A new approach for manufacturing and processing targets used to produce ^{99m}Tc with cyclotrons

L. Matei[1*], G. McRae[2], R. Galea[3], K. Moore[3], D. Niculae[4], L. Craciun[4], G. Surette[2], S.Langille[2], P. Keeping[2], C. St Louis[2], W. Gelbart[5], B. Abeysekera[6], R.R. Johnson[7]

[1]*Best Theratronics, 413 March Rd, Ottawa, ON, CANADA*
[2] *Carleton University, 1125 Colonel By Dr., Ottawa, ON, CANADA*
[3] *National Research Council, Ionizing Radiation Standards Group, 1200 Montreal Rd, Ottawa, ON, CANADA*
[4] *"Horia Hulubei" National Inst. for Physics and Nuclear Engineering, 30 Reactorului St. Magurele, IF, ROMANIA*
[5] *Advanced System Design, 5295 Bear Bay Rd, Garden Bay, BC, CANADA*
[6] *PharmaSpect, 4559 Grassmere St, Burnaby, BC, CANADA*
[7] *Best Cyclotron Systems Inc. (BCSI), 8765 Ash St., Vancouver, BC, CANADA*

Introduction

Alternative methods for producing the medical imaging isotope ^{99m}Tc are actively being developed around the world in anticipation of the imminent shutdown of the National Research Universal (NRU) reactor in Chalk River, Ontario, Canada and the high flux reactor (HFR) in Petten, Holland. Currently, these reactors produce up to 80% of the world supply through fission. The most promising alternative methods involve accelerators that focus Bremsstrahlung radiation or protons on metallic targets comprised of ^{100}Mo and a supporting material used to conduct heat away during irradiation. After irradiation, the targets must be processed quickly to separate and purify the ^{99m}Tc. This paper describes a new approach for manufacturing targets for the (p,2n) nuclear reaction on ^{100}Mo and the foundation for the subsequent commercial separation and purification of the ^{99m}Tc produced. This approach provides a direct route for radiopharmaceutical synthesis of ^{99m}Tc that can be incorporated into routine production in regional nuclear medicine facilities possessing medical cyclotrons.

The targets used to produce ^{99m}Tc are subject to a number of operational constraints. They must withstand the temperatures generated by high-power irradiation and be fashioned to accommodate temperature gradients from *in situ* cooling. The targets must be maintained below the volatilization temperatures of any molybdenum trioxide (MoO_3) or technetium oxides that may be generated because of oxygen ingress during the irradiation. The targets must be resilient, which means they cannot disintegrate during irradiation or post-processing, because of the radioactive nature of the products. Yet, the targets must be easily post-processed to separate the ^{99m}Tc. In addition, the method used to manufacture the targets must be reliable and

reproducible and not wasteful of the ^{100}Mo, because of its cost (~$2/mg). Any manufacturing process should be able to function remotely in a shielded facility to accommodate the possibility of radioactive recycled target feedstock.

The preferred supporting material for the targets is copper because of its high thermal conductivity and ease of machining. The challenge with metallic supports in general, and a copper support in particular, has been attaching the molybdenum in a reliable and reproducible way to produce targets that can meet the operation constraints.

There are a number of methods that have been proposed for large-scale target manufacturing including electrophoresis deposition, pressing and sintering, electroplating and carburization [1]. Developing methods for routine production of targets is an active area of industrial research [2, 3]. From the industrial perspective, plasma spraying showed promising results initially, but the process became very expensive requiring customized equipment in order to reduce losses because of overspray, which necessitated a large inventory of expensive feedstock [4].

The choice of support material constrains the post-irradiation processing to purify the ^{99m}Tc. Generally, the large amount of supporting metal complicates the chemical processes used to recover the small amount of ^{99m}Tc produced.

