REPORT

on the

2nd Research Coordination Meeting

on

“Accelerator-based Alternatives to Non-HEU Production of $^{99}\text{Mo}/^{99}\text{mTc}$”

7-11 October 2013
Legnaro, Italy
1. INTRODUCTION

Due to the widespread availability of $^{99m}$-Technetium ($^{99m}$Tc) generators supplied from fission production of $^{99}$Molybdenum ($^{99}$Mo), alternative sources of supply such as the production of technetium radioisotopes directly from conventional medical cyclotrons has long been neglected. Given the shortage of $^{99}$Mo caused by the unexpected prolonged shutdown of the Chalk River and Petten reactors, and the permanent cessation of $^{99}$Mo production at Chalk River in 2016, the need to explore alternative methods of producing technetium radioisotopes has gained significant interest. This would allow continued use of all existing radiopharmaceuticals designed for $^{99m}$Tc in nuclear medicine in case of another shortage. By taking advantage of this alternative, we would not need to reinvent 50 years of radiopharmaceutical development.

There are several potential methods for the production of $^{99m}$Tc from accelerators. These have been explored in a recent publication "The Supply of Medical Radioisotopes: Review of Potential Molybdenum-99/Technetium-99m Production Technologies" produced by the Nuclear Energy Agency in 2010. In that publication, it was noted that the direct cyclotron production of $^{99m}$Tc is a recommended short term solution. It was noted by the expert panel assembled to assess this CRP that the direct production may also be a longer term solution and is quite sufficient to manufacture $^{99m}$Tc on-site for supplying regional radiopharmacies and may supplement, or in some instances, even replace $^{99}$Mo generators.

In this CRP, the focus will be 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 reach of many commercial cyclotrons. For example, a higher current cyclotron has been used to produce 350 GBq (>9 Ci) of $^{99m}$Tc which could supply a large metropolitan area (18 MeV protons, 250µA, 6 hour irradiation). Higher yields can be reached with higher energy cyclotrons and/or with a more intense beam current.

However, there are several considerations which may play into the practicality of this production method. The six hour half-life of the $^{99m}$Tc is a factor which constrains the time (and therefore the distance) from production to use. The distribution model and the ability to make use of existing distribution networks will influence the practicality. A local distribution model would include a small accelerator and lower power target and producing only enough for the local vicinity, whereas a regional or national distribution model would include a larger accelerator and higher power targets distributing the $^{99m}$Tc more widely. There are other implications to these models such as delivery schedules and the influence of irradiation parameters on isotopically enriched molybdenum supply and recovery. Another aspect to the practicality is the cost per MBq of accelerator produced $^{99m}$Tc when compared to the current price of the generator produced material. Although an exact estimate is probably not possible at this time, rough estimates put the price per MBq at about the same level as the generator produced material although this will depend again on the distribution model chosen and whether existing cyclotron facilities can use the time when the cyclotron is not occupied with other radionuclide production for the production of $^{99m}$Tc. $^{100}$Mo is a naturally occurring isotope of molybdenum and is sold by a commercial isotope supplier (greater than 99% enrichment).

Outstanding Issues:

Patient dose and specific activity: there is an impact on the purity of the final $^{99m}$Tc product both from the isotopic impurities of the enriched molybdenum starting material and the incident proton energy.

Regulatory: there are several approaches to isolating and purifying the $^{99m}$Tc extracted from the target material. A more complete understanding regarding reproducibility, purity and efficiency for these approaches is needed using prescribed metrics for direct inter-laboratory comparisons.
The stability of the isolated $^{99m}$Tc pertechnetate solution as a function of time and the stability of the prepared radiopharmaceutical will affect the shelf life of the product and must be assessed.

The impact of specific activity ($^{99m}$Tc/all Tc isotopes including $^{99g}$Tc) has to be determined in order to define the shelf-life of the accelerator produced $^{99m}$Tc in comparison to generator produced $^{99m}$Tc in the formulation of radiopharmaceutical kits.

The path to recovery of the enriched $^{100}$Mo target material should be optimized and involves tracking the isotopic composition and chemical/radionuclidic impurities in order to determine recycling protocols.

2. ACHIEVEMENTS

Publications resulting from work accomplished during this period of the CRP can be found in the individual country reports.

Production

The feasibility of accelerator production of $^{99m}$Tc based on the $^{100}$Mo(p,2n)$^{99m}$Tc reaction was studied including production of all possible Tc contaminants by using theoretical yield calculations for the reactions energetically allowed.

Achievements and new knowledge obtained in this area were:

- The list of the reactions involved in accelerator production of $^{99m}$Tc up to 30 MeV proton energy on enriched $^{100}$Mo target was determined.
- Cross section data of all the reaction routes relevant to the accelerator Tc production up to 30 MeV were collected. In addition to experimental data, results of nuclear model codes are used.
- The trends of production yields, number of produced nuclides, relative activity and relative physical radiation doses (assuming all energy is absorbed) were determined.
- New experiments were performed to determine the excitation function of the two main reactions $^{100}$Mo(p,2n)$^{99m}$Tc and $^{100}$Mo(p,x)$^{99}$Mo.
- Production yields were also measured using different experimental conditions and were compared with predicted values.
- Experimental cross section data were analyzed and averaged fit values were calculated for the two main reactions from the selected datasets.
- A comparison of theoretical results of EMPIRE calculation code, MENDL-2p and TENDL-2012 data library was conducted. After a comparison of the available experimental results to theoretical predictions, data from the TENDL library were selected for use in the calculation.
- Results provided by the reaction network calculation were analyzed and final conclusions were deduced regarding production conditions and quality of the $^{99m}$Tc.
- A reaction network calculation tool was developed to predict the achievable yields of the main product and to study the amount of contaminating Tc radionuclides based on the selected experimental and theoretical cross section data.
- High $^{100}$Mo enrichment levels are required for good quality-level production of accelerator $^{99m}$Tc. However, other $^{97}$Tc contaminants arise from (p,xn) reactions on the other $^{99}$Mo isotopes and thus it is the absolute amounts of the other Mo isotopes which are important rather than overall $^{100}$Mo content.
- The other technetium isotopes produced in addition to $^{99m}$Tc has an impact on both dosimetry and specific activity aspects.

Target Preparation

Target systems for a number of different cyclotrons have been developed and tested. Target designs for various 15-30 MeV cyclotrons were discussed. Test irradiations have been completed for both enriched and natural Mo-metallic, oxide and carbide mounted on various backing materials.
Several ways of preparing Mo targets for Tc production using the $^{100}$Mo(p,2n)$^{99m}$Tc reaction were reported. Target plate manufacturing methods centred on four approaches: i) Attempts to electroplate Mo metal under aqueous conditions, ii) press and sintering, iii) electrophoretic deposition and iv) carburization.

Aqueous electroplating was largely found to give inadequate coatings which were too thin or non-adherent or contained Mo-oxides that were unsuitable for further development as a stand-alone method for target preparation.

Successful irradiations have been performed at some level using press and sinter, electrophoretic deposition and pressed powder target (metal, oxides or carbides) techniques. Maximum beam currents and heat transfer capabilities of these targets are under investigation.

The self-supporting targets ranged in thickness from 500-2000 µm have been produced by pressing $^{100}$Mo powder using molds allowing simultaneous air removal during pressing process. The ~100 µm $^{99m}$Mo targets in a metallic form on copper backing were prepared by sputtering (magnetron) technique. No stress at micro-structure level has been observed. Additionally, two non-solid target approaches were discussed, with preliminary results on the irradiation of solutions of Na$_2$MoO$_4$ and direct irradiation of Mo-oxide.

Liquid targets composed of dissolved sodium molybdate (Na$_2$MoO$_4$·2H$_2$O) in deionized water were reported. A target vessel was made of niobium with a Havar window.

Direct powder irradiation by placing material in a specially designed ceramic vessel was proposed for cyclotrons with vertical beam lines. The vessel design allows target material dissolution after irradiation and transfer of the dissolved target material. Targets can be produced either from the metallic powder or from the aqueous $^{100}$MoO$_3$ solution which is dried directly in the vessel before irradiation.

**Chemical Isolation**

Various physico-chemical separation methods have been reported. Since different target materials (e.g. Mo metal, MoO$_3$, Mo$_2$C and sodium molybdate solution etc.) were used for irradiation by different groups, it was necessary to follow different separation methods. Many separation methods were tried where Mo content and/or $^{99m}$Tc activity was lower than the typical production run.

Traditional MEK solvent extraction method has been tried in combination of a purification column (alumina/ activated SiO$_2$) with more than 90% recovery in about 30 min. Various types of ion exchange resin have been reported in combination with a purification column. Different ion exchange resins were used, including Dowex-1, PEG coated C-18 SPE cartridge, TEVA resin, OASIS HLB Plus- PEG-2000 and AnaLig® Tc-02 resins. Other resins are being tested for separation properties. For purification, simple alumina, activated SiO$_2$, SepPak alumina and Dowex-1 columns have been utilized by various groups in order to remove traces of Mo, which might come from the primary column. 80% to more than 90% recovery has been reported in 30 min to less than 1h. GBq (Ci) amounts of $^{99m}$Tc have been recovered from the irradiated target by the PEG coated polystyrene columns. Column chromatography was also used to separate Tc produced in liquid targets and was found to separate all contaminates including $^{22}$Na.

A thermochromatographic method has been successfully demonstrated with 97% separation yield in 45 minutes total. This method also includes a “clean-up” step with a C18 cartridge.

It has also been demonstrated that it is possible to have a primary separation of Mo and Tc isotopes with precipitation of Mo as MoO$_3$ hydrate or ammonium phosphomolybdate, the latter having better efficiency. It has been suggested that following the primary separation, further purification of the
supernatant (containing TcO$_4^-$ and traces of Mo) can be effected to remove the traces of Mo from the bulk of TcO$_4^-$ by ABEC resin, HDEHP or ZrO$_2$ column.

**Radiation Dosimetry and assessment of radionuclidic impurities**

Studies were conducted in order to determine the radiation dosimetry of cyclotron produced $^{99m}$Tc and ultimately the impact of radionuclidic impurities on patient dose:

- a tool was developed to predict the level of radionuclidic impurities based on $^{100}$Mo composition and irradiation conditions
- a set of experiments were performed to measure the impurities produced by proton irradiation of highly enriched $^{95}$Mo, $^{96}$Mo, $^{97}$Mo, $^{98}$Mo and $^{100}$Mo.

Enriched molybdenum targets of $^{95}$Mo, $^{96}$Mo, $^{97}$Mo, $^{98}$Mo and $^{100}$Mo were bombarded with a range of proton energies from 10 to 24 MeV. The thick target yields of $^{94}$Tc, $^{94m}$Tc, $^{95}$Tc, $^{95m}$Tc, $^{96m}$Tc and $^{97}$Tc were derived from their activities measured by γ spectroscopy using a high purity Ge detector and corresponded well with recently published values.

Presence of the long lived Tc isotopes such as $^{99g}$Tc, $^{98}$Tc and $^{97g}$Tc are essentially only important regarding the achievable specific activity (SA), while the shorter lived Tc contaminants can also contribute to the patient dose in addition to SA. Due to the decay characteristics of the contaminating technetium radionuclides, half-lives, type and energy of the emitted radiations, the $^{93g}$Tc, $^{94m}$Tc, $^{94g}$Tc, $^{95m}$Tc, $^{95g}$Tc, $^{96m}$Tc and $^{96g}$Tc could give rise to most of the additional patient dose. Selecting a bombarding proton energy lower than 25 MeV, the contaminating Tc isotopes can be produced in (p,n), (p,2n) and (p,3n) reactions on different stable Mo targets. To minimize the amount of the shorter lived contaminating Tc isotopes the composition of the enriched target material should be chosen carefully. Preferably the amount of $^{94}$Mo, $^{95}$Mo and $^{96}$Mo should be kept below 0.005% if possible. In that case the additional physical dose can be kept below 1%. The actual value also depends on the bombarding energy, target thickness, irradiation and cooling time.

This data demonstrates that cyclotron production of $^{99m}$Tc, using highly enriched $^{100}$Mo targets and 15–24 MeV incident proton energy, will result in a product of acceptable radionuclidic purity for applications in nuclear medicine. It was determined that at >20 MeV proton energy, more care must be taken regarding the contribution from other Mo impurities by specifying enrichment requirements.

**Translational achievements: Pre-clinical and clinical trials**

Studies were conducted assessing the image quality of cyclotron produced Tc using phantoms, small animal studies and preliminary human trials.

Quality control procedures were developed for cyclotron produced Tc based on existing generator produced Tc.

Bio-distribution studies of cyclotron-produced $^{99m}$Tc labelled radiopharmaceuticals were conducted. The uptake kinetics and bio-distribution patterns of the cyclotron- and $^{99}$Mo/$^{99m}$Tc generator-produced $^{99m}$Tc radiopharmaceuticals, were compared in various animal models. Matching images and identical biodistribution patterns in animals confirmed that cyclotron- and generator-produced $^{99m}$Tc radiopharmaceuticals were biologically equivalent. Different radiopharmaceuticals were tested including: $^{99m}$Tc-pertechnetate, $^{99m}$Tc-MDP, and $^{99m}$Tc-MIBI.

Formal clinical trial evaluations were performed using cyclotron produced $^{99m}$Tc. The CTA, “A Prospective Phase I Study of Cyclotron-Produced $^{99m}$Tc Pertechnetate (CPERT) in Patients with Thyroid Cancer” was approved by Health Canada (September 2011). Whole body [$^{99m}$Tc]-pertechnetate imaging was performed using modified SNM procedure guidelines. This study is
completed and demonstrated the safety of CPERT and confirmed an equivalent general biodistribution pattern of CPERT with reactor-based \([^{99m}\text{Tc}]\)-pertechnetate.

**Recycling**

For most solid target recycling, the waste solution containing \(^{100}\text{Mo}\) in NaOH and radioactive impurities was left to decay prior to reprocessing. The recovered solution was purified by ion exchange chromatography. The eluate containing ‘molybic acids’ was evaporated to dryness, and the resulting molybdenum trioxide reduced to molybdenum metal.

Additionally the Mo target material separated by several methods may be recovered via precipitation as ammonium poly molybdate phosphate. This precipitation method avoids the need for column purification. By heating this material the Mo-oxide is formed. Recoveries of >90% can be obtained using this method.

For \(\text{MoO}_3\) and \(\text{Mo}_2\text{C}\) targets, the final Mo form (typically \(\text{MoO}_3\)) is usable for the preparation of new targets for irradiation with typical “lifecycle” efficiencies of >85%.

For liquid or salt targets which are dissolved post irradiation, the molybdenum is recovered at the end of processing in \(\text{NH}_4\text{OH}\). This solution was analyzed by gamma spectrometry to determine the efficiency of enriched molybdenum recovery which was >90%.

### 3. WORKPLAN

**Current Progress and Plans for the second phase of the CRP**

The participants agreed to the following work plan concerning \(^{99m}\text{Tc}\) for the second half of this CRP is divided in several subjects as described below. The overlapping and participation between the individual countries is described in the table below:

<table>
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<tr>
<th>Participant</th>
<th>Production</th>
<th>Target</th>
<th>Chemistry</th>
<th>Labelling</th>
<th>Dosimetry</th>
<th>Recycling</th>
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<td><strong>ARMENIA</strong></td>
<td>- We will conduct thick target yield (TTY) measurements – real measurement under C18 proton beam the yield for low intensity and thin target. We will also measure final product radiological and isotopic purity measurements.</td>
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| **CANADA (TRIUMF)**| - Yield measurements have been conducted at 18 MeV resulting in 9Ci at 200 uA for 6 hours.  
- Yield measurements will be conducted at 22 and 16 MeV and compared with literature data (measured and theoretical). |
| **CANADA (University of Alberta)** | - Cross section data and yields as a function of irradiation time for proton energy ranges 10-18 MeV have been completed.  
- TR24 currently being commissioned and 18-24 MeV measurements will be conducted |
| **HUNGARY (ATOMKI)** | - Evaluation of available measured experimental cross sections data is essentially complete, however, the quality of the data is difficult to determine.  
- In the next period, will work on theoretical calculation tool as a function of beam energy and target material composition. |
| **INDIA**          | - Completed irradiation measurements with thin Mo natural foils and investigated production rate of co-produced impurities up to 18 MeV  
- Will conduct measurements up to 20MeV.  
- In the future will look at decay of product material and amounts of co-produced contaminants.  
- Impurity levels in the purified product as a function of time will be studied. |
ITALY (INFN)
- Critical review of experimental data already available for a set of Mo isotopes of interest for proton-induced accelerator production of Tc completed, published paper, one submitted. Have compared theoretical data with available experimental data.
- New cross sections data for proton energy range from 10 MeV up to 18 MeV complete. In the next period, plan to extend to 25-30 MeV. Yield measurement of $^{99m}$Tc as well as for other radionuclides in progress, preliminary estimated yields.
- Calculation tool for estimation of Tc radioisotopes production vs. energy range irradiation time and beam currents based on experimental data first. Developed but not user friendly yet-
collaboration with Vancouver and Hungary

POLAND (POLATOM, University of Warsaw and Institute of Nuclear Chemistry and Technology)
- Determination of the most effective irradiation parameters for $^{100}$M(p,xn) $^{99m}$Tc reaction, the beam energy and time of irradiation as collaboration with Czech republic ongoing,
- Irradiations of the enriched, self-supporting $^{100}$Mo targets with protons of the energy ranging from 10 up to 25 MeV in collaboration with CRP partners.

UNITED STATES (Washington University)
- Irradiation of Mo-oxide and carbide targets completed and yields of $^{99m}$Tc and other Tc isotopes will be measured at this energy profile measured
- Will work on preparation of metallic targets in the next period
- The final product will be analyzed for radionuclidic and radiochemical purity

Target Development

ARMENIA
- Targetry for Mo and MoO$_3$ will be investigated. We will make different designs of targets from these 2 materials, also with sintering and different gluing compounds, investigating their hardness, thermo conductivity, dissolubility and other parameters.

BRAZIL
- We will work on different preparations of an isotopically enriched Molybdenum accelerator target. We will also design, develop and test a target holder system for the production of $^{99m}$Tc via $^{100}$Mo (p,2n) $^{99m}$Tc using a particle accelerator (cyclotron).

CANADA (TRIUMF)
- Slanted target developed based on electrophoretic and sintering – undergoing patent application. Details to be provided at next RCM

CANADA (University of Alberta)
- Development of a reliable and robust $^{100}$Mo target system capable of operating at 24 MeV and 250 µA (potentially 500 µA).
- ACSI provided pneumatic Mo target system with remote loading and unloading has been tested. During the next period will test with irradiated targets

INDIA
- Prepared metallic targets, cannot test at high current at this time.
- Will also investigate preparation of metallic targets by electrodeposition
- Will potentially test targets on new cyclotron

ITALY (INFN)
- Preliminary design of the target system complete ,
- System to be tested at low/intermediate power over the next period.
- Preliminary tests conducted on difference deposition techniques, experiments ongoing
JAPAN
- Focussed on target system for horizontal beam using ceramic target holder
- In next period will evaluate durability and stability of this system for $^{99m}$Tc and other isotopes

KINGDOM OF SAUDI ARABIA
- Will switch target systems from CS30 to C-30.
- Need to conduct target modification to complete this
- Will conduct irradiation experiments in the next period

POLAND
- Obtained pressed powder self-supporting targets
- need to test and also still working on electrodeposition and other techniques,

SYRIA
- Liquid target experiments conducted,
- Tested pressing and sintered targets experiments ongoing
- Will investigate current limits for these targets during the next period

USA (Washington University)
- Method developed for synthesis of Mo$_2$C, pressed power targets created
- Will investigate production of metallic targets during next period.

Chemical Isolation

ARMENIA
- We will develop the present system based on the MEK and centrifuge extractor technology, make some automatic control, some robotics for irradiated target material transportation e.g. from container to “hot” cell.

BRAZIL
- Will develop chemical processing methods to purify $^{99m}$Tc from irradiated accelerator target
- Chemical process automation to be developed

CANADA (TRIUMF)
- Have decided on AnaLiG$^\text{TM}$ column as separation column material, clean product obtained, no carrier materials break through,
- Will look for co-produced Ruthenium isotopes during next period

CANADA (University of Alberta)
- Optimize and validate an automated $^{99m}$Tc recovery system in a GMP environment.

INDIA
- A suitable separation technique for Mo/Tc separation has been standardized using MEK\$
- Quality control studies of the purified product (determination of chemical and radiochemical impurities) conducted
- levels of Nb or Zr radionuclide impurity in the final product determined. Found in Mo fraction – will investigate separation of Nb and Zr from Mo
- During the next period, the separation technique standardized will be translated into a user-friendly automated computer controlled system for separation of Mo/Tc where operation does not require expert operator, direct chemical and radioactivity handling.

ITALY (INFN - LNL (Legnaro National Laboratories))
- Radiochemical separation purification QC procedures to assess the production quality of $^{99m}$Tc, as well as optimization studies on separation/purification processes aimed at $^{99m}$Tc production are progress with Pavia University,
- starting to test separation technique, hope to have procedure by the end of the period,
- Semi-automatic system (home-made) to be tested in Pavia,
- Will also test different separation techniques

**POLAND**
- Dissolution conditions for powder and foil determined - can be reached in 30-40 minutes
- Chromatography using RV PEGylated C-18 was efficient and confirmed in laboratory conditions using radioactive Mo and Tc
- Also looked at targets dissolved in strong nitric acid, and precipitation with polyphosphate – tested separation of Tc using ZrO\textsubscript{2} beads – good conditions for separation, however only conducted on trace amounts
- All methods allowed for recovered, have been using electrochemical dissolution, promising results, can be adopted for recovery of Mo
- Assessment of quality of obtained $^{99m}$Tc in the chemical form of pertechnetate for its further use in radiopharmaceuticals for diagnostic application, including determination of labelling efficiency and biodistribution of $^{99m}$Tc - radiopharmaceuticals prepared using cyclotron-produced $^{99m}$Tc, will be conducted during the next CRP
- Assessment of dosimetry of accelerator produced $^{99m}$Tc will be conducted in collaboration with CRP partners.

**ITALY (University of Pavia)**
- Developed a separation method using low activity samples
- Have separation methods of low activity samples, will compare with other methods, then will automate with collaboration with Ferrara during next period

**JAPAN**
- Separated $^{99m}$Tc and used for radiolabeling,
- need additional experiments and kits,
- will look at other resins for separation
- Working on semi-automated system

**KINGDOM OF SAUDI ARABIA**
- separation experiments for Tc/Mo to be conducted
- will work on ion exchange techniques for the next period

**USA (Washington University)**
- We have investigated the use of a dry distillation technique for the separation of $^{99m}$Tc from the $^{100}$Mo target material
- Comparisons will be made to the conventional ion exchange method over the next period
- An automated purification system will be developed for the more robust and efficient separation technique

**SYRIA**
- Separation system set up for separation of Tc and Mo
- recovery using preconditioned acidic alumina resin developed for liquid targets,
- in the next period, system will be set up for analysis of Mo recovery and measurement recycling efficiency – based on a voltammetric method

**Kit labelling**

As a group we proposal to explore the utility of a product monograph for cyclotron produced pertechnetate.
BRAZIL
- We will work on the quality control of $^{99m}$Tc pertechnetate produced in cyclotron in comparison to generator-produced $^{99m}$Tc pertechnetate from $^{99}$Mo (fission) and on labeling cold kits evaluating their imaging quality.

CANADA (TRIUMF)
- Labelling of acidic, basic and neutral radiopharmaceuticals meet standard QC,
- During the next period will do the same experiment at the end of shelf life – make sure the behaviour is the same as freshly prepared Tc

CANADA (University of Alberta)
- Label a variety of radiopharmaceuticals, perform all relevant QA/QC and confirm their shelf life.

INDIA
- Development of new quality control protocols to control the level of such contaminants (the presence of other metals and any oxidant (including H$_2$O$_2$) species etc.) are completed
- Conducted labelling efficiency of various Tc-radiopharmaceutical kits with cyclotron-produced pertechnetate
- Potentially will look at image quality with cyclotron produced $^{99m}$Tc-radiopharmaceutical will be compared with the generator produced $^{99m}$Tc-radiopharmaceutical over the next period
- Over the next period, will do additional irradiations, separation and will do animal imaging studies

ITALY (INFN)
- We have investigated $^{99}$Tc impact on labeling efficiency test with a set of widely used pharmaceutical kits using generator-based Tc.
- We have performed imaging tests in proper phantoms and impact on images quality vs. the $^{99g}$Tc/$^{99m}$Tc isomeric ratio using the generator-produced Tc and the YAP-(S)PET-CT imaging system for small animals.
- During the next period we will conduct similar work with accelerator Tc

ITALY (University of Pavia)
- During the next period, our laboratory, will verify if the final product matches the authority requests with our nuclear medicine hospital collaborations, either Pavia or Ferrara

JAPAN
- We have evaluated labelling efficiency for 1 compound with using commercially available kits (HMDP)
- During the next period, we will potentially evaluate additional kits

KINGDOM OF SAUDI ARABIA
- During the next period, we will characterize contaminants and their effect, if any, on radiolabeling efficiency using various commercial $^{99m}$Tc -radiopharmaceutical kits, especially HMPAO kit.

POLAND
- We will work on the assessment of quality of obtained $^{99m}$Tc in the chemical form of pertechnetate for its further use in radiopharmaceuticals for diagnostic application, including determination of labelling efficiency and biodistribution of $^{99m}$Tc -radiopharmaceuticals prepared using cyclotron-produced $^{99m}$Tc.
- We are currently manufacturing kits for Tc labeling, testing kits on generator, will conduct tests in parallel on cyclotron Tc with the same validated procedures

USA (Washington University)
- Quality control procedures are partially developed and comparisons will be made between generator produced $^{99m}$Tc and the one produced on our cyclotron.
- MDP had been successfully radiolabeled with our cyclotron produced $^{99m}$Tc
- Over the next period, additional radiolabeling of various common Tc radiopharmaceuticals will be investigated and compared to generator produced $^{99m}$Tc. With collaborations with Canada

**Dosimetry**

**BRAZIL**
- Over the next period Biological evaluation of $^{99m}$Tc produced by accelerators: cytotoxicity, genetoxicity, hemocomatibility, etc.
- We will also study the influence of the radionuclidic impurities for the total doses in different organs.

**CANADA (TRIUMF)**
- We have measured the $\gamma$-spectroscopy composition for isolated Tc isotopes for thick targets at 18 MeV at various timepoints. These results will be used to renormalize the theoretical calculations for radiation exposure to the patient.
- This data is part of a submitted publication and will be reported at the next RCM

**CANADA (University of Alberta)**
- Determined radionuclidic purity of $^{99m}$Tc produced up to 18 MeV
- During the next period will determine radionuclidic purity of $^{99m}$Tc produced up to 24 MeV
- During next period will estimate the radiation dosimetry of existing radiopharmaceutical using cyclotron produced $^{99m}$Tc
- During next period will determine impact on shelf life due to radiolytic decomposition

**HUNGARY**
- Performing dosimetry measurements at 17 MeV proton energy
- provide calculated data for any bombardment energy – no experimental data - may do natural target material in collaboration with CRP partners

**ITALY (INFN)**
- have conducted an independent evaluation of theoretical radionuclide production by >99% enriched molybdenum samples by means of nuclear model codes
- during the next period will conduct a comparison between theoretical and experimental data (when available)
- Dosimetric calculation considering different energy windows, irradiation times, and beam currents (looking for appropriate CRP collaborators)
- Will potentially conduct in vivo experiments

**ITALY (University of Pavia)**
- During the next period the product isotope impurities will be measured and evaluated making a comparison with the results obtained by the different separation methods and irradiation parameters tested (continuation of previous work, MEK completed and other separation techniques will be evaluated).

**KINGDOM OF SAUDI ARABIA**
- During the next period, the isotopic composition of the recovered $^{99m}$Tc will be measured using MCA at different time intervals for 24 hours.

**POLAND**
- During the next period will conduct assessment isotopic composition of accelerator produced $^{99m}$Tc
- During next period will also look at distribution of radiopharmaceuticals in animal models to assess real(true) dosimetry in collaboration with Vancouver CRP partners
USA (Washington University)
- We have examined the production of radionuclide impurities by gamma spectroscopy as various beam energies.
- During the next period we will investigate the impact of isotopic composition and purity of the $^{100}$Mo target material on production of other Tc isotopes which may impact dosimetry.

SYRIA
- We have assessed impurities ($^{22}$Na and others) produced in the liquid targets,
- During the next period we will use our HPGe to measure radioisotope impurities

Target recovery

ARMENIA
- We will prepare a “standard” recovery system and search for more effective ways to recycle $^{100}$Mo.

BRAZIL
- During the next period our group will investigate recovery of $^{100}$Mo from chemical processing and analysis of radionuclidic impurities in the final $^{99m}$Tc after chemical purification.

CANADA (TRIUMF)
- We will continue to refine our ability to recover and isolate molybdate from the waste solution and convert to Mo metal.
- We have demonstrated our ability to recover Mo back into the metal form, 85% recovery and will continue to optimize.
- During the next period, we will continue to assay for radionuclidic impurities and their impact on the timing of recovery.

