

Full Length Research Paper

Cyclotron production of ^{89}Zr : A potent radionuclide for positron emission tomography

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In the present study, zirconium-89 ($T_{1/2} = 3.27$ day, $I_{\beta^+} = 23\%$, $E_{\beta^+} = 0.897$ MeV) was produced through the $^{89}\text{Y}(p,n)$ nuclear reaction at the Agricultural, Medical and Industrial Research School (AMIRS) Cyclotron (Cyclone-30, IBA, Belgium), irradiating Y_2O_3 with 15 MeV proton beam energy and 20 μA current for 20 min. The experimental yield of about 69.77 MBq ^{89}Zr per μAh was obtained. The radiochemical separation of ^{89}Zr from the irradiated Y_2O_3 target was done through the anion exchange chromatography with an overall of 95% process. The intended use of ^{89}Zr is to label monoclonal antibodies (MoAbs) for tumor imaging using positron emission tomography (PET).

Key words: Anion exchange chromatography, production, zirconium-89, separation.

INTRODUCTION

The Zirconium-89 radionuclide has a real medical interest because ^{89}Zr decays by positron emission ($T_{1/2} = 3.27$ day, $I_{\beta^+} = 23\%$, $E_{\beta^+} = 0.897$ MeV) and by electron capture (77%) to stable ^{89}Y (Uddin et al., 2008).

The ^{89}Zr radioisotope is used in the field of tumor diagnostics, tumor therapy and the investigation of the bio-kinetic (Uddin et al., 2005). Also, zirconium-89 has been suggested as a suitable positron emitter for labeling antibodies (O'Brien, 1983; Link et al., 1986; Zweit et al., 1991).

The short-lived organic β^+ -emitters are often used in positron emission tomography (PET). For studying slow metabolic processes, for example, long-term kinetics and bio-distribution of antibodies, longer lived β^+ -emitters are needed. The ^{89}Zr is an important positron emitter because it has an appropriate half-life of 78.41 h and the positron branching is not so low (23%). This radionuclide has already been used for labeling monoclonal antibodies for tumor imaging (Kandil et al., 2007).

The cross sections of various reactions, in order to produce ^{89}Zr , as a therapeutic radionuclide, have been

measured by several authors. The zirconium-89 production via $^{89}\text{Y}(p, n)^{89}\text{Zr}$ reaction has been studied by Uddin et al. (2005), with 4 to 79 MeV proton beam energy, and also Zweit et al. (1991) has reported the production yield of ^{89}Zr via $^{89}\text{Y}(d, 2n)^{89}\text{Zr}$ reaction. Uddin et al. (2008) has used natural target (Zirconium), in order to produce ^{89}Zr , via $^{nat}\text{Zr}(p, pnx)^{89}\text{Zr}$ reaction below 50 MeV proton energy range. Kandil et al. (2007) and Lewis et al. (1980) have studied the ^{89}Zr production yield, via $^{nat}\text{Sr}(\alpha, xn)^{89}\text{Zr}$ and $^{90}\text{Zr}(n, xn)^{89}\text{Zr}$ reactions respectively, below 30 MeV projectile energy. Omara et al. (2009) and Steyn et al. (2011) have measured the cross section of $^{89}\text{Y}(p, n)^{89}\text{Zr}$ reaction with 5 to 18 MeV and 24 to 65 MeV proton energy respectively. Their data were compared with present investigation. The liquid-liquid (LLX) and solid-liquid (SLX) extraction technique were used for separation of zirconium and yttrium in chloride solutions (Dutta et al., 2009). The anion exchange chromatography technique was used for radiochemical separation of ^{89}Zr from the irradiated yttrium target (Zweit et al., 1991). The exchange chromatography and solvent extraction techniques were also used by Kandil et al. (2007).

