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Development of medicine-intended isotope production technologies at Yerevan Physics Institute

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Abstract. Accelerator-based ^{99m}Tc and ^{123}I isotopes production technologies were created and developed at A.Alikhanyan National Science Laboratory (former Yerevan Physics Institute - YerPhI). The method involves the irradiation of natural molybdenum (for ^{99m}Tc production) and natural xenon (for ^{123}I production) using high-intensity bremsstrahlung photons from the electron beam of the LUE50 linear electron accelerator located at the YerPhI. We have developed and tested the extraction of ^{99m}Tc and ^{123}I from the irradiated natural MoO_3 and natural Xe, respectively. The production method has been developed and shown to be successful. The current activity is devoted to creation and development of the technology of direct production ^{99m}Tc on the ^{100}Mo as target materials using the proton beam from an IBA C18/18 cyclotron. The proton cyclotron C18/18 (producer – IBA, Belgium) was purchased and will be installed nearby AANL (YerPhI) till end 2014. The 18 MeV protons will be used to investigate accelerator-based schemes for the direct production of ^{99m}Tc. Main topics of studies will include experimental measurement of ^{99m}Tc production yield for different energies of protons, irradiation times, intensities, development of new methods of ^{99m}Tc extraction from irradiated materials, development of target preparation technology, development of target material recovery methods for multiple use and others.

1 Introduction

In the last decade many scientific centers are working hard to find alternative technologies of Mo/Tc production, in particular using charged particles accelerators [1-8]. There are a few small linear accelerators at A.Alikhanyan National Science Laboratory (the Yerevan Physics Institute) working for applied research, technology development and other areas. In particular the injector of ring accelerator is enough powerful linac with energy up to E_e=75 MeV [1]. It was used as a source of intensive electron beam for ^{99}Mo/^{99m}Tc and ^{123}I production technology development. The future plans are based on a C18 cyclotron which will be commissioned till the end of 2014.

2 ^{99}Mo/^{99m}Tc production

^{99m}Tc is the most widely used isotope in nuclear medicine today [2,3] with over 30 million diagnostic medical imaging scans every year around the world [4,5]. ^{99m}Tc decays to the ground state ^{99g}Tc with a half-life of 6 hours by emitting a 140 keV photon that is detected by imaging detectors. With the short half-life of ^{99m}Tc it is important that the production takes place within close proximity of the hospitals or clinics in which it will be used.

Fortunately, ^{99}Mo decays predominantly to ^{99m}Tc with a half-life of 66 hours as shown in Figure 1. Medical centers or commercial radiopharmaceutical distributors typically purchase ^{99}Mo/^{99m}Tc generators from which ^{99m}Tc (and as a by-product also ^{99g}Tc) can be extracted periodically in a simple chemical process as it accumulates from the decay of the ^{99}Mo parent. The ^{99m}Tc is then bound into the pharmaceuticals for use in the imaging procedure [4–7]. According to the Scientific Centre of Radiation Medicine and Burns at Armenian Ministry of Health, the need in Armenia for ^{99m}Tc isotope is approximately 5,000 doses per year. Presently, Armenia gets this isotope from abroad with a frequency of 1-2 generators ^{99}Mo/^{99m}Tc every 1–1.5 months. This is sufficient for 60–70 patients per generator or about 800 patients per year. Thus there is an urgent need for a constant and reliable supply of this ^{99m}Tc isotope. This

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work will alleviate part of the gap between the need or demand and the supply of ^{99m}Tc isotope in Armenia.
In the spring of 2009, the National Research Universal (NRU) reactor in Chalk River was shut down for more than a year for repairs related to heavy water leaks. This caused an unprecedented shortage of medical isotopes, most importantly ^{99m}Tc and prompted investigations on alternative methods of isotope production. One of the considered options was photonuclear reactions [8–11]. Metastable ^{99m}Tc could be obtained in photonuclear reactions by the irradiation of ^{100}Mo by an intense photon beam (see Figure 2).
This method, while successful, does not provide a sufficient specific activity to be used for mass production and therefore it not used by standard Mo/Tc generators. It could, however, meet the demand for local and regional city clinics.