After irradiation, the ^{99m}Tc must ultimately be recovered as sodium pertechentate (Na^{99m}TcO$_4$) to fit with the current commercial radiopharmaceutical supply chain. This is most often accomplished by a series of separations based on differences in physical and chemical properties of the components. As an example, molybdenum and technetium have been separated by their different sublimation temperatures [5, 6, 7], and dry distillation has been used to separate ^{99m}Tc from neutron-irradiated MoO_3

*Corresponding author, E-mail: lidia.matei@teambest.com

[8]. The latter process was used to develop a Mo/Tc generator for MoO_3 targets irradiated with linear accelerators [8]. Dry distillation has become a standard procedure for separation of radioiodine from tellurium targets [9].

This paper describes the experimental validation of an industrial process for production of targets composed of a Mo layer and a copper support, and shows how the targets can be chemically processed post-irradiation to separate ^{99m}Tc from ^{100}Mo.

Material and Methods

Target manufacturing

Solid targets were manufactured by pressing molybdenum powder into copper (C10100, 99.997%, Thysenkrupp Materials, Finland) with forces sufficient to cause the powder to coalesce into metal layers with >95% theoretical density. The shape of the Mo layer was determined by the geometry of the pressing die. An illustration of the components used to press molybdenum targets is shown in FIG.1.

FIGURE 1. Assembly drawing of the pressing apparatus

Circular targets were manufactured with natural molybdenum (^{nat}Mo, 99.9%, 3-5µm, Alpha Aesar, USA) to test basic production parameters influencing reliability during irradiation and post-processing, including layer thickness and pressing pressures. Circular ^{100}Mo targets (99.03%, ISOFLEX, USA) were manufactured by pressing 200 mg of ^{100}Mo with a force of 350 kN into the central area (10 mm diameter) of a copper disk of diameter 24 mm and thickness 1.6 mm. The targets were irradiated with a cyclotron proton beam: normal incidence, 15 MeV at 50 µA. The backs of the targets were cooled with water flowing at 8 L/min.

Elliptical targets designed for large-scale production at high currents were made using the same manufacturing process, except the die was elliptical and the applied force was 400 kN.

Chemical processing

After irradiation, the targets were placed in a quartz tube (CanSci, Canada) (FIG. 2) that is similar to the tube used by Fonslet for the separation of radioiodine from TeO_2 targets [9].
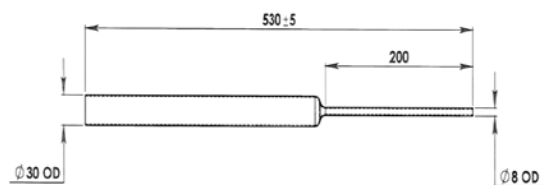

FIGURE 2. Drawing of the quartz tube designed to hold a 55 mm x 20 mm target.

The left end of the tube was connected to an oxygen supply flowing at 10 mL/min. The other end of the tube was partially sealed with quartz wool, but otherwise it was open to the atmosphere. The quartz tube was placed inside a horizontal tube furnace (model 55035A, Lindberg) and the first 23 cm heated to 850°C. The result was a temperature gradient along the tube from 850°C at the inlet to room temperature at the outlet.

The method used to separate and purify technetium relies at this stage on the different vapour pressures of Tc oxides and MoO_3 formed in the presence of oxygen at these elevated temperatures. Tc is oxidized to its anhydride ditechnetium heptoxide (Tc_2O_7, b.p. 319°C; m.p. 110.9°C):

$$4Tc + 7O_2 \rightarrow 2Tc_2O_7$$
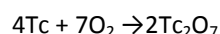
Under these conditions, Mo is completely oxidized to MoO_3, which sublimes at 750°C. The flowing oxygen oxidizes the Mo and Tc and carries the oxides to cooler regions of the quartz tube as described by Tachimory [7].

To simulate the separation process, a solution containing 70 MBq of ^{99m}Tc (Cardinal Health, Canada) as sodium pertechnetate ($Na^{99m}TcO_4$, >99% radiochemical purity) was placed on a Cu/Mo target and evaporated to dryness with a hot plate. The 'spiked' target was then introduced into the quartz tube.

