PRODUCTION OF MEDICAL ISOTOPES WITH ELECTRON LINACS*

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Abstract

Radioisotopes play important roles in numerous areas ranging from medical applications to national security and basic research. Radionuclide production technology for medical applications has been pursued since the early 1900s both commercially and in nuclear science centers. Many medical isotopes are now in routine production and are used in day-to-day medical procedures. Despite these advancements, research is accelerating around the world to improve the existing production methodologies as well as to develop novel radionuclides for new medical applications. Electron linear accelerators (linacs) represent a unique method for the production of radioisotopes. Even though the basic technology has been around for decades, only recently have electron linacs capable of producing photons with sufficient energy and flux for radioisotope production become available. Housed in Argonne National Laboratory's Low Energy Accelerator Facility (LEAF) is a newly upgraded 55 MeV/25-kW electron linear accelerator, capable of producing a wide range of radioisotopes. This talk will focus on the work being performed for the production of the medical isotopes ^{99}Mo (^{99}Mo/^{99m}Tc generator), ^{67}Cu, and ^{47}Sc.

INTRODUCTION

Medical isotopes are generally categorized as therapeutic, diagnostic, or both (theranostic/theragnostic). Radiation therapy relies on the destructive effects of radiation to disable unwanted cells and tissues in a biological system – ideally to combat cancer [1]. Beta-emitting nuclides of the appropriate energy and half-life such as ^{47}Sc, ^{67}Cu, ^{186}Re, and ^{188}Re are of interest. A general rule for a beta-therapy is that ~0.2 mm of tissue (~2-20 cells) is penetrated per 100 keV, making the β^-_{max} energy a crucial factor when treating diseases. Diagnostic procedures rely on the penetrating gamma or an annihilation induced by the injected radioisotope (such as ^{18}F, ^{44}Sc, ^{64}Cu, or ^{99m}Tc). Current medical single photon emission diagnostic cameras (SPECT) are optimized for ^{99m}Tc (140 keV) energies and as such, gamma emissions similar to 140 keV are most desired for these procedures. Positron emission tomography (PET) detects the duel 511 keV annihilation emission from positron emitters.

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Radioisotopes that have image-able gamma emissions and alpha or beta emissions suitable for localized cell destruction are referred to as theranostic agents and are of extreme interest to the medical community. Theranostic agents help minimize healthcare costs, hospital visits, and inconveniences to the patients as they allow for real-time assessment of the treatments.

The electron linac is useful for producing radioisotopes having high specific activity with increased yields. In particular, exploration of the (γ,p) reaction may be able to overcome the shortcomings of the low specific activity usually associated with neutron transmutation.

Argonne National Laboratory's Low Energy Accelerator Facility (LEAF) houses a newly upgraded 55 MeV/25-kW electron linear accelerator (linac), capable of producing a number of medical isotopes through photonuclear reactions that are difficult or otherwise impossible to make [2-4]. Parameters of the linac are provided in Table 1.

Table 1: Parameters of the Argonne Linac

Parameter	Value	Unit
Maximum beam energy	55	MeV
Minimum beam energy	20	MeV
Maximum average beam power	25	kW
RF frequency	1300	MHz
Repetition rate	240	Hz
Length of RF pulse	6.5	μs
Maximum beam pulse width	5	μs
Beam energy spread	3	%

ELECTRON LINAC PRODUCED RADIOISOTOPES

Photonuclear-reaction yields of radioactive isotopes depend on the production of high-energy photons generated by interactions of high-energy electrons with a high-Z material (i.e., a converter) to produce Bremsstrahlung radiation. Production yields are controlled by the electron beam flux, target size, length of irradiation, and reaction cross section. The reaction cross section is one of the most important parameters for estimating efficacy and efficiency of photonuclear reactions. A great deal of work has been done to create experimental cross-sectional data bases for (γ,n) reactions (usually leading towards low specific activity radioisotopes); however, even this database is still incomplete [5-7]. The (γ,p) reactions (that lead to high specific activity radioisotopes) is much less extensively investigated and requires considerable additional investigation.