2.1 Experimental layout for irradiation

The linear electron accelerator (LUE50) at YerPhI was designed, built, and used for many years as an injector for the Yerevan electron synchrotron [1]. The electron beam of that accelerator is converted to photons via bremsstrahlung. Several significant upgrades were needed to the machine in order to use it for ^{99m}Tc production. These included the electron gun and a new high intensity metallic cathode with slightly modified gun electrodes. The result was that the maximum beam intensity was increased from an initial 3 μA to 10 μA. An electron beam of E_e = 40 MeV was obtained using two of the three sections of the accelerator. The electron beam was transported to the target as a beam spot of 12 mm diameter (as measured by a vibrating wire scanner). The beam pulse length was ~1.1 μsec with a repetition frequency of f = 50 Hz.
A special experimental setup [12,13] shown in Figure 3 has been designed and mounted for material irradiation that provides remote controlled motion of the target module across the beam direction adjusting the center of the target to the beam axis. The target body module (Figure 4) was made of copper. A thick tantalum plate has been installed on the entrance window to convert the electron beam to photons. Beam intensity was measured by the Faraday cup (No. 1 in Figure.3). At an electron beam energy of E_e = 40 MeV, and a beam current I_e ~ 10 μA, the total beam power is P = 400 W. The target module and Faraday cup were cooled by water and air. To avoid charge leakage from the Faraday cup, only pure distilled water (with high specific resistance 0.2 MOhm·cm) was used in the cooling system. The data acquisition and visualization of irradiation parameters were done via LabVIEW.
The oxide of natural molybdenum MoO_3 was used for the irradiation. The abundance of the stable isotope, ^{100}Mo / ^{nat}Mo is 9.63%.

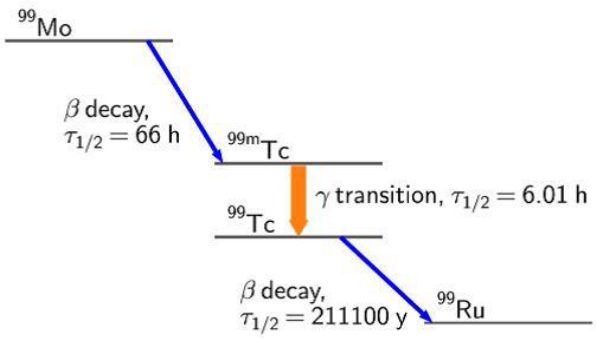

Figure1. The decay scheme ^{99}Mo into ^{99m}Tc [7].

$$\gamma + {}^{100}\mathrm{Mo} \rightarrow {}^{99}\mathrm{Mo} + \mathrm{n} \quad \text{Threshold} = 9.1\ \text{MeV}$$

$$\downarrow$$

$$T_{1/2} \sim 66\ \text{hours} \rightarrow {}^{99m}\mathrm{Tc}\ (T_{1/2} \sim 6\ \text{hours})$$

Figure 2. The ^{99m}Tc production chain on ^{100}Mo target.

The irradiated material was packed in a special aluminum capsule (Figure 5) by pressed powder covered by thin copper foil.

2.2 Investigation of specific activity

One of the main parameters for the production of radioisotopes is the resulting specific activity normalized to the mass of the main isotope (^{100}Mo in our case), the beam current, and the duration of irradiation – Bq/mg·μA·h. The data available for the specific activity of ^{99}Mo published by different experimental groups have a very large variance (90 to 3200 Bq/mg·μA·h [9]).

