Applied Radiation and Isotopes 127 (2017) 214–226

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

A preliminary study for the production of high specific activity radionuclides for nuclear medicine obtained with the isotope separation on line technique

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HIGHLIGHTS

- The use of ISOL method for radionuclides production is proposed.
- ISOL method allows to produce carrier-free radionuclides for nuclear medicine.
- Tests with stable ion beams were produced as a proof of concept.
- Sodium Chloride is suitable as material for targets for Sr and Y beams.
- Activated Carbon can be compacted with PVA to have a solid target for I_2 beams.

ARTICLE INFO

Keywords:
Radionuclides
Radiopharmaceuticals
ISOL
SPES
Specific activity

ABSTRACT

Radiopharmaceuticals represent a fundamental tool for nuclear medicine procedures, both for diagnostic and therapeutic purposes. The present work aims to explore the Isotope Separation On-Line (ISOL) technique for the production of carrier-free radionuclides for nuclear medicine at SPES, a nuclear physics facility under construction at INFN-LNL. Stable ion beams of strontium, yttrium and iodine were produced using the SPES test bench (Front-End) to simulate the production of ^{89}Sr, ^{90}Y, ^{125}I and ^{131}I and collected with good efficiency on suitable targets.

1. Introduction

Radiopharmaceuticals are medicines that deliver a predefined amount of radiation to a target tissue for diagnostic or therapeutic procedures depending on the mechanism of decay. High penetrating radiation, such as γ emission, is mainly used for early diagnosis of tumors and inflammatory diseases (Azaiez et al., 2014). On the other hand particulate emission such as α and β^- emissions, which are capable of inducing cell death, are used for anticancer therapy and pathological conditions such as rheumatoid arthritis. The final goal of radionuclide therapy is to deliver a cytotoxic level of radiation onto a disease site (Handbook of Nuclear Chemistry, 2011).

Radiopharmaceuticals are consequently usually made of two parts: a "radioactive core" and a "carrier system"; the latter allows the deposition of radiation onto the malignant cell population thus avoiding damage to healthy tissues.

However, the physical production of the aforementioned "radioactive core" is regarded as one of the main problems. High costs of production, low reaction cross sections and product purity of current techniques are responsible for this difficulty. This is particularly true in the case of β^- emitting radionuclides.

These radionuclides are usually produced mainly by direct bombardment in dedicated targets using neutrons from nuclear reactors. By means of these reactions it is possible to produce a large number of isotopes and different nuclei in the target. The chemical methods to extract the desired radionuclide are not able to purify it from isotopic contaminants.

Thus specific activity, defined as the ratio between the activity (in terms of radioactivity) of the radioisotope and the mass of the element taken into account (Welch and Redvanly, 2003), is very low and carrier-added radionuclides are produced.

High specific activity is essential both for therapeutic and diagnostic radiopharmaceuticals. This fact should be especially emphasized in the case of radioimmunotherapy (RIT) and peptide receptor radionuclide therapy (PRRT), since cancerous cells have only a few selective sites. High specific activity is required to block these sites with tumor-seeking

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http://dx.doi.org/10.1016/j.apradiso.2017.06.022
Received 2 November 2016; Received in revised form 22 April 2017; Accepted 14 June 2017
Available online 17 June 2017

Fig. 1. BestC70 cyclotron recently installed at LNL in the SPES building.

agents which carry the radioactive isotope and not the "cold isotope", which exerts no therapeutic effect (Welch and Redvanly, 2003).

The use of accelerators and beam purification techniques based on the ISOL (Isotope Separation On-Line) technique might be an efficient way to produce radionuclides for radiopharmaceutical applications; selecting different beams from a production target (mass selection) guarantees the possibility to produce carrier-free radionuclides.

2. ISOL method for the production of radiopharmaceuticals at SPES

The ISOL technique is already established as one of the main techniques for the on-line production of high intensity and high quality radioactive ion beams (Nilsson, 2013). The construction of SPES (Selective Production of Exotic Species) a second generation ISOL facility at INFN-LNL (Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali di Legnaro) will allow the production of radioactive ion beams of neutron-rich nuclei with high purity in the mass range between 80 and 160 amu (Monetti et al., 2015).

At SPES the production of the radioactive isotopes is obtained by nuclear reactions induced by 40 MeV protons accelerated by a cyclotron, recently installed at LNL (Fig. 1), that collide with a multi-foil target consisting of disks of uranium carbide (UC_X) dispersed in carbon (Corradetti et al., 2013) and properly spaced in order to dissipate the deposited beam power (8 kW). The uranium contained in the target material will be ^{238}U, ensuring that the radioactive isotopes produced will belong to a group of elements having atomic numbers between 28 and 57 (elements placed between nickel and lanthanum in the periodic table). In particular, most of the produced nuclides will be neutron-rich, according to the chart of nuclides of Fig. 2.