CANADA (University of Alberta)
- We have designed and tested a system for recycling of $^{100}$Mo and evaluate the quality of $^{100}$Mo after multiple irradiations using Bioscan reform with a homemade resin,
- We have evaluated the recycled Mo (up to 4 cycles) and will report on additional parameters at the end of the next period

INDIA
- We have recovered MoO$_3$ and will work on conversion to metal with the help of CRP partners.
- During the next period, we will continue to optimize this process with help from CRP partners

JAPAN
- We have a recovery system for $^{100}$Mo recycling in use
- During the next period we will continue to use to confirm efficacy of recovery from ceramic target.

KINGDOM OF SAUDI ARABIA
- During the next period, the process of recovering metallic $^{100}$Mo will be attempted using gaseous hydrogen reduction and new electrodeposition techniques using Pt-gauze

ITALY (INFN)
- We have begun testing our first irradiation tests on $^{100}$Mo-enriched samples at low power, to get small quantity of $^{99m}$Tc production using the standard Chattopadhyay method,
- Attempts at recovery of $^{100}$Mo are in progress in collaboration with Pavia and will be reported during the next period
ITALY (University of Pavia)
- During the next period, we will determine the recovery yield and will measure impurities using different techniques present at the laboratory.

POLAND
- During the next period we will develop methods of the $^{100}$Mo recovery from solution after extraction of $^{99m}$Tc from the bulk target material and transformation of molybdenum to metallic form followed by assessment of the effects of isotopic composition of recovered $^{100}$Mo on the quality of $^{99m}$Tc obtained by its irradiation.

USA (Washington University)
- During the next period, our group will investigate the recycling of the enriched $^{100}$Mo target material and determine the effect of recycling on the build-up of other contaminants which may affect the purity of the produced $^{99m}$Tc.

HUNGARY
- We have published theoretical yields for Tc and other isotopes from enriched different Mo targets
- We have collected the experimental cross section data for the reactions involved in the production process
- Selection of the possible best cross section results predicted by different theoretical models for those reactions for which no experimental data are available.
- To build up a dedicated database containing cross section data (from threshold up to 30 MeV) for the reactions can be important regarding the $^{99m}$Tc production
- Determine the amount of different radionuclide produced during irradiation as function of bombarding energy, irradiation time and cooling time for the different available target enrichments.
- Analysis of the calculated radionuclide profiles in order to determine optimal production parameters.
- Determination of the maximal (theoretical) specific activity for various irradiation parameters and target compositions.
- Determine the time dependence of the specific activity of the $^{99m}$Tc product

JAPAN
- We are currently developing the target vessel adaptable for conventional horizontal beam, including automated process as same manner of the vertical irradiation method with $^{100}$Mo oxide target and will report at the next CRM
- By using the products obtained by the above method, we will confirm the quality of the $^{99m}$Tc, especially its radionuclidic/radiochemical purities, as well as the labelling efficiencies for various compounds.
- During the next period, we will also attempt to develop a $^{100}$Mo recycling method to reduce running cost, and evaluate its effect on the $^{99m}$Tc quality, particularly in the repeated use.
4. SUMMARY OF COUNTRY REPORTS

CANADA: TRIUMF

The entire cycle of target production, irradiation, chemical separation, recovery of target material and preparation of targets using the recycled $^{100}$Mo have been performed. In addition theoretical calculations for the excitation functions for ($p$,n), ($p$,2n) and ($p$,3n) reactions were performed covering the energy range from 6 MeV up to 24 MeV. Based on these results the production of the various Tc-isotopes was performed using standard commercially available $^{100}$Mo enrichments including the distributions of accompanying Mo-isotopes. These results were used to estimate the radiation dosimetry for several radiopharmaceuticals kits in comparison to generator produced $^{99m}$Tc. These results have been published in peer reviewed papers.

During the development program a number of systems were established including a process for manufacturing a Mo-metal target, a transfer system for sending the target to the cyclotron and retrieving it. A target dissolution and an automated chemical separation system were constructed making use of the Analig® resin which provides pure Tc-isotopes. A recovery protocol was initiated whereby $^{100}$Mo from previously irradiated targets could be recovered at greater than 85%. To date we have produced greater than 350 GBq (9 Ci) of $^{99m}$Tc on the TR19 cyclotron multiple times.

Based on our results with preparing radiopharmaceutical kits for anionic, cationic and neutral radiopharmaceuticals $^{99g}$Tc does not interfere with labeling for freshly prepared $^{99m}$Tc. In addition labeled kits pass all QC tests for standard kits.

CANADA: University of Alberta

Researchers at the University of Alberta have demonstrated that cyclotron produced $^{99m}$Tc for the molecular imaging community is feasible. Milestones completed that led to the validation of a complete target recycling program began with the measurement of production cross-sections for the $^{100}$Mo($p$,2n)$^{99m}$Tc and $^{100}$Mo($p$,2n)$^{99g}$Tc reactions up to a proton energy of 18 MeV. Following a thermal modelling of 18 MeV protons on molybdenum, a $^{100}$Mo/$^{99m}$Tc target system was designed and tested for a TR19 cyclotron (18 MeV, 100 μA). This included the development of a robust sintering and bonding method for $^{100}$Mo on an aluminum target support plate that achieved a Mo density of ca. 8.2 g cm$^{-3}$. Following Mo dissolution with H$_2$O$_2$, target processing was automated using a modified Bioscan Reform module for the separation of $^{99m}$Tc and recovery of uncontaminated $^{100}$Mo-oxide. In order to reclaim the enriched $^{100}$Mo, a process was developed to convert the recovered $^{100}$Mo-oxide to $^{100}$Mo metal for target recycling using an 1100°C rotary furnace (reduced under H$_2$). Appropriate QC protocols were developed for $^{99m}$Tc pertechnetate, followed by animal biodistribution studies for a variety of Tc-radiopharmaceuticals. A clinical trial showing equivalence was completed with cyclotron-based $^{99m}$Tc: “A Prospective Phase I Study of Cyclotron-produced $^{99m}$Tc Pertechnetate in Patients with Thyroid Cancer”.

HUNGARY

Possibility of accelerator production of $^{99m}$Tc based on the $^{100}$Mo($p$,2n)$^{99m}$Tc reaction was studied by using yield calculations for the reactions energetically allowed. After determining the list of the reactions involved in accelerator production of $^{99m}$Tc up to 30 MeV proton energy on enriched $^{100}$Mo target a reaction network calculation was build up to study the achievable yields of the main product and the amount of contaminating radionuclides. The trends of production yields, number of produced nuclides, relative activity and relative physical doses were determined. New experiments were performed to determine the excitation function of the two main reactions $^{100}$Mo($p$,2n)$^{99m}$Tc and $^{100}$Mo($p$,pn)$^{99}$Mo. An earlier experiment was re-evaluated by using up to date nuclear decay data. Averaged fit values were calculated for the two main reactions from selected datasets. Comparison of MENDL-2p and TENDL-2012 data library was done. Results provided by the reaction network calculation were analyzed and final conclusions were deduced regarding production conditions and
quality of the accelerator produced $^{99m}$Tc. Comparison of accelerator and generator produced $^{99m}$Tc was done.

INDIA

The direct production of $^{99m}$Tc through (p, 2n) reaction on a natural molybdenum target was investigated. Extrapolated thick target yield of $^{99m}$Tc from the irradiation of an enriched $^{100}$Mo target for 1h, 3h and 6h irradiation as a function of incident proton energy (up to 18MeV) was calculated from the irradiated natural molybdenum targets. Separation of technetium radionuclide from the irradiated target by a new method using Dowex-1 ion exchange resin as well as well as by the standard solvent extraction (methyl ethyl ketone) method was studied. The quality of the final pertechnetate solution was assessed. Recovery of target material as molybdenum trioxide has been achieved.

ITALY: INFN-LNL

The work carried out focused on different topics. The first one was to analyze, from a theoretical point of view (but always having a benchmark to experimental data of excitation functions measurements) the in-target yields of all Tc nuclides expected from the $^{98}$Mo(p,x) reactions, taking into account the real isotopic composition for the Mo enriched material. Moreover, a detailed estimation about the post EOB evolution of main quality parameters of accelerator-Tc, related to generator-Tc with the results published in peer-reviewed journals. As a parallel activity, excitation functions measurements are currently focused on the two main reaction channels: $^{100}$Mo(p, pn) $^{99}$Mo and $^{100}$Mo(p, 2n) $^{99m}$Tc, which completion of data for the entire energy range of interest (~ 8-35 MeV) is scheduled to be completed in 2014. Excitation function measurements on either $^{99}$Tc, or other nuclides of interest are scheduled as well. Pharmaceuticals studies have also been performed with a set of kits, labelled with $^{99m}$Tc eluted from standard Mo/Tc generators at 24 h and longer time intervals, in order to mimic the higher $^{99}$Tc/$^{99m}$Tc isomeric ratios expected from accelerator produced $^{99m}$Tc. Moreover, first imaging tests using phantoms and $^{99m}$Tc (in carrier free conditions) eluted from standard Mo/Tc generators at 24 h and longer time intervals, have been investigated. First chemical separation/purification tests using the MEK method on enriched Mo irradiated foils have been conducted. At last, first results have been achieved on Mo deposition as multilayered films on backing material using the physical evaporative deposition technique at UHV at the super conductivity and surface treatments lab at LNL.

ITALY: PAVIA

The University of Pavia, with Laboratory of Nuclear Energy Applied (LENA) and Radiochemistry Area, has tested different approaches starting from an enriched $^{100}$Mo target with 18MeV protons. The research involves the radiochemical purity of the final product, the evaluation of $^{99}$Tc production and the recycling of the enriched molybdenum. The research involves also the Cyclotron of the European Commission Joint Research Centre. The accelerator is a Scanditronix MC40, the laboratory of Accelerator and Applied Superconductivity Laboratory – L.A.S.A. (associated to INFN sez. Mi), INFN-LNL (Legnaro National Laboratories) and the University of Ferrara (INFN sez. Fe). The targets were prepared at Legnaro Laboratory using several enriched $^{100}$Mo foils of 25 micron separated by aluminum foils. Considering references for $^{99m}$Tc production by accelerator the irradiation parameters chosen were: energy: 18.5 MeV, current: 100 nA and irradiation time: 1 h. After the irradiation, Mo foils were dissolved in acid (different acids and concentrations), basic (NaOH in different concentrations with or without H$_2$O$_2$) and finally with only H$_2$O$_2$ and heat. Different approaches were tested for separations of $^{99m}$Tc, together with different approaches for the recovery of Mo oxide after MEK separation. The one that showed the best results was the precipitation of ammonium isopolymolibdate at pH 2-4. After filtration (trapped on the filter), it is possible to choose the final oxidation state, either as Mo oxide or as metallic deposition. In order to obtain Mo oxide the ammonium salt was calcinated at about 700°C. Evaluation of $^{99}$Tc was made with two methods, NAA and ICP/MS. Promising results were obtained using 18 MeV protons on enriched $^{100}$Mo targets.
with dissolution using hot H$_2$O$_2$ followed by 6N NaOH and finally separated with MEK. The solution obtained was free from radionuclidic impurities apart the presence of other Tc isotopes.

**JAPAN**

Remote $^{99m}$Tc production by proton bombardment of $^{100}$Mo was successfully performed using MoO$_3$ salt as a target material and target vessel for vertical beam line. $^{100}$MoO$_3$ could be delivered as aqueous solution, dried in the target vessel by heat, bombarded then re-dissolved for recovery. To apply this procedure in general, a ceramic target vessel was also developed and evaluated using $^{89}$Zr as a model radionuclide. The ceramic target vessel enables the use of acidic/alkaline solution for delivery/recovery of target, including $^{99m}$Tc production.

**KINGDOM OF SAUDI ARABIA**

We have designed a target to be cooled by both water and helium channels and control system, which remotely controls the target from the cyclotron room. In addition, and in order to ensure that the beam is spread over the target area, a beam diagnostic tool (collimator system) was fabricated and used. Moreover, several natural and enriched Mo ($^{nat/100}$Mo) targets in metallic and oxide form were prepared by hydraulically pressing $^{nat/100}$Mo powder (150-200 mg) into the circular cavity aluminum target plates at 5000 psi. This was followed by heating in a furnace at 450$^\circ$C for four hours. For quality control, each target was examined microscopically to ensure its smoothness and homogeneity. To insure stability against high energy and current, $^{nat}$Mo targets in metallic form were irradiated and the isotopic composition measured using gamma spectrometry (MCA, Ge-Li detector) and found to be in agreement with previously published results. $^{99m}$Tc was produced by the bombardment of enriched $^{100}$Mo targets with variable energy protons (15-23 MeV) from the CS-30 cyclotron external beam using the $^{100}$Mo(p,2n) $^{99m}$Tc nuclear reaction. The proton current was 1 $\mu$A and the irradiation time was 10 minutes. The irradiated targets were measured using gamma spectrometry to determine the isotopic composition of the recovered $^{99m}$Tc. The yield of $^{99m}$Tc has increased dramatically when increasing the energy from 15 to 23 MeV. However, the activity of $^{99}$Mo increased from 0.38 to 6.44% when increasing energy from 15 to 23 MeV. Additional radiopharmaceutical testing will be developed during the next work period.

**POLAND**

Target preparation: the relatively thick Mo targets (pellets) for irradiation at the 25-16 MeV energy range have been prepared by the powder pressing technique at the Heavy Ion Laboratory. The thin foils required for the stacked foil experiment are planned to be produced by rolling technique. Upgrades to the PETtrace machine at Heavy Ion Laboratory will include an external beam line that will allow irradiation of the solid target. It is expected to be finished by the end of 2013, with the first irradiations to be performed at the beginning of 2014.

Methods for target preparation by electrodeposition and pressed pellet, using various masses and pressures have been tested at Radioisotope Centre POLATOM.

Target dissolution: dissolution of Mo powder and Mo foil in alkaline medium has been achieved in around 30-40 min at Radioisotope Centre POLATOM. The electrochemical dissolution of Mo foil was investigated reaching 85% separation yield in 3 M NaOH. The method can be potentially adapted to Mo recovery. Good separation yield of $^{99m}$Tc from Mo was also achieved using RPC-18 (OASIS Plus HLB, 225 mg) column modified with polyethylene glycol PEG-2000. Using $^{99}$Mo-$^{99m}$Tc spike solution loaded with high excess of “cold” Mo, the recovery of $^{99m}$Tc was at the level of 90%.

Two strategies such as (1) dissolving in nitric acid with precipitation of MoO$_3$ or (2) precipitation of insoluble heteropolyacid - ammonium molybdenum phosphate hydrate (AMP) followed by sorption on zirconium oxide are proposed by the Institute of Nuclear Chemistry and Technology to separate $^{99m}$Tc from molybdate solution. After AMP protocol optimization, the contamination of
MoO$_4^{2-}$ was below 0.3 mg/mL. If necessary, additional purification steps can be applied. Proposed methods are simple and quick.

**SYRIA**

Multiple methods and experiments have been carried out to produce a suitable target for high current irradiation for $^{99m}$Tc production (> 100 μA). Different electroplating baxes have been used for target support electroplating. The quality of the different electroplated Mo layers on copper substrate was not suitable for high current proton beam and high activity $^{99m}$Tc production. The thickness obtained by different electroplating procedures did not exceed 2-3 μm having a total surface of 10 cm$^2$. Tests on pressed, then sintered molybdenum oxide were performed in order to prepare a molybdenum target.

Another method for the production of $^{99m}$Tc based on a liquid target has been explored. The irradiation has been carried out on a small volume niobium target of 1 ml with a HAVAR window. Column chromatography for the separation of $^{99m}$Tc and recovery of enriched molybdenum has been tested. Gamma spectrometry has been used to determine the separation efficiency.

**USA**

During the first half of the CRP, we have conducted a study of the $^{100}$Mo(p,2n)$^{99m}$Tc reaction on a medical cyclotron using $^{100}$Mo$_2$C. This is the first report of this compound being used as a target for this reaction. $^{100}$Mo$_2$C, a refractory carbide with high thermal conductivity, properties which underscore its use on a cyclotron, was synthesized using $^{100}$MoO$_3$. Its ease of oxidation back to $^{100}$MoO$_3$ under air at elevated temperatures facilitates the use of thermo-chromatography, a high temperature gas phase separation technique for the separation and isolation of $^{99m}$Tc. Activity yields for $^{99m}$Tc averaged 84% of the calculated theoretical yields (15 MeV, 10 μA). Additionally, the per cent recovery of MoO$_3$, the precursor for Mo$_2$C, was consistently high at 85%, ensuring a good life cycle for this target material.

**5. CONCLUSIONS**

Cyclotron production of $^{99m}$Tc by the proton bombardment of enriched $^{100}$Mo has moved beyond the proof-of-concept stage. Significant progress has been made in the development of target systems that can be operated remotely or automatically. These include liquid targets, ones based on the use of oxides or carbides of molybdenum and molybdenum metal. Production yields for high beam current indicate that a single cyclotron can potentially meet the needs of a local community. Comparable chemistry systems for the isolation of $^{99m}$Tc from the $^{100}$Mo target matrix have been explored with approaches that are based on established literature for liquid-liquid extraction, dry distillation and ion chromatography. Efficient recovery procedures have been established that result in >85% recovery of the target material in usable forms for preparing targets for future irradiation.

Labelling results and established quality control procedures indicate that standard radiopharmaceuticals can be prepared that meet the criteria for use in humans. Theoretical calculations have been performed for the estimated co-production of other Tc-isotopes. These results will be compared with experimental results as they become available.

The next stage will see the continued development and implementation of these processes for preclinical imaging and ultimately clinical trials.

**Recommendations**

- Future efforts should focus on developing detailed procedures for chemical separation and recycling of enriched target materials.
• Acquisition of sufficient data should be pursued to enable the creation of a Monograph on the specification for the safe use of cyclotron produced $^{99m}$Tc-pertechnetate for human use.
• Develop a path forward to understand the economic implications for cyclotron produced $^{99m}$Tc.
• Interim Reports from the participants should be provided by the end of 2014 calendar year.
• The 3rd RCM: to be held Vienna, June 2015.

**Preliminary Procedures**  *See Individual Country Reports>*

**Target preparation**
- metallic targets have been prepared by Canada (TRIUMF), Canada (University of Alberta), Poland, Kingdom of Saudi Arabia, Italy INFN-LNL;
- oxide targets have been prepared by Japan, Syria, Kingdom of Saudi Arabia;
- solution targets have been prepared by Syria;
- carbide targets have been prepared by USA

**Tc/Mo separation**
- ion exchange techniques have been developed by Canada (TRIUMF), Canada (University of Alberta), Japan, India, Poland, Syria;
- solvent extraction techniques have been developed by India, Italy (Pavia), Armenia;
- thermochromatographic techniques have been developed by USA

**Mo recovery**
- Recovery of Mo from a solution using ion exchange has been developed by Canada (TRIUMF), Canada (University of Alberta), Syria, India, Japan
- Recovery of Mo from a solution using precipitation has been developed by Poland, Italy (Pavia)
- Recovery of Mo using solvent extraction has been developed by India

**Mo-oxide reduction***
- Reduction of Mo using hydrogen reduction has been developed by Canada (TRIUMF), Canada (University of Alberta)

*be sure to follow all appropriate safety protocols when handling hydrogen*
Individual Country Reports
ACCELERATOR BASED TECHNOLOGIES OF ISOTOPES PRODUCTION IN ARMENIA – CURRENT STATUS AND FUTURE PLANS

A.E. Avetisyan, Armenia

Abstract. Since 2008 A.Alikhanyan National Science Laboratory (the Yerevan Physics Institute) started an activity in the area of development of accelerator based medicine intended isotopes production technologies. The first step has been carried out by use of linear electron accelerator LUE50. Under financial support of ISTC an experimental layout has been mounted and theoretical and experimental investigation of \( ^{99}\text{Mo}/^{99m}\text{Tc} \) and \( ^{123}\text{I} \) trial production via photonuclear reaction has been carried out under electron beam with energy \( E_e=40 \text{ MeV} \). The full cycle of extraction from irradiated material was chosen, purchased, built and executed. The next steps are planned to do under proton beam from C18 cyclotron which will be mounted and commissioned close to end of 2013. Technology of irradiation, cooling, target preparation, isotope extraction and target material recovery are targets of our investigation for next year.

1. Introduction

A.Alikhanyan National Science Laboratory (the Yerevan Physics Institute) was founded in 1943 for an activity in an area of high energy particles and cosmic ray investigation. On the first stage it was based on a high altitude cosmic ray stations (~2000 and 3000 m s.l.a.). Since 1967 the ring synchrotron with 4.5 GeV energy of electrons has been commissioned. Till 2000 a lot of fundamental investigation in the area of photoproduction and electroproduction has been done using that accelerator. Besides ring accelerator a few small linear accelerator are working for applied research, technology development and other areas. In particular the injector of ring accelerator is enough powerful linac with energy up to \( E_e=75 \text{ MeV} \) (see Fig.1)[1]. It was used as a source of intensive electron beam for \( ^{99}\text{Mo}/^{99m}\text{Tc} \) and \( ^{123}\text{I} \) production technology development.

![Fig.1. Ring accelerator tunnel and experimental layout on the end of linac beampipe.](image-url)
2. $^{99}$Mo/$^{99m}$Tc production

2.1. Production option

The $^{99m}$Tc is derived as a daughter isotope from $^{99}$Mo decay (see Fig. 2).

![Fig. 2. $^{99}$Mo decay chain.](image1)

One of considered options of alternative methods of $^{99m}$Tc production was a photonuclear reaction [2-6]. Metastable $^{99m}$Tc could be obtained in the photonuclear reaction by irradiation of $^{100}$Mo under intensive photon beam (see Fig. 3.).

![Fig. 3. $^{99m}$Tc production chain under photo beam.](image2)

For this option the electron beam should be converted to a photon beam via bremsstrahlung. This method cannot provide high specific activity and therefore does not permit the use of standard Mo/Tc generators but could cover the demand for regional and city clinics.

To use its electron beam for photon-induced reactions the electron gun had to be upgraded. A new high intensity metallic cathode was installed with slightly modified gun electrodes so that the maximum intensity was increased from 3 µA to ~10 µA. From 3 accelerator sections 2 were in use providing $E_e = 40$ MeV electron energy. The electron beam was transported to the target magnetic optics in a way that the beam spot diameter on the target was 12 mm, measured by luminofore frame or vibrating wire scanner [7]. The beam pulse length was ~1.1 µsec, repetition frequency f=50 Hz.

2.2. Experimental layout for irradiation

A special experimental setup [8] (see Fig. 4) 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 (Fig. 5) was fabricated of copper. A thick tantalum plate has been installed on the entrance window to convert the electron beam to photons. A Monte-Carlo simulation of an optimal thickness of the converter has been performed. The optimum thickness of the tantalum radiator is about 2 mm (0.5 r.l.).

For direct measurement of the beam intensity, the Faraday cup (1 on Fig. 4) has been used.

At an electron beam energy of \( E_e = 40 \text{ MeV} \), and a beam intensity \( I_e \approx 10 \mu\text{A} \), the total power of the beam is \( P = 400 \text{ W} \). 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 M\( \Omega \text{m} \)) was used in the cooling system. The water temperature and beam current were displayed on a computer monitor. The Data Acquisition and visualization of these parameters were displayed by LabView software.
2.3. Irradiation modes

The oxide of natural molybdenum MoO₃ was used for the irradiation. The abundance of the stable isotope, $^{100}$Mo/$^{99}$Mo is 9.63%. The irradiated material was packed in a special aluminum capsule (Fig. 6). Two styles of target materials were used – a stack of pressed pellets (left) and full length pressed powder (right) covered by thin copper foil with 0.045 g/cm² areal density. First one was used to measure the dependence of excitation energy on the depth of target, and the second one was used for the trial production.

![Fig. 6. Target capsule for different tasks with pellets (left) and full amount (18 g) pressed powder of MoO₃ (right).](image)

The energy spectra from the irradiated materials were measured by a 3M3/3-X 905-4 type NaI(Tl) detector (producer- ORTEC) and an HPGe(ORTEC) detector.

2.4. Investigation of excited specific activity.

One of the main parameters for the production of radioisotopes is the resulting specific activity normalized to the mass of irradiated material, the beam current, and the duration of irradiation – Bq/mg·µA·h. The data on the specific activity of $^{99}$Mo published by different experimental groups has a very large variance (from 90 to 3200 Bq/mg·µA·h [4]).

The irradiation has been performed with a beam intensity of $I_e = 5.5$ µA for 5 hours. The energy spectrum from the irradiated material measured by the NaI(Tl) detector is shown in Fig. 7. The spectrum was fit by a Gaussian function; parameters of the fit are presented on the right top corner of the histogram. The mean value of the Gaussian function is $E_\gamma \sim 140$ keV. Two peaks are seen in the spectrum with energies $E \sim 140$ keV from $^{99m}$Tc and $E \sim 180$ keV from $^{99}$Mo.

The normalized specific activity calculated from this spectrum is $A \approx 3000$ Bq/mg·µA·h which is close to the maximum value of the published range of results.
2.5. Investigation of the depth dependence

To find an optimal thickness for the irradiated material inside the target capsule, we investigated the dependence of the excitation activity on the depth of the target material. A Monte-Carlo simulation (Fig. 8) using GEANT-4 was used to analyze the number of escaped photonuclear neutrons from the MoO$_3$ target.

To further test these simulation results a special experiment has been done. A number of identical pellets, 2 g natural MoO$_3$ each, have been fabricated and then irradiated under electron beam with energy $E_e=40$ MeV and beam intensity $I_e\sim8\mu$A for 2.5 hours. Then activity of each pellet was measured by NaI(Tl) detector once per day for 4 days. Results of the measurements after 15.7, 37.8, 62.7 and 84.3 hours are presented in Fig. 9. Each point shows the number of gamma-quanta under photo peak in the respective energy spectra from the irradiated material.
Fig. 9. The dependence of measured activity on depth of natural MoO$_3$ target after EOB:

- 15.7 hours, • - 37.8 hours, ▲ - 62.7 hours, ▼ - 84.3 hours.

The data in Fig. 9 show that with increasing the thickness of the target, the activity of each pellet is reduced. Self-absorption of the photons limits the thickness of the target.

Thus, the determination of the optimum length for the target will provide economic benefits in the production of isotopes $^{99m}$Tc. This is particularly important for the irradiation of enriched $^{100}$Mo.

2.6. Trial production of $^{99m}$Tc

For the low specific activity option only direct extraction of $^{99m}$Tc from the irradiated material is a reasonable option. For that, a centrifuge extractor with Methyl Ethyl Ketone (MEK) solvent technology was chosen. This technology has been successfully used for many years in Russia [9]. The irradiated MoO$_3$ is dissolved in KOH alkali and then MEK liquid is added to that solution. The irradiated MoO$_3$ dissolves in KOH while $^{99m}$Tc dissolves in MEK so that we have mixture of two solutions with very different densities. The centrifuge extractor was designed at the A.N. Frumkin Institute of Physical Chemistry and Electrochemistry in Moscow [10] 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 semi-automated system commissioned from the Moscow “Federal center of nuclear medicine projects design and development” and developed by FMBA (Russian company) was installed in a “hot” cell shown in Fig. 10.
The natural MoO$_3$ is a powder with a density 4.96 g/cm$^3$. After pressing, its density became ~2.4 g/cm$^3$. The natural MoO$_3$ target of 20 g mass and areal density 0.8 g/cm$^2$ has been irradiated under electron beam with energy $E_e = 40$ MeV and average intensity $I_e \sim 9.5 \, \mu A$ for a duration of $T=100$ hours. 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 ~ 80 mCi.

On subsequent days a new allotment of $^{99m}$Tc is produced from the $^{99}$Mo decay and extracted daily for a period of 5-6 days with a coefficient of extraction of $k \sim 0.7$ in comparison to the previous day.

3. $^{123}$I production

$^{131}$I-containing preparations are widely used in order to examine thyroid glands and kidneys. The long lifetime of $^{131}$I (8 days) and accompanying $\beta$-decay has made the use of $^{131}$I dangerous for life. Recently, other iodine isotopes such as $^{123}$I were produced in several countries. It is short-lived and radiates only via $\gamma$-rays and X-rays, which decrease the absorbed dosage of radiation patients by approximately 100 times. Production of $^{123}$I isotope now are based on hundreds MeV proton accelerators and tens of MeV cyclotron beams of protons, deuterons, $^3$He, and $^4$He. In both cases, together with $^{123}$I, there are undesirable isotopes produced with activities exceeding that of $^{123}$I a thousand times. This requires having a remote control system for target handling, very thick biological shielding, and a special system for removing radioactive waste. The operations costs for accelerators or cyclotrons as mentioned above and their associated systems for radioactivity handling/management is significantly higher in comparison to the operations costs of electron accelerators.

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

$$\gamma + ^{124}\text{Xe} \rightarrow ^{123}\text{Xe} \rightarrow ^{123}\text{I} \quad (T_{1/2} = 13.3 \, \text{hours})$$

The effective cross-section for this reaction is rather high; for photons of approximately 15 MeV the cross section is 450 mbarn. The width of the excitation curve is about 5 MeV. So the effective energy of electrons should be 25-35 MeV. For the higher energy, the number of hard photons increases as well as the number of undesired nuclear reactions. The yield of $^{123}$I could exceed 200 $\mu$Ci/$\mu A*h* g$ of $^{124}$Xe. Experiments performed at JINR (Dubna, Russia) on a 10 g target of pure xenon $^{124}$Xe irradiated...
in the course of 8 hours by an electron beam of 25 MeV and current of 20 µA, yield 200 mCi activity of $^{123}$I [11].

