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Analyzing of Production Conditions of ^{89}Zr in the Particle Accelerator

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Abstract. Nowadays 89Zr is outstanding PET radionuclide with its physical half-life (t1/2 ~ 78 hours), useful decay specifications and so that it is suitable for antibody-based immuno-PET. Relatively oscillated positrons' low decay energies supply to take high-resolution. 89Zr-labeled radiopharmaceuticals, especially as 89Zr-labeled antibodies applications are getting increase day by day.

In this study, calculations about production of 89Zr were done and used (p,n) reaction of 89Y target system. For this Q-value, Threshold Energy, Minimum Coulomb Barrier Energy of the reaction were calculated then the cross-sections of this reaction were found using Empire3.2/MALTA code. After determining the irradiation calculations, the bombardment performed. The irradiation was performed in Ankara Sarayköy Nuclear Research and Training Center, proton accelerator. The cyclotron is IBA type Cyclone-30. Then separation part was done with Dowex resine system. After separation 89Zr from the irradiated target system, radioactive 89Zr was obtained purely..

Keywords: 89Zr, 89Y, Cyclone-30, Empire3.2/MALTA, Radionuclide, Dowex, PET Radionuclides

89Zr'un Proton Hızlandırıcıda Üretim Koşullarının İncelenmesi

Özet. ^{89}Zr, uygun bozunum özellikleri, fiziksel yarı ömrü (t1/2 ~ 78 saat) nedeniyle artan ilgi görmüştür ve bu nedenle de antikor temelli immüno-PET için uygun görülmektedir. Relatif olarak salınan pozitronların düşük bozunum enerjisi yüksek çözünürlüklü görüntü alınmasını sağlar. ^{89}Zr-işaretli radyofarmasötiklerinin insanda kullanımı özellikle ^{89}Zr işaretli antikorlar olarak immuno-PET de kullanımı günden güne artmaktadır.

Bu çalışmada, ^{89}Zr üretimi ile ilgili hesaplamalar yapılmış ve ^{89}Y hedef sisteminin kullanıldığı (p, n) reaksiyonu kullanılmıştır. Bunun için reaksiyon sonucu Bağ Enerjisi, Eşik Enerjisi, Minimum Coulomb Bariyeri Enerjisi hesaplanmış, daha sonra bu reaksiyonun tesir kesitleri Empire3.2/MALTA kodu kullanılarak bulunmuştur. Işınlama hesaplamaları belirlendikten sonra proton bombardımanı yapılmıştır. Bu ışınlama Ankara Sarayköy Nükleer Araştırma ve Eğitim Merkezi'ndeki proton hızlandırıcısında gerçekleştirilmiştir. Kullanılan siklotron IBA tipi Siklon-30'dur. Daha sonra ayırma kısmı Dowex reçine sistemi ile yapılmıştır. Işınlanmış ^{89}Zr, hedef sistemden ayrıldıktan sonra, radyoaktif ^{89}Zr saf olarak elde edilmiştir.

Anahtar Kelimeler: ^{89}Zr, ^{89}Y, Siklon-30, Empire3.2/MALTA, Radyonüklid, Dowex, PET Radyonüklidleri

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1. INTRODUCTION

Positron Emission Tomography (PET) uses short-lived organic β^+-emitters however, in the case of the slow metabolic processes, longer-lived β^+-emitters are needed. ^{89}Zr is an important positron releasing radionuclide with its half-life of 78.41 hours and approximately 23% low positron energy emission. Besides its chemistry is useful labeling of antibodies (mAbs) for PET imaging in radio-immunotherapy and personal medicine. In nuclear medicine, usage of ^{89}Zr as a PET radionuclide increased recently [1, 2, 3, 4, 6, 16, 18, 21]. ^{89}Zr decays to ^{89m}Y with 22.7% of positron emission (β^+ decay) and 77.3% of electron capture (EC). Because of EC, about 15-keV low energy X-ray irradiation is also seen. Moreover, there is 909-keV energy gamma radiation with this decay. 511 keV energy annihilation photons are far away from noise relatively and this situation causes to increase the quality of image. In addition ^{89}Zr with 902 keV positron energy and 78.41 hours half-life is more ideal PET radionuclide than ^{18}F with 110 minute half-life for production and transportation to the hospital [12, 21].

^{89}Zr can produce in medical cyclotrons with proton or deuteron irradiation with ^{89}Y(p,n)^{89}Zr or ^{89}Y(d,2n)^{89}Zr reaction [13, 23]. ^{89}Zr is a specific radionuclide, which can be used in immuno-PET applications with monoclonal antibodies (mAbs) in-vivo monitoring and quantifications [2, 12], and with the half-life of 78.41 hours is an ideal time to connect the antibodies to the target tissue [20, 23, 24].

