

Fig 2. Comparision Between the Data of Levkovskii and ALICE

Table 3.

Decay Parameters Used For Assay

Nuclide	Half-life	Gamma Radiation	Abundance(%)
^{64}Cu	12.7 hr	1345.8 keV	0.48
^{67}Cu	2.58 d	184.6 keV	48.6
		300.2 keV	0.797
^{62}Zn	9.26 hr	596.7 keV	25.7
^{65}Zn	244.1 d	1115.5 keV	50.75
^{67}Ga	3.261 d	184.6 keV	20.4
		300.2 keV	16.6

Copper Monitor Foils: After irradiation, all of the targets were stored at the accelerator building overnight to permit the short lived products to decay before transportation to the radiochemistry laboratories for processing. The copper monitor foils were removed from the target assembly and the area directly in front of the target material was removed for chemical processing and counting to determine the proton intensity. Copper-64 from the reaction $^{65}Cu(p,pn)^{64}Cu$ and ^{62}Zn from the sum of the $^{65}Cu(p,4n)^{62}Zn$ and $^{63}Cu(p,2n)^{62}Zn$ reactions were used to calculate the integrated beam currents. 380 mb was used for the $^{65}Cu(p,pn)^{64}Cu$ cross section while 87 mb was used for the sum of the (p,4n) and (p,2n) reactions that lead to production of ^{62}Zn.[13]

The monitor foils were dissolved in 5 ml of 6 M HCl containing a few drops of H_2O_2. After warming to destroy excess H_2O_2 the solution was adjusted to 9 M in HCl and loaded onto a 7 ml AG 1-X8 anion exchange resin which was conditioned with 9 M HCl. The column was washed with 15 ml of 9 M HCl and the copper removed from the column with 30 ml of 2 M HCl. The Zn isotopes were then stripped from the column with 30 ml of 2 M HNO_3. The copper and zinc fractions were then assayed for ^{64}Cu and ^{62}Zn respectively. A chemical yield of 98% was determined based on gamma counting of the separated fractions. The beam currents were also integrated electronically during the target irradiations. These results were compared to those derived from the monitor foils and found to lie within 5% of the average of the two monitor foil values. All three of the derived beam current values for each target irradiation were averaged to give the values listed in Table 2.

Zinc Target Chemistry: Because both ^{67}Cu and ^{67}Ga have the same gamma emissions, but with different branching rates, the chemistry on the zinc targets was designed to separate the ^{67}Cu from the ^{67}Ga to determine production yields. The chemistry was patterned after Kraus and Nelson[14] and did not separate other non-interfering radionuclides.

The zinc targets Nos. 1, 3, and 5 along with their aluminum holders were each dissolved in ~ 50 ml of 6 M HCl containing a few drops of H_2O_2. After warming to destroy excess H_2O_2 the solution was adjusted to 9 M in HCl and loaded onto a 15 ml AG 1-X8 anion exchange resin conditioned with 9 M HCl. The column was washed with 30 ml of 9 M HCl, then copper and gallium isotopes were eluted from the column with 100 ml of 2 M HCl. The eluant was then evaporated to dryness, dissolved in 3 ml of 12 M HCl and loaded onto a 3 ml AG 50W-X8 cation exchange column. The copper isotopes were stripped from the resin with 12 M HCl and then assayed for ^{67}Cu. The gallium was removed from the cation column with 1 M HCl. Zinc target marerials were then stripped from the anion column with 30 ml of 2 M HNO_3, assayed, and saved for future fabrication of new targets.