The motivation of the present work was the production of ^{89}Zr by coating of Y_2O_3 via sedimentation method on a pure copper substrate that has sufficient stability at

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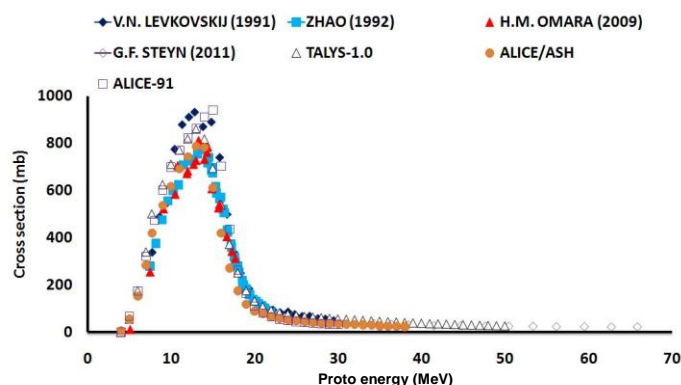


Figure 1. Excitation function of $^{89}\text{Y}(p,n)^{89}\text{Zr}$ reaction by TALYS-0.1, ALICE/91, ALICE/ASH (Hybrid Models) codes and experimental data.

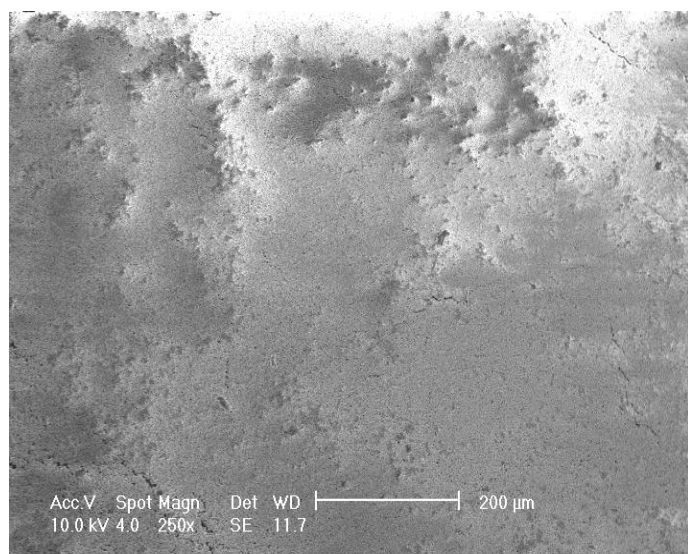


Figure 2. SEM of Yttrium oxide deposit on the Cu backing (435 mg Y_2O_3 , 130.5 mg EC and 4 ml acetone suspensions and 103.42 μm thickness).

high-power beam bombardment and separation of zirconium from Y_2O_3 with high radionuclidic purity using ion-exchange chromatography.

EXCITATION FUNCTION

Excitation functions of the proton-induced reaction on yttrium-89 were calculated by ALICE/91, ALICE/ASH (Hybrid Model) and TALYS- 1.0 codes (Sadeghi et al., 2011; Taghilo et al., 2011), and compared to existing data presented in Figure 1 (Levkovskij, 1991; Zhao, 1992; Omara et al., 2009; Steyn et al., 2011). The evaluation of the acquired data showed that the best range of the energy is 15 to 5 MeV. To avoid isotope and non-isotope impurities and to attain full benefit energy

range without decreasing production yield considerably, 13 to 8 MeV energy range was considered.

EXPERIMENTALS

Target preparation

To obtain the optimum physical dimensions of the target such as the thickness some estimation from the SRIM 2006 code (The Stopping and Range of Ions in Matter); were performed (Ziegler, 2006). Enhancement the projectile energy, increase the production yield the beam current and the time of bombardment. The calculated required target thickness is 743.39 μm for 90° geometry (Sadeghi et al., 2010).