The location of ^{99m}Tc along the length of the quartz tube was determined with a Geiger-Muller (GM) tube coupled to a computer controlled linear actuator (Velmex Unislide), which was used to measure radioactivity every 2 cm, as shown in FIG. 3. The quartz tube was positioned 25 mm from the collimator of the GM.

FIGURE 3. Apparatus used to measure activity with a Geiger Muller (GM) tube along the length of the quartz tube (QT) after Mo/Tc separation.

Subsequent experiments included a chemical pre-processing step to mitigate the chemical contamination from the relatively excessive copper. In these experiments, the target (191 mg ^{nat}Mo) was partially dissolved with 8 mL of 30% H_2O_2, which was then transferred to a ceramic boat where it was mixed with 70 MBq of Na^{99m}TcO$_4$ (Cardinal Health, Canada) and evaporated to dryness. The ceramic boat and its contents were placed in the quartz tube, which was heated and exposed to flowing oxygen as described above and, in a similar way, the Tc activity was determined along the length of the tube.

^{99m}Tc produced by irradiation of circular ^{100}Mo targets using a proton beam

Experiments were performed in which Tc was generated *in situ* by irradiating circular targets containing ^{100}Mo deposited on a copper support. The targets were irradiated for 1 hour with a proton beam of 15 MeV and 50 µA. The irradiated target was partially dissolved with 30% H_2O_2 and this 'raw' solution transferred to a quartz tube (5 cm diameter, 70 cm length) heated to 850°C in a tube furnace (STF 1200 Across International, USA). Oxygen flowed down the quartz tube at 40 mL/min for 30 min after which the quartz tube was allowed to cool before its length was scanned for ^{99m}Tc and ^{99}Mo with Radio Thin Layer Chromatography (RadioTLC) (Raytest, Germany). 'Purified' Na^{99m}TcO$_4$ was recovered by washing the section of the quartz tube showing highest levels of ^{99m}Tc with 1 M NaOH solution.

The isotopic compositions of the raw and purified solutions obtained after irradiation and processing of the target were determined from their gamma spectra measured with a High Purity Germanium detector (HPGe, Canberra) calibrated with a standard ^{152}Eu source. Point sources were prepared by spotting 37 MBq of solution in the center of a paper disk (Whatman 3 MM, diameter 25 mm). The radioactive point sources were positioned 43 cm from the detector and spectra acquired for 100 s to 300 s.

The Na^{99m}TcO$_4$ solution was assessed for radiochemical and chemical purity. The radiochemical purity of the purified Na^{99m}TcO$_4$ solution was assessed with RadioTLC using silica-impregnated fibreglass strips (2 cm x 100 cm iTLC-SG, Merck) as the stationary phase and acetone as the mobile phase. The presence of Mo in the Na^{99m}TcO$_4$ solution was determined with a colourimetric strip test (EM-Quant Mo test kit, Millipore). The presence of copper was determined qualitatively by adding a few drops of concentrated NH$_4$OH solution and checking for the formation of blue [Cu(H$_2$O)$_2$(NH$_3$)$_4$](OH)$_2$ (*Schweitzer reagent*).

Results and Discussion

Figure 4 shows a circular target before and after irradiation.

FIGURE 4. Circular ^{100}Mo target before (left) and after (right) irradiation for 1 h with 15 MeV protons at 50 µA

Before irradiation the targets were subjected to mechanical shock tests and thermal gradients with no observable effect.

After irradiation, 6.6 GBq (End of Bombardment (EOB) decay corrected) was measured at 140 KeV, which is characteristic of ^{99m}Tc. After irradiation there was no indication of any degradation of the target.