The stainless still target cell for Xe irradiation has been prepared (Fig. 11, left) and installed in the experimental layout under electron beam (Fig. 11, right). The cell has been filled by natural Xe using cryogenic condensation method till 230 bar of pressure on room temperature. Just after filling the tendency of pressure in the target cell was the increasing due to the equalization of temperature in the target body volume. To avoid the overpressure the remaining part of gas was transferred to the gasholder. The weighting of target cell shows that accumulated amount of Xe is about 40 grams. The control weighting during one week didn’t show any leakage. Simultaneously the pressure control shows a divergence to both sides repeating the daily fluctuation of the room air temperature.

The Xe target has been irradiated under electron beam. The following parameters have been achieved:

- Amount of natural Xe gas - ~40 gram
- Xe pressure in the stainless still cylinder - ~200 bar
- Beam energy – 40 MeV
- Beam current - ~9 µA
- Duration of irradiation – 12 hours.
- Target pressure was increased during irradiation – up to 250 bars.

![Fig. 11. The stainless steel target sell (left) installed in a target module (right).](image)

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 activity for EOB was

$$ A_{tot} = 7 \times 10^5 \text{Bq} \approx 20 \text{mcCi} $$

The main often use parameter of yield of irradiation is 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

$$ Y = 143 \text{Bq/mg*µA*h} $$

4. Future plans

The development of commercially feasible accelerator based production of medical isotopes in nearest future will be possible by use of proton cyclotron C18 (see Fig. 12) (producer – IBA, Belgium) to be installed nearby AANL (YerPhi) in fall of 2013. The main task of that cyclotron is
short life isotopes production such as $^{18}\text{F}$ for PET. In addition the 18 MeV protons will be used to investigate accelerator-based schemes for the direct production of $^{99m}\text{Tc}$ [12-21].

We propose the $^{99m}\text{Tc}$ direct production method (avoiding $^{99}\text{Mo}$ stage) using proton beams from that C18 cyclotron. That is in a coincidence with the goals of Coordinated Research Project (CRP) sponsored by the IAEA.

4.1. Proposed activity

The theory and technology of $^{99m}\text{Tc}$ direct production method (avoiding $^{99}\text{Mo}$ stage) using metallic $^{100}\text{Mo}$ target is well known and published in many articles. Monte-Carlo simulation should be done to tune irradiation parameters and estimate final product yield. On the first step we will use a standard solid target module [22] to irradiate different target materials such as metallic Mo and powder of MoO$_3$. For that we are in a close contact with experts from IBA Molecular and use their consulting. Then may be a special target module with higher level of cooling should be designed and constructed because the IBA standard module could utilize no more than 500 W. The thin foils of enriched $^{100}\text{Mo}$ have been used in above mentioned articles. We are going to investigate an opportunity of $^{100}\text{MoO}_3$ suitability for that production too. The reason is that a present technology of extraction is based on use of MoO$_3$. The problem is that even pressed powder of MoO$_3$ cannot provide necessary high temperature conductivity; therefore much more intensive cooling should be applied.

All other technology components for $^{99m}\text{Tc}$ production are ready from the previous irradiation experiments with the electron beam. An existent facility of $^{99m}\text{Tc}$ extraction from the irradiated material, specialized building with “hot” rooms and radiochemical purity testing system by use of HPGe detector will be used in the proposed project. Some investment will be required for radiology and chemical purities testing, packing, and certifying. The efficiency of $^{99m}\text{Tc}$ production under proton beam from cyclotron expected to be as minimum 10 times larger than that under electron beam due to much higher beam intensity from cyclotron; duration of irradiation will be only 2-3 hours instead of 100 hours for electron beam. The estimated produced activity of $^{99m}\text{Tc}$ is expected to be ~1-2 Ci per day (1 irradiation per day with max. 2-3 hours of duration) which is even more than current daily demand of Armenian clinics.

Concerning this method authors of published results always note the short life time of $^{99m}\text{Tc}$ as a disadvantage; thus the transportation to a long distance is impossible. That is drawback for production and distribution of isotopes to many remote clinics and for export to abroad. If the task is to fulfill a local demand of a few clinics but in the one and the same city – this way could be reasonable especially taking into account that medicine intended cyclotrons are currently in wide use. This technology could be the best solution for Armenia where only 2-3 clinics use $^{99m}\text{Tc}$ and all of them are in a car driving short distance, and this technology could cover whole demand with much lower price.

The new method using $^{100}\text{MoO}_3$ targets [23] published in the last volume of Nuclear Medicine and Biology is seen as very perspective option, and we will try to master that method too.

4.2. Detailed plan of activity

- Theoretical calculation and Monte-Carlo simulation of nuclear processes in different target materials under proton beam from C18 cyclotron.
- Calculation of excitation function under different energies of protons for $^{nat}\text{MoO}_3$, enriched $^{100}\text{MoO}_3$, metallic $^{nat}\text{Mo}$ and enriched $^{100}\text{Mo}$ for following reactions
  
  $^{100}\text{MoO}_3(p,2n)^{99m}\text{Tc}$, $^{100}\text{MoO}_3(p,2p)^{99}\text{Nb}$, $^{100}\text{MoO}_3(p,pn)^{99}\text{Mo}$,
  $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$, $^{100}\text{Mo}(p,2p)^{98}\text{Mo}$,
  $^{100}\text{Mo}(p, pn)^{98}\text{Mo}$, $^{100}\text{Mo}(p,2p)^{99}\text{Nb}$,
  $^{100}\text{Mo}(p, pn)^{99}\text{Mo}$, $^{90}\text{Mo}(p,2p)^{99m}\text{Tc}$
- R&D of Mo and MoO$_3$ targets, construction, test under real proton beam from C18 cyclotron.
• $^{99m}$Tc real yield measurement depending of protons energy, beam intensity and duration of irradiation
• Comparison of our experimental results with published theory and experimental results
• Further development of $^{99m}$Tc extraction technology from irradiated material
• Further development of target material Mo recovery for multiple uses.
• Test of chemical and radionuclide impurities of final $^{99m}$Tc product.
• Creation of trial production covering full of a part of demand of Armenian clinics.
• Test of chemical and radionuclide impurities of final $^{99m}$Tc product.

The part of above mentioned points is already in progress. The real work with proton beam will start on spring 2014.

One of the proposed way to prepare a pillet from powder style material (e.g. Mo or MoO$_3$) is the use of some compound to “glue” microparticles of material. That compound should be with high adhesive and thermoconductivity proprieties. On the first step we use 10% of silber powder (see Fig. 13).

The investigations of their physical and chemical properties are in progress.

Another point is remote controlled devices for technology processes such as transportation of irradiated material from contayner to hot cell. The design of that machine is completed, mounting is started (see fig. 14).
Conclusion

The Yerevan team has enough good experience in the area of photonuclear method of isotopes production and it is absolute beginner of cyclotron based area. In general we repeat and master all the experience is accumulated by the community of experts in that area – using in particular the infrastructure from previous activity, and will do some owner investigations soon. In general they will be in the area of technology development, implementation of results to a trial and real production scheme to cover a demand of Armenian clinics.

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ACCELERATOR-BASED ALTERNATIVES TO NON-HEU PRODUCTION OF $^{99m}$Mo/$^{99m}$Tc

Carlos Leonel Zapparoli Junior, Jair Mengatti, Brazil

1. Introduction

IPEN (Instituto de Pesquisas Energéticas e Nucleares) is the biggest nuclear research institute of the Brazilian Nuclear Commission CNEN (Comissão Nacional de Energia Nuclear). IPEN, located in the city of São Paulo, produces almost all radiopharmaceuticals used in Brazil. IPEN has a research pool type reactor of 5 MW (IEA-R1) and two cyclotrons for producing radioisotopes for nuclear medicine use.

The Radiopharmacy Center of IPEN-CNEN/SP-Brazil has an established radioisotope production program to supply radiopharmaceuticals to the Nuclear Medicine community in Brazil. IPEN provides radiopharmaceuticals for more than 350 users (hospitals, clinics, etc.) in the country. These radiopharmaceuticals are prepared with radioisotopes produced in both a Nuclear Reactor and Cyclotron accelerators.

Among the radioisotopes used for medical application, $^{99m}$Tc is the most used, responsible for more than eighty percent of the total applications and is delivered in the form of homemade $^{99}$Mo/$^{99m}$Tc generators. IPEN imports all the $^{99}$Mo used in Brazil and up to 2009 the principal supplier was Nordion from Canada. At that time IPEN imported 450 Ci (6-days calibration) per week of $^{99}$Mo. Nowadays IPEN imports nearly 390 Ci of $^{99}$Mo every week from different suppliers.

In the past, IPEN developed the route for producing $^{99}$Mo by neutron activation of Mo-98 targets in the IEA-R1 Research Reactor. IPEN has a processing cell for this $^{99}$Mo producing route, using the gel generator technique but it was demonstrated to be not feasible to the size of medicine application needs existing in Brazil.

2. $^{99}$Mo projects at IPEN

The long term solution is the production of $^{99}$Mo through the fission of Low Enriched Uranium-235 (LEU) targets. This solution is only possible due to the decision of the Brazilian government of constructing a new Nuclear Reactor, the so called BMR (Multipurpose Brazilian Reactor). The Reactor will have a power of 30 MW and will be constructed at Iperó, a city 100 km from São Paulo. The routes of $^{99}$Mo production are being developed: (1) alkaline dissolution of U-Al LEU targets and (2) acid dissolution of metallic LEU targets (Figure 2).
The mid-term project consists on the production of $^{98}$Mo (n,γ) $^{99}$Mo using the existing IEA-R1m Reactor. The methodology employed is the separation of $^{99m}$Tc from $^{99}$Mo through the solvent extraction technique with metilethylketone (MEK). The $^{99m}$Tc will then be distributed to the clinics near IPEN, in Sao Paulo city, and later monodoses will be prepared by labeling the lyophilized kits with $^{99m}$Tc. Figure 2 represents the mid-term strategies for the production of $^{99}$Mo via neutronic activation based on early experiences. Future perspectives on development of mid-term actions would be mainly dependent on the new configuration of IEA-
The objectives of joining this CRP were to obtain technical information about the production of $^{99}$Tc using a Accelerator-based production of $^{99m}$Mo/$^{99m}$Tc. LEU targets already made available from this CRP and to get the support from IAEA and the developers of technology in order to get access to the technical information involved in the production of $^{99m}$Mo/$^{99m}$Tc, such as preparation of the $^{100}$Mo target, waste management, the chemical process of the irradiated U target, purification of $^{99m}$Tc and quality control of the final product. This information will help in the decision on the production route that will be adopted by IPEN in Brazil. The interaction and technical cooperation was also made possible through IAEA. These efforts will be specified in this report.

3. Status on Specific Research Objective

The implementation design is divided into steps which comprise the definition of the target type, irradiation conditions in the cyclotron, separation chemistry of $^{99m}$Tc, quality control $^{99m}$Tc.

3.1 Definition of target

Preliminary studies conducted in the literature on work done by researchers can observe that in general the targets used for irradiation cyclotron accelerator are prepared by compressing hydraulic or $^{100}$Mo sintered from metal oxides and salts pure or mixtures containing other compounds. There are some articles relating to electrodeposition of Mo which serve as references for the studies begin preparation of the target to be used in the system of irradiation targets solids used for the production of $^{67}$Ga and $^{201}$Tl. Some factors are very important and should be evaluated on the characteristics of
the target as prepared by electrodeposition layer thickness electrodeposited Mo, mass, mechanical strength and by heating during irradiation [3-6].

3.2 Irradiation conditions

The irradiation conditions will be studied after the definition of the target obtained by electrodeposition. The system existing in the cyclotron irradiation of IPEN station comprises a solid target irradiation with an inclination of 45 °C with water cooling system. The irradiation conditions such as current, irradiation time and reducing the energy will be based on operating experience for the production of the cyclotron. The beam energy in accordance with literature starts with 12 and ends with 14-15 KeV, current 20-30 µA for irradiations of 1 to 3 hours mass of 170-180 mg of molybdenum.

3.3 Chemical separation of $^{99m}$Tc

The separation of $^{99m}$Tc target following procedures established by several authors based on the target dissolution followed by solvent extraction or by using resins or acidic and basic alumina to separate the $^{99m}$Tc from other impurities formed during irradiation.

3.4 Quality Control

The quality of reagents used in the preparation of the target and solutions and the final product are very important aspects that must be evaluated in the project. The reagents employed as a raw material must have a high degree of purity to decrease the amount of impurity obtained at the end of the irradiation processes and separation of $^{99m}$Tc. Especially the degree of enrichment of $^{100}$Mo after irradiation could produce some radioisotopes of Technetium unwanted end product. The most important qualities controls to assess the purity of the $^{99m}$Tc are obtained radionuclidic and radiochemical analyzes demonstrating the purity and yield of the process and labelling with cold kits.

3.5 Work plan for next phase

- Define the route for target preparation
- Preparation of natural and enriched targets sample ($^{100}$Mo)
- Perform experiments with irradiated natural and enriched targets ($^{100}$Mo) samples
- Definition of the chemical processing route for $^{99m}$Tc production
- Definition of cyclotron parameters for irradiation

Quality control - labelling cold kits in order to evaluated the biological uptake i

4. Conclusion

The participation in the meetings is very important, from the learning point of view and also opening doors for future cooperation.

Brazil is planning to continue the project assembling a cold pilot plant that will be upgraded for use of tracers of the most important nuclides. There are still some areas where the assistance of IAEA is necessary.

Obtain technical information about the production of $^{99m}$Tc using accelerators by irradiating enriched $^{100}$Mo target. This information will help in the decision on the production route that will be adopted by IPEN in Brazil.
REFERENCE


CYCLOTRON PRODUCTION OF $^{99m}$Tc: FROM THEORY TO PRACTICE

Thomas Ruth, Canada

Summary

The entire cycle of target production, irradiation, chemical separation, recovery of target material and preparation of targets using the recycled $^{100}$Mo have been performed. In addition theoretical calculations for the excitation functions for $(p,n)$, $(p,2n)$ and $(p,3n)$ reactions were performed covering the energy range from 6 MeV up to 24 MeV. Based on these results the production of the various Tc-isotopes was performed using standard commercially available $^{100}$Mo enrichments including the distributions of accompanying Mo-isotopes. These results were used to estimate the radiation dosimetry for several radiopharmaceuticals kits in comparison to generator produced $^{99m}$Tc. These results have been published in peer reviewed papers.

During the development program a number of systems were established including a process for manufacturing a Mo-metal target, a transfer system for sending the target to the cyclotron and retrieving it. Target dissolution and automated chemical separation systems were constructed. A recovery protocol was initiated whereby $^{100}$Mo from previously irradiated targets could be recovered at greater than 85%.

This process was established for two types of cyclotrons, the 16.5 MeV PETTrace from GE Healthcare and an ACSI 19 MeV TR19 cyclotron.

To date we have produced greater than 350GBq (>9 Ci) of $^{99m}$Tc have been accomplished multiple times on the TR19 cyclotron.

Based on our results with preparing radiopharmaceutical kits for anionic (MDP), cationic (MIBI) and neutral (HMPAO) radiopharmaceuticals, the level of $^{99}$Tc present does not interfere with labeling. Labeled kits pass all existing QC criteria as indicated in the product documentation provided by the kit manufacturers.

The separation chemistry based on the Analig® resin provides pure pertechnetate in physiological (0.9% w/v) saline. There is no evidence of any non Tc radionuclidic impurities.

From our theoretical calculations, the percent enrichment of $^{100}$Mo affects yield of $^{99m}$Tc, in which the amount of $^{100}$Mo present in the target is proportional to the yield of $^{99m}$Tc. However, the percent abundance of other Mo-isotopes, specifically $^{94-97}$Mo, determines the quantity of other Tc-isotopes produced. The presence of addition Tc isotopes severely influences radiation dosimetry.

Depending upon the proton beam energy and irradiation time, the relative proportions of Tc-isotopes produced impact radiation dosimetry and thus the shelf-life. Despite this, estimates suggest that the shelf-life of cyclotron-produced pertechnetate will be at least 12 hours. The actual shelf-life will have to be determined with further experimentation.

Introduction

Feasibility of cyclotron production of $^{99m}$Tc via the $^{100}$Mo(p,2n)$^{99m}$Tc reaction was demonstrated in the early seventies (Beaver and Hupf 1971). Subsequently, a number of theoretical and experimental studies investigated cross sections, yields, as well as other aspects of accelerator-based isotope production (see for example: Sholten et al. 1999, Takacs et al. 2003, Gagnon et al 2011).

The Government of Canada funded four projects based on accelerators to investigate the commercial production of $^{98}$Mo and/or $^{99m}$Tc. Two were based on the photo transmutation of $^{100}$Mo into $^{99}$Mo ($^{100}$Mo($\gamma$,n)$^{99}$Mo) and two based on proton irradiation of $^{100}$Mo to produce $^{99m}$Tc directly.
($^{100}$Mo(p,2n)$^{99m}$Tc). One of the cyclotron teams involved collaborations between the University of Alberta, the University of Sherbrooke and ACSI. The other team is a collaboration amongst TRIUMF, BC Cancer Agency, the Lawson Health Research Institute in London, Ontario and the Centre for Probe Development and Commercialization (CPDC) in Hamilton, Ontario. The TRIUMF consortium aimed to investigate the use of existing PET cyclotrons as the platform.

Overall Technical Goals for Cyclotron-based Production included:

- Establish optimal irradiation conditions to maximize yield and purity which involves defining the beam energy range (effecting yield and purity), current (which effects yield)
- Target characteristics (the enrichment of $^{100}$Mo, the isotopic composition of other Mo isotopes which will impact purity, establish the target plate capable of being irradiated at high beam current, the encapsulation of the target to enable target transfer, and establish the ability to recycle the enriched $^{100}$Mo)
- The optimal time of irradiation will impact the production, cooling)

Specific Goals

In addition to performing theoretical calculations and determine excitation functions for the possible radionuclides from the irradiation of Mo isotopes the actual production quantities of $^{99m}$Tc needed to be established under production conditions. In addition to the production rates for $^{99m}$Tc, the mix of impurities that are produced need to be identified and quantified. These results will impact the shelf-life and ultimately radiation dosimetry associated with this approach.

The ability to label certain radiopharmaceutical kits is highly dependent upon the specific activity of the $^{99m}$Tc (the ratio of $^{99m}$Tc to all Tc –isotopes including $^{99g}$Tc).

The radionuclide mix in the production of $^{99m}$Tc has implications in production and disposal of waste, in recycling of the enriched $^{100}$Mo target material and patient radiation dose that could be associated with any radionuclidic impurities in the final radiopharmaceutical.

The US Pharmacopeia defines $^{99m}$Tc as being derived from fission produced $^{99}$Mo while the European Pharmacopeia includes the production of $^{99}$Mo by other routes. Thus to allow acceptance of the cyclotron produced $^{99m}$Tc, the regulatory authorities have to understand the implications of the quality of cyclotron produced material on the safety and efficacy for the patient.

With all of these parameters in mind the production specifications need to be established which define the energy window(s), length of irradiation, establishing transport criteria, the shelf-life, and the protocol for recycling of target materials.

Ultimately whether this approach will be adopted into widespread use will depend upon the economic factors associated with providing healthcare.

For these studies the aim was to demonstrate that existing medical cyclotrons could be used to produce sufficient quantities of $^{99m}$Tc to be commercially viable. We chose two platforms, the 16.5 MeV for the GE PETtrace and 18 MeV for the ACSI TR-19 cyclotrons, both of which are widely available throughout the world.

Progress as of October 2013

During the past period (April 2012-October 2013) we have finalized target production process for the TR19 as well as completing the target transfer capsules for the TR19 and the PETtrace. The TR9 target is based on a slanted target while the PETtrace uses an orthogonal target due to space constraints.
The target preparation for the TR19 makes use of electrophoretic approach to deposit the molybdenum metal on a tantalum metal surface followed by sintering at 1700 C. This process produces a robust target that has been tested to 260 µA. The PETtrace target has been tested to 130 µA and up to 100 µA for the Mo plate.

![Tantalum target plate with Mo coating adjacent to the 2 halves of the target transfer chamber. When coupled and inserted at the cyclotron, the beam would enter at a grazing angle from the bottom orifice (with "o"-ring).](image1)

![Enriched Mo-100 target irradiated at 100 µA with 16.5 MeV protons on a PETtrace.](image2)

Using these targets we have produced 350 Gbq (>9 Ci) of $^{99m}$Tc multiple times and have followed the decay over several days to ascertain the composition of the Tc-isotopic mix. Table1 shows the comparison between our measurements, those of Lebeda, et al. and the theoretical measurements of Celler, et al.
TABLE 1. THE POTENTIAL TC-ISOTOPE CONTAMINANTS FOUND IN DIRECT PRODUCTION FROM $^{100}$MO.

<table>
<thead>
<tr>
<th>Tc-isotope(t $^\frac{1}{2}$)</th>
<th>Theor. (Empire)</th>
<th>CycloTech99</th>
<th>Lebeda, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>96 (4.28 d)</td>
<td>0.020</td>
<td>0.052</td>
<td>0.012</td>
</tr>
<tr>
<td>95g (20 h)</td>
<td>0.0097</td>
<td>0.025</td>
<td>0.0062</td>
</tr>
<tr>
<td>94g (4.88 h)</td>
<td>0.028</td>
<td>0.026</td>
<td>0.028</td>
</tr>
</tbody>
</table>

It should be noted that our results are for the 18-10 MeV energy range while the theoretical and the Lebeda results cover the 24-10 MeV range. The target enrichment used was of similar composition with respect to the lighter Mo-isotopes.

As part of our efforts to understand production parameters we have operated the TR19 at >200 µA on target for more than 6 hours with a peak beam current of 260 µA. During this 6 hour run we have lower the beam current to 200 µA on the Mo target while running 60 µA on a standard water target for F-18 production demonstrated that those facilities with dual beam capability can produce Tc-99m without interfering with their PET radionuclide production program. It should be noted that the beam currents indicated here are not limitations. The TR19 has been modified to be capable of producing 300 µA. Once this level has been established routinely we will move to this higher level.

The target transfer capsule has been designed to not only hold the target plate during transfer between hot cell and cyclotron but to also serve as the dissolution vessel. The electrophoretic plated targets are porous in nature and can be dissolved from the tantalum backing with the addition H$_2$O$_2$. The solution is transferred and prepared by drying and taken up in base before adding to a pegylated ion column where the pertechnetate is trapped allowing molybdate and other ions to pass through to the waste.

Following elution we have found a chemically pure Tc product. Colorimetric assays looked for alumina and molybdenum. Depending upon the isotopic composition of the Mo target material will dictate the Tc-isotopic impurities.

The molybdate in the waste solution can be purified via ion exchange and reduced to metal powder suitable for introduction into the electrophoretic plating system by temperature stepped hydrogen reduction. To date we have demonstrated a recovery efficiency of 85% with a range of 80-90%. This was for a small number of relatively small samples, with the expectancy that the efficiency will be higher for bulk solutions. While the recovered molybdenum was chemically pure we have not determined the isotopic composition of the Mo. However expectations are that this will not be different from the starting material at the level of production we anticipate.

The initial automated chemistry was designed and built in-house. However recognising the need to have a system that will meet GMP specifications we have engaged a commercial partner to prepare a chemistry system that will use disposable units as illustrated in the figure below.
Fig. 2. An example of a disposable reagent kit for the separation and isolation of $^{99m}\text{Tc}$

We have labeled cold kits (acidic, basic and neutral) with cyclotron produced $^{99m}\text{Tc}$ and found that they labeled well and the labeled radiopharmaceuticals met the quality criteria.

We performed phantom studies to investigate the characteristics of images derived from cyclotron-Tc samples and to compare them with $^{99m}\text{Tc}$ from a generator.

Results indicate that:

- For early images - acquired on Day 1-2:
  - All images (and profiles) corresponding to photopeak and lower energy windows from the cyclotron and reactor samples were almost identical.
  - A small additional scatter component could be noticed in the photopeak and lower energy windows in the cyclotron sample.
  - In the photopeak and lower energy windows there was a 3-6% increase in counts in the cyclotron sample as compared to the reactor sample.
  - The counts in the upper energy window from the cyclotron sample were four times higher than those from the reactor.
  - The higher photon counts for cyclotron samples was due to other Tc isotopes, i.e., $^{94g}\text{Tc}, \, ^{95g}\text{Tc}, \, ^{96g}\text{Tc}, \text{ and } ^{97m}\text{Tc}$.

- For late images - acquired on Day 5:
  - For the reactor sample the counts were at the baseline level, which means no $^{99m}\text{Tc}$ was left after 5 days.
  - Counts from the cyclotron sample were 50% higher than the background due to other-Tc radioisotopes.
  - Because the majority of contaminant photons have high energy, in the late images of the cyclotron sample they showed only as uniform scatter background.
  - Theoretical yields estimation indicates that the cyclotron samples measured on Day 5 are composed of: 78.1% of $^{97m}\text{Tc}$, 19.9% of $^{96g}\text{Tc}$ and 2% of $^{95m+9g}\text{Tc}$.

The outcomes of the consortium efforts included:

- Calculated theoretical yields for (p,x) reactions of the various molybdenum isotopes that could potentially be found in enriched $^{100}\text{Mo}$. This established theoretical $^{99m}\text{Tc}$ yields and radionuclidic impurities. See Phys. Med. Biol. 56 (2011) 5469–5484 for details;

- A manufacturing process for $^{100}\text{Mo}$ target plates using novel $^{100}\text{Mo}$ coating methods;

- Design, assembly and installation of target stations at TRIUMF (using a CP42 cyclotron), the BC Cancer Agency (operating an ACSI TR19) and GE PETtrace cyclotrons at Centre for
Probe Development and Commercialization (CPDC - Hamilton, ON) and Lawson Health Research Institute (LHRI - London, ON);

- Mitigated risks associated with unique specifications for various cyclotrons at various institutions. For example, the GE PETrace cyclotrons at CPDC (vaulted) and LHRI (self-shielded) maintain the same capabilities, but exhibit unique specifications in their upgrades and operations.

- Design, assembly and installation of target transfer systems to move solid targets from the cyclotron to a shielded workspace (hotcell) at BCCA, CPDC, & LHRI;

- The Development of new, automated purification methods to extract and purify $^{99m}$Tc at greater than 90% efficiency from irradiated targets. See Nuc. Med. Biol. 39 (2012) 551-559 for details;

- Demonstration that high (GBq/Curie-quantity) production yields are achievable with radionuclidic purity in excess of 99.7%;

- The reconstitution of commercial technetium kits and demonstration that the resulting preparations were well within existing quality control (QC) standards; Despite this, the presence of minute quantities of other Tc isotopes, evidence suggests that radionuclidic purity of cyclotron-produced $^{99m}$Tc will not meet existing USP/EP standards. Radionuclidic impurities can be controlled through the isotopic purity of the $^{100}$Mo feedstock, cyclotron irradiation energy, irradiation time and transport/distribution time.


- Development of an efficient method to recycle $^{100}$Mo with over 90% recoveries in order to make the production process economically competitive

- Images corresponding to the 140 keV photopeak window obtained from the cyclotron-produced technetium acquired up to 24h post irradiations are of the same quality as those from generator. In agreement with our theoretical predictions, later images show increases in count rates originating from other technetium isotopes.

References:


ACCELERATOR-BASED ALTERNATIVES TO NON-HEU PRODUCTION OF $^{99}$Mo/$^{99m}$Tc

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A. Background

The University of Alberta has substantially completed their new cyclotron facility, the Medical Isotope and Cyclotron Facility (MICF) to help address the expected problems in the supply of $^{99}$Mo/$^{99m}$Tc generators from of aging nuclear reactors. We have developed a unique approach to demonstrate that cyclotron produced $^{99m}$Tc is feasible. Studies are ongoing to demonstrate that it can be brought into use at full commercial scale (with our partners Advanced Cyclotron Systems Inc. (ACSI) and the Centre Hospitalier Universitaire de Sherbrooke (CHUS).

Presented in this this project report is the work completed up to September 2013, with projections to the end of this CRP.

B. Infrastructure

MICF will house state-of-art GMP radiopharmacy manufacturing rooms (Edmonton Radiopharmaceutical Centre), radiopharmaceutical chemistry research labs, cyclotron targetry and engineering labs and a 500µA, 24 MeV cyclotron (TR24 from ACSI) with 4 external beam lines and 2 automated solid target loading stations. Cyclotron commissioning is ongoing and is expected to be completed by the end of 2013.

As part of MICF, a laboratory was completed and dedicated to target research and development with a focus on solid targets. To facilitate access and integration with cyclotron operations, this laboratory is ideally situated adjacent to the cyclotron operator room, the cyclotron engineering room, and the solid target hotcell room for automated download of irradiated solid targets.

Specific to the preparation of $^{100}$Mo targets for the cyclotron production of $^{99m}$Tc, the target research and development lab is equipped with a 1600°C tube furnace for target sintering and a 25 ton heated (to ~600°C) press for bonding of the sintered molybdenum onto a target support plate. The lab is also equipped to reclaim the $^{100}$Mo following chemical separation performed within the MICF radiopharmacy. As our approach opts to use molybdenum metal as a target material, molybdate isolation will be performed by lyophilization with subsequent reduction to be performed using our 1100°C rotary furnace. For characterization purposes, the lab facility is also equipped with a high purity germanium detector which will be used to evaluate the radionuclidic purity of both the $^{99m}$Tc product and the recycled $^{100}$Mo. This lab will also house an ICP-MS unit which can be used for assessing the $^{99m}$Tc specific activity, as well as the isotopic composition of the enriched $^{100}$Mo target material.

