

Development of cost effective method for production of ^{64}Cu from $^{\text{nat}}\text{Ni}$

Z. Szűcs^{1*}, S. Takács¹, B. Alirezapour^{1,2}

¹Institute for Nuclear Research, Hung. Acad. Sci., Bem ter 18/C, 4026 Debrecen, Hungary,

zszucs@atomki.mta.hu

²Radiopharmaceutical Research and Development Lab, Nuclear Science Research School, Nuclear Science and Technology Research Institute, Tehran, 11365-3486, Iran.

Abstract

A $^{\text{nat}}\text{Ni}$ foil was used for the production of ^{64}Cu via $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ nuclear reaction when the necessary investment for target material (350 mg) is 50 times less using the $^{\text{nat}}\text{Ni}$ instead of ^{64}Ni . The produced 32.2 ± 1.8 MBq of “no carrier added” ^{64}Cu is sufficient for 10 mice trials on small animal PET. The radionuclide contamination was less than 13 ± 12 kBq for ^{55}Co and 4 ± 2 kBq for ^{57}Ni comparing to minimum detectable activity and only 52 ± 2 kBq of ^{61}Cu was in ^{64}Cu due to the modified ion exchange separation. The concentration of Fe(III) was maintained under 1.7 ppm by precipitation and filtering of $\text{Fe}(\text{OH})_3$ due to the chemical purity was required.

Keywords

^{64}Cu , ^{61}Cu , ^{55}Co , ^{57}Ni , elimination of Fe(III), $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ reaction

Introduction

The copper is one of the most important trace elements in the biosphere. Its importance in blood system and chelate bonds to the bioactive macro-peptides is well known. The nuclear medical applications of copper radioisotope such as ^{64}Cu also have wide literature. The ^{64}Cu which decay by β^- and electron capture modes while emitting both beta minus and positron particles in high abundance (38.5% β^- and 61.5% EC with 17.6% β^+) with a half-life of 12.7 hours. It can play an important role of bi-functional radioisotopes for both positron emission tomography (PET) imaging and targeted radionuclide therapy of cancer. [1] The half-life of ^{64}Cu allows producing

this isotope at regional or national cyclotron facilities and distributing to local nuclear medicine departments with the loss of approximately not more than one half-life. In addition, the longer half-life is compatible with the time scales required for the optimal bio-distribution of slower clearing agents, such as monoclonal antibodies (mAbs), nanoparticles, and higher molecular weight polypeptides requiring longer imaging times [2]. The ^{64}Cu suits better for high resolution PET imaging with its low mean energy (278 keV) β^+ - emission and very low intensity but high energy gamma-ray (1345.7 keV, 0.47%) than ^{61}Cu and ^{62}Cu . Its 191 keV mean energy β^- - emission, nearly identical to that of the ^{67}Cu beta-emitter, is suitable for the radionuclide therapy of small tumors. Besides, the electron capture decay mode with its associated Auger emissions can yield more efficient cell killing when the ^{64}Cu nuclide is deposited in the cell nucleus [3]. Copper-64 can be produced with a nuclear reactor via the thermal neutron capture reaction using the $^{63}\text{Cu}(n,\gamma)^{64}\text{Cu}$ reaction or with fast neutron reaction via the $^{64}\text{Zn}(n,p)^{64}\text{Cu}$ reaction [4,5]. The ^{64}Cu produced by thermal neutron irradiation is readily available at many reactor sites; however, its specific activity is too low for labeling antigen or receptor targeted compounds [6]. For production of no-carrier-added (NCA) ^{64}Cu for medical use several routes have been investigated at medium energy cyclotrons [7,8,9]. Therefore we focused our study on production of Copper-64 using lower energy biomedical cyclotrons. The most common nuclear reactions for production of ^{64}Cu by cyclotrons are $^{68}\text{Zn}(p,\alpha n)^{64}\text{Cu}$, $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ and $^{\text{nat}}\text{Ni}(p,n)^{64}\text{Cu}$ [10]. Due to the materials and the available beam parameters at the Institute for Nuclear Research (Atomki) (proton $E=2.5\text{-}18$ MeV, $40\mu\text{A}$ intensity) [11], it was selected the $^{\text{nat}}\text{Ni}(p,n)^{64}\text{Cu}$ reaction to produce ^{64}Cu radionuclide for diagnostic study according to the literature [12]. In this paper we present a cheap method for production of ^{64}Cu due to the selection of target material and an easy process for separation of Cu radioisotopes in the range of tens of MBq scale, the amount that can be useful for small animal PET investigation. The interpreted precipitation and filtration steps to reduce the concentration of free Fe(III) to 1.7 ppm is also necessary due to the strong competition of Fe(III) ions in case of receptor imaging for PET investigations.

