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NOVEL METHODS FOR THE PRODUCTION OF RADIONUCLIDES OF MEDICAL INTEREST WITH ACCELERATORS

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Abstract

Radionuclides for radiopharmaceuticals preparation are currently produced in cyclotrons, generators or nuclear reactors. However, none of these modes is free from serious issues, like: high costs of targets, production of undesired radionuclide contaminants, long and expensive separation methods and formation of long-lived radioactive wastes. For this purpose, novel methods are being developed for the production of highly pure radionuclides. The ISOL (Isotope Separation On-Line) method can be applied to produce high purity radionuclides of medium and heavy masses. ISOL is nowadays established as a major method for the production of high intensity and high quality radioactive ion beams for nuclear physics studies. The SPES-ISOLPHARM project at INFN-LNL (Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali di Legnaro) aims to provide a feasibility study for an innovative technology for the production of high specific activity radionuclides based on the ISOL method. The ongoing experimental activities on primary and secondary (ion collectors) targets production, construction and testing of the selection and transport apparatus is here presented.

INTRODUCTION

Radiopharmaceuticals are medicines that deliver a predefined amount of radiation to a target tissue for diagnostic or therapeutic purposes depending on the mechanism of decay. Radiopharmaceuticals are usually made of two parts: a "radioactive core" and a "carrier system"; the latter allows the irradiation of malignant cell populations, avoiding damage to healthy tissues [1].

Beta-emitting radionuclides are usually produced mainly by direct reaction in dedicated targets using neutrons from nuclear reactors. By means of those 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 leads to the presence of a considerable amount of carrier. In this case, the specific activity, which is the ratio between the activity of the radioisotope and the mass of the element taken into account, is very low.

The global network of accelerators used for the production of medical radioisotopes, in particular cyclotrons, has seen a rapid expansion over the last decade, with a huge increase on the number of installed machines [2].

The accelerators based on the ISOL (Isotope Separation On-Line) technique [3] might be an efficient way to produce radioisotopes for radiopharmaceuticals application, thanks to the mass separation, which guarantees the possibility to produce radioisotopes with high specific activity, close to theoretical value.

THE ISOLPHARM PROJECT

At INFN-LNL (Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali di Legnaro), the SPES (Selective Production of Exotic Species) facility will allow the production of radioactive ion beams of neutron-rich nuclei with high purity, in the range of mass between 80 and 160 amu [4].

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, that will collide a multi-foil target with discs of different materials, mostly uranium carbide [5], properly spaced to dissipate the heat (8 kW) generated by the reaction. Most of the produced nuclides will be neutron-rich (uranium fission) but using different target materials it could be possible to produce proton-rich isotopes. The reaction products will be extracted from the target by evaporation at high temperature (about 2000 °C), and then forced to pass through a transfer tube towards an ionization cavity, where they will be ionized to the 1+ state. Once ionized, these isotopes will be accelerated through an electrode at high potential (up to 40 kV).

The ground-breaking idea of the ISOLPHARM method was granted an International patent (INFN). The driving idea is the obtainment of carrier-free radioisotopes, to be used as radiopharmaceutical precursors, thanks to the extreme purity of ISOL radioactive beams.

The formed beam will be focused using different electromagnetic systems and 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. In Fig. 1 a general scheme of the process is shown.