Argonne National Laboratory has developed irradiation parameters, targetry, and purification methods for the radioisotopes listed in Table 2.

Table 2: Radiometals produced at Argonne with an Electron Linac

Isotope	Production route	Half-Life
^{99}Mo	^{235}U(γ,f)	2.75 d
^{99}Mo	^{100}Mo(γ,n)	2.75 d
^{67}Cu	^{68}Zn(γ,p)	2.83 d
^{47}Sc	^{48}Ti(γ,p)	3.35 d

^{99}Mo

Argonne National Laboratory with support from the National Nuclear Security Administration's (NNSA) Office of Material Management and Minimization (M^3) is developing technologies to accelerate the domestic production of ^{99}Mo.

Technetium-99m is distributed worldwide in a generator system where ^{99}Mo decays to ^{99m}Tc. Technetium-99m is the most widely used radioisotope in nuclear medicine. It has ideal characteristics such as a sufficiently short half-life (6 hrs) and single gamma emission (140 keV) for single-photon emission computed tomography (SPECT) imaging. SPECT utilizes gamma emissions from select radioisotopes such as ^{99m}Tc (140 keV) to collect multiple 2D images that can later be combined into 3D images that map the interior of a patient. Information such as this provides insight to diseases and will help doctors develop cures for certain ailments.

^{99}Mo from Accelerator-driven subcritical fission of a low-enriched uranyl (LEU) sulfate solution. The LEU uranyl sulfate solution was housed in stainless steel vessel with a water reflector. A water-cooled tantalum convertor was located towards the center of the stainless steel vessel. Predominately fast neutrons were generated by bombarding high-energy electrons (35 MeV, 10 kW, 15 hrs irradiation) onto the tantalum convertor. The neutrons were thermalized by the aqueous LEU uranyl sulfate solution (5 L, 0.63 M uranyl sulfate, pH = 1) and surrounding water reflector, inducing fission of ^{235}U to produce ^{99}Mo (6.1% fission yield) [8].

Radioactive gases (mainly Xe, Kr and I radioisotopes) produced during the irradiation were collected and stored for decay.

The LEU target solution was remotely processed using a LabVIEW®-based control system. The solution was purified with an extraction column (TiO_2, 110 µm particle size, Sachtopore) where ^{99}Mo was retained. The eluted solution was stored for future irradiations. The column was washed with sulfuric acid (pH 1) and then water, and ^{99}Mo was stripped with NaOH (0.1 M). The resultant solution was acidified to pH 2 with nitric acid and further purified with a concentration column (TiO_2, 40 µm particle size, Sachtopore). The column was washed with HNO_3 (0.01 M) and water, and the product stripped with NaOH (1 M) to obtain 25 mL of ^{99}Mo product.

Final purification was performed by acidifying the solution with 10 M HNO_3 to 1 M HNO_3 and using the LEU Modified Cintichem process (LMC). Purified ^{99}Mo was recovered as sodium molybdate in ~55 mL of ~0.2 M NaOH. Figure 1 depicts the gamma ray spectrum of the irradiated solution and the final purified product. The chemical yield of ^{99}Mo was >80% (1.4 Ci ^{99}Mo). The product was shipped to a Tc-generator manufacturer for testing and was shown to meet the European Pharmacopeia (EUP) purity specifications, fit into the existing supply chain, was successfully loaded onto a commercial ^{99}Mo/^{99m}Tc generator and the eluted product was successfully tested with two commercial radiopharmaceutical kits [9].

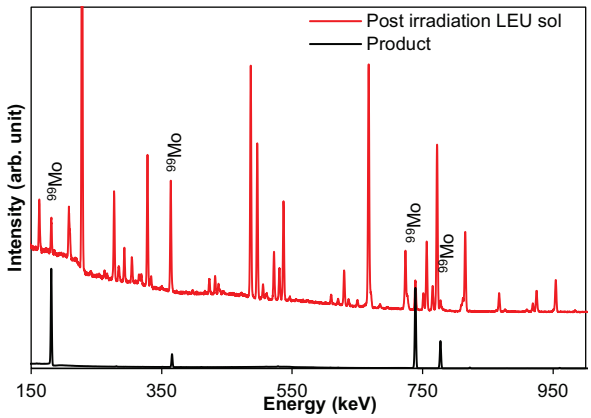

Figure 1: Gamma ray spectrum of the irradiated LEU target solution and the final product after a series of purification steps.