C. Status of $^{99m}$Tc Research at the University of Alberta

3.1 Separation of technetium and molybdenum

After the production of $^{99m}$Tc via the $^{100}$Mo(p,2n)$^{99m}$Tc reaction, there is a requirement for separating $^{99m}$Tc from bulk $^{100}$Mo. Although a number of separation methods have been demonstrated, the possibility of using a cartridge-based system is particularly attractive for routine use in a good manufacturing practice (GMP) regulatory environment.

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1 This report was presented as a poster to the Society of Nuclear Medicine and Molecular Imaging Annual Meeting, Vancouver, Canada, June 8-12, 2013.
Materials and methods

Relative decay-corrected radioactivity was determined via \( \mu \)-ray spectrometry using a HPGE-detector (Ortec model GEM35P4-S). PEG concentration in the final product was evaluated by iodine visualization TLC. Resin functionalization was evaluated by elemental analysis (carbon content).

Separation Technology

Separations were performed on an automated chemistry unit. Resins were evaluated with regard to \([^{99m}Tc]\)pertechnetate and \([^{99}Mo]\)molybdate adsorption and desorption. \([^{99m}Tc]\)pertechnetate and \([^{99}Mo]\)molybdate was obtained from generators (Edmonton Radiopharmaceutical Centre), eluted using NaCl and \((\text{NH}_4)_2\text{CO}_3\) (1.5M) respectively. All commercial resins were activated according to the manufacturer’s specification, and \((\text{NH}_4)_2\text{CO}_3\) (3M, 20 mL) was used to condition all resins before loading of pertechnetate and molybdate. Loading solutions consisted of \((\text{NH}_4)_2\text{CO}_3\) (1.5M) \([^{99m}Tc]\)pertechnetate or \([^{99}Mo]\)molybdate in NaCl. After loading, the resins were washed with \(\text{Na}_2\text{CO}_3\) (1M, 3 mL), and then elution was performed with deionized water (D.I. H\(_2\)O) (10 mL) unless otherwise stated. C-18 cartridges containing 3 g of resin were coated by pouring PEG3000 solution through the cartridge and then washing with D.I. H\(_2\)O. Separations were performed a loading solution containing 300 mg Mo powder dissolved in 10 mL H\(_2\)O and 10 mL \((\text{NH}_4)_2\text{CO}_3\) (3 M). After loading, the column was washed with 5 mL \((\text{NH}_4)_2\text{CO}_3\) (1 M) followed by 1.5 mL D.I. H\(_2\)O. The \([^{99m}Tc]\)TcO\(_4^-\) was eluted using 10 mL D.I. H\(_2\)O and passed through a strong cation exchange column and an alumina column. The \([^{99m}Tc]\)TcO\(_4^-\) was eluted from the alumina column using 10 mL of isotonic saline.

Synthesis of PS-DVB-PEG resin

PS-DVB-PEG resin synthesis consisted of grafting polyethylene glycol (PEG) to polystyrene beads according to previously published methods. In short, a 500 mL, three necked round bottom flask with magnetic stirrer and condenser was capped with a drying tube. It was put in an oil bath on a heat/stir plate and was equipped with thermometer. Chloromethylated polystyrene: 1% divinylbenzene copolymer beads (3.0 – 3.5 g) were pre-swelled in diethylene glycol dimethyl ether (anhydrous, 99.5%, 40 mL) or THF (anhydrous, with inhibitor, ≥99.9%, 60 mL) by stirring for 15 min at room temperature. Polyethyleneglycol methyl ether (average MW 2,000 or 5,000, 20-25 g) was added to the system, and NaH (600 mg) was slowly added over 30 min. The oil bath was then heated to 70°C (gentle reflux for THF) for 17 hours. The NaH was quenched with isopropanol (IPA, ≥99.5%) until no reaction could be noticed. The resin was then washed with IPA and twice with deionized water and filtered using a Buchner funnel.

Results

Commercial SPE cartridges

We evaluated commercial reversed phase resins for their potential of separating pertechnetate from molybdate. Pertechnetate adsorbed strongly on the RP-SPE cartridge Chromabond® HR-P (Macherey-Nagel GmbH & Co.) however none of the solvents used (H\(_2\)O, MeCN, DCM and DMSO) were successful in desorbing the pertechnetate. In addition 0.4% of the \(^{99}\text{Mo}\) was adsorbed on the HR-P cartridge. Oasis® HLB (Waters Inc.) was successful in retaining pertechnetate but acetonitrile was needed for desorption. It was however encouraging that no \([^{99}\text{Mo}]\)molybdate breakthrough to the Tc fraction was observed. Waters tC18 plus and Phenomenex Strata® C18-U did not successfully retain pertechnetate.

PS-DVB-PEG resin

Total synthesis time was 20 hours, and the yield of the synthesis was over 2.5 g PS-DVB-PEG resin per g polystyrene starting material. Elemental analysis indicated a carbon content of 69-76%.
Recovery of $^{99m}$Tc was $82 \pm 9\%$ (n=5, all different batches). The “in-house” produced PEG resins showed similar adsorption characteristics as ABEC™ resin obtained from Eichrom Technologies LLC, however elution profiles of the pertechnetate were more variable between batches of the in-house synthesized resin. These interesting differences could not be attributed to synthesis or resin analysis (elemental analysis). To determine the adsorption due to PEG grafted on the beads, PS-DVB-Cl and PS-DVB-OH were included in the study. As expected, pertechnetate did not adsorb on the resins. The PEG resins all exhibited very low $^{99}$Mo retention and thus low breakthrough to the Tc fraction. The highest breakthrough observed was 0.08% for any PS-DVB-PEG resin.

**C18-PEG resins**

C-18 cartridges containing 3 g of resin were coated by pouring PEG3000 solution through the cartridge and then washing with deionized water (D.I. H$_2$O). PEG concentration in the final product was evaluated by iodine visualization TLC.

Recovery of $^{99m}$Tc was $92 \pm 4\%$ (n=4). Greater than 99.5% of the $^{99}$Mo was present in the load/wash fractions (n=2) thus allowing for minimal losses in terms of recycling enriched $^{100}$Mo. PEG3000 concentration in the final product was lower than the limit of detection for our TLC spot test (0.1 mg/mL), pH was 6 and the product was clear and colorless.

**Conclusions:**

We developed a practical and easily accessible system for separation of $^{99m}$Tc-pertechnetate, with good recovery yields for $[^{99m}\text{Tc}]\text{TcO}_4^-$ and promising features for molybdenum recovery. The final product passed appropriate QC tests.

**3.2 Summary of Molybdenum Target Sintering Results**

Our work towards sintering a molybdenum target has progressed steadily. We have tested various parameters to optimize the sintering process, including the type of atmosphere used and the temperature of the oven, the substrate on which the molybdenum is sintered, and the pressure at which the molybdenum is pressed. We have also worked on developing an efficient method to shape the molybdenum powder prior to pressing and sintering.

We found the best results when the molybdenum was sintered at 1600°C under a reducing atmosphere (5% H$_2$ in Ar) for 4 hours, with the resulting molybdenum achieving a density of ca. 8.2gcm$^{-3}$. Molybdenum sintered at lower temperatures (1200-1400°C) achieved less than half of its maximum density (4.2±2gcm$^{-3}$ vs. 10.2 gcm$^{-3}$); it remained powdery and brittle. Increasing the time for the sintering process had negligible benefits. An inert atmosphere produced variable results.

Some of the substrates that were tested as supports to hold the molybdenum during sintering were sensitive to an inert atmosphere. Tantalum warped under a nitrogen atmosphere. Tungsten showed signs of embrittlement after multiple uses. Glassy carbon and quartz were effectively destroyed at high temperatures, regardless of the atmosphere. Aluminum oxide fared much better, and could withstand elevated temperatures and different atmospheres; it was deemed the best substrate for further studies.

A method was developed to shape and press the molybdenum prior to putting it on the aluminum oxide and sintering. The molybdenum powder was spread over a glassy-carbon based template, the powder was transferred to a steel or tantalum brick, and pressed hydraulically to compress the powder at ca. 8000 psi. The pressed target was then transferred as a sheet onto the aluminum oxide plate for sintering. This process helped maintain targets of consistent quality and prevented the targets from bonding to the aluminum oxide. To prevent contamination of the enriched molybdenum, the materials of the template and the bricks used for pressing need to be carefully controlled.
D. Research Plan for 2013/2014

Our main objective for final period in this CRP is to develop the technological, regulatory and commercial bases for cyclotron-based $^{99m}$Tc supply to the medical community. It is hoped that this target and processing technology will lead to a reliable alternative source of $^{99m}$Tc, as well as provide a platform for the supply other biologically important radioisotopes for research and clinical applications.

Researchers at the University of Alberta will demonstrate that significant quantities of $^{99m}$Tc can be produced on a routine basis from a cyclotron. Our main milestones to be achieved in order to meet this objective are:

- Test the $^{100}$Mo target system capable of operating up to 500 µA with 24 MeV protons.
- Determine radionuclidic purity of $^{99m}$Tc produced with 24 MeV protons. In order to reduce the radionuclidic impurities from cyclotron produced $^{99m}$Tc a new batch of $^{99}$Mo (99.8%) was purchased from Isoflex (www.isoflex.com).
- Develop and demonstrate a $^{100}$Mo recycling process and determine the cost-effectiveness of the $^{100}$Mo recycling.
- Align and demonstrate the complete commercially viable supply chain, from raw materials to patient.
- Develop a standard cost-effective facility-wide solution; including equipment, infrastructure, work flow and licensing, and the development of fully automated GMP compliant target processing and $^{99m}$Tc recovery system.
- Continue the evaluation of cyclotron produced $^{99m}$Tc radiopharmaceuticals in animals and in patients.

Publications, Patents, Posters and Invited Presentations (2012-2013)

Publications

1. K. Gagnon, J.S. Wilson, S.A. McQuarrie, (2012), Letter to the Editor: Experimental cross section measurements for the $^{100}$Mo(p,x)$^{101}$Tc, $^{96}$Nb, and $^{97}$Nb reactions in the energy range of 10 to 18 MeV, Nucl. Med. Biol. 39:923–925.


Patents, Report of Inventions

1. Target preparation and recycling molybdenum for the cyclotron production of $^{99m}$Tc. J Wilson, K Gagnon, SA McQuarrie (Report of Invention, patent filed), 4 April 2011.
Invited Presentations


4. J.D. Andersson, K. Gagnon, J.S. Wilson, J. Romaniuk, D.N. Abrams, S.A. McQuarrie, Separation of molybdenum and technetium, Presented at the 14th International Workshop on Targetry and Target Chemistry, Mexico, August 2012.

5. K. Gagnon, J. Wilson, A.J.B. McEwan, D.N. Abrams, J. Romaniuk, J.D. Andersson, S.A. McQuarrie, Overview of $^{99m}\text{Tc}$ production at the University of Alberta, Presented at the 14th International Workshop on Targetry and Target Chemistry, Mexico, August 2012.


NUCLEAR DATA AND CYCLOTRON PRODUCTION OF $^{99m}$Tc

S. Takacs, Hungary

Abstract. Possibility of accelerator production of $^{99m}$Tc based on the $^{100}$Mo(p,2n)$^{99m}$Tc reaction was studied by using yield calculations for the reactions energetically allowed. After determining the list of the reactions involved in accelerator production of $^{99m}$Tc up to 30 MeV proton energy on enriched $^{100}$Mo target a reaction network calculation was build up to study the achievable yields of the main product and the amount of contaminating radionuclides. The trends of production yields, number of produced nuclides, relative activity and relative physical doses were determined. New experiment was performed to determine the excitation function of the two main reactions $^{100}$Mo(p,2n)$^{99m}$Tc and $^{100}$Mo(p,x)$^{99}$Mo. An earlier experiment was re-evaluated by using up to date nuclear decay data. Averaged fit values were calculated for the two main reactions from selected datasets. Comparison of MENDL-2p and TENDL-2012 data library was done. Results provided by the reaction network calculation was analyzed and final conclusions were deduced regarding production conditions and quality of the accelerator produced $^{99m}$Tc. Comparison of accelerator and generator produced $^{99m}$Tc was done.

Accepted work plan for Atomki

- Collection and selection of the experimental cross section data for the reactions involved in the production process (depending on the bombarding energy the number of important reactions can be around 50)
- Selection of the possible best cross section results predicted by different theoretical models for those reactions for which no experimental data are available.
- To build up a dedicated database containing cross section data (from threshold up to 30 MeV) for the reactions can be important regarding the $^{99m}$Tc production
- Determine the amount of different radionuclide produced during irradiation as function of bombarding energy, irradiation time and cooling time for the different available target enrichments.
- Analysis of the calculated radionuclide profiles in order to determine optimal production parameters.
- Determination of the maximal (theoretical) specific activity for various irradiation parameters and target compositions.
- Determine the time dependence of the specific activity of the $^{99m}$Tc product

1. Measurement and selection of experimental cross section data

Proton induced experimental cross section data measured on enriched and natural molybdenum targets are available in literature but do not cover all the nuclear reactions which are involved in accelerator production of $^{99m}$Tc. The quality and consistency of the available data are not satisfactory. Therefore data should be analyzed carefully and the erroneous data should be selected to be able to provide a more reliable data set. For proton bombardment of molybdenum two main reactions should be investigated the $^{100}$Mo(p,2n)$^{99m}$Tc and the $^{100}$Mo(p,x)$^{99}$Mo. During experiments one can easily introduce systematic errors which could result in incorrect amplitude of the presented excitation function.

The most probably error sources are:
- beam current measurement or charge integration
- detector efficiency calibration
- target thickness measurement
- use of out dated decay data
- problematic peak area determination due to interfering reactions or gamma-lines

To identify hidden systematic errors in an experiment is not trivial. One should know all the experimental parameters and conditions to be able to judge the results which are partly or not at all published.
In order to be able to select among the available datasets, or at least to be able to give stronger arguments for the selection/de-selection, we performed a new measurement using natural molybdenum target and well controlled experimental circumstances. Beside the new experiment cross section data were recalculated in one of our earlier measurement using the original spectra and two different evaluation methods with updated decay parameters.

In the experiment to minimize the systematic error which can be introduce with beam current measurement a Faraday-cap type target holder equipped with electron suppressor was used. For irradiation the stacked target technique was used. The target foils were arranged carefully. Behind each Mo target foil a thin Ti foil was inserted that served as capture foil and monitor foil as well. This way not only a few point but the complete excitation function of the $^{nat}\text{Ti}(p,x)^{48}\text{V}$ monitor reaction and $^{nat}\text{Ti}(p,x)^{46}\text{Sc}$ reaction induced in the Ti foils were determined and compared with recommended values. The Ti foils collected the possible recoiled reaction products from the Mo foils. Using this method the systematic error that could be originating from beam current measurement was minimized.

The detector efficiency was carefully determined by using standard calibrated gamma-sources. The shape consistency of the efficiency curve was checked by measuring different energy gamma lines of the same radionuclide in the high and low energy region and the deduced cross sections were compared with each other. The agreement among the cross section data deduced from different gamma lines confirms that the shape of the detector efficiency curve is correct. The absolute values of the efficiency curve can be checked by comparing the values of the beam current deduced from Faraday-cup measurement and from the use of monitor reactions.

Using high purity natural molybdenum foil as target material with shiny surface and well defined areal geometry the uncertainty of the number of target atoms was minimized.

For data evaluation the nuclear decay data were taken from the latest evaluation work published in the series of Nuclear Data Sheets.

Figure 1 shows the comparison of the monitor reaction and the cross section data deduced in our new experimental work. The agreement among the data point and the curve is excellent that means no hidden systematic error is included in the beam current measurement.
Fig. 1. Comparison of monitor reaction with data deduced in this work.

2. The $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ reaction

The excitation function of the main reaction $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ has been measured several times in the past resulting a not really consistent database. The available data are collected and are shown in Fig 2 including our new dataset measured on natural molybdenum target as well as the re-evaluated data published in 2003. Since in practice no 100% enriched $^{100}\text{Mo}$ target exists the experimental data represent the sum of the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ main reaction and the $^{98}\text{Mo}(p,\gamma)^{99m}\text{Tc}$ capture reaction. The maximum cross section of the $^{98}\text{Mo}(p,\gamma)^{99m}\text{Tc}$ reaction is three orders of magnitude lower than the one of the main reaction, which is below the uncertainties of the presented data, therefore can be neglected. Considering enriched $^{100}\text{Mo}$ target in which the abundance of $^{98}\text{Mo}$ isotope is below 1% the importance of the (p,\gamma) reaction is still lower.

The experimental data measured by different groups are spread over a factor of two at the maximum of the excitation function due to hidden systematic errors. Some data sets are obviously not correct. Removing the dataset measured by Lagunas-Solar et al. in 1991 and data of Khandaker reported in 2006 the remaining ones have “only amplitude” problems.
Most of the available experimental works were performed on natural molybdenum target that requires special attention for the 140.51 keV peak area analyses. Using natural molybdenum target the 140.51 keV peak is a complex peak includes contribution from direct and decay production of $^{99m}$Tc, prompt gamma-line of the decaying longer lived $^{99}$Mo and above 9 MeV where the $^{94}$Mo(p,n$\alpha$)$^{90}$Nb reaction become energetically possible the contribution of decaying $^{90}$Nb which has a 140 keV gamma-line that cannot be resolved by the usual measuring technique.

All these contributions to the 140.51 keV gamma-line should be identified and carefully separated. Due to the statistical nature of radioactive decay the separation of different contributions to the total measured peak area of 140 keV unavoidable introduces additional uncertainties that result in larger scattering of the deduced cross section data points in the 15 – 25 MeV energy region.

Data presented in Fig 2. as Takacs 2003 were re-evaluated using up to date decay parameters and updated monitor reaction which resulted in 8% higher and more narrow excitation function. The new shape is in accordance with the excitation function determined in the new experiment.

The other available experimental data sets can be sorted into different groups. Data of Lagunas-Solar 1991 and Khandaker 2006 are shifted and have unusual shape, therefore they are discarded. Data of Lagunas-Solar 1996 and Challan 2007 form the “high group”. Data of Scholten 1999, and Khandaker 2007 form the “low group”. The normalized data of Levkovskij 1991, Lebeda 2010, Tarkanyi 2012, the re-evaluated data of Takacs 2003 and data of this work form the “middle group”. Data of Gagnon 2011 are in between the high group and the middle group. Data points in one group are in agreement with each other within the reported errors. The differences among the groups can be explained only by hidden systematic errors and therefore it is difficult to find a non-subjective reason to renormalize the published data. Since there is no real scientific
argument to decide which group corresponds best to the real excitation function the “middle group” that includes most results was chosen for further considerations.

Using the five selected data sets an average was calculated by cubic spline method and presented in Fig. 3 as new fit of the experimental data. In the later calculation this “averaged” data were included for the $^{100}$Mo($p,2n$)$^{99m}$Tc reaction.

3. The $^{100}$Mo($p,x$)$^{99}$Mo reaction

The presented experimental cross sections are cumulative cross section. The two reactions are $^{100}$Mo($p,pn+d$)$^{99}$Mo and the $^{100}$Mo($p,2p$)$^{99}$Nb→$^{99}$Mo. The cross sections for the main reaction are considerably higher than those of the ($p,2p$) reaction. Due to the short half-lives of the $^{99m}$Nb and $^{99g}$Nb the available experimental cross section for production of $^{99}$Mo are cumulative, include the production via decay of $^{99}$Nb. The available data are collected in Fig 4 together with the result of the new measurement of this work and the re-evaluated data published in 2003. The new results and the re-evaluated data are in good agreement with each other. The only difference between the original Takacs 2003 and the re-evaluated data set is the missing small bump on the newly calculated excitation function around 22 MeV. Selecting 7 data series a new spline fit was calculated over the data points. The selected data are: normalized data of Levkovskij 1991, Lebeda 2010, Chodash 2011, Gagnon 2011, Re-evaluation of Takacs 2003, 3 series of data sets included in the work of Tarkanyi 2012 and the results of this work.
Figure 5 represents the selected data sets and the newly calculated fit with estimated ±12% error band around it. An average of 12% uncertainty corresponds to ±20 mb uncertainty, above 25 MeV proton energy, where the excitation function has a quasi-flat region.

Beside the above discussed main reactions experimental data for the other reactions involved in the real accelerator production of $^{99m}$Tc are very scarce. To perform calculation for estimating the amount and purity of the produced $^{99m}$Tc cross section data of a large network of nuclear reactions are needed. Since no experimental cross section data are available for most of the remaining reactions involved in the production theoretical cross section data were used in the calculations. The required cross section data can be taken as result of different model calculation available in different data libraries or can be calculated by using different computer codes. Model calculation with specially adjusted input parameters can provide better results.
Fig. 5. Selected experimental cross section for the $^{100}\text{Mo}(p,x)^{99}\text{Mo}$ cumulative reaction and the calculated spline fit. An average of 12% uncertainty corresponds to ±20 mb uncertainty above 25 MeV proton energy where the excitation function has a flat region.

Data of two data libraries were compared to the experimental data available on the Internet. The TENDL-2012 based on TALYS calculations and MENDL-2p based on ALLICE-IPPE calculation code. Both libraries provide cross section data for the reactions included in the reaction network calculation for estimating the amount of $^{99m}\text{Tc}$ and other reaction products. Since experimental data measured on different enriched molybdenum isotopes available only for a few reactions and direct comparison of experimental data with model calculation is not possible for every reaction. The data provided in the data libraries were scaled to natural abundances of the Mo and cross section data measured on different stable isotope of Mo resulting from the same reaction product were summed up. The linear combinations of theoretical results were compared with the experimental data measured on natural Mo target. The general conclusion is that the MENDL-2p performs less adequately and the estimations are not so satisfactory. Additionally the MENDL-2p calculation do not provide separate data for ground states and excited states instead only the sum of the two cross section data are given. Because of these two drawbacks data from the TENDL-2012 data library are used in our calculation except for the two main reactions $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ and $^{100}\text{Mo}(p,pn)^{99}\text{Mo}$ for which the fitted experimental data were used.

Comparing some of the available experimental data and the corresponding data from TENDL-2012 library as a general conclusion is drawn that the agreement for ground state data is better than the agreement for data of meta-stable states. The theory generally underestimates the cross section of meta stable states with some exemption. Examples for experimental and theoretical cross sections are presented in figures 7 - 13. The experimental cross section data measured for the $^{nat}\text{Mo}(p,x)^{96m+g}\text{Tc}$ reaction is compared with the linear combination of the data from TENDL-2012 database in Fig. 6. Regarding that the theoretical excitation functions used in the calculation have deviation from the real cross section values in average 20% in both directions, in a few cases even higher deviation exist, the received result should be considered as “good approximation”. However, the deduced trends and relative values as function of bombarding energy and/or irradiation time describe well the real situation.
Fig. 6. Comparison of experimental data measured for the \( ^{nat}Mo(p,x)^{96m+g}Tc \) reaction with result of TALYS calculation taken from TENDL-2012 data library.

On the figures Fig. 7 – Fig. 13 the excitation functions for producing Tc radionuclides are collected by mass number of molybdenum target nuclides including experimental data only for comparison.

Fig. 7. Excitation function of proton induced reactions on \(^{100}Mo\) target for producing Tc radioisotopes. Reactions with threshold energies below 30 MeV are considered. For comparison some experimental data are also given.
Fig. 8. Excitation function of proton induced reactions on $^{98}$Mo target for producing Tc radioisotopes. Reactions with threshold energies below 30 MeV are considered.

Fig. 9. Excitation function of proton induced reactions on $^{97}$Mo target for producing Tc radioisotopes. Reactions with threshold energies below 30 MeV are considered.
Fig. 10. Excitation function of proton induced reactions on $^{96}$Mo target for producing Tc radioisotopes. Reactions with threshold energies below 30 MeV are considered.

Fig. 11. Excitation function of proton induced reactions on $^{95}$Mo target for producing Tc radioisotopes. Reactions with threshold energies below 30 MeV are considered.
Fig. 12: Excitation function of proton induced reactions on $^{94}$Mo target for producing Tc radioisotopes. Reactions with threshold energies below 30 MeV are considered.

Fig. 13: Excitation function of proton induced reactions on $^{92}$Mo target for producing Tc radioisotopes. Reactions with threshold energies below 30 MeV are considered.

Analysis of the excitation function of the main reaction $^{100}$Mo(p,2n)$^{99m}$Tc can provide the first constrain for the bombarding energy. Due to the shape of the (p,2n) reaction the bombarding energy
should not be higher than 25 MeV. Above that energy the cross section is low and with increasing proton energy the amount of co-produced contaminating radioisotopes in the target material is increasing much rapidly than the amount of $^{99m}$Tc. To avoid the long lived $^{98}$Tc contamination one should lower the initial bombarding proton energy below the threshold of the $^{100}$Mo(p,3n)$^{98}$Tc reaction, which is just below 17 MeV. By doing that the achievable amount of $^{99m}$Tc is reduced but the amount of co-produced $^{98}$Tc radioisotopes is reduced to zero which improves considerably the contamination level of the product.

4. $^{99}$Mo/$^{99m}$Tc Generator produced $^{99m}$Tc

Regarding the Tc contamination of fission produced $^{99m}$Tc only the unavoidable $^{99g}$Tc is present in the freshly eluted solution as contamination. Both the $^{99m}$Tc and $^{99g}$Tc are produced only by decay of $^{99}$Mo. The number of $^{99}$Tc radionuclide in ground state and in excited state is increasing by time according to the decay rule. Due to the 6 h half-life of $^{99m}$Tc its amount reaches a maximum after 22.9 hour decay time, while the amount of $^{99g}$Tc continues to rise. In the clinical practice the $^{99}$Mo generator column is eluted every 24 h, which gives approximately the maximal $^{99m}$Tc activity at each time.

![Graph showing the time dependence of the growth of $^{99m}$Tc and $^{99g}$Tc produced by decaying $^{99}$Mo in the $^{99}$Mo/$^{99m}$Tc generator](image)

Fig. 14. The time dependence of the growth of $^{99m}$Tc and $^{99g}$Tc produced by decaying $^{99}$Mo in the $^{99}$Mo/$^{99m}$Tc generator

After elution no more decay of $^{99}$Mo feeds the amount of $^{99m}$Tc instead the amount of $^{99m}$Tc decreases according to the decay law, while the amount of $^{99g}$Tc continues to increase due to decay of the $^{99m}$Tc isomer state, therefore the ratio of the radionuclides in the two states are changing more rapidly after elution. Figure 15 shows the time dependence of the ratio of the two states $^{99g}$Tc/$^{99m}$Tc. The ratio at zero time corresponds to the decay branching ratio of $^{99}$Mo and increasing till the elution. Applying 24 h decay time the ratio, the amount of $^{99g}$Tc/$^{99m}$Tc reaches 2.5 when the elution takes place. After elution the ratio is increasing more rapidly with time.
Fig. 15. Time dependence of $^{99g}\text{Tc}/^{99m}\text{Tc}$ ratio from fission produced $^{99}\text{Mo}/^{99m}\text{Tc}$ generator

5. Accelerator production of $^{99m}\text{Tc}$

The $^{99}\text{Mo}/^{99m}\text{Tc}$ generator produced Tc contains only $^{99m}\text{Tc}$ and $^{99g}\text{Tc}$ radionuclides no other mass Tc radionuclides are present. While for accelerator produced $^{99m}\text{Tc}$ presence of other mass Tc radionuclides is unavoidable. Considering 100% enriched $^{100}\text{Mo}$ target the amount of co-produced Tc radioisotopes growing rapidly with increasing bombarding energy and the longer lived Tc isotopes are accumulating with longer irradiation time. In the real production case the highly enriched $^{100}\text{Mo}$ target material contains other lower mass Mo isotopes too, on which different unwanted nuclear reactions take place at any chosen bombarding proton energy. The threshold energy of the $^{100}\text{Mo}$(p,2n)$^{99}\text{Tc}$ reaction is 7.79 MeV therefore the bombarding energy should be higher than 7.8 MeV. And because there are several other reactions with threshold energy lower than 7.8 MeV on the different stable isotopes of molybdenum production of unwanted radionuclides is unavoidable. To estimate the amount of different reaction products and their activity a calculation tool was developed. The calculation includes direct and indirect production of the involved radioisotopes considering every possible decay chain. To calculate the production rates cross sections data were taken from TENDL-2012 data library except for the two main reactions. The yields of the reaction products were estimated for all reactions on the stable isotopes of molybdenum with threshold energy up to 30 MeV. Table 1 shows the reaction products and their threshold energies on different molybdenum target isotopes. When more than one reaction routes exists for production of a certain radionuclides on the same target isotope only the lowest threshold energies is listed (i.e. for reactions (p,α) and (p,2p2n)). Setting the bombarding proton energy limit to 30 MeV the number of reactions in Table 1 is 160. Considering the reactions leading to radionuclides in isomer state the total number of the reactions is more than 200. The number of reactions which are included in the calculation network at 17 MeV proton energy is around 140.
TABLE 1. LIST OF REACTION PRODUCTS AND THE CORRESPONDING LOWEST THRESHOLD ENERGY, GIVEN IN MEV, FOR 30 MEV PROTON BOMBARDING ENERGY. DATA ARE TAKEN FROM NNDC Q-VALUE CALCULATOR. REACTIONS LEADING TO ISOMER STATE OF A REACTION PRODUCT ARE NOT LISTED HERE. DATA IN BOLD CORRESPOND THRESHOLD ENERGY LESS THAN 17 MEV.

