DEVELOPMENTS IN ALPHA EMITTING RADIOISOTOPE PRODUCTION AT THE JOINT RESEARCH CENTRE (JRC) OF THE EUROPEAN COMMISSION

K. Abbas[a], A. Alfarano[a,b], Z. Alfassi[c], C. Apostolidis[d], C. Birattari[b], M. Bonardi[b], N. Gibson[a], F. Groppi[b], U. Holzwarth[a], E. Menapace[e], A. Morgenstern[d], S. Morzenti[b] and H. Stamm[a]

[a]Institute for Health and Consumer Protection, Joint Research Centre, European Commission, I-21020 Ispra (VA), Italy
[b]LASA, Radiochemistry Laboratory, University and INFN, via F.lli Cervi 201, I-20090 Segrate, Milan, Italy
[c] Department of Nuclear Engineering, Ben Gurion University, Beer Sheva, 84105 Israel
[d]Institute for Transuranium Elements, Joint Research Centre, P.O. Box 2340, 76125 Karlsruhe, Germany
[e]ENEA, Division for Advanced Physics Technologies, Via Don Fiammelli 2, 40128 Bologna, Italy

Abstract

Alpha emitting radioisotopes are promising candidates for radiotherapy of several tumour types due to the high linear energy transfer (LET) of alpha particles in biological tissues. For this purpose research on productions of ^{225}Ac (via ^{226}Ra(p,2n)^{225}Ac) and of ^{211}At (via ^{209}Bi(α,2n)^{211}At) is undertaken. The research activities aim at improving production techniques and radiochemical processing yield in order to enhance the availability of these radioisotopes for medical application. Theoretical calculations and experimental validation have been used to optimise production conditions and to test alternative production routes. Our results and the current interest in investigating other alpha emitters for radioisotope therapy demonstrate the need for flexible cyclotrons like the Scanditronix MC40 Cyclotron of the JRC-IHCP at Ispra, capable of accelerating a range of light particles (protons, deuterons, alphas, ^{3}He^{2+}), with high extracted beam currents.

INTRODUCTION

There has been a growing interest in therapy with radioisotopes in recent years due to the commercial availability of radiopharmaceuticals. The radioisotopes are produced by nuclear reactors or by particle accelerators such as cyclotrons. In fact intense research is going on nowadays for new radioisotope production routes using cyclotrons since their number is increasing while nuclear reactors are shutting down.

The JRC Cyclotron is a Scanditronix variable energy MC40 machine. It accelerates protons and alpha particles up to 40 MeV, ^{3}He^{2+} to 53 MeV and deuterons up to 20 MeV. Depending on the target and the accelerated particles, the external beam intensity can reach 60 μA. The JRC Cyclotron is the only such accelerator in the south of Europe that is largely devoted to research. The Cyclotron facilities include three irradiation halls with seven beamlines and several dedicated laboratories, which are equipped with glove boxes and with instrumentation such as gamma and alpha spectrometers, necessary not only for cyclotron activation studies, but also for radiochemical separations.

Alpha emitting radioisotopes are therapeutically very effective due to the high linear energy transfer of alpha particles in biological tissues. In fact the range of alpha particles in human tissue is in the range of 60 to 100 um. Therefore the alpha particle energy is deposited within a few cell diameters. When the radiopharmaceutical (labelled with an alpha emitter) is well targeted to tumour tissue, it permits killing mainly of the cancer cells without severe damage to the healthy surrounding tissue.

The research aims at improving production techniques and radiochemical processing yield in order to enhance the availability of these radioisotopes for medical applications. Theoretical calculations and experimental validation have been used to optimise production conditions. In the following, studies for production of ^{225}Ac and ^{211}At, two radionuclides of particular interest for therapeutic applications, are presented.

^{225}Ac PRODUCTION ROUTES

Although several alpha-emitting nuclides are being considered for Targeted Alpha Therapy (TAT) [1], the use of ^{213}Bi ($T_{1/2}$ = 46 min), available through the decay chain of ^{225}Ac ($T_{1/2}$ = 10 days), presently seems the most promising. Several pre-clinical and clinical studies have shown the feasibility of TAT using ^{213}Bi for the treatment of various types of cancer [2, 3, 4 and 5] and infectious diseases [6]. However, so far the main impediment for the widespread use of ^{213}Bi in radiotherapy has been the limited availability of the mother nuclide ^{225}Ac. This nuclide can be obtained only in limited quantities (approx. 1 Ci per year) by radiochemical separation from ^{229}Th sources available at the Institute for Transuranium Elements in Karlsruhe, Germany and Oak Ridge National Laboratory, USA [7 and 8]. In order to meet increasing

radioisotope demand for large scale clinical studies and the treatment of a large number of patients, alternative ways of producing ^{225}Ac are being discussed, mainly through irradiation of ^{226}Ra targets using protons, neutrons or gamma rays.

