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Cyclotron production of ^{64}Cu by deuteron irradiation of ^{64}Zn

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Abstract

The short-lived (12.7 h half-life) ^{64}Cu radioisotope is both a β^+ and a β^- emitter. This property makes ^{64}Cu a promising candidate for novel medical applications, since it can be used simultaneously for therapeutic application of radiolabelled biomolecules and for diagnosis with PET. Following previous work on ^{64}Cu production by deuteron irradiation of natural zinc, we report here the production of this radioisotope by deuteron irradiation of enriched ^{64}Zn. In addition, yields of other radioisotopes such as ^{61}Cu, ^{67}Cu, ^{65}Zn, ^{69m}Zn, ^{66}Ga and ^{67}Ga, which were co-produced in this process, were also measured. The evaporation code ALICE-91 and the transport code SRIM 2003 were used to determine the excitation functions and the stopping power, respectively. All the nuclear reactions yielding the above-mentioned radioisotopes were taken into account in the calculations both for the natural and enriched Zn targets. The experimental and calculated yields were shown to be in reasonable agreement. The work was carried out at the Scanditronix MC-40 Cyclotron of the Institute for Health and Consumer Protection of the Joint Research Centre of the European Commission (Ispra site, Italy). The irradiations were carried out with 19.5 MeV deuterons, the maximum deuteron energy obtainable with the MC-40 cyclotron.

Keywords: ^{64}Cu; ^{61}Cu; ^{66}Ga; ^{67}Ga; Target yield; Radioisotope production; Cyclotron; PET; Therapy

1. Introduction

The characteristics of ^{64}Cu (12.7 h half-life, 39% β^- 578 keV end point, 61% β^+/EC, with a γ-ray emission at 1345.84 keV at 0.473% branching ratio, in addition to the 511 keV annihilation peak), make ^{64}Cu a radioisotope suitable for labelling of a wide range of radiopharmaceuticals, for both PET imaging, and radioimmunotherapy (Firestone et al., 1998). The maximum range of β^+ particle with 653 keV end point energy in soft tissue is ~2.7 mm and the "average" range is ~1 mm. Cu(II) forms a class of stable complexes and chelates with dithiocarbamates (DTC) like ethylmethyl-DTC, with thiosemicarbazones like PTSM, ATSM, and especially with azamacrocyclic chelants (cyclens), like DOTA, DOTP and SarAr. Over the past several years, the behaviour of these compounds of copper has been investigated in cell cultures, rats and humans (Sun and Anderson, 2004).

The usual method for ^{64}Cu production is based on proton irradiation of ^{64}Ni using cyclotrons (Szelecsénil et al., 1993; McCarthy et al., 1997). The method based on fast neutron irradiation of ^{64}Zn through ^{64}Zn(n,p) reaction has been studied and revealed a low yield and contamination with ^{67}Cu (Hetherington et al., 1986; Zinn et al., 1994) while the method of thermal neutron irradiation of ^{63}Cu in a nuclear reactor leads to low specific activity. Among the possible methods for production of NCA ^{64}Cu (and ^{61}Cu), deuteron irradiation of natural zinc targets has been reported (Neirincks, 1977; Abbas et al., 2001; Groppi et al., 2004; Bonardi et al., 2001; Hilgers et al., 2003) and revealed that ^{64}Cu is co-produced with several other radioisotopes including ^{66}Ga and ^{67}Ga. Therefore, handling of the irradiated Zn target has to be performed in highly radiation-shielded cells.

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In the present paper, we have studied the cyclotron production of ^{64}Cu by deuteron irradiation of enriched ^{64}Zn, in order to avoid the co-production of Ga and other undesired radioisotopes. In case of future commercialisation of ^{64}Cu-based radiopharmaceuticals, the cost of ^{64}Zn is much lower than that of ^{64}Ni, therefore this method may be cost effective. Moreover, this method would reduce the radioactive waste stream as compared with irradiation of natural Zn. Following theoretical calculations using the evaporation code Alice 91 (Blann, 1996) and SRIM 2003 (Ziegler, 2003) for excitation functions and stopping power predictions, respectively, irradiation of enriched ^{64}Zn at 19.5 MeV deuteron were carried out and the results are reported in this paper. The work was performed at the Cyclotron Laboratory of the Institute for Health and Consumer Protection of the Joint Research Centre of the European Commission (Ispra site, Italy).

