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FEATURES OF THE COPPER-64 ISOTOPE PRODUCTION USING THE MGC-20 CYCLOTRON AT ST. PETERSBURG POLYTECHNICAL UNIVERSITY

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Abstract. The article deals with the technology of ^{64}Cu isotope production by cyclotron proton irradiation of nickel foil of natural isotopic composition. In order to produce the ^{64}Cu isotope, three nickel samples were irradiated with 13 MeV protons (beam current was 4 μA) for three hours using the MGC-20 cyclotron at SPbPU. After irradiation the samples were subjected to multistage radiochemical treatment aimed at refining the chemical form suitable for measuring the activities of ^{64}Cu isotope and impurities. According to gamma spectrometric analysis, the ^{64}Cu activity value was 30 MBq. The performed calculations of induced ^{64}Cu isotope activity were based on the initial data and took into account the experimental conditions. A comparison of the experimental data with calculation results showed a good agreement between them.

Keywords: copper-64 isotope, cyclotron irradiation, natural nickel foil, comparison

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ОСОБЕННОСТИ ПОЛУЧЕНИЯ ИЗОТОПА МЕДИ-64 НА ЦИКЛОТРОНЕ МГЦ-20 САНКТ-ПЕТЕРБУРГСКОГО ПОЛИТЕХНИЧЕСКОГО УНИВЕРСИТЕТА

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Аннотация. В статье рассматривается технология получения изотопа ^{64}Cu путем циклотронного облучения протонами никелевой фольги природного изотопного состава. С целью наработки изотопа ^{64}Cu, три образца тонкой никелевой фольги в виде дисков были облучены протонами с энергией 13 МэВ (ток пучка − 4 мкА) на циклотроне МГЦ-20 СПбПУ в течение трех часов. По окончании облучения эти образцы подвергали многоэтапной радиохимической обработке, направленной на получение химической формы, удобной для измерения активности примесей и изотопа ^{64}Cu, образованных в результате облучения. По данным гамма-спектрометрического анализа значение активности этого изотопа составило 30 МБк. Сравнение данных эксперимента с результатами выполненных расчетов наведенной активности изотопа ^{64}Cu, базирующихся на исходных данных и учитывающих условия эксперимента, показало хорошее согласие между ними.

Ключевые слова: изотоп меди-64, циклотронное облучение, природные никелевые фольги, сравнение.

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Introduction

Molecular imaging has become a major tool for treating diseases such as cancer, not only providing a means for non-invasive imaging of physiological processes in living organisms at cellular and molecular levels, but also yielding valuable data for early detection and stage classification of diseases, understanding its biology, and assessing therapeutic efficacy. Different imaging techniques, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET), are used for assessing specific molecular targets in biomedical and clinical applications. In particular, among diverse molecular imaging techniques, PET imaging has flourished over the past decade, as augmenting the technology with positron-emitting radiopharmaceuticals allows to image living systems with high spatial sensitivity of measurement and accurate quantification [1].

A particular radioisotope is chosen as a PET radiopharmaceutical depending on its physicochemical characteristics, availability for extraction and production, and the time scale of the biological process to be investigated. The copper-64 isotope (^{64}Cu), which has a half-life of 12.7 hours, is a radiopharmaceutical with unique properties. It can decay by three different schemes: by electron capture (EC), as well as by β^- and β^+ decays. The corresponding yields of the processes are (%): 43.5 (EC), 17. 5 (β^+) and 38.4 (β^-). Because this isotope emits both β^+ and β^- particles, it can be used for both PET imaging and directed radionuclide therapy [2—4].

Increased efforts have been made over the past two decades to design new radiopharmaceuticals based on ^{64}Cu, largely thanks to the well-known copper chemistry. This isotope was attached to various molecules producing radiopharmaceuticals used for both imaging and therapy. Below we present a brief list of ^{64}Cu radiopharmaceuticals and their applications in medicine [5, 6]:

^{64}Cu-ATSM for imaging hypoxia and lung cancer;

^{64}Cu-Trastuzumab for imaging and therapy of breast cancer;

^{64}Cu-PSMA-617 for imaging of hypoxia and lung cancer;

^{64}Cu-AE105 for imaging of lung cancer, colon cancer and bladder cancer.

