CYCLOTRON PRODUCTION OF POSITRON EMITTING RADIOMETALS

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Abstract

The increase in use of Positron Emission Tomography (PET) for medical imaging has led to the development of numerous radiopharmaceuticals for use in preclinical and clinical research for oncology, cardiology and neurology [1]. While many of these biological processes can be investigated with probes radiolabeled with the more commonly used positron emitters, ^{18}F ($t_{1/2}$ = 110 min) and ^{11}C ($t_{1/2}$ = 20 min), imaging at longer timepoints requires radionuclides with longer half-lives. Thus, the production and purification of longer-lived position emitting radiometals has been explored to allow for imaging of peptides, antibodies and nanoparticles. This brief review will focus on the production and purification of ^{64}Cu ($t_{1/2}$ = 12.7 h) and ^{89}Zr ($t_{1/2}$ = 3.27 d).

INTRODUCTION

Positron Emission Tomography (PET), with its high sensitivity and resolution, is growing rapidly as an imaging technology for the diagnosis of many disease states. The success of this modality is reliant on the development of effective imaging compounds. Initially, research in this area was focused on the relatively short-lived PET isotopes ^{11}C and ^{18}F, but the short half-lives of these isotopes limit radiopharmaceutical development to those that probe rapid biological processes. To overcome these limitations, there has been a rise in alternative radionuclide tracer development in recent years. Below, in Table 1, are some examples of radiometals for use in nuclear imaging (all data from [2]).

Table 1: Examples of Positron Emitting Radiometals

Isotope	Production Route	Half-Life
^{64}Cu	^{64}Ni(p,n)	12.7 h
^{68}Ga	^{68}Ge Generator	68 min
^{86}Y	^{86}Sr(p,n)	14.7 h
^{89}Zr	^{Nat}Y(p,n)	3.27 d

While ^{68}Ga use has also increased recently, this short review will focus on the cyclotron produced isotopes, namely ^{64}Cu and ^{89}Zr.

Washington University in St. Louis has been producing and distributing longer-lived PET radionuclides to the research community for over 15 years. The radionuclides that have been produced include ^{64}Cu, $^{76/77}$Br, ^{66}Ga, ^{86}Y, ^{124}I, and ^{89}Zr. Presently, ^{64}Cu and ^{89}Zr are produced on a regular basis (weekly and biweekly respectively), while ^{86}Y and ^{76}Br are produced intermittently in lower quantities. The recent increase in production and shipping of ^{64}Cu to external institutions is illustrated in Figure 1 and is mainly due to the increase in clinical trials with this isotope.

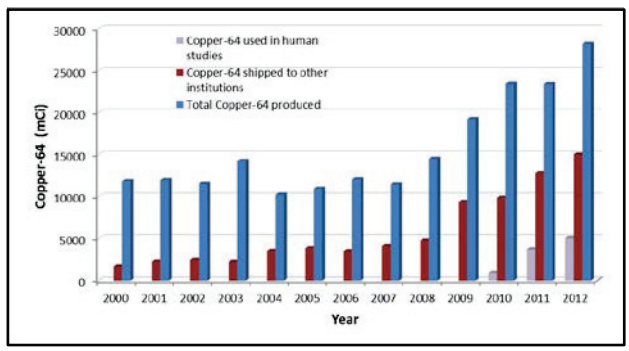

Figure 1: Production and Distribution of ^{64}Cu from Washington University in St. Louis.

TARGET PREPARATION AND BOMBARDMENT

Radiometal production starts with preparation of the target material on a suitable support for cyclotron bombardment. This may be an electroplated deposit, pressed powder pellet, or a foil placed in a suitable holder.

Preparation of ^{64}Ni Targets for Production of ^{64}Cu

Targets are prepared for ^{64}Cu production as per McCarthy *et al* [3]. Briefly ^{64}Ni metal is dissolved in 10 ml of 6.0 M nitric acid. The solution is then evaporated to dryness. The residue is dissolved in 1 ml of concentrated sulphuric acid and 5 mL deionized water and evaporated until slurry is formed. The resulting solution is diluted in 5 ml of deionized water. The pH was then adjusted to 9 with concentrated ammonium hydroxide (25%). Then 0.2 g of ammonium sulphate is added to the solution. This solution was transferred to an electrolytic cell with a graphite electrode as anode and a gold disc (target backing) as cathode. The cathode is cleaned with 6N HNO_3 to remove any metal residue on the surface. The cell is operated at 2.5 V with a starting current between 70-80 mA/cm^2. Final target weights are typically between 20 and 80 mg with a spot diameter of 5 mm.