When the comparison of gamma scintillation or Single-Photon Emission Computed Tomography (SPECT), PET is higher attenuation correction, resolution and sensitivity [10, 17, 20, 21, 22]. According to that, ^{89}Zr-labeled antibodies used in tumor detection at preclinic and clinic, successively [7, 8, 9]. On the other hand ^{89}Zr-labeled antibodies with cancer detection and research, there is also a potential for usage in autoimmune diseases [5, 15]. There are also more studies about labeled of white-blood cells, cytokines and labeling of these cells are also important [11, 14, 19].

2. MATERIALS and METHODS

2.1. Calculation of Q-value, Threshold Energy and Minimum Coulomb Barrier Energy of ^{89}Y(p,n)^{89}Zr Reaction

$$Q = [m_P + m_T - (m_X + m_R)]c^2 \text{ MeV}$$

- m_P is projectile mass in MeV/c^2,
- m_T is target mass in MeV/c^2,
- m_X is emitted particle mass in MeV/c^2,
- m_R is residual nucleus mass in MeV/c^2,
- c is the speed of the light.

After calculating the Q-value, the Threshold Energy (E_{Th}) is,

$$E_{Th} = -Q\frac{m_P + m_T}{m_T} \text{ MeV}$$

Threshold energy for the reaction, which occurs at this energy level, is significant. The other necessary term is Minimum Coulomb Barrier Energy ($E_{cb_{\min}}$) so,

$$E_{cb_{\min}} = 1.109(A_P + A_T)\frac{Z_P Z_T}{A_T(A_P^{1/3} + A_T^{1/3})} \text{ MeV}$$

- A_P is atomic number of projectile,
- A_T is atomic number of target,
- Z_p is mass number of projectile,
- Z_T is mass number of target.

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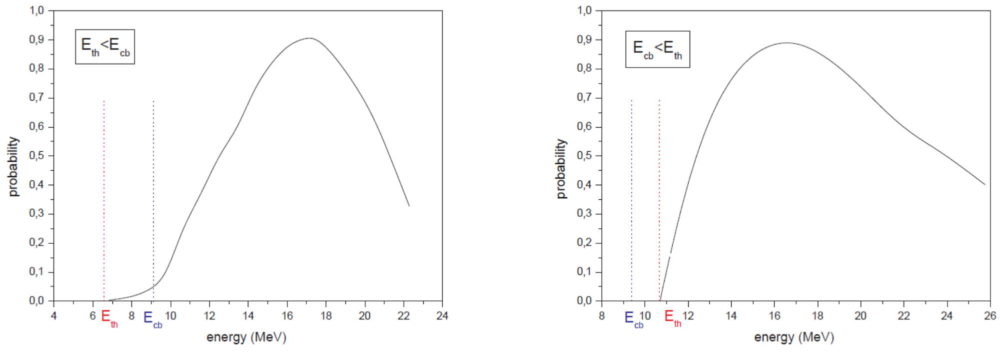

Figure 1. Comparison of Threshold Energy and Minimum Coulomb Barrier Energy

2.2. Nuclear Cross-section and Irradiation Yield

The general formula of the nuclear cross-section is,

$$\sigma_R = \pi r_0^2 (A_p^{1/3} + A_T^{1/3})^2$$

where r_0 is radius of nucleus and about 1.6 fm and the unit of this total cross-section is barn (10^{-24} cm^2). In this project, all the cross-sections of the reactions will be calculated by Empire3.2/MALTA code.

The rate of production is given by the simplest equation,

$$R = n_T I \sigma$$

Nonetheless, the cross-section is not always constant and function of energy so that the more exact expression is,

$$R = n_T I \int_{E_s}^{E_0} \frac{\sigma(E)}{dE/dx} dE$$

- *R is the number of nuclei formed per second,*

- *n_T is the target thickness in nuclei/cm^2,*

- *I is the incident particle flux per second and is related to the beam current,*

- *σ is the reaction cross-section, or probability of interaction, expressed in cm^2 and is a function of energy,*

- *E is the energy of the incident particles,*

- x is the distance travelled by the particle and

- $\int_{E_s}^{E_0}$ is the integral from the initial energy to the final energy of the incident particle along its path.

$$n_T = \frac{\rho x}{A_T} N_A$$

is the equation of target thickness also and,

- *A_T is the atomic weight of the target material in grams,*

- *ρ is the density in g/cm3,*

- *N_A is Avogadro's number and*

- *x is the distance the particle travels through the material in cm.*

Then the overall rate of production is,

$$-\frac{dn}{dt} = n_T I \int_{E_s}^{E_0} \frac{\sigma(E)}{dE/dx} dE - \lambda N$$

- λ is the decay constant and is equal to ln $2/t_{1/2}$ ($t_{1/2}$ is half-life),

- t is the irradiation time in seconds and

- N is the number of produced nuclei in the target.