^{99}Mo Production from ^{100}Mo. Beam energies in the range of 32-42 MeV are optimum for the ^{100}Mo(γ,n)^{99}Mo reaction. Sintered metallic Mo disks (25, 1 mm thick, 12 mm diameter) were irradiated (42 MeV, 8 kW, 6.5 day irradiation) with direct electron beam (no convertor) inside of a He-cooled target assembly [10]. The beam position was monitored with optical transition radiation (OTR) cameras throughout the irradiation. The image of the beam on the entrance window was captured by a charge-coupled device (CCD) camera equipped with a 180 mm focal length lens. The cameras were positioned away from the target and housed within a windowed lead and borated polyethylene shielded box to avoid camera failure. Mirrors were used to provide line-of-sight for the shielded cameras [11].

Six of the 25 Mo disks were ^{100}Mo enriched disks, all other disks were natural Mo. The enriched disks were positioned from slot 5 – 10 from the incident beam (position 1 was closest to the beam entrance window, Fig. 2.). The target holder was delivered to a hot cell in a shielded vessel and the six enriched disks were dissolved with hydrogen peroxide (50% Sn-stabilized). A saturated solution of KOH was added to convert the Mo-peroxo species to $KMoO_4$. An orange precipitate formed, indicating the presence of iron. The mixture was heated to destroy excess peroxide and condense the solution to the desired volume. After cooling, the solution was filtered through a syringe filter

(0.3 μm) resulting in a clear solution with a light orange tint (observed through yellow leaded glass). The activity of the final product was 12.4 Ci of ^{99}Mo [11].

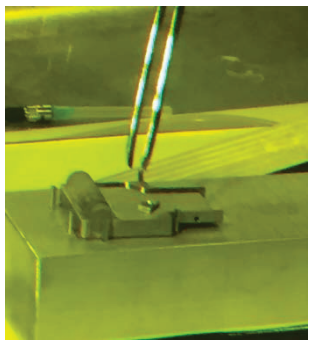

Figure 2: Half-shell of Mo target holder with irradiated Mo target disks. Disks are being extracted for processing.

Natural Mo disks in positions 4, 18, 21, 24, and 25 were counted one month post irradiation and the activities corrected to end of bombardment. Experimental activities were compared with MCNPX calculations. The total activity of the six enriched disks was determined by dividing the total activity of the six dissolved disks based on the predicted activity distribution from MCNPX calculations and allocating that activity to the individual enriched disks. Experimental activities were found to be 74% of theoretical activities [11].

Associated with the production is the recovery and recycle of enriched material. Enriched target materials are expensive (^{100}Mo ~$700/g) and in order to economically produce radioisotopes, must be recycled. Argonne has developed several methods for the recovery of ^{100}Mo from spent low specific activity ^{99}Mo generator systems. Molybdenum can be precipitated in the presence of acid as MoO_3 [12] or as a polyoxometallate in the presence of an associated counter ion (tetra alkyl ammonium salt) [13]. Both solids can then be dried and reduced to Mo metal. An alternative method is solvent extraction of Mo with tri-butyl phosphate (TBP), followed by solidification and thermal reduction to Mo metal [14]. All methods demonstrate excellent purity and recovery (>98%) of Mo.

^{67}Cu

There is an ever pressing need for new theranostic radiopharmaceuticals. Copper-67 presents a very interesting radioisotope with properties ($t_{½}$ = 2.576 days; β^-: 141 keV; γ: 91.3, 93.31, and 184.6 keV) that makes it suitable for both therapy and diagnostic imaging. The half-life is also very amicable for regional shipping. Copper-64 the positron emitting diagnostic pair to ^{67}Cu and is currently being applied in medical research and clinical practice [15, 16].