The thick zinc target No. 0 and aluminum holder were dissolved in ~ 50 ml of 6 M HCl containing a few drops of H_2O_2. After warming to destroy excess H_2O_2 the solution was adjusted to 9 M in HCl and loaded onto a 75 ml AG 1-X8 anion exchange resin conditioned with 9 M HCl. The column was washed with 150 ml of 9 M HCl, then copper and gallium isotopes were removed from the column with 500 ml of 2 M HCl. The eluant was then evaporated to dryness. The residue was dissolved in 3 ml of 12 M HCl and loaded onto a 10 ml AG 1-X8 anion exchange column. The copper isotopes were stripped from the resin with 350 ml of 12 M HCl, and assayed for ^{67}Cu. The gallium was removed from the anion column with 1 M HCl. The natural zinc target material was not recovered. A chemical yield of 90% was determined based on gamma counting of the separated fractions after chemical separation of the copper and gallium. Results for all 4 targets are listed in Table 4.

It is apparent that as the enrichment of ^{70}Zn increases the production of ^{67}Cu also increases and the production of ^{67}Ga decreases. Table 5. shows the production of ^{67}Cu as a function of the enrichment and weight of ^{70}Zn target material.

Table 4.

Recovered nuclides by target

Target	Enrichment	^{67}Cu	^{67}Ga	^{65}Zn
1A	99.72	54.4 kBq	N/D	N/D
1B	99.72	260 kBq	N/D	1.11 kBq
1C	99.72	298 kBq	12.0 kBq	N/D
3	natural	7.4 kBq	840 kBq	95.5 kBq
5	71.6	385 kBq	4 MBq	33.3 kBq
0	natural	75.9 kBq	18.2 MBq	821 kBq

Table 5.

^{67}Cu Production yields

Target No.	^{67}Cu Act.(kBq)	Wgt.of ^{70}Zn in Target(mg)	Activity Produced kBq/mg/hr	Yield kBq/mg/hr/mA
1A	54.4	10.0	16.3	8.14
1B	260	10.0	77.7	15.5
1C	298	10.0	35.9	8.88
3	7.4	0.065	114	20.0
5	385	7.66	50.3	9.62
0	75.9	1.69	44.8	8.51

Results and Discussion

Yield Calculations: Table 5. lists yields by target in kBq/mg ^{70}Zn in target/hr of irradiation/mA current. The high value for target #3 is unexplained and may be due to unseparated ^{67}Ga. The value for target 1B may be due to suspect high electronic beam current integration and was the reason for use of copper monitor foils for the other targets. The average yields for the other 4 targets is 8.88 kBq/ mg ^{70}Zn/hr/mA. Target thickness up to 0.5 mm has no effect on production yields although higher yields were expected based on cross section versus energy data.

Thick target yields versus thin target yields: Calculations based on the Ziegler, ALICE, and Levkovskii data indicate that with a proton energy of 22 MeV incident on the face of the zinc target, production will continue to occur through at least 0.625 mm of target. Target # 0 was 0.5 mm thick and the production rate was within the same range as the thin targets. This indicates that one may extrapolate yields from a thin (0.025 mm) target to a thick (0.625 mm) target provided that they have the same irradiation parameters.

Table VI. lists the ^{67}Cu yields from the current production facilities. The calculated apparent cross section for LAMPF is based on typical yields from 1993 production irradiations. Apparent production cross sections for BLIP were calculated from production information provided by Brookhaven National Laboratory. Brookhaven National Laboratory has previously measured a nuclear cross section of 14 mb on non-production type targets. The value for IBF is the average of 4 measurements ranging from 12.4 mb to 15.4 mb. Our average value of 13.6 mb for the $^{70}Zn(p,\alpha)^{67}Cu$ reaction at 18.5 MeV, although slightly higher than the 11 mb reported by Levkovskii, confirms his work. The cross section for production at the High Flux Isotope Reactor is comparable to that of LAMPF but significantly lower than either BLIP or IBF. Both BLIP and LAMPF have high beam currents and the capability of irradiating large mass targets so that the lower production cross sections can be overcome.

Table 6.

