CYCLOTRON PRODUCTION OF Tc-99m

Ken Buckley, TRIUMF, Vancouver, Canada

Abstract

Concern over past and impending shortages has led to renewed interest in the cyclotron production of Technetium-99m (Tc-99m) - the most used radionuclide in Nuclear Medicine. TRIUMF has led a collaboration to implement the irradiation of Molybdenum-100 (Mo-100) solid targets on cyclotrons previously used only for the production of PET radionuclides. Solid targetry and target transfer systems have been implemented on the GE Medical Systems PETtrace at two centres and the ACSI TRPET at one centre. Irradiations have occurred at 100 μA on the PETtrace and 230 μA on the TRPET. Progress continues towards the design goals of 130 μA and 300 μA respectively. Due to the presence of other molybdenum isotopes in the enriched Mo-100 target material the purity of the resulting technetium is affected by beam energy and irradiation time.

INTRODUCTION

The radioisotope Tc-99m is used in approximately 80% of nuclear medicine imaging procedures at a volume equivalent to approximately one scan per second worldwide [1]. Tc-99m with a half-life of 6 hours is also the decay product of molybdenum-99 which has a half-life of 66 hours. The Mo-99/Tc-99m generator was developed at Brookhaven National Laboratory in 1958 [2]. The generator consists of an alumina column loaded with molybdenum-99. As the Mo-99 decays the Tc-99m builds up on the column and can be eluted by simply rinsing the column with saline yielding Tc-99m in the form of pertechnetate. The development of the generator allowed the simple distribution of Tc-99m to a large geographic area. This easy availability, combined with the desirable decay characteristics of a 140 keV gamma ray and 6 hour half-life have led to the popularity of Tc-99m in clinical nuclear medicine.

Starting in 2009 the National Research Universal (NRU) reactor at Chalk River Laboratories in Ontario Canada was off line for 15 months. This reactor previously supplied 30 % of the world's supply of Mo-99 and is one of 5 that at the time supplied the world's demand for Mo-99. The coincident shutdown of the Petten reactor in the Netherlands resulted in a shortage of Tc-99m in nuclear medicine clinics around the world and raised concerns over the potential fragility of the supply. This concern, coupled to the use of weapons grade highly enriched uranium as the target material for the reactor production of Mo-99, resulted in an effort to develop alternative sources of Tc-99m. The Canadian government funded two consecutive programs through the federal agency Natural Resources Canada. TRIUMF has led a collaboration of four institutions through the Non-reactor Isotope Supply Program and the Isotope Technology Acceleration Program. The collaborators are the British Columbia Cancer (BCCA) Agency in Vancouver British Columbia, the Center for Probe Development and Commercialization (CPDC) in Hamilton Ontario, and the Lawson Health Research Institute (LHRI) in London Ontario. These facilities produce only PET isotopes which, almost exclusively, are produced by irradiating liquids and gases which are easily transported through sealed small diameter (eg. ≤ 3mm) piping. The target material, and produced radioisotopes, are always fully contained while in the cyclotron facility and thus do not typically pose a radioactive contamination hazard. As such the required radiation protection practices are significantly less onerous than those of a commercial production facility irradiating and transporting solid targets.

The feasibility of direct production of Tc-99m was first reported by Beaver & Hupf in 1971 employing the Mo-100(p,2n)Tc-99m reaction [3]. Low current irradiations with molybdenum of both natural isotopic abundance and enriched in mass 100 indicated sufficient production rates that compact commercial medical cyclotrons could supply a metropolitan area. Presumably due to the availability and low cost of Mo-99/Tc-99m generators there was little effort to develop molybdenum targets with high current capabilities, until Targholizadeh reported a thick molybdenum target produced by electrospray [4].

CYCLOTRON FACILITIES

The CPDC & LHRI have GE Medical Systems PETtrace 880 cyclotrons capable of delivering 130 μA of 16.5 MeV protons. The BCCA has an ACSI TRPET cyclotron capable of delivering 300 μA of 19 MeV protons. The intention of this project is to fully utilize the beam power of the cyclotrons.

PETtrace Cyclotron Description

The PETtrace 880 cyclotron is an H- machine with an internal PIG source and dual beam extraction probes allowing simultaneous irradiation of two targets. Targets are arranged on the periphery of the vacuum tank on individual beam ports. There are six ports identified as 1 through 6. One extraction probe serves target ports 1-3 while the other extraction probe serves ports 4-6. Each port has a set of beam collimators followed by a vacuum isolation valve and each port is electrically isolated allowing measurement of the beam current striking the target. The beam port diameter is 15 mm. Radiographs of irradiated target plates were performed according to the method of Avila-Rodriguez [5] to confirm the beam distribution.