The biochemistry of free copper and zinc (the decay product of ^{67}Cu) are well known as they are essential elements and do not have acutely toxic effects nor do they bioaccumulate. The chelation and biochemistry of promising copper complexes have been extensively studied [17-20]. However, a reliable supply of ^{67}Cu has been hindered by the development and use of ^{67}Cu-based radiopharmaceuticals and in turn the development of ^{67}Cu-based radiopharmaceuticals has been hindered by supply.

Copper-67 can be produced by several different methods including proton beams, nuclear reactors, and electron linacs. Photonuclear production with an electron linac was chosen as the best method to produce high specific activity ^{67}Cu compared to the other methods mentioned. The use of an electron accelerator to produce high-energy Bremsstrahlung to induce a photonuclear reaction on ^{68}Zn has been demonstrated in the literature [21-24].

At Argonne, ^{67}Cu was produced by the ^{68}Zn(γ,p) reaction. The target material is a solid metallic Zn cylinder with large volumes (20-28 cm^3, ~100 g of Zn). In test cases, natural zinc targets were prepared by subliming Zn shot from an alumina crucible into a specially designed sublimation apparatus. Generally two sublimations were required to collect enough mass before a 100 g target could be cast (Fig. 3.).

Figure 3: Sublimed zinc prepared to be casted into a target (left). A 100 g Zn target ready for irradiation (right).

Irradiations generally used a 36 MeV beam and the energy and length of irradiation varied from each experiment (generally from 3-10 kW). Batches of 10 mCi or less of ^{67}Cu were produced from natural Zn in order to develop the targetry and purification chemistry.

Many isotope processing and purification procedures require dissolution of the entire target material. Instead, Zn is sublimed from ^{67}Cu, removing the need for large volumes of reagents, and allowing for recycling of the expensive ^{68}Zn, when enriched targets are used. Copper has a non-negligible vapour pressure; therefore tin metal was used as a holdback agent during sublimation. Sublimations were performed under vacuum (<20 mTorr) at elevated temperatures (~600 °C). The temperature was controlled with a standard temperature controller with ramp rate (3 °C/min) and soak periods (4 hrs soak at temp) set during processing. After sublimation, the residual ^{67}Cu (now a Cu/Sn alloy) was dissolved with HCl (8 M, 10 mL) and HNO_3 (concentrated, 1 mL) under boiling conditions. The resulting solution was loaded onto an AG1-X8 (Bio-Rad) ion exchange column in HCl (8M). The column was washed with three full column volumes of HCl (8 M). Copper-67 was then eluted with HCl (2 M) in approximately 8 mL. Gamma analysis of the processed solution revealed a very clean spectrum [25].

The target material can be recycled by melting the sublimed Zn into a fresh alumina crucible at 500 °C under a blanket of $H_2/Ar_{(g)}$ (2.5% H_2). The Zn target is then ready

for another irradiation. Natural Zn targets were disposed of and not used in subsequent production trials.

^{47}Sc

Scandium-47 has a half-life ($t_{1/2}$ = 3.3 days) and emissions (average β^- = 162 keV; γ = 159.4 keV, ~68%) that make it very attractive as a theranostic agent. Its production has been explored with fast neutron reactions on titanium (^{47}Ti and natural) targets [26], high energy proton reaction on ^{48}Ti [27-28], and a ^{47}Ca/^{47}Sc generator [29], but until recently little work has been conducted on photonuclear production from ^{48}Ti targets [30]. With this new attention and the added effort in developing a generator system for ^{47}Sc's diagnostic PET imaging radioisotope pair, ^{44}Sc [31], we have developed a facile ^{47}Sc-purification method from titanium dioxide (TiO_2) targets.