The ^{64}Ni target is irradiated at a beam current of 20 µA for 60 to 80 µA-h with a Cyclotron Corporation CS-15 positive ion cyclotron, with a pneumatically-controlled cylinder sealing the back of the disc and providing cooling with recirculating chilled water. After irradiation,

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the cylinder is retracted, and the disk is ejected into a transfer line via pressurized nitrogen. The disc is brought up from the cyclotron vault to a shielded cell using vacuum. The target is then transferred manually to the processing hotcell.

Preparation of Y Foils for Production of ^{89}Zr

For the production of ^{89}Zr, a 0.64 mm thick ^{nat}Y disc is placed inside a niobium target holder. Nb was selected because of its high melting temperature (Tm = 2,468 °C) and high chemical inertness. Before each target holder was reused, it was scrubbed by hand using a cotton swab dipped in a slurry of Al_2O_3 powder and water. The target holder was placed in 6 M HCl for 1–4 h for cleaning and oven dried before mounting in the CS-15 cyclotron. During bombardment (typically 20 µA for 40 to 60 µA-h), the target holder assembly is cooled on the beam side by a He gas jet and on the reverse side by flowing chilled water. Following irradiation, the target remains in the solid target station for several hours to allow for the decay of short-lived contaminants, (^{89m}Zr) prior to processing as described below.

PURIFICATION

Following irradiation of the targets, the radionuclide of interest is separated from the target material by chemical processing.

Purification of ^{64}Cu

^{64}Cu is purified via an in-house automated system using a procedure adapted from the manual separation described in McCarthy *et al* [3] for use in a hotcell with remote operation [4].

The automated purification module consists of a series of PTFE or Kel-F based solenoid valves that direct liquid, gas, and vacuum flow. Processing of the irradiated enriched ^{64}Ni targets involves the dissolution of the nickel in 6M HCl in a custom made, heated PTFE vessel (30 min), active cooling of the dissolved nickel solution with a vortex tube (20 min), then recovery of the nickel via ion chromatography with 6M HCl, followed by an additional 6M HCl rinse of the dissolution vessel for higher recovery and removal of nickel from the resin, and elution of copper from the resin with 0.5M HCl. The entire chromatography process takes 40 minutes, and the liquid level is monitored via a camera to prevent the resin from drying out. The collected ^{64}Cu solution is then evaporated under argon (20 min) and reconstituted in 0.1M HCl. Another camera monitors the progress of the evaporation. Three radiation detectors are located by the dissolution vessel, column, and nickel recovery vial and provide real-time feedback on how well the process is proceeding. On average, the entire process takes about 2 hours from target introduction. The components required for these steps are located within the hot cell shown in Figure 2, while the control components and computer are located outside of the hot cell.

Figure 2: ^{64}Cu purification system.

The components are controlled using a USB digital input output (DIO) data acquisition unit and digital output modules. The in-house developed control program is easy to navigate and affords the operator flexibility during the synthesis. At the launching of the program, a series of dialog windows guide the operator in the preliminary preparation of the module. Once this procedure is fulfilled, the module is ready to start the synthesis. The operator also has the possibility to pause / abort the synthesis at any time during the sequence if a critical condition occurs. A diagnostic window is available to the operator for troubleshooting during synthesis, permitting the remote actuation of each step in the sequential procedure if adjustment is required due to a faulty condition.

Typical recoveries with this system are 96% or better of starting radioactivity and 98.6% of enriched ^{64}Ni target material.

Purification of ^{89}Zr

We have automated the ^{89}Zr purification method of Holland et al [5] on an in-house constructed system [6]. Using a custom software program made in LabVIEW, running on a laptop outside the hot cell 10 mL 2 M HCl is added to the dissolution vessel to dissolve the ^{nat}Y target. After waiting ~1 h for complete dissolution, the dissolved target is transferred to the separation column containing 100 mg of hydroxamate resin) through tubing using compressed air. Then, the Y is eluted from the column in 10 mL 2 M HCl and collected in a waste vial, leaving the ^{89}Zr bound on the column.