The Institute for Transuranium Elements (ITU) of the JRC in collaboration with the cyclotron of the Forschungszentrum Karlsruhe, Germany, has demonstrated the feasibility of the production of ^{225}Ac in a cyclotron based on the reaction ^{226}Ra(p,2n)^{225}Ac. The excitation function of this reaction was determined by irradiation of a series of identical Ra-targets containing 12.5 µg ^{226}Ra. The targets were irradiated for 7 h with a proton current of 10 µA and incident proton energies were varied between 8.8 and 24.8 MeV using silver foils of varying thickness for energy attenuation. Radiochemical analysis of activation products was performed by extraction chromatographic separation followed by alpha- and gamma spectrometry. The experimentally determined cross sections are shown in Fig. 1 in comparison with model calculations using ALICE and EMPIRE-II codes (www.nea.org**)**. The experimentally determined cross sections are in good agreement with the model calculations. Maximum yields of ^{225}Ac were obtained at incident proton energies of 16.8 MeV.

The feasibility of large scale ^{225}Ac production in the mCi range was tested by irradiation of Ra-targets containing ca. 30 mg of ^{226}Ra in a $BaCl_2$ matrix. Targets were irradiated at constant proton energies of approx. 16 MeV with varying irradiation times. Irradiation of 30.1 mg ^{226}Ra with 15.9 MeV protons for 45.3 hours at a proton current of 50 µA yielded a clinically useful activity of 13.1 mCi of ^{225}Ac. Radiochemical purification yielded a high purity ^{225}Ac product suitable for pre-clinical and clinical TAT studies.

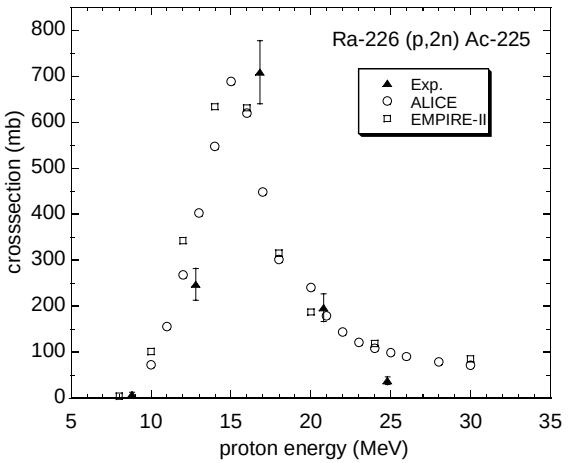

Fig. 1: Comparison of experimental (triangles) and theoretical (ALICE code, circles; EMPIRE-II code, squares) excitation function of the reaction ^{226}Ra(p,2n)^{225}A c

^{211}At PRODUCTION ROUTES

Astatine does not exist as a stable isotope. Therefore no cold chemistry can be performed to understand better the chemistry of this isotope, and widespread use of ^{211}At is hampered by lack of knowledge, in particular on radiochemical labelling. The JRC Cyclotron is currently active in the production of research quantities of ^{211}At for optimising production routes, improving targetry, and for radiochemistry research. Since the potential of ^{211}At for therapeutic biomedical applications is recognised [9, 10], it is planned to strengthen this activity, and to produce quantities large enough for clinical trials of cancer drugs based on ^{211}At. Contributions may also be made to the definition and formulation of standards for production and Quality Control of the related pharmaceutical.