The cyclotron vacuum is achieved by a single oil diffusion pump that affords a typical beam-on operating pressure of 1E-5 mbar.

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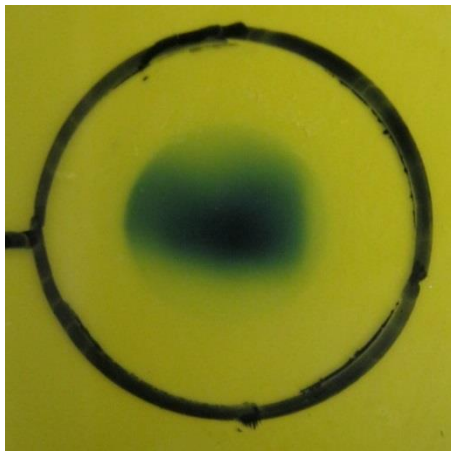

Figure 1: Photo of a radiograph made with Gafchromic EBT2 radiographic film. The tantalum plate radiographed was irradiated for one hour at 130 μA on the LHRI PETtrace. The beam shadow is collimated at 15mm dia.

The PETtrace is available with local shielding allowing installation without construction of a shielding vault. The PETtrace at LHRI is configured this way. The PETtrace at CPDC is installed in a vault.

TRPET Cyclotron Description

The ACSI TRPET cyclotron is a 19 MeV H- cyclotron with an external ion source and dual beam extraction probes. Beam is extracted out opposite sides of the cyclotron. At BCCA the cyclotron has been upgraded to 300 μA and is configured with a four port target selector mounted immediately on one side of the cyclotron. On the other side of the cyclotron the beam port is connected to a switching magnet allowing the beam to be directed to a 2 m long horizontal beam line terminated with another four port target selector, or directed to a downward sloping beam line terminated with a solid target station. Cyclotron vacuum is provided by a cryopump. The ion source and injection line are pumped by a turbo pump and cyropump respectively. The beamline is pumped by a turbopump. All systems operate at pressures on the order of 5E-7 Torr.

The solid target station was designed by our collaboration expressly for Tc-99m production. Local shielding of all target stations is provided. The local shielding of the solid target station was provided by DPace. All other components were provided by ACSI.

TARGET STATIONS

PETtrace Target Station

A target station was designed for the PETtrace that is mounted to target port 2. The target station accepts the target capsule (36 mm diameter by 54 mm long) delivered in the transfer tube and moves it horizontally over the beam port. Subsequently tubes delivering cooling water are inserted into the back of the target capsule pushing the capsule onto the flange of the beam port and forming a vacuum seal. The small volume between the target capsule and the beam port vacuum valve is not pumped separately but rather released into the cyclotron vacuum tank when the vacuum valve is opened. Due to the relative volumes of the vacuum tank and the beam port the cyclotron vacuum is only momentarily perturbed to 1E-3 mbar. Sensors on the target station indicate that the target capsule is in place on the beam port and that the cooling services are connected. The target control system then exhibits a signal to the cyclotron control system to indicate the beam port can be opened and the capsule irradiated. Similarly the cyclotron control system exhibits a signal to indicate the beam port valve is opened.

The concentric cooling tubes deliver water at 6-8 Lpm over the back of the target plate. Assuming the theoretical density of molybdenum, the water flow was calculated to limit the target temperature to ~300 C at maximum beam current. No attempts have been made to measure the actual target plate temperature during irradiation.

The target capsule itself contains the target plate, a small disk with the molybdenum-100 coating. Initial irradiations were conducted with an electrophoretically deposited coating thick enough to degrade the beam to 10 MeV where the cross-section for the production of Tc-99m drops near zero.[6] [7] These coatings have a density significantly less than theoretical and proved to have insufficient heat conduction, operating up to only 40 μA before showing signs of failure. Higher density coatings have now been produced and successfully irradiated up to 100 μA.

Figure 2: PETtrace target area on locally-shielded cyclotron. The Tc-99m production target is second from the bottom. The transfer tube is obscured by the target station and not visible in the photo.

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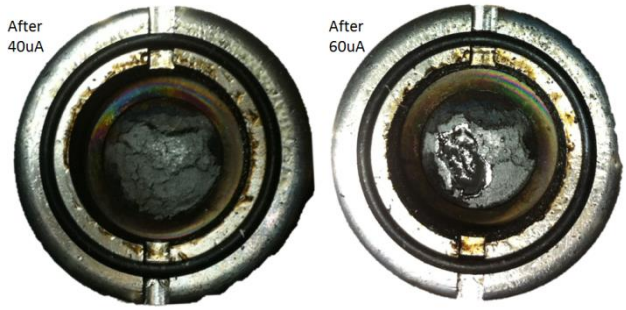

Figure 3: PETtrace target plates showing failure of the molybdenum coatings above 40 μA.