For all, the yield of the nuclear reaction is,

$$Y_{EOB} = \frac{N_A I}{A_T}(1-e^{-\lambda t})\int_{E_s}^{E_0} \frac{\sigma(E)}{S_T(E)} dE$$

- $S_T(E)$ *is the stopping power,* dE/dx *actually.*

2.3. Energy Loss after bombardment, Stopping Power and Range of Ions in Matter

For Bethe and Bloch (Bethe et al., 1932), stopping power with the simplest form is,

$$S = \frac{4\pi e^4 Z_1^2 Z_2}{mv^2}[\ln(\frac{2mv^2}{I}) + \ln(\frac{1}{1-\beta^2}) - \beta^2 - \frac{C}{Z_2}]$$

MeV/cm

- m is the mass of electron,

- Z_1 and Z_2 are the atomic numbers of the particle and target,

- e is the electron charge,

- v is the velocity of the particle,

- I is the ionization (excitation) potential,

- β is v/c and v is the speed of particle in cm/s and

- C/Z_2 is the shell correction.

2.4. SRIM (Stopping Powers and Ranges in All Elements, 2013)

SRIM is the program, which can calculate and simulate the energies of the charged or uncharged particles in the system. These particles can be electrons, protons, neutrons, helium, deuterium or tritium. According to SRIM2013, it gives the range of the projectile into the target depends on stopping power.

2.5. Reaction Q-values and Threshold Energies for ^{89}Y+^{1}H

According to Table 1, the reaction Q-value is about 3.6 MeV and so the reactions occur after this energy level. Also from the equations (1) and (2), the results are about -4 MeV and 4.1 MeV. Then the Coulomb Barrier energy (3) for this reaction is 8 MeV. Since Threshold Energy is smaller than Minimum Coulomb Barrier Energy, the reaction initiates at the Threshold Energy level.

Table 1. Q-values and Threshold Energies for different reactions of ^{89}Y+p until 15 MeV

Reaction Products	Q-value (keV)	Threshold Energy (keV)
^{90}Zr+γ	8353.380	0.0
^{86}Sr+α	1678.100	0.0
^{89}Y+p	0.0	0.0
^{89}Zr+n	-3615.110	3656.070
^{82}Kr+2α	-4679.690	4732.720
^{88}Sr+2p	-7076.770	7156.970
^{85}Rb+p+α	-7966.740	8057.020
^{88}Y+d	-9257.150	9362.060
^{85}Sr+n+α	-9813.140	9924.350
^{87}Sr+^{3}He	-10471.360	10590.030
^{78}Se+3α	-10669.020	10789.930
^{88}Y+n+p	-11481.720	11611.840
^{87}Y+t	-12351.640	12491.610
^{88}Zr+2n	-12934.490	13081.070
^{81}Br+p+2α	-14583.330	14748.600
^{84}Kr+2p+α	-14983.700	15153.500

2.6. Cross-sections for the Reaction of ^{89}Y+^{1}H

According to Empire3.2, the cross-sections of some reactions of ^{89}Y+p are below;

Table 2. Cross-sections of the different reactions after the proton bombardment to the target of ^{89}Y (*=the main reaction)

Energy (MeV)	(p,γ) reaction cross-section (mb)	(p,n) reaction cross-section (mb)*	(p,2n) reaction cross-section (mb)	(p,d) reaction cross-section (mb)	(p,2p) reaction cross-section (mb)	(p,α) reaction cross-section (mb)
10	0.22577	654.357	0	0	0	0.48568
11	0.18951	681.768	0	5.1E-08	5.8E-06	0.85182
12	0.19406	709.748	0	5.2E-05	0.00156	1.78121
13	0.17922	684.621	0	0.00182	0.03143	3.83865
14	0.17308	682.809	30.3097	0.17112	0.23038	8.97375
15	0.16944	619.156	106.859	4.38041	1.07919	17.9847

From Table 2, the probable radiochemical purities will be ^{90}Zr, ^{89}Zr, ^{88}Zr, ^{88}Y, ^{88}Sr and ^{86}Sr using Table 1. The reactions' cross-sections except the main reaction (p,n), is too small to produce another impurity so they are negligible.