Another property of the isotope in question makes its ionic form ($^{64}Cu^{2+}$ ions) particularly valuable for medical applications, i.e., for PET imaging of various cancers. In contrast to most conventional radiopharmaceuticals, it is not necessary to attach the radioisotope to expensive carrier molecules in the case of $^{64}Cu^{2+}$, which greatly reduces the costs for the production technology. Bypassing the radiolabeling stage gives a unique advantage over the traditional technique, since standard radiochemical processing is sufficient after irradiating the target to obtain the composition of radiotracer acceptable for PET imaging [7, 8].

Another important characteristic of the ^{64}Cu isotope is that it can be obtained both at a cyclotron and a nuclear reactor. The latter technology is based on two nuclear reactions capturing the neutrons *n*:

$$^{63}\text{Cu}(n, \gamma)^{64}\text{Cu (thermal) and } ^{64}\text{Zn}(n, p)^{64}\text{Cu (fast)},$$

where γ are gamma quanta, *p* are protons.

Large-scale production of the ^{64}Cu isotope takes advantage of the first reaction (thermal neutron capture). The main limitation of this approach is the low specific activity of the isotope against other active impurities of the target, which makes such technology unsuitable for preparing radiopharmaceuticals in practice.

The fast neutron capture reaction also has many limitations. Fast neutron flux in the reactor core is generally unavailable for isotope production. Most research reactors in the world are also limited by requirements on the target volume of the target, which, in turn, imposes restrictions on the activity of the resulting ^{64}Cu isotope [8].

However, ^{64}Cu can be produced in a cyclotron via a nuclear reaction ^{64}Ni(p, n)^{64}Cu through irradiation with protons of enriched or natural nickel. Automated modules are now available for rapid and highly efficient separation of ^{64}Cu from ^{64}Ni and other radioisotopes by ion-exchange chromatography. The majority of preclinical and clinical studies available have used ^{64}Cu produced in the cyclotron by this technology. When it comes to developed countries with advanced cyclotron equipment, this route is likely optimal for producing the required isotope for regular clinical practice [9, 10]. Notably, all studies on this subject concern copper production with targets from enriched nickel isotope ^{64}Ni, which is extremely expensive. Selecting a natural mixture of nickel isotopes can be considerably more cost-effective.

The goal of this study consisted in obtaining data on the activation of nickel targets with natural isotopic composition.

This was achieved by the following steps:

foil made of natural nickel was irradiated with 13 MeV protons at the MGC-20 cyclotron of Peter the Great St. Petersburg Polytechnic University (SPbPU);

irradiated foil was subjected to radiochemical processing to separate the resulting radioisotopes;

activity of the ^{64}Cu isotope was measured;

experimental data were compared with computational results.

Methods

Foil irradiation. Proton energies from 10 to 15 MeV are sufficient for obtaining ^{64}Cu [11]. We chose an energy of 13 MeV at the MGC-20 cyclotron at SPbPU. Three layers of nickel foil with natural isotopic composition (natural mixture), each 100 μm thick, were used as targets; their total thickness was 300 μm, each sample weighed 0.09 g. The samples were disc-shaped, 12 mm in diameter (with an area of 1.13 cm^2).

To additionally purify the foil prior to irradiation, it was first washed three times with heptane (C_7H_{16}, saturated hydrocarbon) and then three times with isopropyl alcohol.

The three nickel discs exposed to radiation were secured with a copper target holder (Fig. 1). Copper was chosen due to its high thermal conductivity ensuring heat removal. The diameter of the irradiated field was determined by the geometry of the holder, amounting to 10 mm. The holder was attached to a water-cooled substrate to prevent overheating of the target.

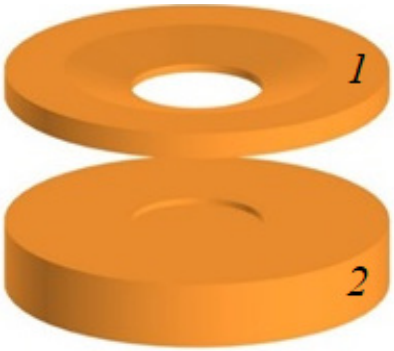

Fig. 1. Copper target holder; three foil discs attached between ring (*1*) and substrate (*2*)

A beam of 13 MeV protons was used for irradiation, the beam current was 4 μA, the irradiation time was 3 hours.