Elliptical targets suitable for high-volume production of ^{99m}Tc with high-power cyclotrons were manufactured (FIG 5). These targets are intended for irradiation in a general-purpose target holder designed to be attached to all makes of cyclotrons found in regional nuclear medicine facilities. The holder orients the target so that the proton beam angle of incidence is 75°. Figure 5 shows that the molybdenum on the front face in the center of the target is in the form of an ellipse (39 mm x 10 mm). During irradiation, the short axis of the ellipse will be at right angles to the beam; the projection of the molybdenum target on a plane perpendicular to the beam matches the circular Gaussian beam profile. The elliptical shape reduces the heat flux associated with high current sources. The molybdenum in the center of the elliptical target is fully dense with thickness 60 µm determined from SEM cross-sections. On the back of the target are cooling channels (FIG. 5).
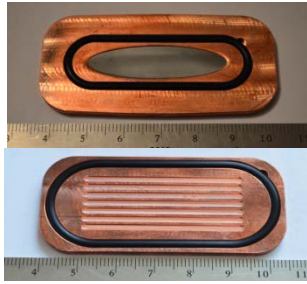
FIGURE 5. The top picture shows the front face of an elliptical Mo target. The bottom picture is of the back face showing the cooling channels.

The elliptical targets were designed for high-volume production of ^{99m}Tc with 15 MeV protons at 400 µA, 15% beam collimation, and cooling water flowing behind at 10 L/min [4]. A thermal simulation of expected temperatures during irradiation is shown in FIG. 6. The center of the target is expected to reach 260°C, which is below the temperatures at which any oxides inadvertently generated *in situ* could volatilize and contaminate the target holder and cyclotron.
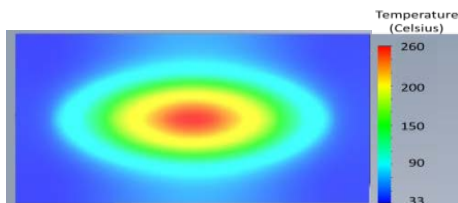

FIGURE 6. Simulation of the target temperature during proton irradiation: 15 MeV, 400 µA, cooling water flowing on the back side at 10L/min.

Like the circular targets, the elliptical targets were readily produced with minimal loss of molybdenum and were able to withstand mechanical shock and thermal gradients.

Chemical processing

The reaction of the target with oxygen at elevated temperature apparently results in mixed oxides of Cu, Mo and Tc. The oxidation of Cu involves two phases: partial oxidation forms Cu_2O (red) and total oxidation produces CuO (black) [10]. The formation of these two oxides is likely accompanied by the formation of mixed oxides including Mo and Tc, which would interfere with the formation of Tc_2O_7 and, thus, confound the separation process, which is optimized to condense Tc_2O_7 in the cooler regions of the quartz tube.

Figure 7 shows the state of the copper support after reaction with oxygen at elevated temperature. At least 60% of the radioactivity was found at the target insertion point or on the target, probably as $Cu(TcO_4)_2$ embedded in Cu_2O.
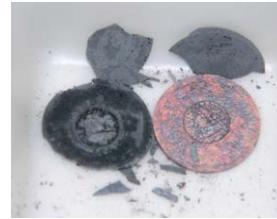

FIGURE 7. Copper target support after reaction with oxygen at 850°C following irradiation with 15 MeV protons at 50 µA. The black material flaked off of the copper support after oxidation; it is most likely CuO.

Other copper reaction products can complicate recycling of the non-transformed ^{100}Mo. CuO and MoO_3 can react to form $CuMoO_4$, which is a yellow-green crystal at 500-700°C [11].

The deleterious effect of copper on the thermal separation process can be appreciated when it is performed with reduced amounts of copper. When a pressed Mo pellet containing 5% Cu and 70 MBq of ^{99m}Tc was processed, 90% of the activity was recovered from the coolest part of the quartz tube. MoO_3 was deposited as yellow-white needle crystals in the 770°C region and black CuO was found at the insertion point of the quartz tube. When the amount of copper was reduced, the Mo/Tc thermal separation process produced good results.

The benefits of eliminating copper suggested a two-step oxidation process. In the first step, the target was immersed in 30% H_2O_2 to create insoluble copper oxides and soluble Mo peroxomolybdates, likely diperoxomolybdate [12], and soluble $HTcO_4$. The solution was decanted leaving the copper, and then evaporated leaving the Mo and Tc for further oxidation by oxygen gas at elevated temperature as per the thermal separation process.