The reaction products will be extracted from the target by evaporation at high temperature (about 2000 °C), and then forced through a transfer tube towards an ionization cavity where they will be ionized to the 1+ state (Manzolaro et al., 2013). Once ionized, these isotopes will be extracted and accelerated by means of at high potential (up to 40 kV). Radioisotope production and extraction from the target are represented in Fig. 3.

The resulting beam will be subsequently steered and focused using different electromagnetic systems and then finally purified in order to have a pure isotope beam without any contaminants. It will therefore be possible to collect the radionuclides of interest using a proper substrate placed at the end of the experimental line. A general scheme of the process is shown in Fig. 4.

The radioisotope production and collection performed with this technique have the capability to produce high specific activity materials using a simple procedure, meeting the requirements of radiopharmaceuticals. It is important to highlight that if the mass separation is performed effectively (ΔM/M at least better than 1/200) only an isobar chain is present in the collection target. The radiopharmaceutical quality is therefore expected to be extremely high. Using this production method, high specific activities, low gamma emitting impurities and very low isotope contamination can be expected. For this reason the ISOL technique is now under study for the production of radionuclides for nuclear medicine.

The radioisotopes produced at SPES using uranium carbide which are interesting from a radiopharmaceutical point of view are: ^{89}Sr (Kuroda, 2012), ^{90}Y (Goffredo et al., 2011), ^{125}I (Schwarz et al., 2012; Rodrigues et al., 2013; Shi et al., 2014), ^{131}I (Wyszomirska, 2012; Chamarthy et al., 2011) and ^{133}Xe (Mathews et al., 2008; Al-Busafi et al., 2012). Feasibility studies using stable ion beams for the production of strontium, yttrium and iodine are described later in this work.

3. ISOLPHARM

The ISOLPHARM project has the aim of performing, in the first instance, a feasibility study to use the RIBs produced at SPES as a new source of extremely pure radionuclides for use in nuclear medicine. The main aim is the obtainment of carrier-free radionuclides thanks to the mass separation followed by the chemical purification; the first process allows the removal of isotopic contaminants, the second of isobaric contaminants. To achieve this objective a wide range of knowledge must be taken into account, ranging from nuclear physics to engineering, technological production and radiopharmacy.

A profitable collaboration is now established between INFN-LNL and the Department of Pharmaceutical and Pharmacological Sciences of the University of Padua. The latter can provide the proper facilities for the chemical and pharmaceutical technological development of the project, so that from the very beginning a pharmaceutical production process can be developed.

It is important to clarify the main objectives of the project. The ISOLPHARM project initially is aimed at the production of radionuclides already present on the market, such as ^{89}Sr, ^{90}Y, ^{125}I, ^{131}I and ^{133}X. Nevertheless this can be regarded as innovative because of the possibility of producing them as carrier-free radionuclides. For example ^{89}Sr is produced by neutron irradiation and so it is carrier added, with very low specific activities values; it is for this reason used nowadays only in the chloride form (Metastron) as bone seeking agents for the palliation of bone metastases (Kuroda, 2012). Carrier-free ^{89}Sr produced with the ISOL method can be regarded as a new and innovative nuclide for molecule labeling and active targeting.

In the present work the results obtained from operating with stable beams already available at INFN-LNL are shown. The SPES test bench was used to produce stable strontium, yttrium and iodine beams, which simulate the production of ^{89}Sr, ^{90}Y, ^{125}I and ^{131}I.

As a second step, the ISOLPHARM project aims to study, as a research facility, the innovative radionuclides coming from a fissile target, as the one installed at SPES, bombarded with protons at high currents and energies. A broad fission spectrum can be obtained (see Fig. 2) and innovative radionuclides can be produced.

4. Experimental apparatus

The experimental apparatus present at LNL allowed the performance of some preliminary tests to verify the production of radionuclides of pharmaceutical grade with the ISOL technique. For this purpose, the SPES test bench, referred to as Front End offline (FE), was used. This apparatus, schematically represented in Fig. 5, has been designed and developed for the SPES project and is aimed at the production of (1+) ion beams. It is currently used in off-line mode, i.e. for the acceleration of stable ion beams; it is not connected to the proton beam line. Once the set up will be completed, it will be moved to a