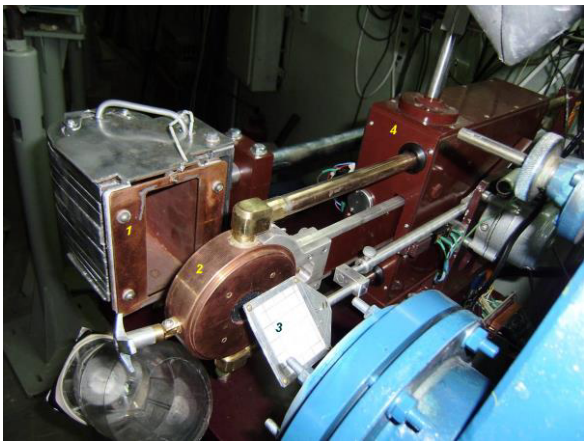

Figure 3. Experimental setup: 1 - Faraday cup, 2 - moveable target module, 3 luminofore for the beam spot size and position along with video TV control and 4 target module moving system.

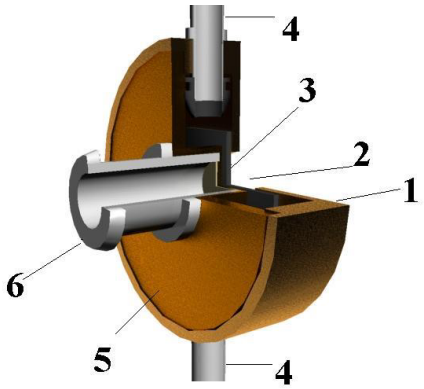

Figure 4. The body of the target module with identified components: 1 is the framework, 2 is the beam entrance window, 3 indicates the tantalum plate, 4 is the water cooling pipe, 5 is cup, and 6 is the target capsule (shown in greater detail in Figure 5).

Figure 5. Target capsule with full amount (18 g) pressed powder of MoO_3.

The irradiation was done with a beam current of Ie = 5.5 μA for 5 hours. The energy spectrum from the irradiated material measured by the NaI(Tl) detector is shown in Figure 6. The spectrum was fit by a Gaussian, the mean value of the Gaussian function is Eγ ~ 140 keV. Two peaks are seen with energies E ~ 140 keV from ^{99m}Tc and E ~ 180 keV from ^{99}Mo.
The normalized specific activity calculated from the measurements reflected in this spectrum was

$$Y \approx 3000 \text{ Bq/mg}\cdot\mu\text{A}\cdot\text{h}$$

which is close to the maximum value of the published range of results [10].

2.3 Trial production of ^{99m}Tc

For the low specific activity case the only reasonable option is the direct extraction of ^{99m}Tc from the irradiated material. For that, a centrifuge extractor based on methyl ethyl ketone (MEK) solvent technology was chosen. The irradiated target is dissolved in KOH alkali, and then MEK liquid is added to that solution. The MoO_3 dissolves in KOH while ^{99m}Tc dissolves in MEK so that we have mixture of two solutions with very different densities.

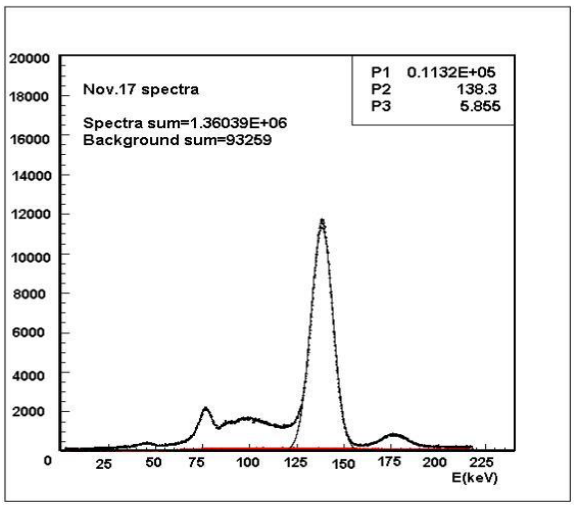

Figure 6. The energy spectrum from the irradiation of the MoO_3 measured with a NaI(Tl) detector.