Radiochemical processing of samples. Following irradiation, nickel foil samples were processed by the following technique to obtain the ^{64}Cu isotope:

samples were held for 12 hours to allow short-lived isotopes to decay; next, the irradiated foil was removed from the cyclotron and placed in a box with lead protection;

three foil samples were dissolved in 5 ml of aqueous HCl solution (molar concentration of the solution was 11.7 M) for 4 hours at 100 °C;

solution was evaporated in a glycerol bath for 1 hour at 185–200 °C to dryness; the resulting precipitate was cooled to room temperature for 20 min;

solid precipitate was dissolved in 4 ml of aqueous HCl solution (concentration of the solution was 6.0 M) for 20 min at room temperature of 25 °C;

20 μl aliquot was removed from a solution of a known volume (obtained at the end of the previous stage) for gamma-spectrometric analysis.

Spectrometric analysis of the sample. Analysis was performed after another 1 hour 14 minutes via a gamma radiation spectrometer equipped with a GEM-FX5825 semiconductor detector based on ultrapure germanium and a DSPec-50 multi-channel digital analyzer.

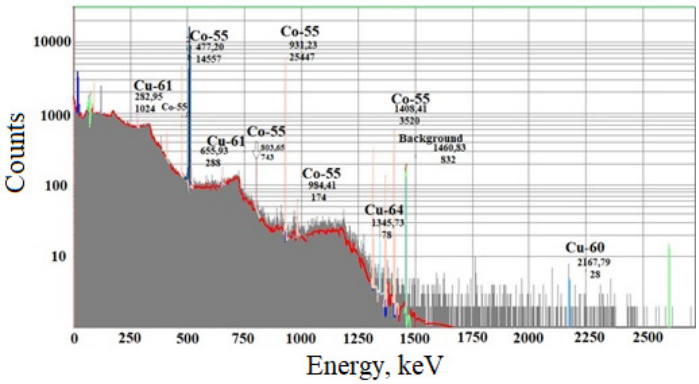

Fig. 2. Spectrum from aliquot (20 μl) obtained from the radiotracer with a natural mixture of nickel isotopes

Experimental results

A peak is observed on the energy spectrum (Fig. 2) at 1345.77 keV, corresponding to ^{64}Cu, suggesting it is present in the sample. The activity of ^{64}Cu in a 20 μl aliquot was 45 kBq (with an error of 30%), while the complete solution (4 ml) contains ^{64}Cu with an activity of 9 MBq. This activity is achieved 21 hours after irradiation. Thus, we can conclude that the activity of ^{64}Cu immediately after the end of irradiation was 30 ± 9 MBq. Further analysis of the data showed that the measurement result obtained is consistent with the computational result (see below).

Simulation of ^{64}Cu yield for natural nickel irradiated with a proton beam

The simulation was carried out using the solution to the equation for passage of protons through matter (Bethe–Bloch formula) and the equation for isotope production in a natural nickel target irradiated with protons in the cyclotron to find the yield of the reaction ^{64}Ni(p, n)^{64}Cu [12]. Natural nickel contains the following isotopes [13]:

^{58}Ni (68.00 %), ^{60}Ni (26.00 %), ^{61}Ni (1.14 %), ^{62}Ni (3.71 %) and ^{64}Ni (0.93 %).

Fig. 3 shows the total activity of ^{64}Cu depending on the thickness of the target made of natural nickel irradiated with protons with an initial kinetic energy of 13 MeV. The line corresponds to the dependence, and the band to its measurement error depending on the error of the reaction cross section. Evidently, the optimal target thickness for producing the maximum isotope activity at this energy is 300–350 μm.