The column is rinsed with 10 mL water, which is collected in the same waste vial, and then ^{89}Zr is eluted in 1 mL 1 M oxalic acid and collected in a product vial as ^{89}Zr-oxalate. A schematic of the automated module for the separation of ^{89}Zr from the yttrium target material is shown in Figure 3.

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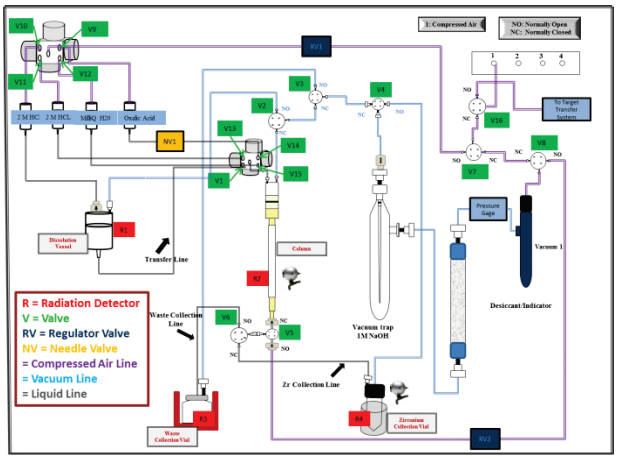

Figure 3: ^{89}Zr purification system.

QUALITY CONTROL

All isotopes undergo quality control procedures including radioisotopic purity and effective specific activity.

Radioisotope Purity

The radiochemical purities of the produced radioisotopes are assayed after end of purification via gamma spectroscopy with a high purity germanium well detector coupled to a multichannel analyzer. "Clean" ^{64}Cu spectra should show only the characteristic gamma ray at 1364 keV and the 511keV annihilation photon, while the ^{89}Zr spectra should display only the 909 keV characteristic gamma ray and the 511 keV annihilation photon. Figure 4 shows a typical high purity ^{89}Zr gamma ray spectrum.

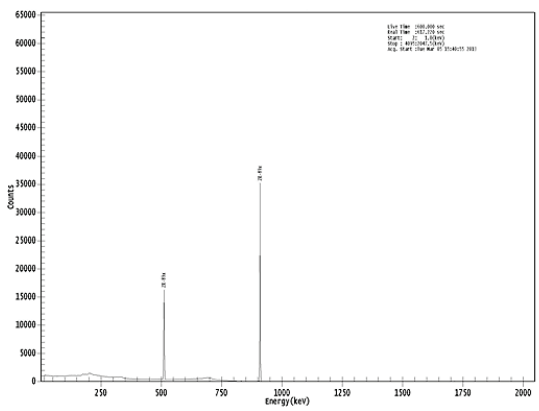

Figure 4: Gamma ray spectrum of ^{89}Zr.

Effective Specific Activity (ESA)

Effective Specific Activity (ESA) for radiometals can be defined as the amount of metals present that will bind to a suitable ligand per unit radioactivity. Determination of ESA involves titration with a suitable chelator. In this manner we can determine the amount of total metals that many interfere with the chemistry of each isotope. For example, below, in Fig. 5, is a titration curve for measurement of ^{64}Cu ESA with TETA.

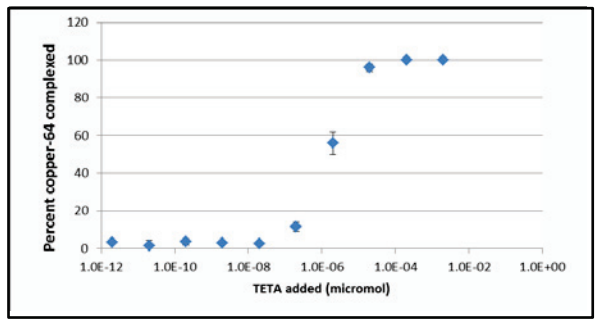

Figure 5: TETA titration for the determination of ESA for ^{64}Cu.

To determine the ESA, the point at which 50% of the radioactivity is complexed and doubled to determine the amount required to complex 100%. The total amount of transition metal complexed is determined and the users are supplied with an ESA in mCi/mmol total metal ions. Typical ESA varies from 7680 to 38400 mCi/µmol total binding metals from ^{64}Cu and from 45 to 1780 mCi/umol for ^{89}Zr.

CONCLUSION

Radiometal isotopes have enabled the investigation of various biological processes in the area of oncology, cardiology and neurology. Widespread use and clinical translation of these radionuclides requires robust optimized target preparation and purification methods for routine production.

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