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Using the reaction network calculation one can model most of the aspects of the accelerator production of \(^{99m}\text{Tc}\) by proton bombardment using highly enriched \(^{100}\text{Mo}\) target.

6. Yield and specific activity estimation of \(^{99m}\text{Tc}\)

To estimate the yield of different radionuclides produced during irradiation of enriched molybdenum target both direct and indirect production were considered. Irradiating the Mo target most of the reaction products are radioactive and decay to other isotope forming a decay chain. The contribution of different production routes leading to the formation of the same reaction product are summed up when estimating the final number of reaction products present in the target at any time. The well-known mathematical formulae describing the formation and decay of stable and radioactive reaction products are used. For activation only the one step direct production is considered. Any secondary reaction that may occur at each level of the newly produced isotopes has been ignored. For indirect production routes one or multiple-step (up to 5 steps decay, or 6 elements) decay chains are considered. Reactions induced by the bombarding proton beam in the molybdenum target leading to the products listed in table 1 and their longer lived isomer states are included in the calculation. The actual differential equation was solved analytically by direct integration, for every different production routes and was applied in the calculation. Calculating the reaction yields or the number of newly formed nuclides in a single irradiation the change in the number of target nuclei during the irradiation process has been considered negligible. The yield calculation uses target thickness corresponds to the proton range from bombarding energy down to 7.8 MeV, the threshold of the \(^{100}\text{Mo}(p,2n)^{99m}\text{Tc}\) reaction. The calculation is divided into 3 main parts regarding time scale. Irradiation time: From start of irradiation till end of bombardment (EOB), that includes the direct and indirect production of the reaction products. Cooling time1: From EOB till the end of separation of Tc isotopes from the irradiated target. During this cooling time period only indirect decay production of Tc and other reaction products take place. Cooling time 2: This cooling period starts when the separation of the Tc isotopes is completed and applied only to follow the decay of the Tc activities. Supposing that only Tc is removed from the dissolved target material by the separation process to follow the decay of the remaining radioactive nuclide species in the target the cooling time starts at EOB.

Estimating the production yield of \(^{99m}\text{Tc}\) and the amount of co-produced stable and radioactive reaction products by calculation highly enriched \(^{100}\text{Mo}\) target material was supposed with isotopic composition: \(^{100}\text{Mo} 99.54\%\), \(^{98}\text{Mo} 0.41\%\), \(^{97}\text{Mo} 0.0016\%\), \(^{96}\text{Mo} 0.0012\%\), \(^{95}\text{Mo} 0.0076\%\), \(^{94}\text{Mo} 0.0051\%\), \(^{92}\text{Mo} 0.006\%\). Cross section data included in the calculation were taken from TENDL-2012 data library except for the \(^{100}\text{Mo}(p,2n)^{99m}\text{Tc}\) and \(^{100}\text{Mo}(p,pn)^{99}\text{Mo}\) reactions for which evaluated experimental cross section data were used.

From figure 16 can be red that the amount of additional Tc radionuclides is growing rapidly with increasing bombarding energy and with longer irradiation time which is investigated in more detailed way below. To keep down the amount of co-produced Tc and other reaction products the irradiation time should be optimized and the bombarding energy should be as low as the possible to be able to produce the requested amount of \(^{99m}\text{Tc}\), and the proton energy should not be higher than the threshold energy of the \(^{100}\text{Mo}(p,3n)^{98}\text{Tc}\) reaction to avoid the production of \(^{98}\text{Tc}\) on the almost 100% abundant \(^{100}\text{Mo}\).

More detailed analysis of the bombarding energy and irradiation time dependences of the yield of \(^{99m}\text{Tc}\) and other reaction products is given in the following section.
Fig. 16. Comparison of the relative Tc content of $^{99}$Mo/$^{99m}$Tc generator and accelerator produced $^{99m}$Tc

7. Results and Discussion

7.1. Quality of accelerator produced $^{99m}$Tc as function production conditions

Detailed calculation on reaction network for production of $^{99m}$Tc by proton bombardment shows that not only the long lived $^{99g}$Tc and $^{98}$Tc co-produced radionuclides have importance regarding the isotopic purity and specific activity of $^{99m}$Tc but other lower mass Tc radionuclides too.

In the following sections data are compared for a 3 h irradiation, 17 – 7.8 MeV bombarding energy, which corresponds to ~430 µm target thickness depending on the porosity of the target, target isotopic composition mentioned above, 1 hour post irradiation processes including separation of Tc radionuclides and 1 h further cooling time including the labeling chemistry. The above defined irradiation and cooling parameters are referred as “standard” parameters in this calculation if not otherwise stated.

Figure 17 shows the estimated absolute number of Tc nuclides with different mass and exited states are present beside the $^{99m}$Tc after an irradiation and handling process with above defined standard parameters. Data in Fig. 17 are normalized for 1µA beam intensity. As it is clearly visible $^{99g}$Tc is the most produced radionuclide. Although the bombarding energy is below the threshold of the $^{100}$Mo(p,3n)$^{98}$Mo reaction relatively large amount of $^{98}$Tc and $^{97m,g}$Tc are present due to the reactions on of lower mass stable isotopes of molybdenum in the target with minor amount. Figure 18 reproduces the relative number of different Tc nuclides scaled to the amount of $^{99m}$Tc. The numerical values are collected in Table 2.
Fig. 17. Number of Tc nuclides with different mass and exited states are present beside $^{99m}$Tc for a 3 h, 17 MeV irradiation, 1 hour post irradiation processes including separation of Tc radionuclides and 1 h further cooling including the labeling chemistry.

Fig. 18. Relative number of Tc radionuclides normalized to the amount of $^{99m}$Tc after a 3 h 17 MeV irradiation, 1 hour cooling till separation of technetium and 1 h further cooling before use of the $^{99m}$Tc labeled product.
TABLE 2. COMPARISON OF THE AMOUNT OF DIFFERENT TC RADIONUCLIDES PRESENT BESIDE $^{99m}$Tc AFTER A 3 H LONG IRRADIATION, 1 HOUR COOLING TILL SEPARATION OF TECHNETIUM AND 1 H FURTHER COOLING AT 17 MEV PROTON BOMBARDING ENERGY AND 432 µM TARGET THICKNESS WHICH CORRESPONDS TO 17 – 7.8 MEV PARTICLE ENERGY.

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For this production condition the number of $^{99g}$Tc is 4.86 times more than the number of $^{99m}$Tc. The amount of the remaining other xxTc is only 0.027 times more than the number of $^{99m}$Tc. It means that the specific activity of $^{99g}$Tc is mainly influenced by the amount of $^{99g}$Tc in this production circumstances. For comparison: for $^{99}$Mo/$^{99m}$Tc generator produced $^{99m}$Tc based on 24 h elution period the amount of $^{99g}$Tc is 2.9 times higher than the amount of $^{99m}$Tc at 1 h after the elution time which is comparable the one that can be reached by accelerator production of $^{99m}$Tc.

However by comparing the physical dose of the contaminating technetium radionuclides in the generator and accelerator produced $^{99m}$Tc the situation is much different. While for the generator produced $^{99m}$Tc only the very long lived $^{99g}$Tc is present as contaminating technetium radionuclide for the accelerator production several other Tc radionuclides are present with shorter and longer half-lives. The total activity of these contaminating Tc radionuclides is about 4 orders of magnitude lower than the activity of $^{99m}$Tc but at the same time about 4 orders of magnitude higher than the activity of the long lived $^{99g}$Tc. The radionuclides $^{93g}$Tc, $^{94m}$Tc, $^{94}$Tc and $^{101}$Tc represent most of the activity. Calculating the physical dose of the different Tc radionuclides and comparing to the dose of $^{99m}$Tc the ratio is even higher. It can be seen in Fig 19 that the relative physical dose for several of the lower mass xxTc radionuclides is significantly higher (5 – 6 order of magnitudes higher) than the relative physical dose for $^{99g}$Tc and only 3 orders of magnitudes lower than the physical dose of $^{99m}$Tc.
Fig. 19. Relative physical dose of the different $^{99m}\text{Tc}$ radionuclides normalized to the physical dose of $^{99m}\text{Tc}$ after a 3 h irradiation time, 1 hour cooling time till separation of technetium and 1 h further cooling time before using the product.

7.2. Comparison of generator and accelerator produced $^{99m}\text{Tc}$

In this section the quality of accelerator produced $^{99m}\text{Tc}$ is compared with generator produced $^{99m}\text{Tc}$. The relative number of contaminating Tc nuclides, the relative activity and the relative physical dose are investigated as function of bombarding energy and irradiation time.

Supposing equal amount of $^{99m}\text{Tc}$ in the samples eluted from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator and produced by an accelerator means:

$$N(99m\text{Tc})_G = N(99m\text{Tc})_A \quad (1)$$

The number of atoms, activities and physical doses can be compared directly with each other.

$$\frac{N(99m\text{Tc})_A}{N(99m\text{Tc})_G} = \frac{N(all\text{ Tc} - 99m\text{Tc})_A}{N(99m\text{Tc})_G} \quad (2)$$

The conditions of generator produced $^{99m}\text{Tc}$ can be harmonized easily with the above defined production conditions for accelerator produced $^{99m}\text{Tc}$ by choosing 1 h cooling time after elution in case of generator produced $^{99m}\text{Tc}$. In that situation the elution time is the same for both the generator and accelerator production and the same 1 h cooling time is applied after elution. In Figure 20 the number of extra technetium atoms are compared in the accelerator produced specimen with those of in the generator produced one. The number of Tc atoms different from the $^{99m}\text{Tc}$ for accelerator production (i.e. $all\text{Tc} - 99m\text{Tc}$) divided by the total number of Tc atoms different from the $^{99m}\text{Tc}$ for generator production (i.e. number of $^{99g}\text{Tc}$). The number of extra Tc atoms in the accelerator produced sample at 14 MeV is 1.58 times more than that of in the generator produced sample. The ratio of the two quantities is increasing slowly up to about 20 MeV above that energy the slope of the curve is steeper and reaches 5.42 at 40 MeV.
When comparing only the $^{99}\text{Tc}$ in the two production methods the ratio is changing between 1.57 and 1.76, that means the amount of technetium contaminants other than $^{99}\text{Tc}$ is growing rapidly by increasing bombarding energy. Up to 17 MeV proton energy the ratio is determined by the amount of $^{99}\text{Tc}$. Above 17 MeV other reaction channels open and the co-produced lower mass technetium isotopes become more dominant. Similar trend can be deduced for the relative activity and relative physical doses with one significant difference (see Fig 21). While the ratio of the number of contaminating Tc atoms for the two production modes changes between 1.58 and 5.42 the ratio of the corresponding activity is 4 to 6 orders of magnitude higher and changing from $4.3 \times 10^4$ to $4.0 \times 10^6$ from 14 to 40 MeV. Due to the shorter half-life of the lower mass extra contaminating Tc isotopes the additional activity is much dominant than that of for the very long half-life $^{99}\text{Tc}$. Calculating the physical dose the situation is even worse. The 4 to 6 orders of magnitude higher activity corresponds to 6 to 7 orders of magnitude higher physical dose due to the decay properties of the contaminating Tc nuclides considered. Table 3 shows the relative number, the relative activity and the relative dose of the contaminating Tc radionuclides for the two production methods supposing that the same amount of $^{99m}\text{Tc}$ is produced by both methods. The ratio of $^{98}\text{Tc}$ acc/gen is also included in the table. Values are compared for supposing a 3 h irradiation time, 1 h cooling time till separation of technetium from the dissolved target material and 1 h further cooling time till use of the accelerator produced $^{99m}\text{Tc}$. For the generator produced $^{99m}\text{Tc}$ 1 h cooling time is considered after the elution with 24 h decay period.

The length of the irradiation time also influences the above ratios. Using longer irradiation time presence of the contaminants with short half-lives becomes less important due to saturation effect.

Figures 22 and 23 show the dependence of the above ratios as function of irradiation time.
Fig. 21. Comparison of the activity and the corresponding physical dose for the contaminating Tc radionuclides produced by accelerator and generator production methods as function of bombarding energy.

Table 3: Relative number, the relative activity and relative dose of the contaminating Tc radionuclides for the two production methods supposing that the same amount of $^{99m}$Tc is produced by both methods. The ration of $^{99g}$Tc acc/gen is also included.

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Fig. 22. Comparison of the number of contaminating Tc atoms of accelerator production to the generator produced ones as function of irradiation time.

Fig. 23. Comparison of the activity and the corresponding physical dose for the contaminating Tc radionuclides produced by using accelerator and generator methods as function of irradiation time.
8. Target recovery

The highly enriched, expensive $^{100}$Mo target material should be recovered and use again after suitable cooling time and proper target preparation. For any very strict target technology the change of the isotopic composition of the enriched material is unavoidable. For 17 MeV bombarding proton energy the required amount of target material is about $2.8 \times 10^{21}$ atoms/cm$^2$ (for a target thickness correspond to energy loss of the proton beam of $17 \pm 7.8$ MeV, $\sim 430 \mu$m). In a 17 MeV and 3 h irradiation cycle the number of reactions occurs on the $^{100}$Mo content of the target is estimated to be $1.5 \times 10^{14}$ 1/µA.

Supposing a beam intensity of 100 µA the number of reactions that takes place on $^{100}$Mo is in the order of $10^{16}$ during a 3 h irradiation. It is 5 orders of magnitude less than the number of $^{100}$Mo atoms in the target. However, during successive reuse and irradiation of the same target material under the same irradiation conditions the small changes are accumulating and the isotopic composition of the target gradually changes. In figure 24 the estimated relative change of the target composition is shown. Lower mass Mo isotopes are produced directly from the higher mass Mo isotopes. Beside direct production of Mo isotopes indirect production by decay of Nb and Zr nuclides should be considered. In the first estimation the balance of “loss” and “gain” is positive only for $^{96}$Mo and $^{97}$Mo isotopes. Due to the initial low amount of $^{97}$Mo in the enriched $^{100}$Mo target material, the relatively high cross section of $^{100}$Mo(p,α)$^{97}$Nb reaction and the short half-life of $^{97}$Nb the relative “gain” is very significant in case of $^{97}$Mo. It is somewhat more than 7 % after 100 times reuse of the same target material (see Fig 25) not considering the loss due to the chemistry. As consequence of gradual increase of the amount of $^{97}$Mo and $^{96}$Mo target isotopes an increase of the amount of produced $^{97m,Tc}$ and $^{96m,Tc}$ contaminating radionuclides occurs. This change in target composition would affect the isotopic composition, specific activity and relative dose of the final product which may invoke regulatory problems. Compensating the mass loss during reprocessing by adding fresh enriched target material the overall change will be less significant.

<table>
<thead>
<tr>
<th>Irradiation time (h)</th>
<th>Relative extra $^{99m}$Tc number</th>
<th>Relative extra $^{99}$Tc activity</th>
<th>Relative extra $^{99}$Tc dose</th>
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<tr>
<td>0.5</td>
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<td>4</td>
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<td>3.9E+04</td>
<td>8.4E+05</td>
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<tr>
<td>5</td>
<td>1.89</td>
<td>3.7E+04</td>
<td>8.1E+05</td>
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<tr>
<td>6</td>
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<td>24</td>
<td>4.62</td>
<td>3.1E+04</td>
<td>6.7E+05</td>
</tr>
</tbody>
</table>
Fig. 24 The estimated relative change of the target composition as function of number of irradiations.

Fig. 25 The estimated relative change of the target composition as function of number of irradiations. The increase of $^{97}$Mo is important.
9. Summary

- The averaged experimental data for the most important reactions $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ and $^{100}\text{Mo}(p,x)^{99}\text{Mo}$ used in the calculation may contain systematic errors that influence the estimated amount of $^{99m}\text{Tc}$.
- Result of nuclear model calculations based on the TALYS code and appropriate input parameters agree with the experimental data of (p,xn) and (p,pn) reactions quite well, but reactions with gamma or complex particles in the exit channel, like (p,γ), (p,αn), etc., are not described so well. Experimental cross section data are not available for all the reactions involved in accelerator production of $^{99m}\text{Tc}$ for those cases only the results of theoretical calculations are available.
- Highly enriched $^{100}\text{Mo}$ as target material is needed for accelerator production of $^{99m}\text{Tc}$ to reduce the amount of contaminating technetium in the product. Activity of the Tc impurities for accelerator production can be several orders of magnitude higher than that of in the generator produced case and very much depend on the composition of the target material, beam energy and irradiation time.
- Only the direct production of $^{99m}\text{Tc}$ can be considered. Avoiding high level of contamination the bombarding energy should be kept low and those energies the yield of indirect production of $^{99m}\text{Tc}$ via the $^{100}\text{Mo}(p,x)^{99}\text{Mo}$ reaction is low.
- The maximum proton energy for production of $^{99m}\text{Tc}$ is proposed to be 17 MeV below the threshold energy of the $^{100}\text{Mo}(p,3n)^{98}\text{Tc}$ reaction.
- The numbers of contaminating Tc atoms, other than $^{99}\text{Tc}$, are increasing rapidly with bombarding energy above 25 MeV.
- Calculations show that in any circumstances the amount of contaminating Tc radionuclides in accelerator produced $^{99m}\text{Tc}$ is higher than for generator produced one based on 24 h elution intervals. The higher contamination level definitely would affect the preparation of $^{99m}\text{Tc}$-chelates.
- In order to reduce the amount of Tc contaminants one should keep down the bombarding energy which result in lower yield of $^{99m}\text{Tc}$. The lower yield would provide $^{99m}\text{Tc}$ only for local or limited regional use.
- The expensive highly enriched $^{100}\text{Mo}$ target material should be handled centralized. Production should be made on daily basis and transport of the $^{99m}\text{Tc}$ product should be organized properly which would require good logistic.
- The accelerator produced $^{99m}\text{Tc}$ product would probably be more costly than the generator one.
- Proper logistic and recovery method should be developed for reuse of the expensive $^{100}\text{Mo}$ enriched material.
- Successive irradiations would change the composition of the original target material by building up the amount of lower mass Mo isotopes and reducing the amount of $^{100}\text{Mo}$. This change in target composition slowly would affect the isotopic composition, relative activity and relative dose of the final product.
- Successive irradiations gradually build up other elements in the target Ru, Nb and Zr up to 100 ppm levels which may invoke additional treatments of the recycled target material.

Table 5. gives a summary of the Estimated amount and quality of the accelerator produced $^{99m}\text{Tc}$ after a 3 h long irradiation at 17 MeV proton bombarding energy, 1 hour cooling till separation of technetium and 1 h further cooling using highly enriched $^{100}\text{Mo}$ target with 432 μm target thickness which corresponds to 17 – 7.8 MeV particle energy. Comparison of accelerator and generator produced $^{99m}\text{Tc}$ is included.
TABLE 5. ESTIMATED AMOUNT AND QUALITY OF $^{99m}$Tc AFTER A 3 H LONG IRRADIATION AT 17 MEV PROTON BOMBARDING ENERGY, 1 HOUR COOLING TILL SEPARATION OF TECHNETIUM AND 1 H FURTHER COOLING USING HIGHLY ENRICHED $^{100}$Mo TARGET WITH 432 $\mu$m TARGET THICKNESS WHICH CORRESPONDS TO 17 – 7.8 MEV PARTICLE ENERGY. COMPARISON OF ACCELERATOR AND GENERATOR PRODUCED $^{99m}$Tc.

<table>
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<tr>
<th>Parameter</th>
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<th>Generator</th>
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<tr>
<td>Bombarding energy</td>
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<td></td>
</tr>
<tr>
<td>Threshold energy</td>
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<td></td>
</tr>
<tr>
<td>Beam intensity $\mu$A</td>
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<tr>
<td>Irradiation time</td>
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<tr>
<td>Cooling time 1</td>
<td>1 h</td>
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<tr>
<td>Cooling time 2 $(1+1)$</td>
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<tr>
<td>Target thickness</td>
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<td>Number of reactions on $^{100}$Mo</td>
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<td>$\Sigma$ $^{xx}$Tc $^{99m}$Tc $^{99g}$Tc $\Sigma - ^{99m}$Tc</td>
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<tr>
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<td>7.84E+08</td>
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<tr>
<td>Physical dose [MeV/s] acc</td>
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<tr>
<td>Relative Phys. Dose acc/gen</td>
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<td>1.652</td>
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References
1. E. Browne and J.K. Tuli, Nuclear Data Sheets for A = 99*, Nuclear Data Sheets 112 (2011) 275–446
4. Q-value Calculator (QCalc), Data Source: Atomic Mass Data Center, NNDC, Brookhaven National Laboratory
Abstract. The direct production of $^{99m}$Tc through (p, 2n) reaction on a natural molybdenum target was investigated. Extrapolated thick target yield of $^{99m}$Tc from the irradiation of an enriched $^{100}$Mo target for 1h, 3h and 6h irradiation as a function of incident proton energy (up to 18MeV) was calculated from the irradiated natural molybdenum targets. Separation of technetium radionuclide from the irradiated target by a new method using Dowex-1 ion exchange resin as well as the standard solvent extraction (methyl ethyl ketone) method was studied. The quality of the final pertechnetate solution was assessed. Recovery of target material as molybdenum trioxide has been achieved.

1. Introduction

It is known that $^{99m}$Tc is the most important radioisotope used in the preparation of radiopharmaceuticals for diagnostic nuclear medicine. More than 80% of the administered radiopharmaceuticals are prepared from this radioisotope. Traditionally $^{99m}$Tc is being obtained indirectly from a radioisotope generator, $^{99}$Mo/$^{99m}$Tc, by decay of its parent radioisotope, $^{99}$Mo. The major amount of $^{99}$Mo used to make the generators is produced by fission of $^{235}$U in a nuclear reactor. Five old reactors (NRU of Canada, HFR of Netherlands, BR2 of Belgium, Safari-1 of South Africa and Osiris of France) meet almost entire global demand of $^{99}$Mo. Because of the steady supply of $^{99}$Mo (and hence $^{99m}$Tc) over the years from these reactors, production of $^{99m}$Tc by the direct route via the $^{99}$Mo(p, 2n)$^{99m}$Tc reaction in a cyclotron did not gain sufficient importance, though the production of large amount of $^{99m}$Tc by this route was demonstrated long back [1]. The renewed interest to study this production route as an alternate source of $^{99m}$Tc started only a few years back when the nuclear medicine community faced the scarcity of $^{99m}$Tc due to planned and unplanned shutdown of a couple of reactors (NRU, Canada; HFR-Patten, Netherlands) which were used to meet the major share of global demand of $^{99}$Mo. So, the researchers started to study thoroughly the various aspects of $^{99m}$Tc production in a cyclotron. Research activities in this direction include the study of the excitation function of $^{99m}$Tc and other isotopic and nonisotopic active/stable isotopes produced concurrently by proton induced reactions on Mo target [2, 3, 4, 5, 6, 7, 8, 9, 10], development of a target irradiation system which can utilize high beam current [11], development of a fast chemical separation method [12, 13, 14], recovery of $^{100}$Mo from the irradiated target [15] and assessment of the directly produced $^{99m}$Tc for the preparation of radiopharmaceuticals [12]. In the present work the authors have studied the yield of $^{99m}$Tc produced from the proton irradiation of a natural molybdenum metal target as a function of incident proton energy, developed a new method of separation of the Tc radioisotopes from the irradiated natural molybdenum target, assessed the quality of the TeO$_4^-$ obtained after the chemical separation and recovered molybdenum from the irradiated target as MoO$_3$.

2. Experimental

2.1 Materials

Reagents such as hydrochloric acid, nitric acid, ammonium carbonate, sodium hydroxide pellets, hydrogen peroxide etc., were of analytical grade and were procured from E. Merck, India. Mo foils and Cu monitor foils were purchased from H. Cross Co. NJ 07074, USA, and Material Research Corporation, New York, USA, respectively. Anion exchanger: Dowex-1x8 (Cl$^-$ form, 200–400 mesh), capacity 3–5 meq/dry g and Mo powder (<150 µm, 99.99%) were purchased from Sigma Chemical Co. St. Louis, MO. 63174, USA. Aluminium oxide, active basic and acidic (100–200 mesh), Brockman grade-1 (Prabhat Chemicals, Mumbai, India) were used in preparing the purification columns. [$^{99}$Mo]Na$_2$MoO$_4$ in 5N NaOH (150mg Mo/ml: 1.11–2.22 GBq/ml) used in optimizing the separation of $^{99m}$Tc from $^{99}$Mo and the cold kits (MDP and MIBI) were obtained from the Radiopharmaceutical Division, BARC and BRIT, Mumbai, India.
Paper chromatography (PC) strips (3 MM Chr, 20 mm width) were purchased from Whatman International Limited, England.

2.2 Target preparation

Two types of targets were irradiated. For irradiation at low beam intensity and for short duration, natural Mo foils (25 micron) in a stack (containing 4-7 foils, 10 mm x 10 mm, with an 8-10 micron thick natural Cu monitor foil placed just before the first Mo foil) were used. Circular (10 mm diameter) Mo pellet targets were used in the irrations of longer duration and at higher beam intensities. These Mo pellets were prepared by pressing about 400 mg natural Mo powder in a dice plunger at 980 MPa pressure.

2.3 Target irradiation

All the irradiation experiments were carried out with 16/18 MeV protons using the cyclotron of Variable Energy Cyclotron Centre (VECC), Kolkata. The beam current was measured by placing a natural copper monitor foil (8-10 mg/cm² thick) in front of the target. For beam current measurement the nat^{64}Cu(p, x)^{2,63,65}Zn cross-section data recommended by International Atomic Energy Agency [16] were used. In case of Mo-foil stack irradiation, stacks containing 4-7 nat^{99}Mo foils (each 25 micron thick) were irradiated with a proton beam (energy window: 8-18 MeV, current: 10-50 nA) for 5 minutes. In order to irradiate the stacked foil targets at lower beam energy, 100 µm, 200 µm, 300 µm, 400 µm thick Mo foils were used in between the Cu monitor foil and the Mo stack, to degrade the proton energy from 18/16 MeV. The actual “on target” beam energy falling on the individual foil in a stack was determined using the energy-range formula and tables [17]. The radioactivity in each Mo foil in the stack was assessed 1.5h after the end of irradiation (EOI). Mo pellet (about 400 mg) targets irradiated at 1-3 µA beam intensity for 1-6 hours were used to standardize the chemical separation of Tc-radionuclides from Mo and other co-produced non-isotopic impurities (e.g. nat^{97,96,95,95m}Nb) and to study the recovery of Mo from the irradiated target.

2.4 Gamma ray spectrometry

The radioactivity of samples was measured on a 30 cc HPGe detector coupled to an ORTEC 92X Spectrum master and a personal computer loaded with ORTEC Maestro II software. The detector used had 10% efficiency relative to a 3” x 3” NaI(Tl) detector and an energy resolution (FWHM) of 1.74 keV at the 1332 keV γ-peak of nat^{60}Co. A standard nat^{152}Eu source was used for the energy as well as for the efficiency calibration. The radionuclides were identified by their characteristic photo peaks and half-lives. In order to avoid any interference of counts from the same gamma energy of another radioisotope, carefully selected characteristic gamma energies of the respective radioisotopes were used for the activity measurement. The gamma energies used for the radioactivity measurement of different radioisotopes are listed in Table 1. All the nuclear data of these radioisotopes used for calculation were taken from the available reference [18]. The radioactivity measurement of all the radioactive samples was carried out at a suitable distance (0.5-25 cm) from the detector so that the dead time is below 10%. Total error in the yield was estimated in the standard way: the independent errors of the linearly contributing processes (beam current measurement-8%, statistical error in the counting-4% and uncertainty in the sample geometry-5%) were summed quadratically and the square root of the sum was taken. Thus, the total error estimated in the yield was about 10.2%.
TABLE 1. NUCLEAR DATA USED IN ESTIMATION OF VARIOUS RADIOISOTOPES

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>$t_{\text{½}}$ (h)</th>
<th>$E_{\gamma}$ (keV)</th>
<th>$I_{\gamma}$ (%)</th>
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<tr>
<td>$^{62}$Zn</td>
<td>9.193 h 548.35</td>
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<td>8.2</td>
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<td>243.93 d</td>
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<td>6.0067 h</td>
<td>140.511</td>
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<td>$^{99}$Mo</td>
<td>65.976</td>
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<td>2.75 h</td>
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<tr>
<td>$^{92m}$Nb</td>
<td>10.15 d 934.44</td>
<td>99.07</td>
<td></td>
</tr>
</tbody>
</table>

Direct counting of foils irradiated for short duration: Radioactivity in the irradiated foils were measured about 1.5h after the EOI in order to estimate the activity of the radioisotopes having shorter half-life (e.g. $^{94m}$Tc having $t_{\text{½}}$ 52 min). Typical assay live times were 300 sec for these samples. The radioactivity in the same irradiated foils were also measured for a longer duration and at a closer distance from the detector at different time points post irradiation in order to obtain a better counting statistics of those radioisotopes having longer half-lives. It is known that if the decay of the radioisotope during the measurement time is ignored, it will result in inaccuracy in radioactivity measurement. It has been calculated that when the measurement time duration is significantly longer compared to the half-life of the radioisotope (i.e. when duration of assay live time is larger than about 3/100th of the half-life of the radioisotope being assayed) the error in the activity estimation is increased beyond 1%. In such situation the actual activity at the start of measurement was calculated using the following formula:

$$A_{\text{SOC}} = \frac{c \cdot \lambda \cdot t_R}{(1-e^{-\lambda t_L}) \cdot \varepsilon \cdot \gamma \cdot t_L} \quad \ldots \ldots (1)$$

where, $A_{\text{SOC}} =$ activity of the sample counted at the start of counting, $c =$ total count of the sample for time $t_L$, $\lambda =$ decay constant of the radioisotope counted, $\varepsilon \gamma =$ detector efficiency for the particular gamma energy counted, $\gamma =$ gamma ray intensity of the characteristic gamma peak of the radioisotope counted $t_R =$ real time of counting, $t_L =$ live time of counting.