The first irradiation was performed in order to prepare an in-house spike for development of a purification method. A water cooled tungsten convertor was used to convert the incident electrons to photons. The convertor consisted of three tungsten disks 0.08" thick and spaced 0.04" apart. Two natural Ti foils (2" × 4" × 0.035" *99.7%*) and 10 g of natural TiO_2 (Sigma Aldrich, >99% A.C.S. grade, ~2" × 2" × 0.125") were irradiated using this target station (Fig. 4). The Ti foils were placed ~0.1875" and 0.625" away from the convertor. The foils were cooled with compressed air forced through a coil submerged in ice water. The TiO_2 was ~1.375" from the convertor and was pressed against a water-cooled plate. The foils and TiO_2 were wrapped in high-grade aluminium foil for containment.

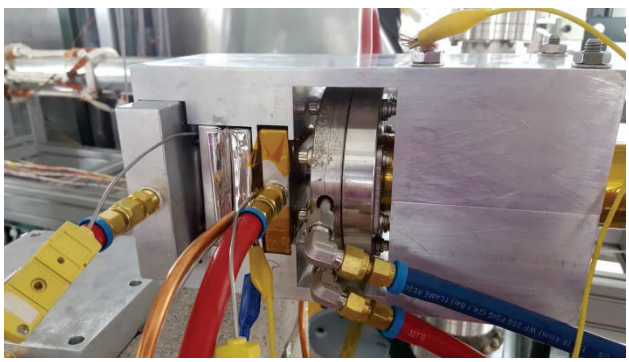

Figure 4: Clam shell target station with targets in place.

The three targets were irradiated with an electron-beam energy of 35 MeV at 2 kW. The beam was on target for three hours.

Post irradiation the samples were counted with a high purity germanium (HPGe) detector after retrieval the following day (Table 3). The titanium plates were scanned by a gamma scanner to verify the beam position and size. The beam spot was within 1 mm of the center of the targets. A small portion of the 10 g of TiO_2 (~0.5 g) was dissolved in fuming concentrated sulfuric acid (~75 mL H_2SO_4 per gram of TiO_2). An aliquot was taken and counted. Activities found in the liquid samples matched the data of the solid TiO_2 sample, within measured uncertainties. A 5 mL aliquot of the liquor was diluted with de-ionized water (18 MΩ) resulting in a stock solution. The stock was purified from the target material by extraction chromatography. In brief, the diluted stock solution was loaded directly onto the column. The column was washed with H_2SO_4 followed by HCl. The product was eluted with dilute HCl.

Table 3: Activities of Radioscandiums Produced

Isotope	Ti foil 1 (μCi)	Ti foil 2 (μCi)	TiO_2(μCi)
^{44}Sc	185.5	216.8	12.7
^{46}Sc	9.9	11.1	5.7
^{47}Sc	1313.3	1532.7	716.1
^{48}Sc	115.1	132.9	67.8

Greater than 98% of the titanium was found in the eluent and combined washes. Radioscandium was eluted from the column with >98% recovery in ten bed volumes of the strip solution. The strip was also analyzed by HPGe and inductively coupled plasma/mass spectrometery (ICP-MS). Expected radioscandiums, ^{24}Na, and ^{40}K were observed in the gamma spectrum of the strip solutions. The ICP-MS data demonstrated excellent purification of scandium with only environmental impurities (Na, B, Si, and Fe) present.

Titanium target material can be recycled by precipitation of titanium from alkaline solutions. The precipitated species can then be heated in a furnace below 600 °C under atmospheric conditions to reclaim TiO_2.

SUMMARY

Argonne has demonstrated photonuclear production of several in demand radioisotopes, ^{99}Mo, ^{67}Cu, and ^{47}Sc. Subcritical fission of a low-enriched uranyl (LEU) sulfate solution produced ^{99}Mo that met purity specifications and demonstrated >80% chemical yield. The product was shipped and passed all tests, fitting into the existing supply chain. Direct production of ^{99}Mo from enriched ^{100}Mo disks demonstrated high production yields and correlated well with theoretical calculations. Production and purification methods for both ^{67}Cu and ^{47}Sc have been developed. Methods for recycling of enriched materials have also been demonstrated.

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