Targets consisted of 435 mg Y_2O_3 of high chemical purity (99.9%, Aldrich), which was deposited on the copper substrate (11.69 cm^2 surface area) by means of a sedimentation method (Rösch et al., 1993). To minimize the thickness of the yttrium oxide layer and to increase heat transfer, the 6° geometry is preferred, in which case a 74.33 μm Y_2O_3 layer is recommended. In this method, ethyl cellulose (EC) was added to yttrium oxide. Then suspensions of this mixture in acetone were obtained by mixing and stirring. To prepare the target, a particular home-made system was constructed. It consists of two plates (19×10×3 cm^3) made of Teflon. The upper plate contains an elliptical window of 11.69 cm^2 . The copper substrate is placed between these two plates, the upper part is fitted on it with six supporting pins and it is sealed by an O-ring fitted-window. The Y_2O_3 suspension solution was stirred for 2 to 3 min and loaded in to cylinder of the upper disk immediately. The window was covered by a plate made of Teflon that includes a small hole. The solution evaporated slowly through the hole at the room temperature after about 12 to 24 h. The scanning electron microscope (SEM) of yttrium oxide which is deposited on the Cu backing is given in Figure 2. Quantity of EC is an important factor for adhering and coating among physical properties of the samples, so the quantity of EC should be optimum. The optimum results are presented in Table 1.

Irradiation

The Y_2O_3 was coated into a target holder and it has bombarded with 15 MeV proton beam energy, extracted from cyclotron of AMIRS for 20 min. The beam current was 20 μA . To protect the target material from reaching excessively high temperatures, during the irradiation, a jet of cooling water flows across the back of copper substrate in direct contact with it, so heat is removed efficiently from the backing. In order to improve the thermal conductivity, copper substrate where included in the back of some grooves. No direct cooling is used over the front of the deposited target.

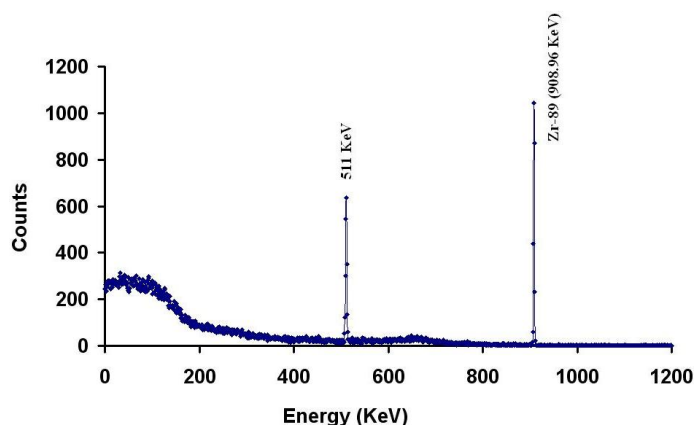
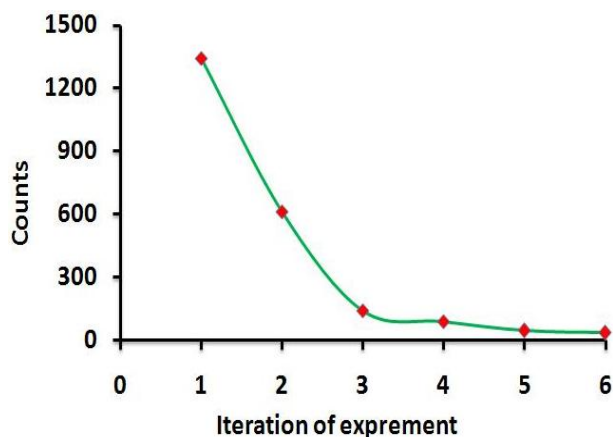
Determination of radionuclidic purity and chemical purity

A 15 MeV proton beam was used to irradiat the Y_2O_3 as a target. The single isotope of ^{89}Zr ($E_\gamma=908.964$, $I_\gamma=100\%$) was observed in the gamma ray spectrum (Figure 3), and therefore, the radionuclidic purity was determined via γ -ray spectroscopy. The spectrum of gamma-ray emitting radionuclides was carried out using a high-purity germanium (HPGe) detector (Canberra™ model GC1020-7500SL). Zirconium-89 was mainly identified via a gamma peak, through single transition from ^{89}Zr first excited state to its ground state of 908.96 keV. The γ -ray spectrum of a highly purified ^{89}Zr sample which is measured with an HPGe detector is presented in Figure 3. The peak area analysis was done using the IPA DAS 2.3 (data acquisition software). The chemical impurity in the separated

Table 1. Influence of EC amount with 4 ml acetone on 435 mg Y_2O_3 .