The centrifuge extractor was designed at the A.N. Frumkin Institute of Physical Chemistry and Electrochemistry in Moscow [14] and allows the separation of the two elements with high purity, followed by the separation of the ^{99m}Tc from MEK by evaporation. The complete automated system, developed by "Federal Center of Nuclear Medicine Projects Design and Development" of Federal Medical – Biological Agency of Russia (FMBA), was commissioned and installed in a "hot" cell shown in Figure 7.
The natural MoO_3 is a powder with an absolute density 4.96 g/cm^3. After pressing, its volume density became ~2.4 g/cm^3. A natural MoO_3 target with a mass of 20 g and areal density ~8 g/cm^2 has been irradiated under electron beam with energy E_e = 40 MeV and average current of I_e ~ 9.5 μA for a duration of T = 100 hours.

Figure 7. The main part of the centrifuge extractor complex.

The irradiated material was then processed by the centrifuge extractor and the first trial amount of ^{99m}Tc has been produced. The decay correction to the EOB (end of bombardment) yielded ~ 2.96·10^9 Bq (80 mCi).
The efficiency of extraction is ~95%, according to the specification of the centrifuge.

3 ^{123}I production

The ^{123}I isotope [15] is short-lived and radiates only γ-rays and X-rays, which decrease the absorbed dosage of radiation patients by approximately 100 times. Production of ^{123}I isotope now is based on hundreds MeV proton linear accelerators and tens of MeV cyclotron beams of protons, deuterons, ^{3}He, and ^{4}He.

The most pure isotope of ^{123}I is produced in the following reaction:

$\gamma + {}^{124}Xe \rightarrow {}^{123}Xe+n$, threshold = 8.3 MeV

$\downarrow$

$T_{1/2} = 2.2$ hours $\quad {}^{123}Xe \rightarrow {}^{123}I$ ($T_{1/2}$ =13.3 hours)

The Xe target has been irradiated under Ee=40 MeV and I_e~9μA electron beam. The following parameters have been achieved:

- Amount of natural Xe gas - ~40 g
- Xe pressure in the stainless steel cylinder - ~200 bar
- Beam energy – 40 MeV
- Beam current - ~9 μA
- Duration of irradiation – 12 hours.
- Target temperature – 20^{o} C max
- Target pressure was increased during irradiation – up to 250 bars.

The Xe target has been removed from beam position a day after irradiation finished. Then all chemical procedures of ^{123}I extraction have been done.

The same parameter as has been mentioned in 2.2 has been investigated namely the total activity after irradiation normalized to the amount of target material (for pure ^{124}Xe), beam current and exposition time - duration of irradiation.

Taking into account that concentration of ^{124}Xe in the natural Xe is only 0.96% and the mass of irradiated gas was only 40 gram – the real mass of irradiated ^{124}Xe was only 40 mg, therefore this parameter for the current irradiation was

$$Y=143\text{Bq/mg}\cdot\mu\text{A}\cdot\text{h}$$

4 ^{99m}Tc direct production under proton beam from cyclotron

For proton beam energies close to 25 MeV ^{99m}Tc can be produced directly via the reaction ^{100}Mo(p,2n)^{99m}Tc [16]. ^{99}Mo can also be produced via ^{100}Mo(p,pn)^{99}Mo, but as will be shown later, the ^{99}Mo decays provide only a small additional contribution to ^{99m}Tc production.

In general the focus is on the direct production of ^{99m}Tc from proton bombardment of enriched molybdenum although other accelerator based technologies are feasible. Usable quantities of ^{99m}Tc can be produced by the ^{100}Mo(p,2n)^{99m}Tc reaction which has a peak in the cross-section at 15-16 MeV, well within the range of many commercial medical cyclotrons. With 150 μA on target using 19 MeV protons for 6 hours, up to 9 Ci (333 GBq) of ^{99m}Tc can be produced 2 to 3 times per day, which is enough to supply a large megalopolis. Higher yields can be reached with higher energy cyclotrons and/or with a more intense beam current. The cross-sections of ^{100}Mo(p,2n)^{99m}Tc reaction is presented on Figure 8[16].