Experimental

The Ni metal foil with natural isotopic composition (chemical purity: 99,9%) and thickness of ~0.5mm (445 mg/cm²) was supplied by GoodFellow, UK. The irradiation was done at the cyclotron of Atomki. The irradiation lasted 3 hours with 15 MeV, 15 μA proton beam. The bombarding proton energy was limited at 15 MeV where the cross section already drops below 1/3 of the maximal value of the cross section of the ⁶⁴Ni(p,n)⁶⁴Cu reaction and to keep down the production of additional radionuclides. At this bombarding energy the range of the protons is about 460 microns that means the beam stops in the target. The target foil was fixed on a water-cooled copper backing for proper temperature maintaining during irradiation. After 8 hours cooling time to decay of the short lived Cu products the activity of the irradiated target was first measured by dose calibrator “AtomLab 100” of SUN Nuclear Corporation, USA, then chemically processed. The irradiated foil was dissolved in 10 mL 6 M HCl to which 8 mL of hydrogen peroxide ((H₂O₂) was added slowly. The dissolution was carried out in ~40 min between 100 – 150°C. After that the solution was evaporated to dryness. The solid residue was dissolved again by 5M HCl. This solution was used for the separation process on an anion-exchange column Dowex 1-8X. The flow rate on the column was 0.5 mL min⁻¹. After the loading process the column was washed 4 times with 5M HCl and 2 times with distilled water. The separated fractions were collected and each of them the radioactivity was measured separately: the results are reported in Table 1. The reagents used in the chemical process were “pro analysis” grade from Sigma Aldrich. The ion-exchanger resin Dowex1-8X, 200-400 mesh was from Supelco. The IC column from BIO-RAD (1.2 cm ID, 20 cm long) was filled with 20 mL pre-treated resin. The resin was chemically treatment before its application by 100 mL 0.1M NaOH and 0.1 M HCl to eliminate the possible hyper-active nodule on the resin. The γ- spectra were measured by using a Canberra HPGe detector (model GC1520), Tenelec and Canberra electronics Nucleus II type analyser card and software. The geometry dependent detector efficiency was determined by calibrated ¹⁵²Eu point source. 10 μL of samples were taken for the measurement from each step of the chemical process.

Table 1: Relative activities of the radioisotopes in the separated fractions, where “L” means the loading fraction, “A” means 5M HCL washing, “W” means distilled water washing. Data is given by the dose calibrator Atomlab 100 in setting ¹⁸F.

| Fraction | L1 | L2 | A1 | A2 | A3 | A4 | W1 | W2 |
|-----------------------|------------------|------------------|------------------------------------|------------------|------------------|----|----|------------------------------------|
| Activity [kBq] | 81 | 81 | 89 | 13690 | 222 | 0 | 0 | 1765 |
| Detected radioisotope | ⁵⁷ Ni | ⁵⁷ Ni | ⁵⁷ Ni, ⁵⁵ Co | ⁵⁵ Co | ⁵⁵ Co | - | - | ⁶⁴ Cu, ⁶¹ Cu |

The last fraction containing the Cu isotopes was evaporated to dryness. Trace amount of Fe(III) visible by the slight yellow color of the liquid was determined in the product. To separate the iron the residue was taken back with distilled water to liquid form and added 3 mL of ammonium hydroxide 25% (NH₄OH). The brown precipitated Fe(OH)₃ was filtered by the 0.22 micron Millipore filter, and the extracted fraction containing ⁶⁴Cu was collected. The amount of radioactivity and radionuclide purity of ⁶⁴Cu was determined by γ -spectrometry as it is described above. The sequential steps of chemical process are showed in Table 2.

Table 2: Chemical process to separate the ⁶⁴Cu from irradiated ^{nat}Ni foil

| Step of process | Chemicals | Description |
|--------------------------------|---|--|
| Dissolution of target material | 10 mL 6M HCl, 8 mL H ₂ O ₂ | Firstly add HCl, after that gently add H ₂ O ₂ in 35-45 min. at 100-150C°. After dissolution evaporate to dryness. |
| Separation by anion exchanger | 20 mL DOWEX1-8X resin, 4x 5mL 5M HCl, 2x 5mL distilled H ₂ O | Take back with 10 mL HCl, load to column, wash it 4 time with HCL, after that 2 times with water. Last fraction evaporates to dryness. |
| Elimination of Fe(III) ion | 1 mL distilled H ₂ O 3mL 25% NH ₄ OH | Take back with 1 mL water, add NH ₄ OH, filtrate it on 0,2 μ m filter. Evaporate the extract to dryness |
| Preparation of final product | 0.5 ml 0.9% NaCl | Take back with 0.5 mL saline. |

Results and Discussion

The strength of complexation of metal ions with chloride ions depends on the concentration of chloride ions. This is the theoretical background for separation of different transition metal ions by ion-chromatography [13]. This method is a powerful tool to get the stock solution of ⁶⁴Cu for labeling procedure in nuclear medicine. The separation of ⁶⁴Cu versus ⁵⁷Ni and ⁵⁵Co radioisotopes was complete, as the radio-chromatogram shows in Table 1. 5M HCL fractions

washed out the target material ^{nat}Ni with ^{57}Ni , after that ^{55}Co . The pure ^{64}Cu ion was eluted by water. The γ -spectra of the different fractions related to Table 1 are reported in Fig. 1.