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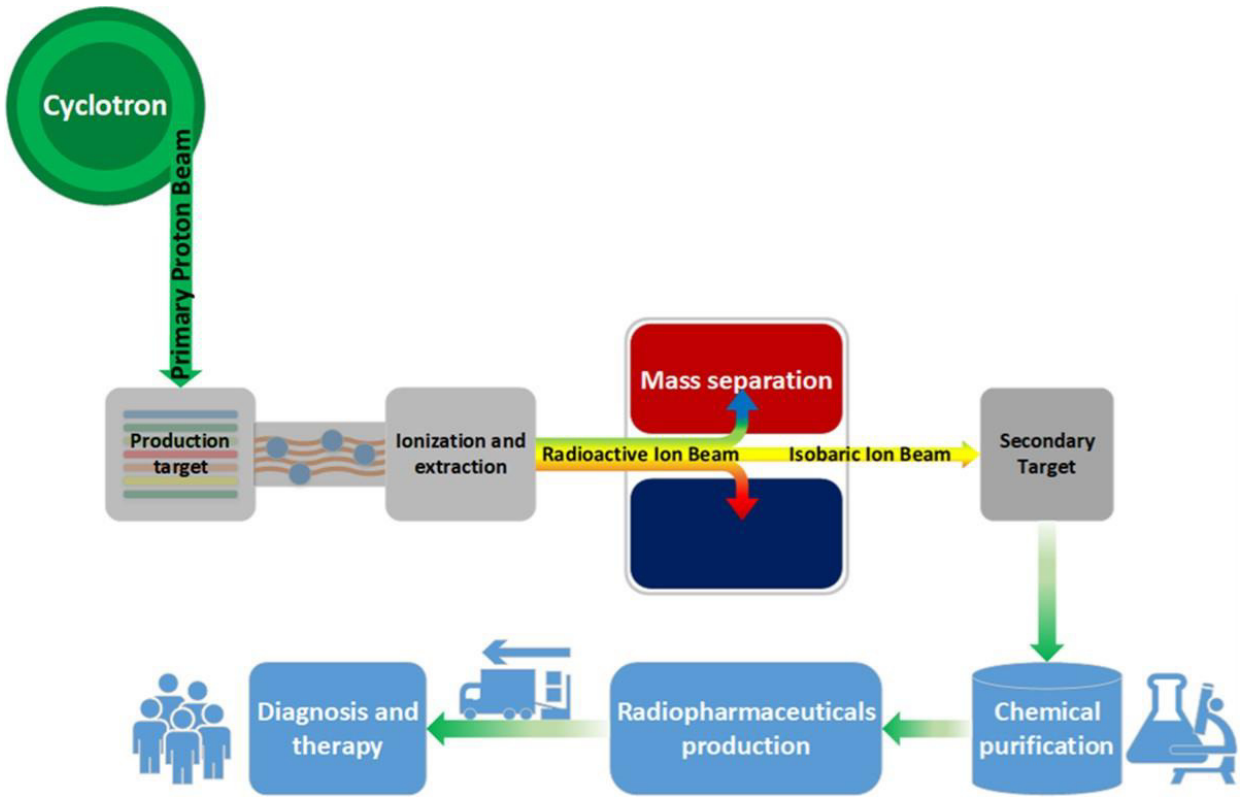

Figure 1: The ISOLPHARM process.

THE SPES FRONT END

The experimental apparatus present at LNL allowed the performance of some preliminary tests. A SPES test bench was used, referred to as offline Front End (FE). This apparatus, shown in Fig. 2, has been designed and developed for the SPES project.

To study the production of a radionuclide with the ISOL technique for the obtainment of a radiopharmaceutical product, stable isotopes of the same element can be used, since they have the same chemical behavior. For this reason, the FE was used to produce stable ion beams and carry out the feasibility tests here reported. The FE is made of five different functional subsystems: the ion source complex, the beam optics subsystem, the Wien filter and two diagnostic boxes.

In offline mode, different methodologies can be used to introduce the stable isotopes to be ionized and accelerated, depending on the physical state of the element. In the case of gases, they are introduced through a controlled gas flow and injected in the ionization source thanks to a calibrated leak; in case of solid materials, they are in the form of soluble salts, dissolved in acidic media and quantitatively deposed and solvent evaporated on a tantalum foil, called mass marker (MM) [6].

The ionization sources used in the FE are of two kinds [7], according to the first ionization potential of the element. For elements of the 1st and 2nd groups, a Surface Ion Source (SIS) is adopted; for elements with higher electronegativity, a Plasma Ion Source (PIS) is necessary.