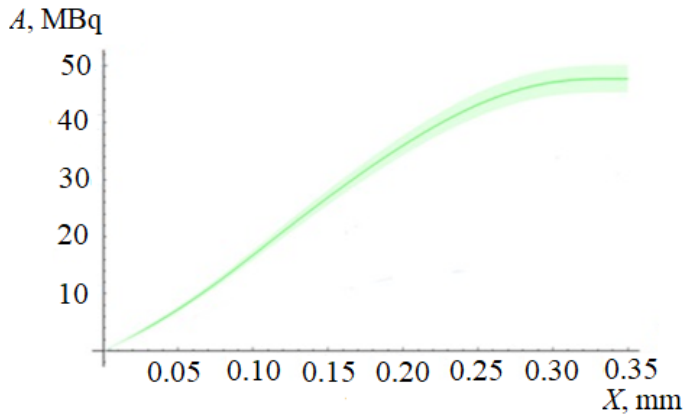

Fig. 3. Computed total activity of ^{64}Cu isotope depending on the thickness of the target made of natural nickel, irradiated by protons with an initial kinetic energy of 13 MeV (irradiation time was 3 h)

The computational results can be used to determine the activity of ^{64}Cu for a 300-μm-thick target irradiated for 3 hours with 13-MeV protons (beam current was 4 μA). The results indicate that the activity of ^{64}Cu amounted to 47 ± 3 MBq. It follows from statistical analysis of the measurement (30 ± 9 MBq) and the computation (47 ± 3 MBq) that the level achieved for the significance of the observed deviation between the computational and measurement results is 0.07 (7%). The achieved level of significance is the probability that the deviation between the computation and measurement due to statistical fluctuations reaches 7% for testing the null hypothesis. The hypothesis is that the observed difference between the computational and measurement data is associated with statistical fluctuations; the level of significance achieved should then be compared with the level of significance chosen in practice to be 0.05. Since the achieved significance level of 0.07 exceeds 0.05, the null hypothesis is confirmed, i.e., the observed difference is indeed associated with statistical fluctuations. Thus, the computed and measured results are in agreement at a significance level of 0.05. We can thus argue that the experimental data agree well with the computational results.

Conclusion

This paper describes the procedure for producing the ^{64}Cu isotope at the MGC-20 cyclotron. Three foils made of natural nickel were irradiated with a 13-MeV proton beam and subsequently subjected to radiochemical processing. The measured activity of the ^{64}Cu isotope was used to obtain the activity value at the end of irradiation, amounting tos 30 ± 9 MBq. The computed activity of the ^{64}Cu isotope under conditions corresponding to the experimental ones amounted to 47 ± 3 MBq. The significance level achieved for the observed deviation of the computational result from the measurement was 0.07. Thus, we have established that the computed and measured results are in agreement at a significance level of 0.05, i.e., the agreement is good.

REFERENCES

1. **Gambhir S. S.,** Molecular imaging of cancer with positron emission tomography, Nat. Rev. Cancer. 2 (9) (2002) 683–693.

2. **Asabella A. N., Cascini G. L., Altini C., et al.,** The copper radioisotopes: A systematic review with special interest to ^{64}Cu, BioMed Res. Int. 2014 (May) (2014) 786463.

3. **Amiot M. N., Be M. M., Branger T., et al.,** Standardization of ^{64}Cu using an improved decay scheme, Nucl. Instr. Meth. Phys. Res. A. 684 (21 August) (2012) 97–104.

4. **Anderson C. J., Riccardo F.,** Copper-64 radiopharmaceuticals for PET imaging of cancer: Advances in preclinical and clinical research, Cancer Biother. Radiopharm. 24 (4) (2009) 379–393.

5. **Holland J. P., Riccardo F., Anderson C. J., Lewis J. S.,** Copper-64 radiopharmaceuticals for oncologic imaging, PET Clinics. 4 (1) (2009) 49–67.

6. **Zhou Y., Li J., Xu X., et al.,** ^{64}Cu-based radiopharmaceuticals in molecular imaging, Technol. Cancer Res. Treat. 18 (February 14) (2019) 1533033819830758.

7. **Boschi A., Martini P., Janevik-Ivanovska E., Duatti A.,** The emerging role of copper-64 radiopharmaceuticals as cancer theranostics, Drug Discov. Today. 23 (8) (2018) 1489–1501.

8. **Chakravarty R., Chakraborty S., Dash A.,** $^{64}Cu^{2+}$ ions as PET probe: An emerging paradigm in molecular imaging of cancer, Molecul. Pharmaceut. 13 (11) (2016) 3601–3612.

9. **Xie Q., Zhu H., Wang F., et al.,** Establishing reliable Cu-64 production process: From target plating to molecular specific tumor micro-PET imaging, Molecules. 22 (4) (2017) 641.