W(EC) (mg)	W (EC)/ W (Y_2O_3) (%)	t^* (μm)	t_d ($mg\cdot cm^{-2}$)	Adhesion	Comments
174	40	102.43	51.31	Tolerable	Porous
152.25	35	79.24	39.7	Excellent	Reflective, smooth
130.5	30	103.42	51.8	Excellent	Porous
87	20	84.57	39.01	Unfavorable	Track, Porous

t^* , Measured mean thickness of the deposit in micrometer; t_d , calculated thickness of the deposit on Cu backing. * The prepared suspensions were manually introduced into the home-made system, so some suspensions were remained in the baker inevitably. Therefore in some cases, despite of more amounts of Y_2O_3/EC , the obtained thickness was less than the coating condition with fewer amounts of Y_2O_3/EC .

**Figure 3.** HPGe spectrum proton irradiated by Y_2O_3 taken 10 days after EOB.**Figure 4.** The washing of filter.

radio-zirconium was measured against yttrium. It was done using the inductively-coupled plasma atomic emission spectroscopy (ICP-AES).

Separation of radio-zirconium from irradiated yttrium oxide

The radiochemical separation of radio-zirconium was attempted via ion-exchange chromatography technique.

Ion-exchange chromatography technique

The method used for the separation of ^{89}Zr from the target is based on the differences in the distribution coefficients for these two elements on an anion-exchange resin at different molarities of HCl (Kraus and Nelson, 1958). Before starting the separation process of yttrium-zirconium, separation of ethyl cellulose from zirconium and yttrium is necessary. Therefore, the irradiated Y_2O_3 target was washed by 100 ml acetone. In this process, EC was dissolved in acetone. Afterwards, the solution was filtered. Ethyl cellulose and acetone were passed from filter but, zirconium and yttrium were remained on it. The zirconium and yttrium were washed from the filter and dissolved in 100 ml hot 12 M HCl. The washing and filtering was repeated for six times as shown in Figure 4. In each time, activity was measured carefully. Figure 4 shows that the activity was decreasing. When the zirconium and yttrium oxide was completely dissolved in HCl, 1 ml of 20% H_2O_2 was added to ensure the oxidation of Zr to Zr(IV). The heating was continued until the solution was completely dry after which it was redissolved in 12 M HCl and left to cool.

For the ion exchange separation, a glass column, 10 cm long by 1.0 cm dia placed behind a 5 cm thick lead shield, was packed with Dowex 1-x8 (Cl⁻) resin (100-200 mesh, BDH Chemicals Ltd Poole, England). The column was primed with 12, 2 and finally 12 M HCl prior to use. After loading, the column was eluted with 12 M HCl at a flow rate of 1.5 ml/min. At this molarity the ^{89}Zr activity remained bound to the resin, whereas ^{89}Y was not absorbed. Against the column, was primed with 20 ml 12 M HCl to ensure that ^{89}Y was separated completely. This process was repeated for ten times. In each section, activity was measured carefully.

The 2 M HCl was used for separation of zirconium from the resin. In this section also, the column was primed with 20 ml 2 M HCl and repeated for six times. In each section, activity was measured carefully as shown in Figure 5.

RESULTS AND DISCUSSION

The zirconium-89 is producible through several reactions as follows: (i) $^{89}Y(p, n)^{89}Zr$, (ii) $^{89}Y(d, 2n)^{89}Zr$, (iii) $^{nat}Zr(p, pnx)^{89}Zr$, (iv) $^{nat}Sr(\alpha, xn)^{89}Zr$ and (v) $^{90}Zr(n, xn)^{89}Zr$. In the present study, the $^{89}Y(p, n)$ reaction was used.