For the simulation of the radionuclide production, at the end of the line, immediately after the second diagnostic box, a substrate of pharmaceutical grade (usually sodium chloride, “irradiation target” in Fig. 2) is positioned in order to collect the desired accelerated stable ions.

COPPER IONIZATION AND DEPOSITION TESTS

Among the radioisotopes that can potentially be produced in the framework of the ISOLPHARM project, ^{64}Cu and ^{67}Cu are a promising theranostic pair [8].

In order to evaluate the capability of the SPES FE to efficiently ionize copper isotopes and extract them into a beam, ionization tests were performed by loading precise amounts of stable natural copper into the ion source, by means of the MM technique which foresees the surface deposition of a small amount of the desired element on a thin tantalum foil that is lately accurately folded and inserted inside a small tubular oven, that replaces the production target. Such oven can be heated by Joule effect, allowing the atomization of the substrate previously deposed on the foil, and the migration of the neutrals towards the ion source. In the case of copper, the PIS was used.

We could verify copper ionization thanks to the analysis of masses composing the beam. A typical mass scan for copper is reported in Fig. 3A. Copper is clearly identified thanks to the two peaks of masses 63 and 65.

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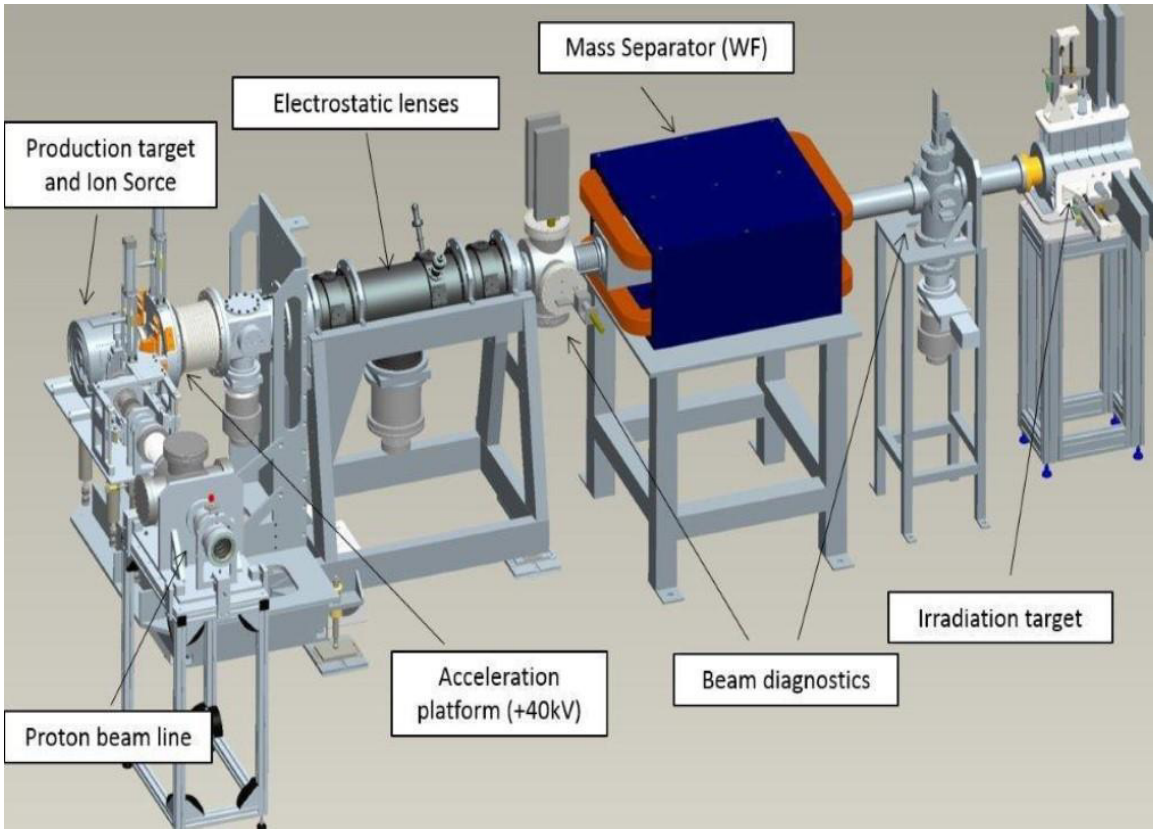

Figure 2: The off-line Front End.