Production rate comparision of various methods

Facility	Reaction	Time	Current	Production Rate kBq/mg/hr/mA	Apparent cross section in mb
LAMPF*	$Zn(p,spall)^{67}Cu$	168 hr	400 μA	2.13×10^{-2}	0.94
BLIP[15]	$Zn(p,x)^{67}Cu$	120 hr	45 μA	3.39×10^{-1}	2.15
IBF**	$^{70}Zn(p,a)^{67}Cu$	1 hr	5 μA	8.88	13.6
HFIR	$^{67}Zn(n,p)^{67}Cu$	168 hr	4×10^{14} n/s/cm2		0.91-1.23

* Historical yields 1992-93 ^{67}Cu production at LANL-LAMPF

** Average of 4 measurements, this work

Conclusions

Useful quantities of ^{67}Cu can be produced via the (p,α) reaction on enriched ^{70}Zn targets using low energy proton accelerators. Enrichments greater than 70% provide the highest yields but will require recovering and reusing the target material. Using this approach, production of ^{67}Cu should be possible at a number of currently operating accelerators at any time during the year, which would alleviate the current sporadic and limited supply of this valuable medical radioisotope.

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References

1. E. BROWNE, R. B. FIRESTONE, and V. S. SHIRLEY, Table of Radioactive Isotopes, John Wiley and Sons, New York, USA, (1986)
2. G. DE NARDO, S. DE NARDO, D. KUKUIS, H. DIRIL,C. SUEY, and C. MEARES, Int. J. Instrum. Part B, Nucl. Med. Biol. 18, (1992), 633
3. D. A. COLE, J. A. MERCER-SMITH, S. A. SCHREYER, J. K. NORMAN, and D. K. LAVALLEE, Nuc. Med. BIOl. 17, (1990), 457
4. D. A. COLE, D. C. MOODY, L. E. ELLINWOOD, M. G. KLEIN, J. A. MERCER-SMITH, A. BRUMBAUGH, R. O. EIKLEBERRY, D. LEWIS, G. SACCOMANNO, J. J. BECKTEL, and D. K. LAVALLEE, New Trends in Radiopharmaceutical Synthesis, Quality Assurance and Regulatory Control, (A. Emran, ed.) Plenum Press, New York, (1991), 109
5. J. A. MERCER-SMITH, J. C. ROBERTS, S. D. FIGARD, and D. K. LAVALLEE, Vol.1 of Targeted Diagnosis and Therapy Series(J. T. Rodwell, ed.), Marcel Dekker, New York, (1988), 317
6. J. C. ROBERTS, S. D. FIGARD, J. A.MERCER-SMITH, Z. V. SVITRA, W. L.ANDERSON, and D. K.LAVALLEE, J. Immunol. Meth., 105, (1987), 153
7. S. V.DESHPANDE, S. J. DE NARDO, C. F. MEARES, M. J. McCALL, G. P. ADAMS, M. K. MOI, and G. L. DE NARDO, J. Nucl. Med. 29, (1988), 217
8. S. MIRZADEH, F. F. KNAPP Jr., Radiochimica Acta, 57, (1992), 193
9. M. BLANN, J. BISPLINGHOFF, Code ALICE/ Livermore 82. Lawrence Livermore National Laboratory-Internal Report UCID-19614, November 5, 1982.
10. J. F. ZIEGLER, J. P.BIERSACK, and V. LITTMARK, The Stopping and Range of Ions in Solids, Pergamon Press, Inc., New York, USA, (1985)
11. V. N. LEVKOVSKII, Activation Cross Section Nuclides of Average Masses(A = 40-100) by Protons and Alpha-Particles with Average Energies (E = 10-50 MeV), Moscow, Russia, (1991)
12. M. BARBIER, Induced Radioactivity, North Holland Publishing Co. , Amsterdam-London, (1969)
13. S. MEGHIR, and L. YAFFE, Ph.D. Thesis, McGill University, Montreal, Quebec, Canada, (1962)
14. K. A.KRAUS, and F.NELSON, Proceedings of the International Conference on the Peaceful Uses of Atomic Energy, 1955, United Nations Vol.7, (1956),113
15. K. KOLSKY, p.c., Brookhaven National Laboratory, (1994)