According to Table 2, ^{89}Zr production yields were calculated as 89.09, 58.36 and 86.47 MBq/ μAh for cross section data of ALICE-91, ALICE/ASH (pre-equilibrium and equilibrium) and TALYS-1.0 (direct, pre-equilibrium and equilibrium) codes, respectively. Within the experimental error range, the presented data is in agreement with the theoretical calculations extracted from ALICE/ASH and TALYS-1.0 codes. It seems that,

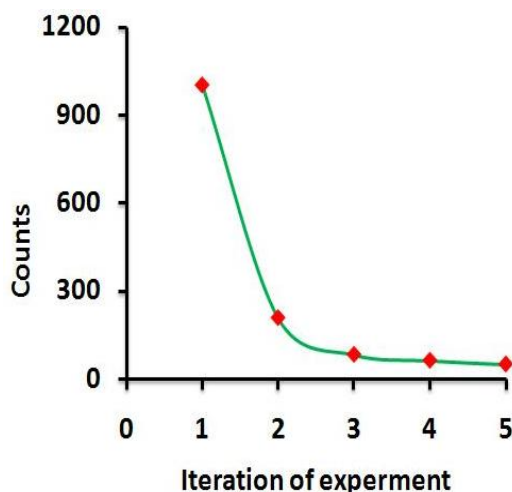


Figure 5. The washing of resin.

Table 2. ^{89}Zr production yield for various reactions.

Reaction	Energy [MeV]	Yield [MBq/ μAh]	Targetery	Reference
$^{89}\text{Y}(\text{p}, \text{n})^{89}\text{Zr}$	12	28	pressing	Kandil et al. (2007)
$^{89}\text{Y}(\text{p}, \text{n})^{89}\text{Zr}$	15	85	Stacked foil	Uddin et al. (2005)
$^{\text{nat}}\text{Sr}(\alpha, \text{xn})^{89}\text{Zr}$	15	0.3	sedimentation	Kandil et al. (2007)
$^{89}\text{Y}(\text{p}, \text{n})^{89}\text{Zr}$	15	69.77	sedimentation	Present work
$^{\text{nat}}\text{Zr}(\text{p}, \text{pxn})^{89}\text{Zr}$	20	25	Stacked foil	Uddin et al. (2008)
$^{89}\text{Y}(\text{d}, 2\text{n})^{89}\text{Zr}$	16	66.6	pressing	Zweit et al. (1991)
$^{89}\text{Y}(\text{p}, \text{n})^{89}\text{Zr}$	15	89.09	-	ALICE-91 code
$^{89}\text{Y}(\text{p}, \text{n})^{89}\text{Zr}$	13	58.36	-	ALIC ASH cdoe
$^{89}\text{Y}(\text{p}, \text{n})^{89}\text{Zr}$	15	86.47	-	TALYS 1.0 code

the ^{89}Zr is the decay product of pre-equilibrium or equilibrium compound systems. Table 2 shows a yield of 69.77 ± 10 MBq/ μAh , which is higher than Kandil et al. (2007) and Zweit et al. (1991) values (28 and 66.6 MBq/ μAh). This may be due to the fact that they used pressing method in their target preparation, they could not produce ^{89}Zr with high beam current as compare to present work. Uddin et al. (2005), has reported the ^{89}Zr production yield as 85 MBq/ μAh by using the stacked foil yttrium target which is much more expensive than present work target.

As well as the previous section separation was done using the ion-exchange chromatography. About $95 \pm 5\%$ of ^{89}Zr was extracted. The concentration of yttrium in the solution after separation was determined by inductively coupled plasma-atomic emission spectrometry (ICP-AES, JY-124) being 40.9 ppm.

Conclusion

^{89}Zr is one of significant interest for the PET. The radionuclide ^{89}Zr was produced by irradiation of Y_2O_3 , as

a thick target that was prepared by means of the sedimentation method and separated in $95 \pm 5\%$ radiochemical yield using anion exchange chromatography. The target was irradiated up to 20 μA current with 15 MeV.

Zirconium was effectively separated from EC and yttrium. Yields of about 69.77 MBq ^{89}Zr per μAh were experimentally obtained. Development of cooling system that contains a circulating flow of chilled helium in front of the target besides the water cooling was used in this study to improve thermal conductivity and so is it expected to allow the use of higher beam current up to 30 μA . The present data was compared with some recent, both theoretical and experimental, published data (Figure 1). It seems that, the ^{89}Zr is the decay product of pre-equilibrium or equilibrium compound systems.

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