The thermal separation process carried out after evaporation provided separation efficiency greater than 85%. MoO_3 deposited as yellow needle crystals at the appropriate place on the quartz tube, while the ^{99m}Tc oxide was carried to the coolest region of the tube. The ^{99m}Tc was washed from the tube with 0.1 M NaOH. Radio-TLC showed Tc as pertechnetate (TcO_4^-) (R_f=0.97) and a radiochemical purity of 95%. No traces of Cu or Mo were identified in the final product. Only a small amount of Cu was converted to CuO during the first oxidation step: 17.7 ppm of Cu^{2+} in the peroxide solution was detected with Atomic Absorption Spectrometry. Thus, the confounding effect of copper was

essentially eliminated with the two-step separation process

Radionuclides found after irradiation

The highest cross-sections for production of ^{99m}Tc by the (p, 2n) reaction on ^{100}Mo lie between 15 MeV and 10 MeV [13]. There are additional non-productive reactions that result in isotopes of Nb, Mo and Tc. The gamma spectrum shown in FIG. 8 of the raw solution obtained after dissolving the irradiated target in peroxide revealed photo-peaks corresponding to ^{99}Mo ($T_{1/2}$=66 h, E=181 keV, 739 keV) and ^{96}Nb ($T_{1/2}$=23.4 h; E =568 keV, 849 keV; 1091 keV, 1497 keV and 1200 keV). Photo-peaks corresponding to ^{62}Zn ($T_{1/2}$=9.1 h, E=596 keV, 548 KeV, 511 KeV) and ^{65}Zn ($T_{1/2}$=8.1 h, E=1115 keV, 511 KeV) were not detected.
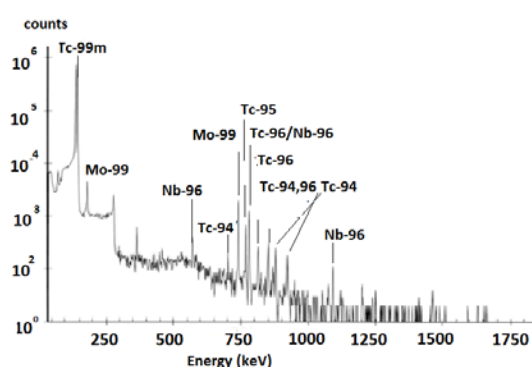

FIGURE 8. Gamma spectrum showing the isotopic composition of the raw solution obtained after dissolution of the irradiated target with peroxide (24 h EOB)

The molybdenum (Mo) and niobium (Nb) isotopes found in the raw solution were removed during the thermal separation process. After 30 min, MoO_3 was seen to deposit on the quartz tube walls as a white powder (FIG. 9) whilst technetium was recovered from the coolest region of the quartz tube in a similar manner to the procedure carried out for the experiments using Tc-spiked Mo.

The ceramic boat contained trace amounts of black copper oxide, but no activity, which indicated complete separation of Tc: radioactivity recovery was greater than 70% of the initial value.
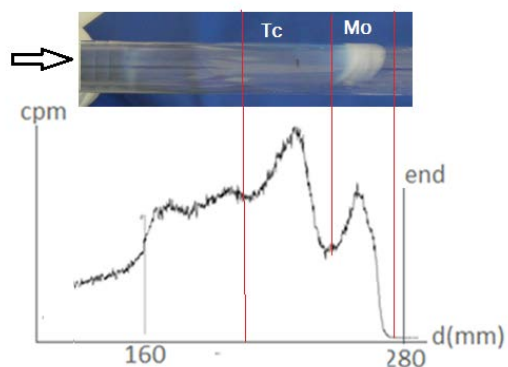

FIGURE 9. Radioactivity along the length of the quartz tube showing the physical separation of activated Mo and Tc isotopes. The arrow indicates the scanning direction from the cold outlet end of the quartz tube towards the sample insertion point. Any radioactivity in the other regions of the tube was below the detection limit.

