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Applied Radiation and Isotopes 62 (2005) 383–387
Applied Radiation and Isotopes
www.elsevier.com/locate/apradiso

Cyclotron production of Ac-225 for targeted alpha therapy[1]

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Received 30 January 2004; received in revised form 31 March 2004; accepted 25 June 2004

Abstract

The feasibility of producing Ac-225 by proton irradiation of Ra-226 in a cyclotron through the reaction Ra-226(p,2n)Ac-225 has been experimentally demonstrated for the first time. Proton energies were varied from 8.8 to 24.8 MeV and cross-sections were determined by radiochemical analysis of reaction yields. Maximum yields were reached at incident proton energies of 16.8 MeV. Radiochemical separation of Ac-225 from the irradiated target yielded a product suitable for targeted alpha therapy of cancer.

Keywords: Targeted alpha therapy; Actinium-225; Radium-226; Cyclotron; Radioisotope production

1. Introduction

Targeted alpha therapy (TAT) is a novel cancer treatment modality, using alpha radiation to selectively destroy tumour cells (Apostolidis et al., 2001). The principle of TAT is based on the coupling of alpha-emitting radionuclides to tumour-selective carrier molecules, e.g. monoclonal antibodies or peptides, allowing the specific targeting of cancer cells. Due to the short path length of alpha particles in human tissue (<100 μm), TAT has the potential of delivering a highly cytotoxic radiation dose to targeted cancer cells, while limiting the damage to surrounding healthy tissue.

Presently a limited number of alpha-emitting nuclides is being considered for TAT (McDevitt et al., 1998), with Bi-213 ($T_{1/2}$ = 46 min), available through the decay chain of Ac-225 ($T_{1/2}$ = 10 days), presently being the most promising. Several pre-clinical and clinical studies have shown the feasibility of TAT for the treatment of various types of cancer (Huber et al., 2003; Jurcic et al., 2002; Allen et al., 2003; Vandenbulcke et al., 2003; Kennel et al., 2002) and infectious diseases (Dadachova et al., 2004). However, so far the bottleneck for the widespread use of Bi-213 in radiotherapy has been the limited availability of the mother nuclide Ac-225. Presently Ac-225 can be obtained only in limited quantities (approx. 1 Ci per year) by radiochemical separation from Th-229 sources, available at the Institute for Transuranium Elements in Karlsruhe, Germany, and Oak Ridge National Laboratory, USA (Apostolidis et al., 2001; Boll et al., 2003). In order to meet the increasing radioisotope demands of large-scale clinical studies, and the treatment of a large number of patients, alternative ways of producing Ac-225 are being discussed, mainly through irradiation of Ra-226 targets

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[1]Dedicated to Prof. Dr. Franz Baumgärtner on the occasion of his 75th birthday.

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doi:10.1016/j.apradiso.2004.06.013

using protons, neutrons or gamma-rays (ITU, 1995; Mirzadeh, 2002; Garland et al., 2003; Liu and Allen, 2003). However, our review of relevant literature failed to yield reports of an experimental demonstration of Ac-225 production on a scale required for clinical applications.

This work describes the first experimental verification of the feasibility of the production of Ac-225 by proton irradiation of highly radioactive Ra-226 targets in a cyclotron through the reaction Ra-226(p,2n)Ac-225. Target preparation and irradiation parameters are described, experimentally determined cross-sections as a function of proton energies are compared with model calculations using the ALICE code. The separation and purification of Ac-225 from irradiated radium targets was performed using extraction chromatography, and quality control of the product was carried out using alpha- and gamma spectrometry.

2. Experimental section

2.1. Target preparation

Ra-226 was obtained as $RaCO_3$ from the Institute for Radiochemistry of the Technical University Munich and from SCK-CEN, Mol. Purification of Ra-226 and preparation of targets for irradiation were performed in a designated, contamination-free hot cell using telemanipulators. The $RaCO_3$ stock material received from SCK-CEN had earlier been used for the production of Ac-227 by neutron irradiation and was found to contain residual traces of Ac-227 that had to be removed before production of Ac-225. For the purification, batches of 300 mg $RaCO_3$ were dissolved in 5 ml 2 M HCl, several times evaporated and re-dissolved in 2 M HCl and dried at 200 °C. The dry residue was re-dissolved in water and evaporated twice, finally re-dissolved in 0.01 M HCl, filtered and loaded onto the extraction chromatographic resin Ln-spec (Eichrom). Under these conditions Ac-227 was extracted on the column, while radium could be washed through the column using 0.1 M HCl. The radium eluate was evaporated and re-dissolved using dilute HCl to make up a radium stock solution that was analysed by ICP-MS for Ac-227 contamination. For the preparation of targets containing μg amounts of Ra-226, aliquots of 10 μl of stock solution were slowly evaporated on thin silver foils and covered with a second silver foil. The silver foil sandwiches were pressed and encapsulated in silver capsules, which were subsequently transferred to a glove box and welded gas-tight. For irradiation experiments using larger amounts of radium, an aliquot of radium stock solution typically containing 30 mg of Ra-226, was mixed with a stock solution containing 300 mg of $BaCl_2$ in dilute HCl. Barium was used as matrix due to the similar chemical properties of Ba and Ra. The mixture was evaporated, the residual solid phase was ground in a mortar and pressed into a pellet of 16 mm in diameter and 0.8–1.0 mm in height. Subsequently, the pellets were enclosed in silver capsules which were welded gas-tight. Before irradiation, the leak-tightness of the targets was controlled by monitoring radon emanation and by performing standard helium diffusion testing (UL500, Leybold). Additionally, targets were heated in 0.1 M HCl at 100 °C for 1 h to ensure mechanical stability and leak-tightness.

2.2. Irradiation conditions

Ra targets were irradiated using a 28 MeV proton beam at the cyclotron of the Forschungszentrum Karlsruhe, Germany. Proton currents were varied from 10 to 50 μA and targets were water cooled. Online capsule leak-tightness control was implemented by continuous monitoring of alpha activity in the water cooling circuit with automatic shutdown in case of target failure. A schematic cross-section of the target is shown in Fig. 1. Series of identical Ra targets containing constant amounts of Ra-226 (12.5 μg) were irradiated for 7 h, with a proton current of 10 μA, to study Ac-225 production yields as a function of incident proton energy. Incident proton energies were varied between 8.8 and 24.8 MeV using silver foils of varying thickness for energy attenuation. Ra targets containing ca. 30 mg of Ra-226 in $BaCl_2$-matrix were irradiated at constant proton energies of approx. 16 MeV with varying irradiation times to study the feasibility of Ac-225 production in the mCi range.

2.3. Processing of irradiated targets and Ac purification

Irradiated radium targets were opened in a hot cell after 2–3 days cooling time. $RaCl_2$, containing Ac-225 and by-products, was dissolved in 0.01 M HCl and

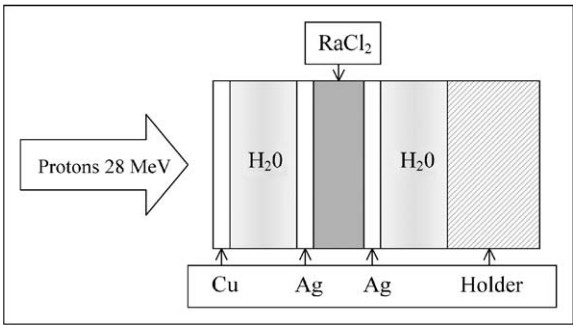

Fig. 1. Schematic view of the target design used for proton irradiation of radium chloride.