From the radioassay data of each foil that was irradiated for 5 min, yields of various radioisotopes were calculated. Then by adding the yield of a particular radioisotope in successive foils, the cumulative yield (in 5 min irradiation) of that radioisotope in the thick target was calculated as a function of incident proton energy. From these data thick target yield for 1h, 3h or 6h irradiation was calculated using the following formula:

$$A_t = A_5 \cdot \frac{\phi}{\phi'} \left(\frac{1-e^{-\lambda t}}{1-e^{-\lambda t_5}}\right) \quad \ldots \ldots (2)$$

where $A_t =$ activity at the end of 1h, 3h or 6h irradiation, $A_5 =$ activity at the end of 5min irradiation, $\lambda =$ decay constant of the isotope under consideration, $\phi =$ proton flux during the 1h, 3h or 6h irradiation, $\phi' =$ proton flux during the 5min irradiation.
2.5 Target dissolution

Irradiated target was dissolved following a reported method [15]. The irradiated target was taken in a conical flask and 3ml H$_2$O$_2$ (30% w/w, E. Merck, India, Purified) was added to it and the flask was heated (50-60 °C) in a water bath. When the target reacted completely with H$_2$O$_2$, the flask was brought to room temperature and 1ml of 3M ammonium carbonate was added drop wise to yield a clear solution.

2.6 Preparation of the basic alumina column (required in MEK separation)

5g of dry basic alumina obtained commercially was used directly for making this column, 80mm (H) x 14 .mm (dia.).

2.7 Anion exchange resin column (7mm×1mm) preparation

A slurry of 15 mg Dowex-1 x 8, Cl$^{-}$ resin in 2ml water was taken in a syringe and pushed into a polypropylene tube (internal diameter 1 mm, the other end of the tube was packed with some glass wool) to make the resin column. Both the ends of the tube were fitted with miniature barbed polypropylene fittings. The column was preconditioned by passing 10 ml of normal saline solution followed by washing with 5ml water.

2.8 Preparation of the acidic alumina column (required in Dowex-1-HNO$_3$ acid separation)

A slurry of 1.5g acidic alumina in 5ml water was poured into a glass column, 12mm (H) x 8mm (dia.), containing a sintered disc at the bottom. Excess liquid was drained off with the help of a vacuum pump and the column was washed thoroughly with 10ml saline. Both the ends of the column were closed with silicon rubber septa having a small hole at the centre for insertion of a needle. Care was taken to avoid entrapment of any air bubbles in the column bed. A liquid trap was connected in-line with the vacuum pump (purchased from Waters, Milford, USA) to prevent any accidental contamination of the pump.

2.9 Chemical separation of the Tc-radionuclides from the irradiated thick $^{99m}$Mo target

2.9.1 Separation by MEK solvent extraction method

The solution obtained after the dissolution of the irradiated target was thoroughly agitated with 5ml MEK in a vortex mixer. After standing for few minutes, the two layers got separated. The upper organic layer containing the Tc radionuclides was collected with a pipette and passed through a basic alumina column to trap any Mo impurity present in the extracted organic layer. The aqueous layer containing the molybdenum target material was preserved for recovery of molybdenum. Aliquots of the radioactive solution were taken from all the radioactive solutions handled before and after the separation for the estimation of separation efficiency using γ-ray spectrometry in an HPGe detector.

2.9.2 Separation by Dowex-1 resin and HNO$_3$ method

The flowchart of this separation procedure is shown in Fig.1. In this method, at first with the help of a vacuum pump the molybdate/pertechnetate solution was allowed to pass through the resin column, which immobilized the pertechnetate and allowed the molybdate to flow. The molybdate solution was collected in the molybdenum collection vial. The Mo line and the resin column were washed with 1ml of water and the washing was also collected in the molybdenum collection vial. The resin column was then washed with 5ml of water and the washing was collected in the waste collection vial. 4ml of 4M HNO$_3$ was passed through the resin column to elute $^{99m}$Tc into the evaporation vial. The HNO$_3$ line & the resin column were washed with 1ml water and the washings were collected in the evaporation vial. The evaporation vial was then
heated while a flow of air was passed through the HNO₃ acid line. HNO₃ was thus evaporated out completely and the evaporated HNO₃ was trapped in a NaOH bath. The evaporation vial was then cooled and the requisite volume (10ml) of saline was added. Sodium pertechnetate in saline thus obtained was passed through a small acidic alumina column (1.5g), a millipore filter (0.22µm) and then collected in a vacuum vial. This method was tried using both molybdate/pertechnetate radioactivity obtained from cyclotron target and reactor production of ⁹⁹Mo.

2.9.3 Niobium removal

This particular study was carried out to study whether niobium radioisotopes (which could be produced through various nuclear reactions and the amount of which depends on the energy of proton as well as the enrichment level of ⁹⁹Mo used) are removed in the two separation methods. For this study, the ⁹²mNb (t₁/₂= 10.15d) tracer required was produced in the cyclotron from nat Nb target through (p, pn) reaction. The irradiated niobium target was dissolved in a mixture of 1ml HF and 0.1ml HNO₃. A small amount of this active solution was deliberately added to the ⁹⁹Mo/⁹⁹mTc activity to find out the presence of Nb in ⁹⁹mTc fraction. For this, an aliquot from the stock solution and from both Mo and ⁹⁹mTc fractions obtained after separation was taken out for radioactivity measurement in the HPGe detector.

Dissolution of irradiated molybdenum in H₂O₂

Basification of the solution of Mo/⁹⁹mTc with ammonium carbonate

Passage of the Mo/⁹⁹mTc solution through a tiny resin column

Washing of the resin column with 3% ammonium carbonate solution

Elution of ⁹⁹mTc with 4ml 4M HNO₃

Removal of HNO₃ by evaporation and trapping in a NaOH trap

Reconstitution of dry residue of ⁹⁹mTc with saline

Collection of ⁹⁹mTc in a vacuum vial after passing through an alumina column via 0.22µm Millipore filter

FIG. 1. Separation and purification of ⁹⁹mTc from the irradiated molybdenum target using Dowex 1 column

2.10 MDP and MIBI Labelling

2 ml of the radioactive Tc-pertechnetate solutions obtained from the two separation methods were added separately to the freeze-dried kit vials of MDP and MIBI. The ⁹⁹mTc-MDP preparation vials were kept at room temperature for 10min while the ⁹⁹mTc-MIBI preparation vials were kept in a boiling water bath for 10min for the completion of the labelling reactions.

2.11 Quality Assessment Tests

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The radioactive pertechnetate solutions obtained from the two separation methods were checked for the clarity, pH, radionuclidic purity (RNP) and radiochemical purity (RCP purity). The clarity of the solution was checked by visual inspection and pH was evaluated using a suitable pH indicating paper.

2.11.1 Radionuclidic purity (RNP) and radiochemical purity (RCP)

The RNP of the final product was estimated using a calibrated HPGe detector. The RCP of radioactive \( \text{TcO}_4^- \) solution was evaluated by paper chromatography using Whatman paper strip (10cm x 1cm) and MEK as mobile phase. The RCP of \( ^{99m}\text{Tc-MDP} \) was evaluated by developing the Whatman paper strip (10cm x 1cm), spotted with the sample, in MEK solvent and saline. The radiochemical purity of \( ^{99m}\text{Tc-MIBI} \) was evaluated by developing the Whatman paper strip (10cm x 1cm), spotted with the sample, in MEK solvent and ethanol.

2.11.2 Chemical purity

MEK, molybdenum and aluminium contents in the final radioactive \( \text{TcO}_4^- \) solution were determined by turbidity/color tests using iodoform, potassium thiocyanate and chromazural-S tests, respectively, as per BRIT, Mumbai, India monograph.

2.11.2.1 MEK content test:

200 µl of 1N NaOH, 200 µl of 0.1N I\(_2\), 50 µl of the test solution and 150 µl distilled water were taken in a test tube. The turbidity produced in the sample was compared with that of the standard (0.1% v/v).

2.11.2.2 Molybdenum content test:

50 µl of the test sample, 50 µl of 10% KCNS and 10% SnCl\(_2\) were taken in a test tube. The orange-red colour produced in the sample was compared with that of the standard (10ppm).

2.11.2.3 Aluminium content test:

10 µl of the test sample, 30 µl of acetate buffer (0.1 M sodium acetate & 0.1 M acetic acid, pH = 4.6) and 10 µl of chromazural-S (2.7 mM) were taken in a test tube. The reddish pink colour produced in the sample was compared with that of the standard (10ppm).

2.11.2.4 Nitrate (NO\(_3^-\)) content test:

The level of nitrate ion in the final radioactive \( \text{TcO}_4^- \) solutions was measured using colorimetric test strips (Merck, Germany, Cat. No. 1.1020.0001). This test strips measure the nitrate ion concentration semi-quantitatively by visual comparison of the reaction zone of the test strip with the fields of a colour scale which can measure 10-500 mg/l of NO\(_3^-\).

2.11.2.5 Hydrogen Peroxide (H\(_2\)O\(_2\)) content test:

Similarly, the presence of hydrogen peroxide in the final radioactive \( \text{TcO}_4^- \) solutions was measured using colorimetric test strips (Merck, Germany, Cat. No. 1.10011.0001). This test strips measure the peroxide concentration semi-quantitatively by visual comparison of the reaction zone of the test strip with the fields of a colour scale which can measure 0.5-25 mg/l of peroxide.
2.12 Recovery of Mo from the irradiated target

The aqueous fraction containing ammonium molybdate obtained after solvent extraction with MEK or the eluate obtained after passing the load solution through the resin column in the Dowex-1 resin and HNO₃ method can be used to recover the enriched target material. In order to standardize the Mo recovery, 500mg of Mo metal was dissolved as per the method described in section 2.5. To this solution 200µCi of $^{99}$Mo was added. Then from this solution the $^{99m}$Tc and $^{99}$Mo fractions were separated by the two separation methods described above. Total $^{99}$Mo activities in the solution before separation and in the Mo fraction obtained after separation were estimated. In the Mo fraction, molybdenum was present as ammonium molybdate. This fraction also contained some ammonium carbonate which was used during Mo metal dissolution step.

2.12.1 Conversion of molybdate to MoO₃

The Mo fraction obtained in each separation process was separately heated in a small vial. Care was taken to avoid any loss of this solution during heating. When all the solvent evaporated out, the dry residue obtained was heated for one hour at about 700 °C. The residue turned light yellow in colour after this heating step. On cooling, the colour of the residue turned gray. The weight of the dry powder obtained was recorded. It was also noted that, commercial MoO₃ also turned yellow on heating.

2.12.2 Characterization of recovered molybdenum compound by X-ray diffraction

Recovered MoO₃ was characterized by X-ray powder diffraction method. For the purpose of comparison, XRD was also performed on commercially available (Loba Chemie, Mumbai, India, GR grade) sample of MoO₃ (unheated and heated at 700°C). The crystalline phases of the powder were identified in the D8 Advance (Bruker, Germany) X-ray diffractometer using monochromatized Cu Kα source (1.5418 angstrom radiation).

3. Results and Discussion

3.1 Stacked foil irradiation: Thick target yield of $^{99m}$Tc

Radioactivity of various Tc radioisotopes produced in each foils in the stacks, irradiated for 5min, was determined from the gamma spectrometry data. Then the yield of Tc radioisotopes in each foil for 5min irradiation with 1µA proton beam was calculated as a function of the incident proton energy. From these data by adding up the radioactivity of the respective radioisotope in successive foils, the thick target yield (TTY) for 5 min irradiation with 1µA proton beam was calculated and plotted as a function of the incident proton energy (Fig.2). Then the TTY of various Tc radionuclides for 1h, 3h, and 6h irradiations at 100µA proton beam were calculated using the equation (2) mentioned under section 2.4 and plotted as a function of the incident proton energy (Fig.3-8).
FIG. 2. Thick target yield of Tc radionuclides formed in 5min irradiation of a natural Mo target with 1µA proton beam.

FIG. 3. Thick target yield of $^{99m}$Tc obtained from 1h, 3h & 6h irradiation of a natural Mo target with 100µA proton beam.

FIG. 4. Thick target yield of $^{99}$Tc obtained from 1h, 3h & 6h irradiation of a natural Mo target with 100µA proton beam.
In the studied range of the proton energy, the yields of all the Tc radioisotopes produced in natural Mo target increase as a function of the incident proton energy. It may be noted that the direct production of all these Tc radioisotopes (except $^{99m}$Tc) can take place through more than one channel. However, $^{99m}$Tc can only be produced directly through $^{100}$Mo(p, 2n) reaction. For this reason the experimental TTY data obtained from this study can be directly extrapolated for enriched $^{100}$Mo target. The TTY of $^{99m}$Tc thus calculated at the end of irradiation (EOI) for 100% enriched $^{100}$Mo target for 1h, 3h, and 6h irradiations is represented in Fig.9. It is evident from this figure that if an 100% enriched $^{100}$Mo target is irradiated at 18→8MeV, 100µA proton beam for 1h, 3h, and 6h, it will produce 44, 119, 204 GBq of $^{99m}$Tc at EOI, respectively.
Several authors have published cross-sectional data for $^{100}\text{Mo}(p, 2n)^{99m}\text{Tc}$ reaction [2, 3, 4, 5, 6, 7]. From the three recently published excitation function data (Tarkanyi et al. [10], Gagnon et al. [9], Lebeda et al., [8]), we have calculated the TTY as a function of the incident proton energy between 18 and 8 MeV using the following formula:

$$Y = F \cdot T \cdot \left[1 - e^{(-\ln 2 \cdot t / 6.01)}\right] \cdot A \cdot \int_{E_2}^{E_1} \left(\frac{\partial \sigma}{\partial E_2}\right)^{-1} \times \cdot \ dE,$$  

$$\cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots \cdots 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FIG.9. Thick target yield of $^{99m}\text{Tc}$ obtained (present work) from 1h, 3h & 6h irradiation of an enriched $^{100}\text{Mo}$ target with 100µA proton beam.

Fig.10 shows a comparison of the TTYs of $^{99m}\text{Tc}$ obtained from our studies to that of Gagnon et al. [9], Labeda et al. [8] and Tarkanyi et al. [10] when 100% enriched $^{100}\text{Mo}$ targets are irradiated with 100µA proton beam for three hours. It is evident that our results are in very good agreement with that of Labeda et al. [8] and Tarkanyi et al. [10].
FIG. 10. Comparison of thick target yield of \(^{99m}\)Tc obtained by various authors in 3h irradiation of an enriched \(^{100}\)Mo target with 100µA proton beam

3.2 Chemical Separation

3.2.1 Dowex-1 resin and HNO\(_3\) method

In the new Dowex-1 resin and HNO\(_3\) method, pertechnetate was bound efficiently (95%) and eluted from the resin with very high yield (90%). \(^{99}\)Mo along with the non-radioactive molybdenum target material ended up in the waste stream. The overall yield of \(^{99m}\)Tc in both the separation methods was about 80%.

3.3 Quality Assessment of Purified \(^{99m}\)Tc

A challenge in the development of cyclotron produced \(^{99m}\)Tc is to ensure that the quality of the final pertechnetate preparation to be equivalent to that obtained from a \(^{99}\)Mo/\(^{99m}\)Tc generator.

At the end of the chemical separation, the product was evaluated for radionuclidic, radiochemical and chemical purity using the standard quality assessment protocols. The quality assessment results are summarized in Table 2. The radiochemical purity of the pertechnetate preparation was found to be 99%. The efficacy in labelling of MDP and MIBI with the pertechnetate solution obtained from either of the separation method was typically more than 95%.

In both the separation processes no \(^{99}\)Mo was detected in the product vial containing radioactive TcO\(_4^–\). It was found from the simulation studies that 99.8% Nb was removed in the washing process and 0.07% of initial amount of Nb was present in eluted \(^{99m}\)Tc obtained in the Dowex method. Nb peak was absent in the organic fraction obtained in the MEK solvent extraction process. So, it can be concluded that Nb will not contaminate the product in either of the separation process. MEK content in the final product was found to be less than 0.1% (v/v). In both the methods of separation, nonradioactive molybdate content in the final pertechnetate solution was within the acceptable limit (less than 10 ppm). Al\(^{3+}\) levels were below the limits (less than 10 ppm) set for generator-produced pertechnetate. For both the processes, the pH of the final product solution was between 6 and 7. Paper chromatography showed that the pertechnetate obtained by processing of the targets irradiated in cyclotron was identical in radiochemical purity with the generator produced pertechnetate and no colloid was formed. The concentration of nitrate ions in the final pertechnetate solution was matching.
with 10 mg/l NO₃⁻ colour zone in the test strip, which is much less than the LD₅₀ value of nitrate (1267 mg/kg, oral-rat). The concentration of H₂O₂ in the final radioactive TcO₄⁻ solutions was matching with 2-5 mg/l H₂O₂ colour zone, which is much less than the LD₅₀ value of peroxide (1232 mg/kg, oral-rat).

**TABLE 2. TYPICAL DATA FOR THE QUALITY CONTROL TESTS OF Na¹⁹⁹⁹MTCO₄ PREPARED IN CYCLOTRON AND FROM ALUMINA COLUMN GENERATOR**

<table>
<thead>
<tr>
<th>Q. C. Parameter</th>
<th>TcO₄⁻ obtained from cyclotron by Dowex-1 MEK method</th>
<th>TcO₄⁻ obtained from Generator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarity</td>
<td>Clear</td>
<td>Clear</td>
</tr>
<tr>
<td>pH</td>
<td>6-7</td>
<td>6-7</td>
</tr>
<tr>
<td>⁹⁹Mo breakthrough</td>
<td>&lt;10⁻⁴% &lt;10⁻⁴%</td>
<td>&lt;10⁻⁴%</td>
</tr>
<tr>
<td>RC Purity</td>
<td>&gt;99 %</td>
<td>&gt;99 %</td>
</tr>
<tr>
<td>Al and Mo</td>
<td>&lt; 10 ppm</td>
<td>&lt; 10 ppm</td>
</tr>
<tr>
<td>Nitrate</td>
<td>&lt; 10ppm</td>
<td>-</td>
</tr>
<tr>
<td>Peroxide level</td>
<td>&lt; 5ppm &lt; 5 ppm</td>
<td>-</td>
</tr>
<tr>
<td>MEK content</td>
<td>-</td>
<td>&lt;0.1% (v/v)</td>
</tr>
</tbody>
</table>

### 3.4 Recovery of Mo from the Irradiated Target

Recovery of molybdate (ammonium molybdate) obtained in the two separation methods was estimated from the counting data and the recovery yield was found to be about 100% in both the methods. Ammonium molybdate when heated seems to break down into MoO₃ and ammonia. Conversion yield of molybdate was estimated by gravimetric method. From the weight of Mo in MoO₃ recovered, the recovery yield of Mo was estimated to be more than 94.5% (n=3).

#### 3.4.1 Characterization of Recovered Molybdenum Compound by X-ray Diffraction

The spectra pattern of the synthesized powder matches with the commercial MoO₃ (unheated and heated at 700°C), but the intensity of the peaks is more close to the commercial heated MoO₃ powder (Fig. 11). The 2θ values for the major peaks at 12.8, 23.6, 25.8, 27.5, 33.6 and 39.2 resemble the JCPDS 85-2405 file, having monoclinic structure (space group P2₁/m, a: 3.954, b: 3.687, c: 7.095). This result confirms that our recovered Mo is chemically in the form of MoO₃.
4. Conclusion

Present study of $^{99m}$Tc yield in stacked foil irradiation shows that proton irradiation of enriched $^{100}$Mo target at 18→8MeV, 100μA proton beam for 1h, 3h, and 6h, will produce 44, 119, 204 GBq of $^{99m}$Tc at EOI, respectively. The new chemical separation method developed recovers more than 80% of $^{99m}$Tc from the irradiated target. The recovered pertechnetate has acceptable radionuclidic, radiochemical and chemical purity for labeling of biomolecules for clinical applications. The chemical separation also ensures more than 94.5% recovery of the costly enriched Mo target material as MoO$_3$.

Acknowledgment

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Abstract. Following preliminary feasibility studies started at Legnaro National Laboratories (LNL) in 2011, the Istituto Nazionale di Fisica Nucleare (INFN) research activities are underway since the kick-off of the IAEA CRP aimed at the alternative, accelerator-driven $^{99m}$Tc production routes. Such an effort is actually being carried out in order to get a mid-term solution to a possible new radionuclide shortage, as occurred in the recent past. The aim is to provide $^{99m}$Tc radionuclide production, in as large as enough amounts, to support the diagnostic needs of Nuclear Medicine Services of the Veneto Region and possibly of neighboring areas in the north of Italy. Such a goal is actually pursued because of the future, high intensity proton cyclotron which will be available in the next coming years at LNL. A summary of activities performed so far is here discussed.

1. Theoretical studies aimed at $^{99m}$Tc direct production by proton accelerators

Since the $^{99m}$Tc shortage occurred in recent years, because of the current reactor-based $^{235}$U(n,f)$^{99}$Mo$\rightarrow$$^{99m}$Tc scheme, it has by now clear that the most promising, alternative production route, to get $^{99m}$Tc radionuclide in as large as enough amounts to fulfill the needs for medical procedures, is through the direct $^{100}$Mo(p,2n) reaction. Regarding this issue, investigations on accelerator-based production routes have started at LNL laboratories in the last few years [1]. In particular, a theoretical study to investigate the feasibility of accelerator-based direct $^{99m}$Tc production, using proton beams on highly enriched $^{100}$Mo metallic targets, has been carried out [2] in order to determine the best irradiation conditions. Indeed such a study falls into the framework of the INFN project aimed at the future accelerator $^{99m}$Tc production by using the next, high performance, cyclotron scheduled to be available at LNL in the next years.

Feasibility studies on the matter have already assessed that $^{100}$Mo enrichment levels as high as 99% at least are required for a future, quality-level production of accelerator $^{99m}$Tc on a routine basis. That is because of the other $^{9x}$Tc contaminants isotopes and/or isomeric states yielded by (p,xn) reactions on remaining $^{9x}$Mo isotopes which may have an impact either on radiation dosimetry, or on the specific activity of the final accelerator-Tc product. However, available studies performed so far were based either on a mix of theoretical-experimental (when available) nuclear data, or on theoretical excitation functions (e.f.) only, but considering simplified assumptions and constraints about the map of long/short-lived radioactive Tc-isotopes produced.

A new theoretical study has therefore decided to be performed, in order to shed light on the matter. Instead of considering optimal and/or desired composition of the material, as well as given irradiation condition, our investigation has started taking into account the real isotopic composition about the $^{100}$Mo-enriched material, as it is currently available on the isotopes market. That is because of the parallel experimental program we launched (see below) about the $^{98}$Mo$^{99m}$Tc e.f. measurements based on the use of the enriched material. The isotopic composition of metallic molybdenum material taken as reference in this study was indeed from the batches provided in 2012 by the ISOFLEX company [3] which, most likely, is the largest world supplier: $^{100}$Mo (99.05%), $^{98}$Mo (0.54%), $^{97}$Mo (0.07%), $^{96}$Mo (0.11%), $^{95}$Mo (0.10%), $^{94}$Mo (0.05%), $^{92}$Mo (0.08%). [3]

The goal of the work carried out was to analyze, from a theoretical point of view (but always having a benchmark to experimental data of excitation functions measurements) the in-target total yields of all Tc nuclides expected from the $^{98}$Mo(p,x) reactions, aimed at the accelerator $^{99m}$Mo$^{99m}$Tc production. All related parameters about the production and purity of the desired isotope, $^{99m}$Tc, have been calculated, regardless any constraint which might simplify the theoretical approach to the problem. A series of in-target quality parameters has thus been calculated for Tc-produced radionuclides at the End Of Beam (EOB) taking into account 200 µA proton beam output current as reference. Moreover,
(which is more important) their evolution at cooling times. The last TENDL 2012 [4] theoretical excitation functions provided by TALYS code, extended up to (p,6n) (p,p5n) and (p,2p4n) levels, were at the purpose used to get a detailed map of all radionuclides expected. TENDL data have indeed been taken into account due to the reasonable agreement assessed with experimental data so far available for (p,xn) reactions.

1.1. $^{100}$Mo(p,x) excitation function for $^{99}$Mo production

$^{99}$Mo may be basically produced by the main $^{100}$Mo(p,pn) reaction. However a contribution is also given by decay product of $^{99m}$Nb ($t_{1/2} \approx 15$ s) and $^{99g}$Nb ($t_{1/2} \approx 2.5$ m), due to the additional (p,2p) reaction. A collection of $^{100}$Mo(p,pn)$^{99}$Mo experimental excitation functions, measured in the last two decades only is plotted in Figure 1. As observed, from the analyses of experimental data, results are consistent up to $\approx 25$ MeV, while at higher proton energies an unusual spread (i.e. uncertainty band) up to 100 mb (including error bars extension) may be noted. Moreover in order to take into account the additional Mo as well as Nb isotopes, yielded by the other (p,x) open reaction routes on $^{100}$Mo isotope, TENDL 2012 [4] cross sections data have been taken in to account as well. As an example, the $^{95}$Nb isotopes and isomeric states up to the (p,2p4n) levels are shown in Figure 2. When available, experimental measurements are plotted as benchmark.

![Figure 2: $^{100}$Mo(p,pn)$^{99}$Mo theoretical cross section evaluation from TENDL 2012 database up to (p,2p4n) level. Benchmark experimental measurements performed by Levkovskij [5] for $^{95m}$+g Nb, $^{96}$Nb and $^{97}$Nb are plotted as well](image)
1.2 Mo(p,xn) excitation function for $^{99m}$Tc production

Such a radionuclide may either be directly produced by the by $^{100}$Mo(p,2n) reaction, or as decay product of $^{100}$Mo. An additional, although minimal, contribution is also from the decay chain $^{99}$Nb $\rightarrow$ $^{99m}$Mo $\rightarrow$ $^{99m}$Tc or $^{98}$Nb $\rightarrow$ $^{98}$Mo $\rightarrow$ $^{99m}$Tc. As known such a reaction has been repeatedly measured over the past 40 year in different experimental campaigns, although with an unusual spread of data, which reason is up to now not clear. In Figure 3 a plot of the more recent experimental data for the $^{100}$Mo(p,2n) reaction, collected in in the last 20 years, is shown. Taking into account the history of different measurements which have been performed so far, using different target material purity as well as isotopic compositions, different experimental set-ups adopted and post-irradiation procedures for samples activity measurements, no clear trend indication about the real cross section values expected for such a reaction route may be drawn, which can give a satisfactory explanation about the spread observed. Also shown in figure for comparison is the last TENDL 2012 evaluation by nuclear code TALYS, which has been used for our theoretical estimation. In Figure 4 is instead shown the plot of all theoretical excitation

FIG.3. Experimental cross section data for $^{100}$Mo(p,2n)$^{99m}$Tc reaction measured in the last 20 years. Shown is also the most recent theoretical cross section evaluation from TENDL 2012 database.

FIG.4. $^{100}$Mo(p,xn)$^{99m}$Tc theoretical cross section evaluation from TENDL 2012 database up to (p,6n) level. Benchmark experimental measurements for $^{99m}$Tc (Gagnon [6]), $^{100}$Tc (Skakun [7]) and $^{99m}$Tc (Takacs [8]) are plotted for comparison.
functions from TENDL 2012 library [4], concerning the $^{100}$Mo(p,X) reaction routes for additional Tc isotopes production, both in ground and isomeric states, are reported up to the (p,6n) level. Experimental excitation functions for $^{99m}$Tc production measured by Takacs [8], $^{99g}$Tc by Gagnon [6] and $^{100}$Tc by Skakun [7] are shown for comparison, as well. In figure 4 it may be noticed that reaction routes for the long-lived contaminants $^{99g}$Tc, $^{98}$Tc and, to some extent, $^{97g}$Tc isotopes are opened up and will be produced by the $^{100}$Mo(p,xn) reactions if operating at 25 MeV.