The well-established production route for ^{211}At ($T_{1/2}$ 7.2 h) is by alpha particle bombardment of pure Bi using a cyclotron. In order to produce no-carrier added (NCA) ^{211}At for metabolic radiotherapy a suitable radiochemical separation of the At radioisotopes from Bi and Po is necessary. The established separation method is by dry distillation of ^{211}At from the irradiated Bi target at high temperature (at least 600^{o}C), which requires expensive equipment with quartz components. In addition, handling of alpha emitters at high temperature requires particularly strict safety measures. The goal of the current work described here is to develop a system for wet radiochemistry. Several short irradiations (2 hours irradiation at 0.5 µA current) of thick Bi targets have been carried out at the JRC Cyclotron. The energy of the alpha particles beam was set to 28 MeV. Liquid/liquid extraction is the method adopted for the separation [11-14]. The irradiated Bi metal is dissolved in a minimum amount of concentrated HNO_3 (less than 1 ml) until the brown fumes of NO_2 are no longer produced. 10ml of 8N HCl is then added to the solution making the solution little more than 7N HCl. The At is removed from the solution leaving behind the Bi and the Po by extraction with 8-10 ml of disopropyl ether (DIPE), pre-equilibrated with 8N HCl. The extraction of At isotopes by the DIPE can be more than 99% efficient with two extractions. However, it is sufficient to do only one extraction since in the first extraction more than 96% of the At is transferred to the DIPE phase. To remove traces of Bi the DIPE phase is washed with 2-3 ml of 8N HCl. This step leads to a loss of At of less than 2%. Bringing At back to the aqueous phase (stripping or back-extraction) must be done at either basic pH or with a reducing agent. The best results are found with both basic pH and a reducing agent such as sodium sulphite or sodium thiosulfate. However if the reducing agent should be avoided due to the requirements of the following labeling procedure, extraction by aqueous NaOH is sufficient. With 1N NaOH back extraction of about 80% is obtained while 0.125N NaOH leads to 50-70% back extraction. The yield depends on the reducing agent and the pH. The At was found to be quantitatively separated from the Bi and ^{210}Po impurities. The radionuclide purity of the final solution and the different fractions produced along the

radiochemical procedure are measured both by gamma spectrometry (which allows easily to distinguish between ^{211}At and ^{210}At) and by alpha spectrometry with a Si surface barrier detector and with two different liquid scintillation counting systems: Beckman LD5000 system and high-resolution alpha-liquid scintillation with $\alpha/\beta/\gamma$ pulse shape analysis (PSA) discrimination (the TRIATHLER "multilabel tester").

The characteristic gamma rays: 328 keV (^{211}At), 569 keV and 897 keV (^{211}Po), 245 keV, 1181 keV, 1436 keV, 1486 keV (^{210}At) are well resolved. Therefore gamma spectrometry can be used to determine the contamination of the ^{211}At preparation with ^{210}At. Due to the larger branching ratio of gamma lines of ^{210}At even a small concentration of ^{210}At can be determined. For the alpha spectrometry measurement with the Si surface barrier detector, the different liquid fractions obtained are deposited on Ag foils, by stirring the Ag foil with the solution of ^{211}At before measurement. Fig 2 shows the alpha spectrum of the ^{211}At fraction in equilibrium with its daughter ^{211}Po.

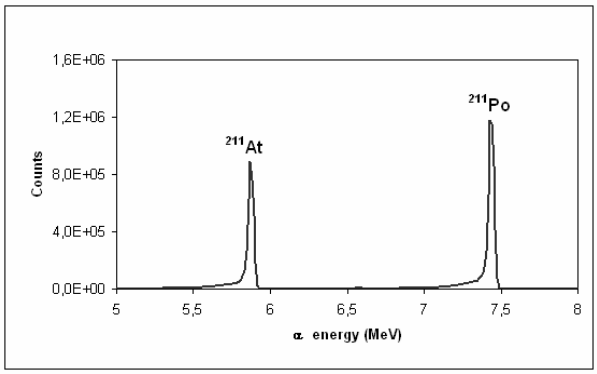

Fig 2: Alpha spectrum of the purified ^{211}At fraction

These alpha spectrometry measurements, although giving highly resolved peaks require a time consuming procedure during the sample preparation stage. In contrast, the liquid scintillation technique and in particular the TRIATHLER "multilabel tester" permits the measurement in a very short time of alpha activities with very high efficiency (about 100%) and without selective effects as a real sample of the extracted solution is used. In this way, it is possible to reduce the time of measurements, especially important for short-lived radionuclides and to reduce radiation dose to personnel, although at the expense of a less well resolved spectrum. This method is not able to separate the alpha line of ^{211}At (at 5868 keV) from the alpha line at 5304 keV of its possible contaminant ^{210}Po (daughter of ^{210}At).

Further long irradiations are planned to improve the present methodology.

CONCLUSION

Routine production of ^{225}Ac through ^{226}Ra cyclotron irradiation is feasible. However it requires the set-up of a designated production facility including hot cells and shielded glove boxes is required, together with other equipment for the safe handling of irradiated ^{226}Ra.

Development of ^{211}At production is carried out at a very limited number of cyclotron sites. The JRC Cyclotron aims to increase test productions, and eventually consider a regular production schedule for use by local clinical research centres or hospitals.

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