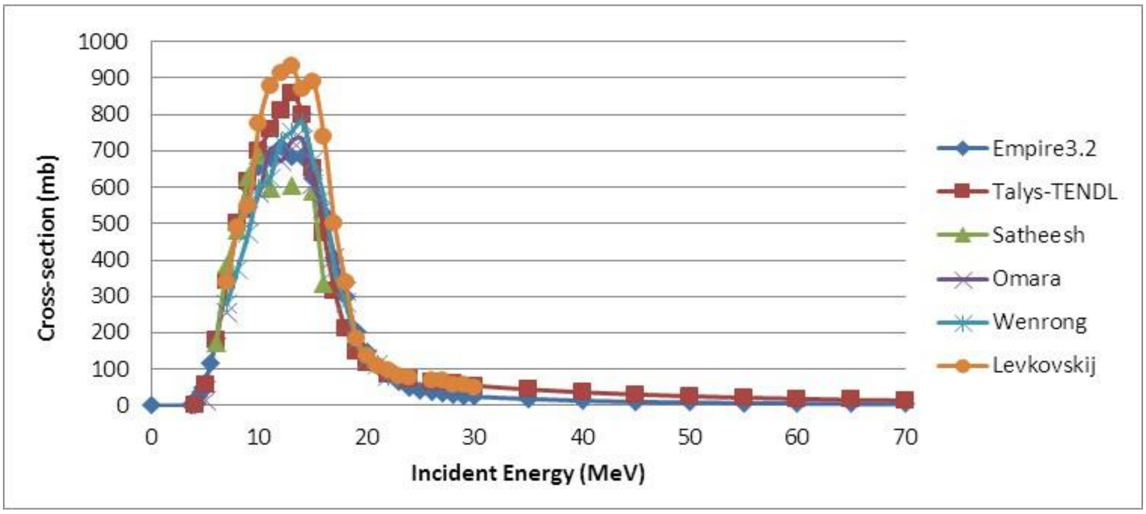

Figure 2. Comparison of the Empire3.2, Talys-TENDL2014 and EXFOR cross-section data for the reaction of $^{89}Y(p,n)^{89}Zr$

When incident energy is increased, different reactions occur directly so minimum energy is always preferable. Furthermore 12 MeV energy range is optimum and other probable reactions are (p,γ), (p,d), (p,2p) and (p,α) but if it is compared, these reactions cross-sections are extremely small from the main reaction. From these results, other isotopes can occur actually like ^{90}Zr, ^{88}Y, ^{88}Sr and ^{86}Sr as seen in Table 1 then ^{90}Zr and ^{86}Sr cannot produce because of the threshold energy of the main reaction.

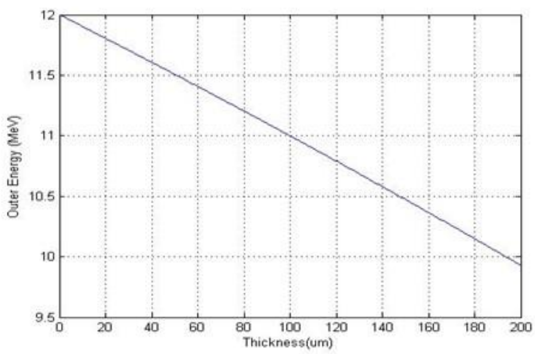

Figure 3. Energy loss with 12 MeV proton beam after target of ^{89}Y using MATLAB code

2.7. Stopping Power of the Target System

From SRIM(2013), the target thickness is the most important parameter and for 12 MeV proton energy, energy loss against thickness result is in Figure 3.

2.8. Rate of Production

The calculations about the bombardment was performed with MATLAB using IAEA data for irradiation. According to Figure 4 to produce ^{89}Zr from ^{89}Y with proton bombardment under 12 MeV in Cyclone-30 cyclotron.

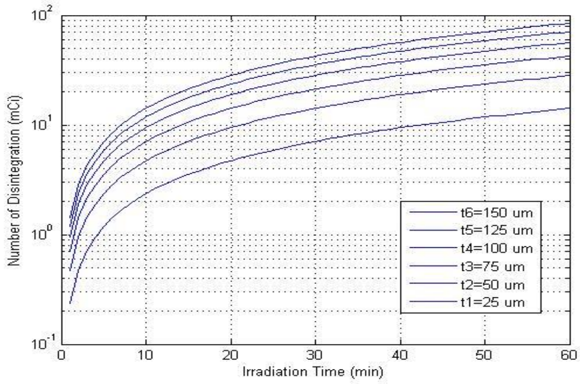

Figure 4. Activity for the irradiation of target ^{89}Y with proton beam for 1 hour.