1.3 Estimation of $^{99}$Mo/$^{99m}$Tc production yields

Starting from the aforementioned TALYS/TENDL 2012 theoretical excitation functions, the first approach followed was to find out the optimal irradiation condition for $^{100}$Mo-enriched metallic molybdenum targets aimed at both $^{99}$Mo and $^{99m}$Tc productions. A calculation tool has been developed, which is able to provide a series of output data, such as, heat power and related power density deposited in the active Mo layer (useful for the engineering design of target), reaction rates normalized per incident proton, production yields, activities, and related ratios. Input parameters are incident energy, beam current, irradiation time, cooling time and isotopic target composition. Cross section as well as stopping power data may be updated in an easy way, including future experimental data as well. The first goal was to assess the optimal thickness of Mo-enriched metallic material required for both $^{99}$Mo and $^{99m}$Tc productions at various incident energies. Such information is indeed important to limit the amount of the highly costly $^{100}$Mo material. In our approach the proton beam incident angle is always kept fixed and normal to target surface. Depending upon the operative heat power and power density level fixed, which, in turn, is related to production-target engineering constraints, indeed it does make no sense to have an arbitrary incident angle. Equivalent molybdenum layer thicknesses deposited on backing material that are required at different impact angles, may indeed be easily estimated afterwards.

In Figure 5 both the $^{99}$Mo and $^{99m}$Tc yields distribution versus sample layer thickness calculated, normalized per incident proton, are plotted in semi-logarithmic scale, for some interesting proton beam energies. As may be noticed, values are within one order of tenth, up to the point where the yield drop off starts, down the energy threshold corresponding to the thick-target production (i.e. energy exit without the useless heat power deposition corresponding to the Bragg peak). Figure 5 also shows the recommended thicknesses for an optimized production, saving target material. In the next Table 1 the optimal $^{100}$Mo-enriched layers recommended for 25, 20 and 15 MeV protons for $^{99m}$Tc production, as well as related integral production yields are reported. Parameters assessing the accelerator $^{99m}$Tc quality produced (i.e. the ratio of $^{99m}$Tc vs. both the $^{99g}$Tc isomer and all Tc nuclides depending upon the energy window) are listed as well. Such parameters, which directly relate the $^{99g}$Tc production quality expected to the proton beam energy selected, have to be as high as possible.
Just looking at such data it may be inferred that the best incident energy for the $^{99m}$Tc accelerator production having final quality as close as possible to that from Mo/Tc generator, lays between 15 and 20 MeV, to get a reasonable balance between $^{99m}$Tc yield and quality level, the contribution from other Tc nuclides reaction rate being minimal. Productions held at proton energies larger than 20 MeV instead causes additional contributions from other Tc contaminants (i.e. mainly $^{98}$Tc, $^{97m+g}$Tc $^{96m+g}$Tc and, at lesser extent, by $^{95m+g}$Tc $^{94m+g}$Tc) produced by reaction routes due to the other Mo target isotopes present, which basically bring a decrease of $^{99m}$Tc/$\Sigma$ xxTc ratio. In-target production yields estimated at EOB at 15 and 20 MeV for the optimized sample thickness are reported in Table 2. The following parameters: i.e. 3 hrs. irradiation time, 200$\mu$A proton beam current and 500 W/cm$^2$ mean power areal density on target have been taken into account as reference. A series of $^{99m}$Tc quality parameters have thus been estimated.

As may be pointed out, almost all of in-target radioactivity at EOB is due to Tc radioisotopes (i.e. about 98% at 15 MeV and 95% at 20 MeV respectively). The $^{99m}$Tc Radio Nuclidic Purity (RNP) is however relatively low (around 40%) even considering the best irradiation parameters (e.g 15 MeV). The reason for that is basically the contribution of the quite short-lived $^{100}$Tc, the presence of which may not be avoided.

At both energies considered, $^{100}$Tc activity contribution ranges from 5 times larger to values almost equal to that provided by $^{99m}$Tc, at increasing irradiation times. That is not however a problem because after 5 mean time $\tau$ (i.e. $\sim$ 1.8 min) it has fully decayed in $^{100}$Ru (stable), which can be chemically separated during target dissolution. Other isotopic contaminants giving contribution to the overall activity instead remain in the final Tc solution (reference case at 20 MeV protons and 3 hrs irradiation). Major contributors are: $^{96m}$Tc, $^{94F}$Tc, $^{92}$Tc, $^{94m}$Tc, $^{93m}$Tc, $^{95g}$Tc, $^{96g}$Tc. On the other hand the activity contribution from the long-lived $^{99g}$Tc, $^{98}$Tc and $^{97g}$Tc, is instead minimal with low impact for radiation dose imparted to patient. However their impact about the isotopic purity, as well as the specific activity of the final accelerator-Tc, is not negligible at all, taking also into account the larger cross section values for them, compared to that of $^{99m}$Tc. This may have an impact on the radiopharmaceutical preparation process.

FIG.5. $^{99}$Mo (left) and $^{99m}$Tc (right) nuclide yields distribution, normalized per incident proton, vs. penetration depth calculated for 99.05% $^{100}$Mo-enriched metallic target at some reference proton energies. The eye-guide lines are to show layer thicknesses selected for an optimal radionuclides production with respect to the thick-target configuration.
TABLE 1. RECOMMENDED $^{100}$Mo-ENRICHED LAYER THICKNESSES AND RELATED INTEGRAL YIELDS (NORMALIZED PER INCIDENT PROTON) FOR $^{99m}$Tc. QUALITY PRODUCTION PARAMETERS EXPECTED ARE ALSO LISTED.

<table>
<thead>
<tr>
<th>Proton Energy (MeV)</th>
<th>Mo optimal layer thickness (µm)</th>
<th>$^{99m}$Tc/p</th>
<th>$^{99m}$Tc/$^{99m+g}$Tc</th>
<th>$^{99m}$Tc/$\Sigma^{xx}$Tc</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>260</td>
<td>2.84·10$^{-4}$</td>
<td>0.235</td>
<td>0.211</td>
</tr>
<tr>
<td>20</td>
<td>570</td>
<td>5.65·10$^{-4}$</td>
<td>0.198</td>
<td>0.170</td>
</tr>
<tr>
<td>25</td>
<td>940</td>
<td>6.70·10$^{-4}$</td>
<td>0.187</td>
<td>0.117</td>
</tr>
</tbody>
</table>

TABLE 2. $^{99m}$Tc IN-TARGET PRODUCTION YIELDS ESTIMATED AT EOB AFTER 3h IRRADIATION, AT 15 AND 20 MEV, 200 µA BEAM CURRENT. 99.05% $^{100}$MO-ENRICHED METALLIC MOLYBDENUM TARGET IN THE OPTIMIZED TARGET CONFIGURATION. A SERIES OF QUALITY PARAMETERS RELATED TO $^{99m}$Tc AND ALL TC ISOTOPES AND ISOMERIC STATES YIELDED ARE LISTED.

<table>
<thead>
<tr>
<th>$^{99m}$Tc production</th>
<th>Ep=15 MeV</th>
<th>Ep=20 MeV</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-target activity</td>
<td>105.6</td>
<td>205.8</td>
</tr>
<tr>
<td>Specific Activity</td>
<td>3.84·10$^7$</td>
<td>2.96·10$^7$</td>
</tr>
<tr>
<td>Tc / TOTAL activity</td>
<td>0.9848</td>
<td>0.9468</td>
</tr>
<tr>
<td>$^{99m}$Tc / TOTAL activity</td>
<td>0.3693</td>
<td>0.3926</td>
</tr>
<tr>
<td>$^{99m}$Tc / $^{99m+g}$Tc</td>
<td>0.1990</td>
<td>0.1665</td>
</tr>
<tr>
<td>Isotopic Purity (IP)</td>
<td>0.1970</td>
<td>0.1520</td>
</tr>
<tr>
<td>Radionuclidic Purity (RNP)</td>
<td>0.3750</td>
<td>0.4147</td>
</tr>
</tbody>
</table>
1.4 Post EOB evolution of quality parameters expected by accelerator-produced Tc

Both the Isotopic Purity (IP), as well as the Radio Nuclidic Purity (RNP) time evolution expected for the accelerator-produced $^{99m}$Tc during decay after EOB is shown in Figure 6, (reference case at 20 MeV protons and 3 hrs irradiation). This is indeed the behavior foreseen, apart from the time needed for the Tc chemical separation from other radioactive and stable isotopes of other chemical species. As shown RNP rise up at values as large as 95% in just a few minutes, mainly because of the quick decay of $^{100}$Tc. Values as high as 99% are however achieved about 0.5 hr after EOB, because of relative contribution to decays from other short-lived (i.e. $T_{1/2} < 1$hr) isotopes (mainly $^{96m}$Tc, $^{94g}$Tc, $^{92}$Tc) up to the maximum limit of RNP= 99.58%. That occurs about 6-7 hours after EOB in case of proton irradiations at energies as low as 15 MeV. However a time window, ranging from 1hr up to about 20 hrs post EOB may be clearly seen where RNP values keep always above 99%. Such a limit for accelerator-produced Tc is indeed quite important, considering that the same parameter for generator-produced Tc is about 99.99%.

On the other hand the ratio $^{99m}$Tc/$^{99m+g}$Tc as high as ~0.2 is achieved at EOB in our theoretical study, which, moreover is close to IP value. As a reference, the $^{99m}$Tc eluted from generators at 24 hrs interval is instead 0.26, as reported in [9]. Taking into account the likely underestimation of the TENDL 2012 (p,2n) excitation function for $^{99m}$Tc production, it may therefore be argued that such a value is in pair with the generator-produced Tc. On the contrary accelerator produced $^{99m}$Tc having RNP values never higher than 99% and IP ones always lower than 10% clearly point out that irradiations at energies basically larger than 20 MeV (i.e. 25 MeV) have to be avoided, even using highly enriched molybdenum material. It may therefore be concluded from such a theoretical study that the optimal proton energy for accelerator-produced $^{99m}$Tc is within the energy 15-20 MeV. More detailed information about the theoretical work performed may be found in the paper by Esposito et al. [2].

2. Assessment of $^{99m}$Tc/$^{99m}$Tc isomeric ratio on the final radiochemical purity and stability of $^{99m}$Tc radiopharmaceuticals

Theoretical investigations and some recent preliminary irradiations tests on $^{100}$Mo-enriched samples, point out that both the $^{99m}$Tc/$^{99m}$Tc nuclide ratio and $^{99m}$Tc specific activity will be basically different in the final accelerator-produced Tc with respect to generator-produced one, because of the additional
Tc contaminant nuclides produced, such as $^{99m}\text{Tc}$, $^{98}\text{Tc}$, $^{97m}\text{Tc}$ and $^{97m}\text{Tc}$. Among them the ground-state, long-lived $\beta$ emitter $^{99m}\text{Tc}$, which will be produced in the largest amount and being useless for diagnostic procedures, might in turn have an impact in the pharmaceutical procedures going to compete with $^{99m}\text{Tc}$ for the formation of the corresponding chemically identical radiopharmaceuticals. The presence of an excess of $^{99m}\text{Tc}$ might thus be responsible for a value of radiochemical purity lower than the standard required for some radiopharmaceutical preparations.

A set of measurements with $^{99m}\text{Tc}$, eluted from a standard $^{99}\text{Mo}/^{99m}\text{Tc}$ generator, were therefore performed in order to check possible impact of different $^{99m}\text{Tc}/^{99m}\text{Tc}$ isomeric ratios on the preparation of different Tc-labeled pharmaceutical kits listed in Table 3. All of them have been labeled with either the first $^{99m}\text{TcO}_4^-$ elute obtained from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (supplied by two different companies) or with elutes up to 72 hours past the last elution.

### TABLE 3. RADIOPHARMACEUTICALS USED IN THE ASSESSMENT STUDY

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Radiopharmaceutical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neurolite</td>
<td>$^{99m}\text{Tc}$-ECD</td>
</tr>
<tr>
<td>2</td>
<td>Stamicis</td>
<td>$^{99m}\text{Tc}$-SESTAMIBI</td>
</tr>
<tr>
<td>3</td>
<td>Technemibi</td>
<td>$^{99m}\text{Tc}$-SESTAMIBI</td>
</tr>
<tr>
<td>4</td>
<td>Cardiolite</td>
<td>$^{99m}\text{Tc}$-SESTAMIBI</td>
</tr>
<tr>
<td>5</td>
<td>TechniScan</td>
<td>$^{99m}\text{Tc}$-MAG3</td>
</tr>
<tr>
<td>6</td>
<td>Pentacis</td>
<td>$^{99m}\text{Tc}$-DTPA</td>
</tr>
<tr>
<td>7</td>
<td>Medronato II</td>
<td>$^{99m}\text{Tc}$-MDP</td>
</tr>
<tr>
<td>8</td>
<td>Osteocis</td>
<td>$^{99m}\text{Tc}$-HMDP</td>
</tr>
<tr>
<td>9</td>
<td>Nanocoll</td>
<td>$^{99m}\text{Tc}$-NANOCOLLOIDS</td>
</tr>
</tbody>
</table>

#### 2.1. Experimental methods

The preparation of radiopharmaceuticals was carried out with sodium pertechnetate eluates coming from two different generators: a "dry" Drytec generator (GE Healthcare, Milan, Italy), and a "wet" Elumatic III generator (IBA-CIS Bio International, Gif Sur Yvette, Cedex France). All generators, with $^{99}\text{Mo}$ calibrated activity of 10 GBq, were eluted with 5 ml of saline solution as indicated by each manufacturer. From each generator we analyzed and compared 3 first elutions performed just after generator delivery, and 3 elutions carried out after 36, 48 and 72 hours from the previous elution. The radiochemical purity (PRC) of radiopharmaceuticals was evaluated immediately after preparation ($t=0$) and at the end of the stability period indicated by the manufacturer. The radiochemical purity and stability was measured using methods specified by manufacturer, with the exception of TechniScan (Mallinckrodt) for which was used the following chromatographic system: mobile phase, 54/45/1 (Physiological / Methanol / glacial acetic acid) and stationary phase, RP-18 (Merck) [10]. Thin–layer chromatography plates were analyzed with a Cyclone instrument equipped with a phosphor imaging screen and an OptiQuant image analysis software (Packard, Meridien, CT).

The determination of $^{99m}\text{Tc}$ in a fresh elute requires an immediate measurement after the elution of the $^{99m}\text{Tc}$ activity and a later measurement of the total activity of $^{99m}\text{Tc}$ (in few months almost all the $^{99}\text{Mo}$ and $^{99m}\text{Tc}$ atoms decay into $^{99}\text{Tc}$). The assessment of $^{99m}\text{Tc}$ activity in the sample has been performed by using a dose calibrator (PET-dose, Comecer, Castelbolognese, Italy), while the evaluation of $^{99m}\text{Tc}$ activity has been performed using the TRI-CARB 2810TR liquid scintillation analyzer (Perkin Elmer Inc., Monza, Italy). Samples for $^{99m}\text{Tc}$ activity measurements were prepared taking an aliquot of 0.8 ml from one of the elutes decayed for 60 days (total volume: 5 ml) and adding 5.4 ml of liquid scintillator (Ultima Gold LLT cocktail, Perkin Elmer Inc., Monza, Italy). The measurement of $^{99m}\text{Tc}$ activity was performed using the 0–295 keV energy window.
2.2. Results and Discussion

Radiochemical purity (RCP) values are reported in Table 4. Data refer to the PRC evaluated immediately after the preparation (t = 0). For sake of simplicity, data at the end of the stability period specified by the manufacturer are not reported. All data are within the specifications required by the manufacturer. In Table 5 are the PRC data are instead reported, obtained from reconstitution of the kits with the first eluate.

### Table 4. RCP of Radiopharmaceuticals at T=0, Prepared with Eluates at 72 Hours from the Previous Elution.

<table>
<thead>
<tr>
<th>No.</th>
<th>PRC (Drytec)</th>
<th>PRC (Elumatic)</th>
<th>PRC (requirements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98.73 ± 1.85</td>
<td>98.68 ± 0.95</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>2</td>
<td>99.40 ± 1.23</td>
<td>99.13 ± 0.63</td>
<td>≥ 94%</td>
</tr>
<tr>
<td>3</td>
<td>98.16 ± 0.11</td>
<td>98.00 ± 0.19</td>
<td>≥ 94%</td>
</tr>
<tr>
<td>4</td>
<td>98.53 ± 0.27</td>
<td>98.11 ± 0.06</td>
<td>≥ 94%</td>
</tr>
<tr>
<td>5</td>
<td>99.31 ± 0.14</td>
<td>99.44 ± 0.14</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>6</td>
<td>99.12 ± 0.33</td>
<td>98.12 ± 1.03</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>7</td>
<td>99.63 ± 0.64</td>
<td>99.11 ± 0.43</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>8</td>
<td>99.13 ± 0.11</td>
<td>99.63 ± 0.64</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>9</td>
<td>98.94 ± 0.41</td>
<td>98.11 ± 0.11</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>10</td>
<td>99.11 ± 0.03</td>
<td>99.03 ± 0.29</td>
<td>≥ 95%</td>
</tr>
</tbody>
</table>

### Table 5. Radiopharmaceuticals RCP at T=0 and at the Expired Time Specified by the Manufacturer, Prepared with the First Eluate; PRCex* Means the Radiochemical Purity at the End of the Expired Time.

<table>
<thead>
<tr>
<th>No.</th>
<th>PRC (t=0)</th>
<th>PRCex*</th>
<th>PRC (t=0)</th>
<th>PRCex*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drytec</td>
<td>Elumatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>99.17 ± 0.25</td>
<td>99.13 ± 0.21</td>
<td>98.38 ± 0.54</td>
<td>98.74 ± 0.25</td>
</tr>
<tr>
<td>2</td>
<td>97.67 ± 1.24</td>
<td>97.71 ± 1.13</td>
<td>97.68 ± 0.56</td>
<td>97.77 ± 0.88</td>
</tr>
<tr>
<td>3</td>
<td>98.65 ± 0.40</td>
<td>98.57 ± 0.57</td>
<td>98.42 ± 1.02</td>
<td>99.03 ± 0.48</td>
</tr>
<tr>
<td>4</td>
<td>98.15 ± 0.11</td>
<td>98.01 ± 0.04</td>
<td>97.99 ± 0.11</td>
<td>98.15 ± 0.14</td>
</tr>
<tr>
<td>5</td>
<td>98.79 ± 0.02</td>
<td>98.11 ± 0.15</td>
<td>98.11 ± 0.62</td>
<td>98.43 ± 0.29</td>
</tr>
<tr>
<td>6</td>
<td>99.03 ± 0.24</td>
<td>99.88 ± 0.11</td>
<td>99.16 ± 0.32</td>
<td>99.19 ± 0.11</td>
</tr>
<tr>
<td>7</td>
<td>98.10 ± 0.13</td>
<td>98.02 ± 0.15</td>
<td>99.13 ± 0.04</td>
<td>98.77 ± 0.08</td>
</tr>
<tr>
<td>8</td>
<td>99.23 ± 0.18</td>
<td>98.15 ± 0.16</td>
<td>99.17 ± 0.12</td>
<td>98.76 ± 0.29</td>
</tr>
<tr>
<td>9</td>
<td>98.22 ± 0.13</td>
<td>98.33 ± 0.39</td>
<td>98.79 ± 0.16</td>
<td>98.92 ± 0.59</td>
</tr>
<tr>
<td>10</td>
<td>99.28 ± 0.07</td>
<td>98.55 ± 0.21</td>
<td>99.11 ± 0.35</td>
<td>99.01 ± 0.32</td>
</tr>
</tbody>
</table>
Results show that the total amount of technetium ($^{99g}$Tc+$^{99m}$Tc), present in the first eluate at 24h and in eluates obtained at longer time intervals up to 72 h did not affect the radiochemical purity of the final products. Table 6 shows an estimation of the total amount of technetium present in an eluate obtained from a $^{99m}$Tc generator with $^{99}$Mo calibrated activity of 10 GBq. The ratio R of three $^{99m}$Tc eluates at 24 hours and two $^{99m}$Tc first eluates at 48 hours have been measured and the results have been $R_{24h} = 3.23 \pm 0.15$ and $R_{48h} = 6.68 \pm 0.31$ respectively. While the experimental value of first eluates at 48 hours are in good agreement with the theoretical value of 6.5, the experimental value of eluates at 24 hours shows a large difference with respect to the theoretical value of 2.55.

This discrepancy could be explained by taking into account the elution efficiency $\epsilon = 0.91$ of $^{99}$Mo generators used in our work. Indeed, the recalculated ratio R at 24 hours is included in the range [2.78 – 3.38] and depends on temporal sequence of previous elutions. Results prove that the radiochemical purity and stability of these radiopharmaceuticals are not affected by the $^{99g}$Tc/$^{99m}$Tc ratio up to values as high as 11.84. A future goal will be to repeat the experiments with $^{99m}$Tc eluates from generators with $^{99}$Mo calibrated activity higher than 10 GBq, in order to check the possible impact of $^{99g}$Tc in higher $^{99m}$Tc activities solutions at different $^{99g}$Tc/$^{99m}$Tc ratio and in the first production in Ci quantities from accelerator produced Tc. More detailed explanations may be found in the paper by Boschi et al. [11]

<table>
<thead>
<tr>
<th>Time from previous elution</th>
<th>$^{99g}$Tc/$^{99m}$Tc ratio</th>
<th>Amount of total Tc found</th>
<th>$^{99g}$Tc/$^{99m}$Tc ratio found</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 hours</td>
<td>11.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 hours</td>
<td>6.50</td>
<td>0.22 ± 0.01</td>
<td>6.68 ± 0.31</td>
</tr>
<tr>
<td>36 hours</td>
<td>4.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td>2.54</td>
<td>0.12 ± 0.01</td>
<td>3.23 ± 0.15</td>
</tr>
</tbody>
</table>

2.3. Possible impact of $^{99g}$Tc/$^{99m}$Tc isomeric ratio on scintigraphic image quality. Determine the allowed limits for $^{99g}$Tc and other Tc-isotopes in the final accelerator-produced Tc.

The quality of a scintigraphic image in diagnostic procedure, in general, and its spatial resolution, in particular, is sensible to the possible presence of other competing gamma- or beta-ray emitters as radionuclide labeling agents. Possible impact on the imaging characteristics could indeed arise from $^{99g}$Tc that, we already know, will anyway be present in larger amounts by the accelerator produced $^{99m}$Tc with respect to generator one; hence the measurements about the influence of the $^{99g}$Tc on the gamma-ray images obtained from Tc$^{99m}$ need to be investigated.

First imaging tests using NEMA NU4 phantoms and $^{99m}$Tc (under $[^{99m}$TcO$_4$] form) eluted from standard Mo/Tc generators at 24 hrs and longer time intervals, have been performed as preliminary approach, in collaboration with Nuclear Medicine Dept of Ferrara University. A preclinical YAP-PET/SPECT-CT integrated imaging system for small animal’s scanner prototype [12] has been at the purpose used. The impact from different $^{99g}$Tc/$^{99m}$Tc ratio R has been investigated, in order to find out the maximum amount of $^{99g}$Tc that could be used without detrimental on the imaging quality. Such a research activity is indeed fundamental to assess the limit (if any) about the future use of the accelerator produced $^{99m}$Tc to label pharmaceuticals used in imaging in nuclear medicine. The same in vivo tests using the accelerator-produced $^{99m}$Tc are expected to be performed at a later stage.
In order to carry out such a work, three $^{99m}$Tc elutes produced by $^{99}$Mo/$^{99m}$Tc generator with increasing ratio R were chosen for imaging studies: 4.16, 9.51 and 15.2, corresponding to an equivalent $^{99m}$Tc/$^{99m}$Tc ratio of 0.194, 0.095 and 0.062 respectively. Each tomographic acquisition has been performed by filling in a NEMA phantom NU 4-2008 with 74 MBq of $^{99m}$Tc-pertechnetate solution. Data have been acquired with the YAP-(S)PET scanner and reconstructed by using a EM-ML algorithm. Reconstructed SPECT images of NEMA phantom are shown in Figure 7 for the aforementioned parameters. The average reconstructed activity along the phantom axis, for the three values of R, is also shown. The visual inspection on the images shows not any significant difference in image quality and radioactivity distribution. Taking into account the $^{99}$Tc specific activity level, first indications achieved point out that the isomeric ratio R seems to have no imaging detectable effects at such an investigation detail.

Moreover, additional experiments have been performed in collaborations with the Physics Dept. of Padua University and INFN branch, as well as with the Istituto Oncologico Veneto (IOV) (the Oncology Research Center of Veneto region, Padua). During 2013 a series of experiments to check the imaging properties of $[^{99m}$TcO4]$^-$ eluted from generator at different $^{99g}$Tc/$^{99m}$Tc isomeric ratio R have been completed. In order to draw quantitative conclusions about the imaging characteristic at different isomeric ratios, a series of measurements of the spatial resolution, the digital resolution and linearity of a gamma-ray imaging system have been conducted. A phantom was constructed, made of a microcirculation system formed by, tiny, capillary tubes, arranged in a parallel array, as shown in Figure 8. The capillary system has basically the following parameters:

- capillary tubes inner diameter: 700 µm;
- visible tube length: 90 mm;
- capillary tubes gap: 10 mm;
- minimal overall volume necessary to maintain liquid circulation: 10ml.
The liquid circulation in the whole system is fed and left constant by a peristaltic pump, in order to keep a homogeneous gamma-ray emission from each capillary tube during the acquisition.

$^{99m}$Tc-based elutes have been obtained from the commercially available generators (GE Healthcare [13] and Mallinckrodt [14]). Desired isomeric ratios R have been obtained after an appropriate time lapse after elution from the generators. About 1 ml of $^{99m}$Tc-pertechnetate solutions diluted in 2000 ml of water, with $^{99m}$Tc/$^{99m}$Tc ratios R=4, R=8 and R=16 (i.e. $^{99m}$Tc/$^{99m+g}$Tc ratio of 0.200, 0.111 and 0.059 respectively), have been used to acquire images for the flat field corrections. $^{99m}$Tc-pertechnetate solutions with a volume of 10 ml and the same isomeric ratios of R=4, R=8 and R=16 have been used afterwards to feed the capillary system for the spatial resolution measurements. The initial total activity of the gamma-ray emission with respect to 140.5 keV line of $^{99m}$Tc was approximately 8 mCi. Images from the emission of $^{99m}$Tc/Tc$^{99m}$ solution in the capillary system at each given isometric ratio R, have been obtained, shown in Figure 9. A position-sensitive high-spatial-resolution gamma camera of LRIM laboratory (gamma camera for small animals), based on a segmented Cs(I) scintillator [15,16], has been used for this purpose. The gamma camera has been previously characterized by measuring the energy response for different areas of the field of view. For each image area, a calculated correction factor was applied for the photo-peak position, in order to get a uniform energy response over the entire field of view. Following such a correction method, the energy resolution has been improved by a factor equal to 2.

FIG. 8. The capillary system and the peristaltic pump
FIG. 9. a) Images of the capillary system with different concentration ratios of Tc$^{99m}$/Tc$^{99g}$. Nine regions of interest where the spatial resolution has been measured are shown with a white broken line; b) an example of the sixth profile (black lines) and the corresponding fits (red lines) to the count statistics of the profile.

TABLE 7. RESULTS FOR THE SPATIAL RESOLUTION OF THE GAMMA CAMERA IN THE WHOLE FOV AT DIFFERENT $^{99m}$Tc/$^{99g}$Tc ISOMERIC RATIOS

<table>
<thead>
<tr>
<th>Layer No</th>
<th>Average FWHM (mm)</th>
<th>Uncertainty (mm)</th>
<th>Average FWHM (mm)</th>
<th>Uncertainty (mm)</th>
<th>Average FWHM (mm)</th>
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<td>4</td>
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<td>0.18</td>
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<tr>
<td>9</td>
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<td>1.72</td>
<td>0.21</td>
<td>1.80</td>
<td>0.21</td>
</tr>
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TABLE 8. OVERALL SPATIAL RESOLUTION OF THE GAMMA CAMERA AT DIFFERENT RATIOS OF $^{99m}$Tc/$^{99g}$TC

<table>
<thead>
<tr>
<th>Ratio R4</th>
<th>Average FWHM (mm)</th>
<th>Uncertainty (mm)</th>
<th>Ratio R8</th>
<th>Average FWHM (mm)</th>
<th>Uncertainty (mm)</th>
<th>Ratio R16</th>
<th>Average FWHM (mm)</th>
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<tr>
<td></td>
<td>1.79</td>
<td>0.16</td>
<td></td>
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<td>0.17</td>
<td></td>
<td>1.80</td>
<td>0.18</td>
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</table>
Images of the capillary system at different isomeric ratios R have then been acquired and 9 regions of interest from each image were used to analyze the spatial resolution. Fits to the count statistics of the profiles have been conducted using the method described in [17,18]. Spatial resolution of the gamma camera at the corresponding peak positions has been calculated. The results for the whole field of view are given in the next Table 7. The overall spatial resolution of the gamma camera, averaged on all measured values in the FOV at different $^{99m}$Tc/$^{99}$Tc isomeric ratios are shown in Table 8. No significant difference (within experimental uncertainty) between the measured gamma-camera spatial resolution values are noticed at these isomeric ratios.

From the imaging performance analyses conducted so far, it may be concluded that the larger presence of the isomer Tc$^{99g}$ in quantities not exceeding the isomeric ratios R=16 do not influence the imaging characteristic of $^{99m}$Tc in the pertechnetate solution. Hence the future accelerator-produced Tc, would generate images with quality comparable to the one of generator-produced $^{99m}$Tc gamma-ray images. That is even more so whether specific activities of accelerator $^{99m}$Tc will be comparable to the generator-produced $^{99m}$Tc. A more important future goal will be to assess the impact of the other accelerator-produced Tc-isotopes on the image quality and to determine their maximum-allowed limits in the final product.