Place of Figure 1.

We can estimate only an upper value of the contamination level by ^{55}Co and ^{57}Ni radioisotopes, for which the minimum detectable activity (MDA) were 13 ± 12 kBq and 4 ± 2 kBq respectively. The calculation was made by using the most intense γ -line of ^{55}Co (931.3 keV, 75%) and of ^{57}Ni (1377.6 keV, 81,7%) by measuring 10 μL of the final product. No traces were indentified in the spectra, therefore the contamination must be less than the MDA values in the end product. However, the one magnitude higher dose-rate of the ^{55}Co isotope comparing to the dose –rate of ^{64}Cu at the end of the bombardment in the irradiated target requires special attention during the separation procedure.

The activity of the ^{64}Cu containing main product was 32.2 ± 1.8 MBq in 0.5 mL sterile saline usually. The amount of the ^{61}Cu radionuclide in the final product was 52 ± 2 kBq, (0.16%), 26 hours after the end of bombardment which value is continue to decrease due to the ratio of half-lives. We have succeeded to improve the quality of the ^{64}Cu final product in this experiment by developing and applying a protocol for removing the iron content from solution [14]. Presence of trace amount of iron ions in the eluted liquid can be explained with the behavior of the anion exchanger resin. During the column preparation as well as the separation process, when the column was washed by HCl, the iron which was in HCl in ppm concentration, enriched on the column too with the Cu ions. That iron content was washed out together with the copper by distilled water in the final step of the separation. After the precipitation and filtration of $\text{Fe}(\text{OH})_3$ the concentration of “free” Fe(III) was 1.7 ppm by estimation of the constant of solubility of $\text{Fe}(\text{OH})_3$ [14]. The elimination of iron ions is extremely important due to its strong competitive behavior with copper during the chelate complexation as well as for receptor imaging of tumor cells [15]. The chemical yield of the wet chemistry and filtration steps was $85\pm 7\%$. This value is based on 8 separation experimental procedures.

Conclusions

This paper describes a cheap small scale production way of ^{64}Cu radionuclide. The necessary amount of metallic Ni target material is only about 350 mg. The cost of 350 mg of enriched ^{64}Ni target material is about \$ 13300 [16], while 10 pieces of 10 mm diameter, 0.5 mm thick natural Ni foil cost only \$250 [17]. It means that the necessary investment for target material is about 50 times less when using $^{\text{nat}}\text{Ni}$ target for irradiation. The amount of produced activity of ^{64}Cu in one run would be eligible for 10 mice trials with small animal PET camera.

Acknowledgement

Authors thank to the International Atomic Energy Agency (IAEA, project N^o: 12005 IRA) for supporting of our study.

References

1. <http://www.nndc.bnl.gov/chart/chartNuc.jsp>
2. Anderson C.J. and Ferdani R. (2009) Cancer Biother. Radiopharm. 24: 379-393
3. Blower P.J., Lewis J.S. and Zweit J. (1996) Nucl. Med. Biol. 23:957-980
4. Herr W., and Bott H. (1950) Z. Naturforsch A. 5a: 629.
5. Herrero P, Hartman JJ, Green MA, Anderson CJ, Welch MJ, Markham J, Bergmann SR. (1996) J Nucl Med. 37:1294-300.
6. Lynn KG, Webber M, Rellig LO, Mills AP, Moodenbaugh AR (1987) NATO ASI ser B169: 161-174.
7. Mirzadeh S., Mausner L.F., and Garland M.A. (2010) In Vértés A., Nagy S., Klencsár Z., Lovas R.G., and Roesch F. (ed) Handbook of Nuclear Chemistry, 2nd edn. Springer
8. Qaim S.M. (2010) In Vértés A., Nagy S., Klencsár Z., Lovas R.G., and Roesch F. (ed) Handbook of Nuclear Chemistry ,2nd edn. Springer
9. Qaim S.M. (2012) Radiochim. Acta 100: 635–651
10. McCarthy D.W., Shefer R.E., Klinkowstein R.E., Bass L.A., Margeneau W.H., Cutler C.S., Anderson C.J. et al (1997) Nucl. Med. Biol. 24: 35-43
11. <http://www.atomki.hu/Accelerators/Cyclotron/beams.html>

12. <https://www-nds.iaea.org/medical/nip57ni7.html>
13. Nelson F., Michelson D.C. (1966) J Chromatog A 25: 414-441.
14. Erdey L.(1966) Introduction of chemical analysis, I. Vol. 8. edition, Tankönyvkiadó, Budapest, (in Hungarian)
15. Wadas T.J., Wong E.H., Weisman J.R., Anderson C.J. (2011). Rev J Chem 110: 2858-2902
16. <http://www.goodfellow.com/catalogue>
17. <http://www.isoflex.com>

Figure 1. γ -spectrum of eluted fractions. 10 μL from each fraction was measured for 300 sec in calibrated position. The y scale show the counts collected during the measuring time.