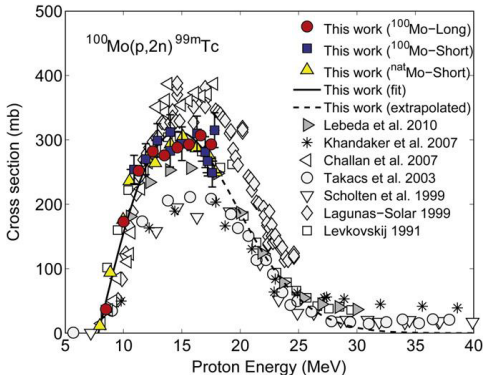

Figure 8. The cross-sections of ^{100}Mo(p,2n)^{99m}Tc reactions.

All above presented results are for metallic molybdenum target. The advantages for that option are high thermal conductivity of metallic plate of target and easy cooling of target during irradiation under high intensity proton beam. The disadvantage of that option is the not high enough efficiency of metallic enriched ^{100}Mo target recovery which creates commercial difficulties due to the very high cost of enriched ^{100}Mo.

The well known and frequently reported technology of Mo powder target preparation is based on following requirements to the target pellets:

- enough strength to be saved during installation under beam, removing and transporting to chemical processing area;
- high thermal conductivity to extract thermal energy to basement plate for cooling.

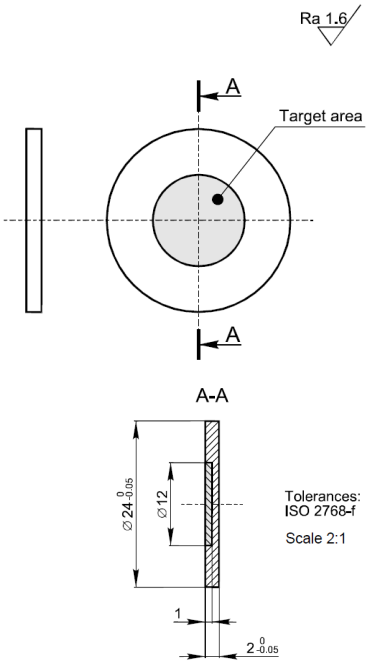

Figure 9. Solid target disc.

The installation disc for solid target with a space for irradiating material is shown in Figure 9. We suggested a new method of Mo pellet preparation. As a material a natural Mo powder was used with granularity 1-20 μm. First of all it is simply pressed under ~0.7 N/m^2 (F=~1000 kg) producing a pellet with diameter ~12 mm and mass ~600 mg (see Figure 10). Then one side of that pellet was processed under laser beam (see Figure 11).
The grooves due to melted Mo powder are working like metallic fixtures in concrete providing enough high mechanical strength and thermal conductivity.

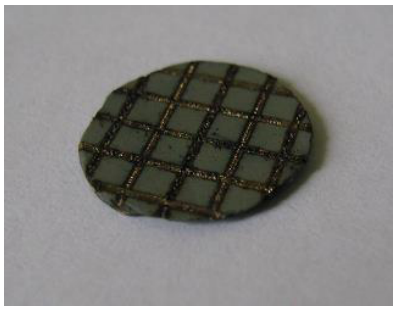

Figure 10. The target pellet processed by laser beam.

Figure 11. The target disc with pressed Mo powder after processing by laser beam (left), zoomed (right).

Conclusion

AANL (YerPhI) started the activity of isotopes production technology just a few years ago in general using present linear electron accelerator. During last years the technologies of 2 types of isotopes were investigated, positive results were achieved. Results were reported in international conferences and published. A new C18/18 cyclotron will be commissioned during December 2014 which we will use also for the master and development of ^{99m}Tc direct production technology – with a target of real production and covering the demand of Armenian clinics.
Implementation of the method which we will develop for ^{99m}Tc direct production could provide enough activity covering the entire demand for ^{99m}Tc in Armenian clinics. Those studies are in line with the goals of Coordinated Research Project (CRP) "Accelerator-based Alternatives to Non-HEU production of Mo-99/Tc-99m" sponsored by the IAEA.

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