Gamma spectrometry performed 8 h post-EOB on a sample of the purified solution containing 37 MBq indicated only the presence of technetium isotopes (FIG. 10).
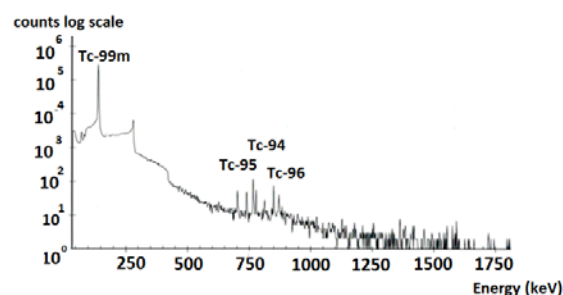

FIGURE 10. Gamma spectrum showing only Tc isotopes in the purified solution (8 h EOB).

Automated process for separation of Tc from irradiated Mo targets

The separation procedure described above is the foundation for an automated method for producing ^{99m}Tc in nuclear medicine imaging facilities. Automation reduces dose to operating personnel by eliminating manual handling of radioactive material. The method can be automated with three main components: a target dissolution unit, a thermal separation unit and a pharmaceutical purification unit (pharma unit).

After irradiation the target is transferred from the target holder pneumatically via a carrier 'rabbit' to the dissolution vessel within the dissolution unit (FIG. 11) where 30% H_2O_2 is added; dissolution takes 5-10 min.
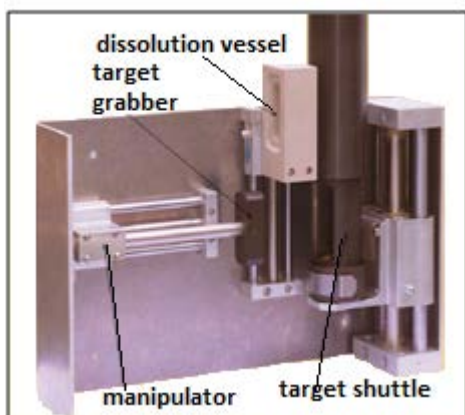
FIGURE 11. Target dissolution unit

The solution is then transferred to the quartz reaction vial in the thermal separation unit by suction through a port located on the top of the dissolution vessel. After completing the transfer, the water is evaporated in vacuum and collected in a waste collection vessel. The reaction vial is also connected to an oxygen gas line and a collection vial (FIG. 12).
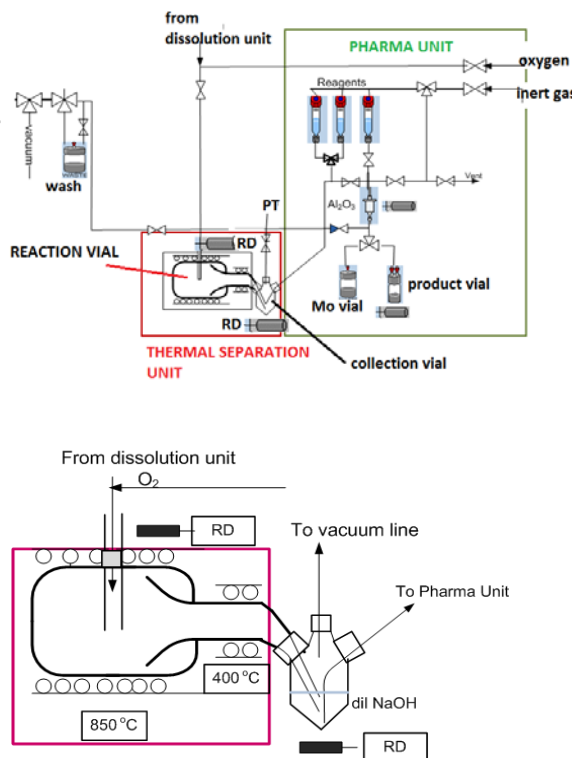

FIGURE 12. Flow diagram for automated separation of Tc from irradiated Mo targets (top). An expanded view of the thermal separation unit is shown in the lower diagram.