10. **Szűcs Z., Takács S., Alirezapour B.,** Development of cost-effective method for production of ^{64}Cu from $^{nat.}$Ni, J. Radioanal. Nucl. Chem. 302 (2) (2014) 1035–1038.

11. **Aslam M. N., Sudár S., Hussain M., et al.,** Charged particle induced reaction cross section data for production of the emerging medically important positron emitter ^{64}Cu: A comprehensive evaluation, Radiochim. Acta. 97 (12) (2009) 669–686.

12. **Tiba A., Berdnikov Ya. A.,** Optimization of the copper-64 isotope production from natural nickel target at a cyclotron, St. Petersburg Polytechnical State University Journal. Physics and Mathematics. 14 (2) (2021) 81–89.

13. **Rosman K. J. R., Taylor P. D. P.,** Isotopic compositions of the elements, Pure Appl. Chem. 70 (1) (1998) 217–235.

СПИСОК ЛИТЕРАТУРЫ

1. **Gambhir S. S.** Molecular imaging of cancer with positron emission tomography // Nature Reviews Cancer. 2002. Vol. 2. No. 9. Pp. 683–693.

2. **Asabella A. N., Cascini G. L., Altini C., Paparella D., Notaristefano A., Rubini G**. The copper radioisotopes: A systematic review with special interest to ^{64}Cu // BioMed Research International. 2014. Vol. 2014. May. P. 786463.

3. **Amiot M. N., Be M. M., Branger T., Cassette P., Lepy M. C., Menesguen Y., DaSilva I.** Standardization of ^{64}Cu using an improved decay scheme // Nuclear Instruments and Methods in Physics Research A. 2012. Vol. 684. 21 August. Pp. 97–104.

4. **Anderson C. J., Riccardo F.** Copper-64 radiopharmaceuticals for PET imaging of cancer: Advances in preclinical and clinical research // Cancer Biotherapy and Radiopharmaceuticals. 2009. Vol. 24. No. 4. Pp. 379–393.

5. **Holland J. P., Riccardo F., Anderson C. J., Lewis J. S.** Copper-64 radiopharmaceuticals for oncologic imaging // PET Clinics. 2009. Vol. 4. No. 1. Pp. 49–67.

6. **Zhou Y., Li J., Xu X., Zhao M., Zhang B., Deng S., Wu Y.** ^{64}Cu-based radiopharmaceuticals in molecular imaging // Technology in Cancer Research & Treatment. 2019. Vol. 18. February 14. P. 1533033819830758.

7. **Boschi A., Martini P., Janevik-Ivanovska E., Duatti A.** The emerging role of copper-64 radiopharmaceuticals as cancer theranostics // Drug Discovery Today. 2018. Vol. 23. No. 8. Pp. 1489–1501.

8. **Chakravarty R., Chakraborty S., Dash A.** $^{64}Cu^{2+}$ ions as PET probe: An emerging paradigm in molecular imaging of cancer // Molecular Pharmaceutics. 2016. Vol. 13. No. 11. Pp. 3601–3612.

9. **Xie Q., Zhu H., Wang F., Meng X., Ren Q., Xia Ch., Yang Zh.** Establishing reliable Cu-64 production process: From target plating to molecular specific tumor micro-PET imaging // Molecules. 2017. Vol. 22. No. 4. P. 641.

10. **Szűcs Z., Takács S., Alirezapour B.** Development of cost-effective method for production of ^{64}Cu from $^{nat.}$Ni // Journal of Radioanalytical and Nuclear Chemistry. 2014. Vol. 302. No. 2. Pp. 1035–1038.

11. **Aslam M. N., Sudár S., Hussain M., Malik A. A., Shah H. A., Qaim S. M.** Charged particle induced reaction cross section data for production of the emerging medically important positron emitter ^{64}Cu: A comprehensive evaluation // Radiochimica Acta. 2009. Vol. 97. No. 12. Pp. 669–686.

12. **Тиба А., Бердников Я. А.** Оптимизация получения изотопа меди-64 из природного никеля на циклотроне // Научно-технические ведомости СПбГПУ. Физико-математические науки. 2021. Т. 14. № 2. С. 81–89.

13. **Rosman K. J. R., Taylor P. D. P.** Isotopic compositions of the elements // Pure and Applied Chemistry. 1998. Vol. 70. No. 1. Pp. 217–235.

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