2.9. Preparation of Dowex Resine

First, the activation of the resine was obtained. For this 10% NaCl solution and 0.2% NaOH was heated at 80 Cº for 2 hours. Then Dowex (1x8) was passed through the mixture with 0.5% HCl solution. Before the elution, the column was conditioned with 12 M HCl. In the first step, the target will be washed with 12 M HCl and will be passed through the resine. It is expected that ^{89}Zr will stay in the resine in this way then after washing the resine with 2 M HCl, ^{89}Zr will also come from there.

3. RESULTS AND DISCUSSION

From all the calculations, it is decided that irradiation parameters were like below;

Table 3. Irradiation Parameters

Target Material	Yttrium metal foil (99.99% pure)
Irradiation Time	30 minutes
Irradiation flux	20 µA ($1.25x10^{14}$ proton/cm^2)
Proton beam angle	6º
Thickness of the target	150 µm
Proton beam energy	15 MeV
Expected activity	10 mCi
Cooling time	1 day

After bombardment, ORTEC LaBr3 scintillation detector performed the counting method. In the first spectroscopy (Figure 5), it is seen that there are 3 main peaks which are annihilation photon (511 keV), ^{89}Zr gamma peak (909 keV) and ^{65}Zn gamma peak (1116 keV) because of copper target plate. Then the impurity was removed using Dowex resine, there are only 2 peaks can be seen in Figure 6.

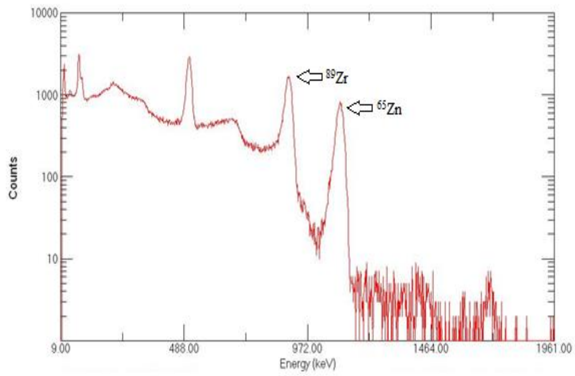

Figure 5. The first gamma spectroscopy of the target after irradiation

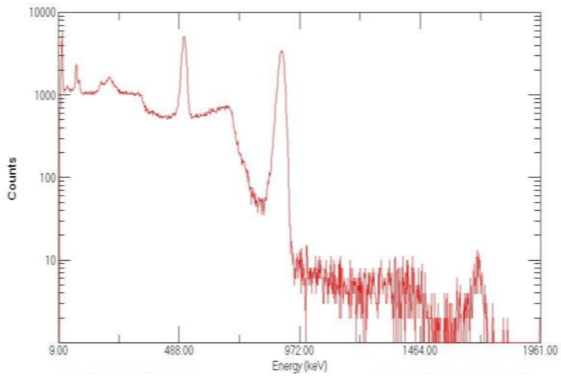

Figure 6. The gamma spectroscopy of target after washing with resine

Totally 3.5 mCi of activity was observed in the dose calibrator after the irradiation. According to the spectrum obtained after the initial washing of the copper target system with 12M HCl, the ^{65}Zn impurity was removed from the system and the amount of residual activity decreased to 2.5 mCi.

This is calculated to be around 7 mCi of ^{89}Zr immediately after irradiation. According to the calculations made, a radiation efficiency of 70% was achieved. It is believed that the cause of the error is caused by the heat spread of the yttrium foil. As a result, ^{89}Zr was obtained in pure form.

4. CONCLUSION

Using new metallic PET radionuclides like 89Zr is increasing all over the world. With a single photon energy and half-life, it is useful and more efficient than other PET radionuclides. To product this radionuclide, there is a nuclear reaction named (p,n) and the target for this reaction is 89Y. IBA Cyclone-30 proton accelerator, which has a 30-MeV maximum energy of protons, is very common in the world and the irradiation was performed in this cyclotron.

To sum up, it is matched that the theoretical data and experimental outputs. It was calculated that after irradiation, it was waited about 10 mCi activity from the target but only 7 mCi total activity was obtained because of the damaged target due to high temperature. Last of all, the irradiation was successfully completed taking radioactive 89Zr without any radiochemical impurity.

5. ACKNOWLEDGMENTS

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