TRPET Target Station

The TRPET target station consists of a vacuum box containing a protection baffle followed by four beam collimators defining the beam size and position. A target flange accepts a target capsule that is rotated and locked into place by pneumatically actuated rollers engaging helical segments on the outside of the target capsule. The target flange provides the vacuum seal and water cooling service connections to the capsule. A roughing pump allows the vacuum envelope to be evacuated before opening a gate valve to the beamline. A nitrogen vent line allows the envelope to be brought to atmospheric pressure prior to removing the target capsule.

The TRPET beam shape is an ellipse approximately 10 mm tall by 20 mm wide. The target plate is held in the capsule at a 10 degree angle to the beam distributing the beam power over an ellipse of approximately 60 mm by 20 mm. Cooling water flow of 8 L/min was calculated to maintain the target plate at approximately 300 degrees C with 300 μA of 18 MeV protons incident, again assuming theoretical density of the molybdenum coating.

The target control system provides a signal to the cyclotron system to indicate the target is in place on the target station.

Radiographs were performed to adjust the collimator positions.

The target capsule (63 mm diameter and 165 mm long) is symmetric about the beam axis allowing the capsule to be engaged in one of two positions, 180 degrees apart. The temperature difference of the target plate was minimal between each direction of water flow. This feature greatly simplifies the alignment of the target capsule with the beam flange.

The molybdenum coating has been successfully irradiated at 230 μA at 18 MeV. The lower power density and thinner molybdenum coating required account for the better performance of the TRPET target over the PETtrace target even with the low density coating.

TRANSFER SYSTEM

The options for a solid target transfer system are either mechanical or pneumatic. We chose to go with a mechanical system in part because of the paradigm of operation of a typical PET cyclotron in which the irradiated material is always fully encapsulated and kept separated from the cyclotron vacuum envelope and laboratory environment. Conventionally a solid target is exposed to the vacuum envelope during irradiation and exposed to the laboratory environment at some point during the transfer from the target station to the processing hot cell. These conditions allow for the potential release of particulate matter that may be highly radioactive. In our view, a mechanical transport system was the least likely to cause widespread distribution of such material.

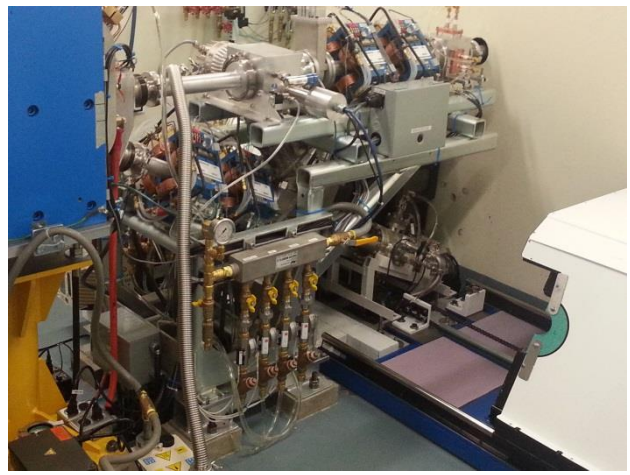

Figure 4: TRPET solid target station below the horizontal beamline and with the local shield open.

The target capsule transfer system is composed of a reel containing 20 m of spring steel tape with a cross-section of 2 x 3 mm. The tape is fed through a pair of rollers that clamp the tape when an air piston is actuated. One roller is driven by a variable speed electric motor to drive the tape forward. The tape drive unit is located in the hot cell and used to push the target capsule to the target station for irradiation and subsequently pull the capsule back after irradiation. To retract the tape the rollers are disengaged and the reel driven in reverse by the same variable speed motor. In this way we are able to push and pull the target capsule from one end and thus are able to enter the target space of the locally shielded PETtrace through the single available penetration. Additional drive force can be supplied to the spring steel tape at intermediate points along the transfer route by a “booster station”. The booster station again uses a pair of rollers that clamp the tape with one roller being driven. These rollers however need to remain open to a width equal to the transfer tube diameter until the capsule has passed, at which time they can be clamped on the tape and driven. We were concerned at first about the regulation of two motors driving the same tape but in practice using the same gearing and same drive voltage on the motors is sufficient as the system will self regulate with the motors sharing the load.

A 39 mm inside diameter flexible plastic duct is used for the transfer tube. The same transfer system is used for the TRPET target capsule with a 76 mm inside diameter tube.