Oxygen is added to the reaction vial, which is enclosed within an insulated oven that is then raised to 850°C. This results in the production of Tc$_2$O$_7$. The reaction vial is equipped with a fun-

nel to direct the Tc$_2$O$_7$ to the inlet of the collection vial, which is maintained at a temperature above the volatilization temperature of Tc$_2$O$_7$ (310°C) to facilitate vapour transfer along the path. A small volume of dilute NaOH added to the collection vial forms sodium pertechnetate:

$$Tc_2O_7 + 2NaOH \rightarrow 2NaTcO_4 + H_2O$$
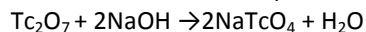
The sodium pertechnetate solution is subsequently transferred by suction to the pharma unit where it is loaded onto a small Alumina-N cartridge from which the purified product is eluted using saline solution.

The movement of the ^{99m}Tc can be followed with radioactivity detectors (RD) placed at strategic points in the thermal separation and pharma units. At the end of the process, ^{100}MoO$_3$ will be recovered as Na$_2$^{100}MoO$_4$ for recycling by washing the reaction vial with a solution of NaOH which is transferred to the Mo recovery vial. The system is fully automated through customized software for complete remote operation. The system is designed to fit in standard isotope production hot cells found in nuclear medicine imaging facilities.

Concluding Remarks

An industrial process is being developed and tested for production of ^{99m}Tc from molybdenum targets irradiated with protons from cyclotrons available to nuclear medicine imaging facilities. The targets were manufacturing by pressing Mo powder into thin metallic layers embedded into solid copper supports. No further processing of the targets was required to ensure the Mo layers remained attached to the copper substrate. The density of the Mo layers approached 100%. The targets were resilient. Before irradiation the targets were subjected to mechanical shock tests and thermal gradients with no observable effect. After irradiation there was no indication of any degradation. Twenty targets per hour could be reliably and consistently produced within design specifications with a molybdenum loss of less than 2%. In addition, post-processing after irradiation for 5 h with 15 MeV protons was shown to produce ^{99m}Tc. Elliptical targets suitable for high-volume production of ^{99m}Tc with high-power cyclotrons have also been manufactured using the same process. Like the circular targets, the elliptical targets were readily produced with minimal losses and withstood mechanical shock and thermal gradients. The elliptical targets were designed to withstand 6 kW generated by 15 MeV protons at 400 µA. Thus, the targets have been shown to meet the

required operation constraints for the intended industrial application.

Direct oxidation of irradiated targets was initially done in flowing oxygen at high temperature, however, this resulted in high levels of copper confounding the subsequent thermal separation. The copper was hypothesized to have formed chemical species with the Mo and Tc, such as $CuMoO_4$ and $Cu(TcO_4)_2$/$CuTcO_4$, which were not suited to the thermal separation designed to isolate Tc as Tc_2O_7.

The confounding effect of copper was overcome with a two-step oxidation process in which the irradiated target was first treated with a solution of hydrogen peroxide. The Mo and Tc are soluble in the peroxide solution, but the copper is not. The peroxide solution containing the Mo and Tc was then evaporated leaving the Mo and Tc for further oxidation by flowing oxygen at high temperature. This two-step oxidation process essentially eliminated Cu from the final products. Washing with NaOH at the end of the process resulted in ^{99m}Tc as $Na^{99m}TcO_4$, with recovery of radioactivity greater than 70%.

Radioactivity of 6.6 GBq was detected following the irradiation of a ^{100}Mo target with 15 MeV protons at 50 µA for 1 hour. The gamma spectroscopy performed on the raw solution obtained after dissolution revealed the presence of Tc isotopes together with ^{99}Mo and ^{96}Nb. No traces of Zn isotopes or Cu were detected in the purified product. Gamma spectroscopy showed that the final product, $Na^{99m}TcO_4$, contained only Tc isotopes. The process described in this paper can be automated with modules that easily fit in standard production hot cells found in nuclear medicine facilities.

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