2. Production of ^{64}Cu by deuteron irradiation of zinc

2.1. Deuteron irradiation of natural zinc

The primary products from deuteron irradiation of natural zinc include ^{64}Cu, ^{61}Cu, ^{67}Cu, ^{65}Zn, ^{69m}Zn, ^{66}Ga, ^{67}Ga, where the production of a given radioisotope may be optimised by adjusting some irradiation parameters, such as the energy of the projectile or the target thickness. The yields (A) are calculated as

$$A = N_v I(1 - e^{-\lambda t}) \int_{E_{Th}}^{E_p} \sigma(E) \left[\left(\frac{dE}{dx} \right)(E) \right]^{-1} dE,$$

where N_v is the number of target atoms for the desired reaction per unit volume, I is the beam intensity, λ is the radioactive constant of the produced isotope ($\lambda = \ln(2)/T_{1/2}$), t is the duration of the irradiation, E_p is the beam energy, E_{Th} is the reaction threshold energy, $\sigma(E)$ is the excitation function and $dE/dx(E)$ is the stopping power of the target material.

Table 1 shows the calculated thick target yields of different radioisotopes versus the energy for deuteron irradiation of natural zinc. The natural isotopic composition of zinc is taken into account in these calculations. The yields of ^{67}Cu, ^{65}Zn and ^{69m}Zn radioisotopes were calculated only for the energy of 19.5 MeV deuterons as they are very low at lower energies. The experimental studies regarding deuterons irradiation of natural Zn (Neirincks 1977; Abbas et al., 2001; Groppi et al., 2004; Bonardi et al., 2001; Hilgers et al., 2003) reported results in good agreement with those shown in Table 1, with significant quantities of ^{66}Ga and ^{67}Ga radioisotopes co-produced with the desired ^{64}Cu radioisotope. ^{66}Ga emits rather intense and high-energy γ-rays, 1039 keV (38.4%) and 2752 keV (23.5%), which consequently requires adequate shielding to protect the operators during radiochemical separations. Ga radioisotopes can be easily chemically separated from Zn or Cu materials, and the ^{67}Ga radioisotope is already in use in medical applications. However, via deuteron irradiation of natural Zn, ^{67}Ga is co-produced with ^{66}Ga and the two radioisotopes cannot be chemically separated, therefore a long decay period is required to reduce the ^{66}Ga activity. In fact, the main dose rate from an activated natural zinc is generated by the Ga radioisotopes, so if ^{67}Ga is not required, the production of these radioisotopes simply causes extra shielding requirements and radioactive waste. For instance, a sample disc of 1 cm diameter containing 37 MBq each of ^{64}Cu, ^{66}Ga and ^{67}Ga would generate a dose rate at 10 cm of about 880 μSv/h of which 93% is due to the Ga radioisotopes. In case of an additional 37 MBq of ^{61}Cu in the sample disc, the contribution of Ga radioisotopes in the generated dose rate is estimated at 70%. ^{61}Cu has, however, a much shorter half-life and decays away rapidly. These dose rates are estimated using MicroShield software (version 5.03a, Grove Software Inc, USA).

2.2. Approach for reduction of Ga radioisotopes

One of the possibilities of reducing the co-production of Ga radioisotopes is to irradiate the natural Zn at low deuteron energies. According to Table 1, by performing an irradiation at 14 MeV instead of 19.5 MeV, the production yield of ^{64}Cu which at low energy takes place mostly through the ^{66}Zn(d,α)^{64}Cu reaction would be reduced by factor 2.5 while the reduction factors for the production of ^{66}Ga and ^{67}Ga would be 3.8 and 1.7, respectively (Fig. 1). In addition, the ^{61}Cu production would be reduced by a factor of 5.1 although its production does not cause problems due to its relatively short half-life (3.4 h). As summarised in Table 1, the ^{66}Ga and ^{67}Ga radioisotopes are created from the ^{66}Zn, ^{67}Zn and ^{68}Zn isotopic components of natural Zn. Therefore, it is possible to produce pure ^{64}Cu free of Ga radioisotopes by deuteron irradiation of ^{64}Zn through the ^{64}Zn(d,2p) reaction. The calculated thick target yields of ^{64}Cu, ^{61}Cu and ^{65}Zn for the case of deuteron irradiation of pure ^{64}Zn are given in Table 2, together with the corresponding yields for natural Zn. In addition to avoiding the production of Ga radioisotopes, deuteron irradiation of ^{64}Zn should, in theory, increase the thick target yield of ^{64}Cu. In this work, the deuteron irradiation of ^{64}Zn of 99.4% isotopic purity was performed to verify the theoretical predictions.

3. Experimental

3.1. Target material

The ^{64}Zn target consisted of a 7 mm diameter disk with a thickness of 325 ± 3 μm (232 mg/cm^2) purchased from ISOFLEX Inc., USA with the following isotopic distribution (atom percent): ^{64}Zn: 99.4 ± 0.1, ^{66}Zn: 0.39, ^{67}Zn: 0.04, ^{68}Zn: 0.15 and ^{70}Zn: <0.02%. ^{48}V activity produced in a disk of pure Ti (99.6% purity, 30 ± 4 μm thickness and 7 mm diameter, Good Fellow) via $^{nat.}$Ti(d, x)^{48}V reaction