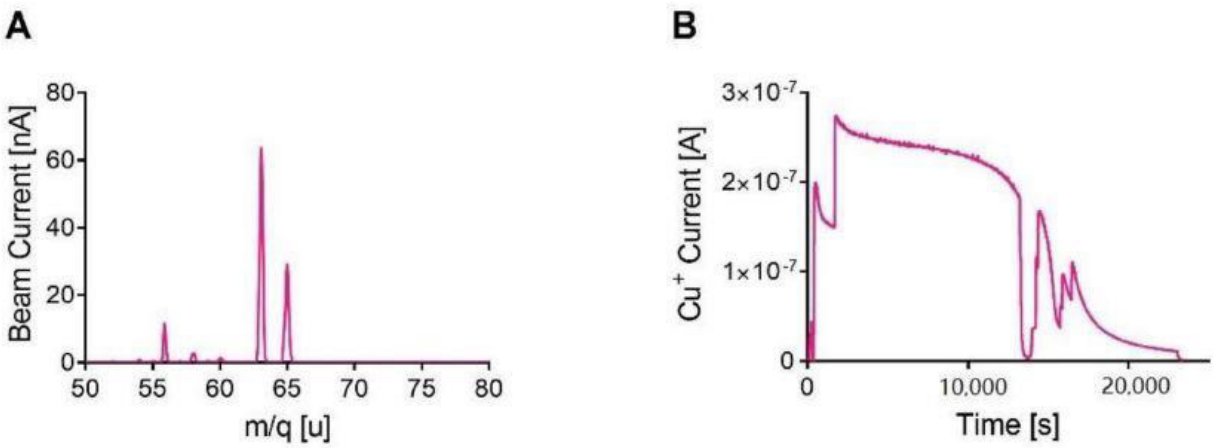

Figure 3: (A) Mass scan of copper beams and (B) trend of copper beam in time during ionization tests.

The ionization efficiency, i.e., the total amount of ^{nat}Cu ionized out of the amount of ^{nat}Cu in the MM, was 7.7 ± 1.3%. In Figure 3B the copper beam current trend is reported.

After the removal of the secondary target at the end of several hours of irradiation, its appearance was as shown in Fig. 4, clearly showing the implantation of the two different masses composing ^{nat}Cu, 63 and 65..

The quantification of copper after the recovery from the beam was made possible thanks to the dissolution of the targets in acidic medium. When diluted nitric acid was used, only a low amount of copper was measured, so the dissolution in concentrated nitric acid and at high temperatures was then applied. In this case the amount of copper recovered was higher (about 50%), but still not the 100% of the copper which was foreseen on the targets. For this reason, further studies are going to be carried out to improve the efficiency of the chemical recovery process.

CONCLUSION

The ISOLPHARM project aims to develop a technique which opens the possibility to produce a wide range of radionuclides with extremely high levels of purity. This is related to the intrinsic high specific activity, because of the

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lack of isotopic contaminants, and radionuclidic and chemical purity, since impurities coming from the beam and from the targets are very limited, compared to those of traditional methods.

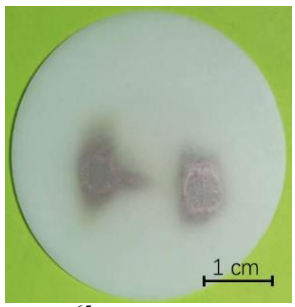

Figure 4: The ^{63}Cu and ^{65}Cu spots on the secondary target from right to left.

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