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Transfer Routes

The hotcell at CPDC is located above the cyclotron vault with a transfer route approximately 12.5 m long, including the elevation change. The route has at least six bends, each of at least 90 degrees. The uncertainty in the number of bends arises from the routing of the conduit down through the cyclotron vault shielding wall. To minimize the neutron leakage through the conduit bank it was specified to provide a dog leg in the conduit however the exact details of the dog leg are not available. The uncertainty in the maximum bend angle arises because the conduit connects to the floor trench at an angle greater than 90 degrees so our transfer tube bends back on itself when making the transition from the hot cell service room trench into the downward conduit to the vault.

The hotcell and cyclotron at LHRI are on the same floor in adjacent rooms permitting a transfer route of approximately 10 m. The route has nine bends, six of which are ninety degrees, none are greater.

At BCCA the hotcell is located on the same floor directly in line with the target station and beamline so the transfer route is very simple with only one ninety degree bend and one 45 degree bend to accommodate elevation changes. The total length of the transfer route at BCCA is 6.5 m.

The theory of pushing a cable bundle through a bend in a conduit shows that the peak force is required immediately at the exit of the bend [8] and once the cable bundle has left the bend the force to move the bundle returns to within ~10% of the force to move the bundle prior to the bend. Due to the constraints of the target space on both the CPDC & LHRI cyclotrons the target station is located immediately at the exit of a ninety degree bend. This has made the transition from the transfer tube into the target station difficult to navigate as any slight misalignment of the transfer tube to the target station is hard to overcome as the force to push on the tape is limited by the buckling of the tape that occurs between the tape drive and the target station. The booster station works very well to mitigate this issue. In principle, any number of such booster stations could be utilized to accommodate an arbitrary transfer route.

DISSOLUTION

The dissolution of the molybdenum metal to recover the technetium takes place in the hot cell. In both the PETtrace and TRPET implementation the target capsule forms the dissolution chamber when the capsule is placed on a header. Dissolution of the molybdenum is carried out by the introduction of a warm 30% peroxide solution and proceeds to complete quantitative dissolution in less than 30 minutes. The solution is then basified by the addition of sodium hydroxide to yield a solution of sodium pertechnetate and sodium molybdate that can subsequently be separated by solid phase extraction with any one of a variety of commercially available resins using an automated chemistry module [9]. The sodium molybdate is not retained by the resin and can thus be reserved for recycling the enriched Mo-100. The key feature of the dissolution apparatus is the ability to handle the evolution of gas and vapour from the exothermic reactions of molybdenum oxidation and peroxide decomposition.

PRODUCTION METRICS

Molybdenum coatings have been made with two different enrichment profiles shown in Table 1. Batch 1 was obtained from Isoflex USA and Batch 2 from Trace Sciences International. While conventional wisdom would suggest that 99.01% Mo-100 would be better, the higher abundance of the molybdenum isotopes lighter than mass 98 lead to long lived technetium impurities that cannot be isolated from the Tc-99m. Due to the relationship of the reaction cross-sections as a function of beam energy, irradiations at higher energy produce proportionally more of these Tc impurities which in turn will contribute greater radiation dose to the patient the longer the irradiation or the longer the decay time from production [10]. Further experimental data is required to fully analyse the acceptable enrichment profile for a given beam energy and irradiation time.

Table 1: Isotopic Abundance of Molybdenum Used for Target Coating.

Isotope	Batch 1	Batch 2
Mo-100	99.01	97.39
Mo-98	0.55	2.58
Mo-97	0.08	0.01
Mo-96	0.11	0.005
Mo-95	0.10	0.005
Mo-94	0.06	0.005
Mo-92	0.09	0.005

Yield data is shown in Table 2 comparing our results to date with the theoretical calculations of Celler et al. [7] and the investigation of cross sections by Tárkányi et al. [11]

Table 2: Comparison of Saturated Production Rates

	PETtrace (GBq/μA)	TRPET (GBq/μA)
Celler	2.8 ± 0.3	3.8 ± 0.4
Tárkányi	3.4 ± 0.3	4.4 ± 0.4
Our Data	1.8 ± 0.2	3.5 ± 0.4

Maximum production to date is 350 GBq (9.4 Ci) after ~7 hours of irradiation on the TRPET at an average current of ~220 μA.

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CONCLUSION

Target stations, transfer systems, and target processing apparatus have been developed for 2 installations of PETtrace cyclotrons (locally-shielded and vaulted) and 1 installation of a TRPET cyclotron with a beamline. The PETtrace target stations have been demonstrated to accept 130 μA of beam current and molybdenum coated target plates have been demonstrated to accept 100 μA to date with plans to continue to 130 μA imminently. Measured production yields on the PETtrace indicate that *120 GBq (3.2* Ci) per 6 hour irradiation is feasible. The TRPET target station and molybdenum coated target plates have been demonstrated to accept 230 μA of beam current at 18 MeV. Measured yields indicate that *525 GBq (14.2* Ci) per 6 hour irradiation is feasible. Mo-100 is fully recovered for recycling.

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