3. Excitation functions (e.f.) experimental measurements on nuclear reaction routes related to the accelerator-based production of $^{99m}$Tc

3.1. Excitation functions and yields for proton irradiation on isotopically enriched $^{100}$Mo

Such an activity, started at the beginning of 2012, is being progressing and performed in collaboration with the physics group of Milan University and INFN Milan section and the EU JRC lab in Ispra (Varese), Italy. Excitation functions measurements are currently focused on the two main reaction channels: $^{100}$Mo(p, pn) $^{99}$Mo and $^{100}$Mo(p, 2n) $^{99m}$Tc, which completion of data taking on the whole energy range of interest (~ 8-35 MeV) is scheduled within 2014. Cross sections data for the production of other nuclides (i.e. $^{96}$Nb, $^{97}$Nb etc.) will be measured as well. In order to limit all possible errors arising from standard post-irradiation gamma spectrometry measurements, we have preferred to use $^{100}$Mo-enriched (99.05% level) molybdenum, in metallic form, as target material, from ISOFLEX Company [3].

The excitation functions have been measured by using the stacked foil technique at different energies. The stack of thin foils consists of alternating high purity aluminum (as recoil catcher and energy degrader foils), highly enriched molybdenum in $^{100}$Mo and one titanium beam monitor foil. $^{100}$Mo targets of nominal thickness of 20-25 µm (i.e. 20.44-25.55 mg/cm$^2$ mass thickness) with a certified enrichment were melted and laminated in the nuclear target laboratory at the Legnaro National Laboratory (LNL-INFN). The experimental value of target thickness was measured accurately by weighting, followed by additional measurements using a high precision thickness meter instrument, in order to assess foils thickness homogeneity.

Stacks were irradiated and activated at the EU JRC lab in Ispra, Italy, by means of a cyclotron (Scanditronix MC40 ) which can deliver protons up to 40 MeV with a beam current up to 60 µA. All irradiations were carried out at different incident energies in the range from 8 MeV to 18 MeV so far, with typically 100 nA beam current and 1 hour irradiation.
The activity of the Radio Nuclides (RN) produced in all irradiated targets was measured by a high purity germanium (HPGe), calibrated, in the same geometric configuration of the targets, by certified calibration sources. In calculating the $^{99m}Tc$ activity, corrections were required to subtract out: (i) the interference of the 140.5102 keV energy peak arising directly from decay of $^{99}Mo$ and (ii) the indirect production of $^{99m}Tc$ as a result of $^{99}Mo$ decay, both during and post-irradiation. Moreover we also verified that no other interferences for the 140.5102 keV peak were present. As an example, in Figure 10 is reported the semi log plot for decay curve at 18 MeV.

The experimental thin-target yields for $^{99}Mo$ and $^{99m}Tc$, shown in Figures 11 were fitted by the software TableCurve 2D for Windows (Systat Software Inc) and related mathematical functions integrated to get the thick-target yields. With such calculated thick-target yields for the production of $^{99}Mo$ and $^{99m}Tc$, the total activity of $^{99m}Tc$ that can be produced may be evaluated as a function of the cooling time and of the irradiation time. In Tables 9-11, as an example, the calculations for three different total absorption energy irradiations are reported. In the next future cross section measurements will be extend up to higher energies up to (30-35 MeV). Results obtained

FIG.10. Decay curve of $^{99}Mo$/$^{99m}Tc$ for the 140.5102 keV gamma ray peak. The proton beam energy on target is 18 MeV.

FIG.11. Experimental thin-target yields for $^{100}Mo(p,x)^{99}Mo$ (left) and $^{100}Mo(p,2n)^{99m}Tc$ (right) nuclear reactions
so far will be submitted for publication in the near future.

TABLE 9: ACTIVITY (GBQ) OF $^{99m}$Tc FOR A CONSTANT BEAM OF 100 $\mu$A CURRENT AS FUNCTION OF THE COOLING AND IRRADIATION TIMES. INCIDENT ENERGY ON THE “TOTAL ABSORPTION TARGET”: 12 MEV.

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<td>51.1</td>
<td>45.5</td>
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TABLE 10: ACTIVITY (GBQ) OF $^{99m}$Tc FOR A CONSTANT BEAM OF 100 $\mu$A CURRENT AS FUNCTION OF THE COOLING AND IRRADIATION TIMES. INCIDENT ENERGY ON THE “TOTAL ABSORPTION TARGET”: 14 MEV.

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<td>116.5</td>
<td>103.8</td>
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TABLE 11: ACTIVITY (GBQ) OF $^{99m}$Tc FOR A CONSTANT BEAM OF 100 $\mu$A CURRENT AS FUNCTION OF THE COOLING AND IRRADIATION TIMES. INCIDENT ENERGY ON THE “TOTAL ABSORPTION TARGET”: 16 MEV.

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<td>168.3</td>
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3.2. Cross section evaluation for innovative $^{99}$Mo production via the ($\alpha$,n) reaction on $^{96}$Zr target

In the framework of activities scheduled by the INFN project aiming at alternative, accelerator production of $^{99}$Mo/$^{99m}$Tc a different reaction route has also been investigated as potential different approach to the production of $^{99}$Mo having high specific activity. The $^{96}$Zr($\alpha$,n)$^{99}$Mo reaction, using the well-known stacked foil technique and natural Zr targets, in the energy range 32.5-6.9 MeV has been evaluated.

Stacked targets were prepared using first Al foils as beam energy degrader and then adding 3-4 times a pattern composed by a natTi foil (10 $\mu$m) as monitor, natZr foil (10 $\mu$m) as target and Al foil as catcher of recoils particles and energy degrader (high-purity foils supplied by Goodfellow, England). Four irradiations were performed at the cyclotron ARRONAX [19], by using the 67 MeV $\alpha$-beam with a current of $\sim$200 nA.

Considering that $^{96}$Zr is 2.8% of natural Zr targets, in order to produce a relevant amounts of $^{99}$Mo activity, the irradiation time was about 4 hours. The activities of irradiated samples were measured without any chemical separation using gamma-ray spectroscopy. All foils were measured at the same
HPGe detector (dead time < 6%), previously calibrated using $^{152}$Eu, $^{241}$Am, $^{109}$Cd point-like sources (supplied by Cerca-Lea, France). The activities at the End Of Instantaneous Bombardment (EOIB) were calculated using the software FitPeaks [20], the effective particle energy in each foil of the stack by using the code SRIM [21] and the cross sections with the well-known activation formula. The beam intensity was monitored by the natTi($\alpha$,x)$^{51}$Cr reaction [22]. Since the amount of $^{51}$Cr recoil atoms were not negligible (~10%), in the calculation of the cross section the total $^{51}$Cr activity resulting from the sum of the activity in the monitor and in the following target foil was used. The overall uncertainty in each cross section was obtained by taking in account the square root of the sum of the squares of the individual uncertainties: reference cross section (8-12%), detector efficiency and sample-detector geometry (5%), statistical errors (2-6%), target thickness (1%), decay data errors (~1%) [23].

The results reported refer to a 100% enriched $^{96}$Zr target. The cross section values measured in the different irradiations show excellent agreement and indicate that the ideal energy range for $^{99}$Mo production is 13-25 MeV. Cross sections results were compared with published experimental data [24], thus finding good agreement in trend, although with a higher peak value. The $^{96}$Zr($\alpha$,n)$^{99}$Mo reaction is an interesting alternative production route of $^{99}$Mo aimed at the realization of $^{99}$Mo/$^{99m}$Tc generators. Using enriched $^{96}$Zr as target, $^{99}$Mo is the only radioactive Mo-isotope produced, while using natural Zr as target, the resulting $^{99}$Mo still has a high Radio Nuclidic Purity (only the radioactive $^{93}$Mo is co-produced), but with lower specific activity. In both cases no Tc-nuclides are directly produced in target and the high purity $^{99m}$Tc results only from the decay of $^{99}$Mo. Detailed results of such an experimental activity will be published in the near future.

4. Technological developments to design and test a high-power (e.g. ~10 kW) $^{100}$Mo-enriched production target. Assessment of viable processes in order to find out the optimal way to molybdenum deposition technique.

The production target is a crucial point, since the high proton currents involved require a target system able to remove the hitting heat power with high efficiency. $^{100}$Mo-enriched metallic molybdenum targets, having thickness around or less than 1 mm deposited on a cooled copper/aluminum/tantalum backing are taken into account. The selection of molybdenum active thickness on Cu/Al/Ta backing has to be performed considering that the proton energy loss per unit path in Mo material is barely constant (about 15 MeV/mm) down to 10 MeV and then rapidly increases (Bragg Peak). On the other hand, the $^{99m}$Tc production is mainly concentrated in the energy range 10-25 MeV and basically drops down below 10 MeV. Therefore after crossing about 1 mm thickness Mo-layer, the proton beam may be fully stopped into the backing layer, being the Tc production contribution under threshold. In such a way, the power delivered to the Mo target can be minimized/optimized.

The selection of backing material will be strictly related to the different techniques (i.e. sintering, plasma spray, Plasma Void Deposition (PVD), Hot Isostatic Pressing (HIP), electroplating, etc.) which might be exploited for the molybdenum deposition on the support plate material. Any of such techniques have advantages and drawbacks in the preparation of dense 100-300 µm at least metallic molybdenum layers.

For all such reasons the preferable candidate material, either for the target holder, or the sample back plate is aluminum (one of the best Al alloys considering the thermal properties, mechanical strength as well as activation products etc.). The choice of better material however mainly depends on the strategy followed for the chemical dissolution of Mo irradiated sample as well. Concerning the beam power areal density hitting the sample, it is preferable to have proton beam parameters not critical, also to avoid possible blistering formation on the target plate due to hydrogen implantation. Levels around 500 W/cm² are considered for a safe operation. A second issue, not less difficult than the previous mentioned, is the target cooling under high power levels. The problem of heat removal from narrow irradiation area is crucial for the effectiveness of the nuclear reaction. The experience gained in the construction of superconductive resonant cavities, for linear accelerators in nuclear physics research activities with heavy ions, has led Legnaro labs to acquire a well-known
and internationally recognized competence and expertise in the surface treatments, thin film coating technology, plasma engineering, electrochemical finishing and vacuum technology for construction of experimental research tools as well as for industrial application. We proposed to have investigation tests on Mo deposition at the Surface Treatments and Superconductivity (STS) lab at LNL.

4.1. Physical Vapour Deposition (PVD) of few hundreds of micron thick films

Thick films of Transition metals can be produced by a plethora of different deposition methods. Sputtering is however only seldom considered as a possible method for depositing thick films. The reason under that is mainly due to the fact that sputtered films are micro-structurally stressed. Sputtering indeed induces tensile or compressive stresses in the film depending on the pressure of the inert gas used for igniting the discharge. Theoretically then it exist a gas pressure that signs the transition between the tensile and the compressive stress. However this working region depends on many other parameters included the film thickness and it is reproducible with difficulty.

Therefore the approach that we have followed consists in the stress relief due to the stress relaxation of one thousands of layered depositions of half a micron thick films. In other words the deposition of a thick film is fragmented in thousands subsequent brief depositions of thin films. Each deposition is spaced by a “relaxation time” in which the film is annealed. The idea under this method is that the stress release for half a micron film is much easier than for a hundred micron film. The hypothesis moreover is that the deposition of a half a micron thin film will be deposited each time onto a “stress free” surface.

In order to investigate the deposition of multilayered stress relieve films, a standard magnetron sputtering in UHV regime has been used. In order to do thousands of depositions, a Labview® program has been built in order to automate the sputtering procedure. A planar target of 2” diameter is used. We have tested Niobium for practicality, but for our experience, nothing relevant will change when we will sputter Molybdenum. Argon is used as inert gas. The sputtering discharge can be ignited in front of a shutter in order to set parameters. Then the gas is left flushing in the chamber that is turbo-pumped across a partially throttled valve. The sputtering supply is controlled by a program that switches the power on and off in a programmable time with programmable intervals, as displayed in the Figure 12.
First tests gave films little thinner than 100 microns deposited in a 4 day process, that do not delaminate. One critical problem to take into account is the absolute cleanliness of the whole operation and the cleaning of the sputtering system. Small particle of dust left on the substrate or flakes coming from the delamination of film from the sputtering chamber, if deposited on the substrate can work as a nucleation of protrusions growing on the deposited film and amplified by the film thickness. For that reason, the substrate holder must be absolutely clean and free of dust.

Sputtering therefore can be a possible technique for the deposition of stress free thick film. The procedure can be adapted for the deposition of Mo100 thick films. The problem of the material lost due to the large cone of sputtering can be eventually solved by the use of suitable shutters and by designing a non-planar source especially suited for a directional deposition.

5. Radiochemical separation/purification processes optimization for 99mTc production

The target prototype, built at the LNL mechanical workshop, will be also used for some preliminary 99mTc production tests using the cyclotron available in Pavia and/or in JRC Ispra labs first. The high power cyclotron at the ARRONAX Center (France) will be used at a later stage.

After bombardment, 100Mo targets will be dissolved by electrochemical dissolution to produce the chemical species $[^{99m}TcO_4^-]$ and $[^{99/100}MoO_4^{2-}]$ and purified by the method of Chattopadhyay. Such a method is based on the retention/elution behavior of pertechnetate and molybdate ions on different ion exchangers as well as the potential to trap preferentially the no-carrier added $[^{99m}TcO_4^-]$ from different media on a tiny column of strong base anion-exchanger (DowexTM 1x8). The radiochemical purity of cyclotron-produced $[^{99m}TcO_4^-]$ will be determined by instant thin-layer chromatography (ITLC) on Whatman 3 chromatographic paper developed with acetone/HCl 2N (80:20). Radionuclide purity of the cyclotron-produced 99mTc will be assessed by μ spectroscopy for the presence of 99Mo and different cyclotron-produced Tc isotopes. The content of tetrabutylammonium bromide (used for the elution of 99mTc) will be estimated by noted standard colorimetric methods by comparing the color intensities of the extracted organic layers of the standard and the test solutions.

The proposed method has also applicability for recovery of expensive 100Mo and decontamination of 99Tc from spent 99Mo waste solution and recovery of 99Tc for research use. The practical problems associated with this apparently simple chemical operation are significant because radiation safety considerations have to be taken into account because of remote handling operations. Main objective of this phase of the project will be to optimize the known extraction procedure for the 99mTc recovery in very high yield and develop a remote control system for the recovery of ready to use Na$[^{99m}TcO_4^-]$ solution.

Such a proposed activity will be performed by radiochemistry/radiopharmacy section of Ferrara University in collaborations with the LENA group at in Pavia.

References:

[3] Isoflex 2012 Batch, Certificate of Analyses Mo-100 enriched molybdenum metallic material (ISOFLEX-USA)
[5] N. Levkovski, Middle mass nuclides (A=40±100) activation cross sections by medium energy (E=10±50 MeV) protons and -particles (experiment and systematics) (Moscow: Inter-Vesti) p 155 (1991)


[13] GE Healthcare S.r.l., via Galeno 36, 20126 Milano, Italy

[14] Mallinckrodt Italia S.P.A., via Rivoltana 2/d, 20090 Segrate (Milano), Italy


Abstract. The University of Pavia, with Laboratory of Nuclear Energy Applied (LENA) and Radiochemistry Area, has tested different productions approach starting from an enriched $^{100}$Mo target with 18MeV protons. The research involves the radiochemical purity of the final product, the evaluation of $^{99m}$Tc production and the recycling of the enriched Molybdenum.

Facilities

The facilities adopted are the Laboratories of the University of Pavia and protons irradiation are performed at the Cyclotron of the European Commission Joint Research Centre. The accelerator is a Scanditronix MC40 Fig.1. It is a highly versatile accelerator with variable particle energy and the capability of accelerating protons and alpha particles (8 - 40MeV) as well as deuterons (4 - 20MeV) and helium-3 nuclei (13 - 53 MeV).

Targets preparations are made in collaboration with the laboratory of Accelerator and Applied Superconductivity Laboratory – L.A.S.A. (associated to INFN sez. Mi), INFN - LNL (Legnaro National Laboratories) and the University of Ferrara (INFN sez. Fe). Table 1 shows facilities and their applications.

<table>
<thead>
<tr>
<th>Facilities</th>
<th>application</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFN - LNL (Legnaro National Laboratories)</td>
<td>Foils preparation</td>
</tr>
<tr>
<td>Laboratory of Accelerator and Applied</td>
<td>Irradiations</td>
</tr>
<tr>
<td>Superconductivity Laboratory – L.A.S.A.</td>
<td></td>
</tr>
<tr>
<td>(associated to INFN sez. Mi),</td>
<td></td>
</tr>
<tr>
<td>University of Pavia and Ferrara (INFN sez. Fe)</td>
<td>Separations</td>
</tr>
<tr>
<td>University of Pavia (INFN sez. Pv)</td>
<td>Recovery and dosimetry</td>
</tr>
</tbody>
</table>
Targets preparation

Targets are few foils $^{100}$Mo enriched of 25 micron stick together and separated by aluminum foils prepared at Legnaro Laboratory. Fig.2

Irradiation

The irradiations made at the JRC of Ispra were fixed with 18MeV of Protons. This energy was chosen considering the references, with the production yields on energy of both $^{99m}$Tc and impurity, and the consideration that many cyclotrons installed inside hospitals, in Italy, are 18MeV accelerators. If we consider the half-life of the isotope we point that a local production could be convenient in case of world production lacks.
The irradiation parameters were:
- Energy: **18.5** MeV
- Current: **100 nA**
- Irradiation time: **1 h**

The final activity expected was about **10 MBq** of Tc-99m for each foil. This activity allowed the manipulation of the radioactive materials after the decay due to the time necessary to transfer the target to Pavia Laboratory, indeed the residual activity is enough to measure all parameter of interest.

**Target dissolution**

Tc should be separated from the bulk and we tested different approaches. Mo foils were dissolved in acid (different acids and concentrations), basic (NaOH in different concentrations with or without \( \text{H}_2\text{O}_2 \)) and finally with only \( \text{H}_2\text{O}_2 \) and heat. In order to have the best yield is important to have the dissolution as fast as possible and in the final form useful for direct separation. After several tests we consider the use of heated \( \text{H}_2\text{O}_2 \) the best choice. Table 2 shows results.

**TABLE. 2 DISSOLUTION RESULTS**

<table>
<thead>
<tr>
<th>Dissolution approach</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNO(_3) at different concentrations</td>
<td>Fast reaction</td>
</tr>
<tr>
<td>HCl at different concentrations</td>
<td>medium</td>
</tr>
<tr>
<td>NaOH 6N</td>
<td>No reaction</td>
</tr>
<tr>
<td>NaOH 6N with ( \text{H}_2\text{O}_2 ) at different concentration</td>
<td>Passivation</td>
</tr>
<tr>
<td>( \text{H}_2\text{O}_2 ) 15% cold</td>
<td>No reaction</td>
</tr>
<tr>
<td>( \text{H}_2\text{O}_2 ) 15% and heating to boiling point</td>
<td>Fast reaction</td>
</tr>
</tbody>
</table>

**Separation**

Tests were performed using well known Methyl ethyl ketone (MEK) separation and exchange resins as AG 1X8 in connection with alumina column Fig4. We have used Waters Sep Pak Alumina A Plus Cartridge, 1710 mg sorbent, 50-330 µm (Activated with H\(_2\)O deionized). The column was rinsed 5 mL of H\(_2\)O. 1% of starting activity was retained on the column. At this stage the aim is to retain Mo and elute \(^{99m}\)Tc. The solution was again passed through Sep-Pack Water Plus QMA in order to concentrate \(^{99m}\)Tc\(_4^+\) on the column and subsequently elute it with saline. Only 10% of \(^{99m}\)Tc is retained. Finally we obtain best results with the separation using Methyl ethyl ketone (MEK) Fig.3 as already describe in precedent report. Table 3 Shows results

**TABLE. 3 SEPARATION RESULTS**

<table>
<thead>
<tr>
<th>Separation technique</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEK</td>
<td>Fast with good separation</td>
</tr>
<tr>
<td>Resin</td>
<td>Presence of interference like Mo isotope in the final products</td>
</tr>
</tbody>
</table>
Recycling

We tested different approaches for the recovery of Mo oxide enriched after Methyl ethyl ketone (MEK) separation. The one that showed best results was the precipitation of ammonium isopolymolibdate at pH 2-4. After filtration with no ashes filter is possible to choose the final oxidation state either as Mo oxide or as metallic deposition. In order to obtain Mo oxide the ammonium salt was calcinated at about 700°C. Future test will be performed to develop also reduction or final target preparation.

Evaluation of $^{99m}$Tc production

We have tested two methods for the determination of $^{99m}$Tc. We have used activation analysis and ICP/MS.
By activation we used the $^{100}$Tc isotope with 15.8 sec (Fig. 6) half-life. The detection limit is higher than ICP/MS (ppm), it can be used only as reference of other techniques. Sensitivity could be increased adopting cycle analysis system. Tested were performed with $5 \times 10^{-2}$ g/g.

Starting from standard solution Eckert & Ziegler containing $5.84 \times 10^{-5}$ g/g of $^{99}$Tc (activity: 185.1 kBq mass: 5.01365 g) it was prepared the solutions for calibration. Determination limits result between 1 and $5 \times 10^{-12}$ g/g.

This measure will be used to determine cross section of $^{99}$Tc productions.

**TABLE 4. CALIBRATION CURVE SAMPLES ICP/MS TECHNIQUE**

<table>
<thead>
<tr>
<th>ID</th>
<th>Fattore di diluizione</th>
<th>g/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc7</td>
<td>1/100 Sol Madre</td>
<td>5.84E-07</td>
</tr>
<tr>
<td>Tc6</td>
<td>1/2 Tc7</td>
<td>2.92E-07</td>
</tr>
<tr>
<td>Tc5</td>
<td>1/5 Tc7</td>
<td>1.17E-07</td>
</tr>
<tr>
<td>Tc4</td>
<td>1/10 Tc7</td>
<td>5.84E-08</td>
</tr>
<tr>
<td>Tc3</td>
<td>1/4 Tc6</td>
<td>2.92E-08</td>
</tr>
<tr>
<td>Tc2</td>
<td>1/5 Tc4</td>
<td>5.84E-09</td>
</tr>
<tr>
<td>Tc1</td>
<td>1/2 Tc3</td>
<td>2.92E-09</td>
</tr>
<tr>
<td>Tc0_5</td>
<td>1/5 Tc1</td>
<td>1.46E-09</td>
</tr>
<tr>
<td>Z1</td>
<td>H2O 3% di HNO3</td>
<td>Blank</td>
</tr>
<tr>
<td>Z2</td>
<td>H2O 3% di HNO3</td>
<td>Blank</td>
</tr>
</tbody>
</table>

**FIG. 5 Calibration curve ICP/MS Technique**
Results and Conclusions

The production of the $^{99m}\text{Tc}$ using $^{100}\text{Mo}$ targets with 18MeV protons gives good results. The best separation methods used is the dissolution with hot $\text{H}_2\text{O}_2$ than in NaOH 6N and finally separated with MEK. Other separation methods tested should be optimize because of the presence of Mo isotope in the final products. The solution obtained is really free from radiochemistry point of view apart the presence of other Tc isotopes like the 97 and 96 and ground. It is easy recover the Mo target in oxide form, than a new preparation of the target is needed considering also the redox reaction to metallic Mo.
REMOTE PRODUCTION OF $^{99m}$Tc BY PROTON BOMBARDMENT OF $^{100}$MoO$_3$. - DESIGN AND EVALUATION OF CERAMIC TARGET VESSEL -

Yasuhisa Fujibayashi, Kotaro Nagatsu, Japan

Abstract. Remote $^{99m}$Tc production by proton bombardment of $^{100}$Mo was successfully performed using MoO$_3$ salt as a target material and target vessel for vertical beam line. $^{100}$MoO$_3$ could be delivered as aqueous solution, dried up in the target vessel by heat, bombarded, then re-dissolved for recovery. To apply this procedure in general, a ceramic target vessel was also developed and evaluated using $^{89}$Zr as a model radionuclide. The ceramic target vessel enables the use of acidic/alkaline solution for delivery/recovery of target, including $^{99m}$Tc production.

AUTOMATED PRODUCTION METHOD

Dissolving + Recovery: ca 15 min x 3 times = 45 min

FIG.1. Automated $^{100}$MoO$_3$ loading/unloading system
As reported in the previous meeting, automated $^{99m}$Tc production system has been developed using MoO$_3$ salt as a target material (Figure 1, Figure 2).

**DEVELOPMENT AND EVALUATION OF CERAMIC TARGET VESSEL (1)**

We developed a “target vessel for in situ preparation” made of alumina ceramic for conducting remote metallic radionuclide production. Alumina, a major ceramic, has noticeable properties as a material for target vessel, namely high temperature tolerance, chemical resistance and high thermal conductivity. In addition, the easiest production can be achieved by using a vertical beam. The target material can be set horizontally in a vertical irradiation system that is capable of holding any form of target material by gravity. Therefore, a raw metallic material, such as a powder, a granule, or noticeably, an enriched species (as purchased) can be irradiated. Such processing would be free from the time consuming, laborious solidification work, such as electroplating, hotpressing, or sintering of enriched materials. Thus, the proficiency of the ceramic target vessel with the vertical irradiation technique through the production of $^{89}$Zr via the $^{89}$Y(p,n) reaction was investigated.

The ceramic target vessel developed in this study is illustrated in Figure 3. The vessel with a conical bottom was made of alumina (99.7% purity of Al$_2$O$_3$, as A-480 S grade, Kyocera, Japan), and the inner volume was approximately 8 mL (ϕ15 mm×44 mm). Two ports made of the same alumina (ϕ6 mm×2 mm×40 mm) were attached to the body with a silicon O-ring and four screws. Each port was connected to a tube made of perfluoro-alkoxyethylene (PFA, ϕ3 mm×2 mm) with a Teflon reducing union. The assembled ceramic vessel was inserted into an aluminum chassis designed for a vertical irradiation system. The chassis had three recesses for lifting it up to the irradiation port. The three fingers catching the recesses were isolated from the ground and connected to an ammeter for monitoring the beam current. Cooling water was supplied from and returned to the upper surface via the bottom of the ceramic vessel. A thin planar ceramic heater (100 W, 50 mm×20 mm×2 mm, Sakaguchi E.H.Voc Corp., Japan) was attached to the exterior bottom of the chassis.
The $^{89}\text{Zr}$ target yield was $57\pm11$ MBq/µAh (1.54±0.29 mCi/µAh, n=10) at EOB. This yield, around 80%–90% of the value (~65 MBq/µAh) expected on the basis of a previous report, suggested that the irradiation of the powdered target was carried out successfully. The approximate 10–20% decrease from the expected value might be caused by the low bulk density of the powdered target or reduced thickness due to the conical shape of the ceramic vessel (low target thickness in proportion to the wider beam radius). The final $^{89}\text{Zr}$ product, ~940 MBq (>25 mCi) on average generated by a nominal 10 µA×2 h irradiation, was obtained in the volume of ~90 µL within 2.5 h from EOB. Such a low-volume extraction was achieved by the use of the prepared small-volume column. This result exceeded the standard for efficient labeling (i.e., >3.7 GBq/mL).

In a preliminary experimental irradiation, the Y powder was apparently oxidized in air; it acquired a brownish-white flake-like appearance and showed less solubility in HCl. The inner ceramic vessel was therefore purged by He prior to irradiation. The efficiency for trapping $^{89}\text{Zr}$ by column separation dropped significantly by changing the Y distributor. Although both Y samples used in this study had 99.9%+chemical purity, the elemental impurities were quite different (based on typical analysis data available from both distributors). The largest contaminant in the Y samples was Fe (220 ppm in New Metal Chemicals) or Ta (300 ppm in GoodFellow's). When using Ta-contaminated Y, ~40% of the activity was found in the waste fraction from the column. A possible explanation is as follows: ferric (III) or tantalum (V) ions could be generated when the corresponding Y powder was dissolved in HCl. Tantalum (V) ions might have a stronger affinity to the column than $\text{Zr}^{4+}$ owing to their higher oxidation state; thus, $\text{Zr}^{4+}$ might be excluded as a result of competition. The radionuclidic purity of Zr-89 in the product was more than 99.9% at 3 h from EOB. A small amount of $^{88}\text{Zr}$ and its daughter $^{88}\text{Y}$ were found in a long-decayed sample. The $^{88}\text{Zr}$ contamination level was estimated to be 0.039% at EOB. No other radionuclidic impurities were found either in the product or waste fraction, such as those originating from impurities in the Y reagent, Pt foil, or Al (alumina ceramic vessel).

The remaining $^{89}\text{Zr}$ activity found in the ceramic vessel was ~5% of the total produced. These losses
were caused by the dead volume from the conical shape (≈0.9 mL) or insufficient dissolution of Y; however, this activity is considered to be negligible for practical purposes of radionuclide production. The ceramic vessel persisted for 10 production runs and is intact and still in use, as confirmed by visual inspection (200 µAh+, 10 µA at maximum). However, after the first irradiation, the inner ceramic wall became darker in color and showed a slight decrease in resistance (initial level: N2000 MΩ, decreased to 10–20 MΩ after the vessel was washed and dried, as measured by a MΩ Hitester; Hioki, Japan). It is well known that alumina ceramic is an excellent insulator because of its high resistance; however, the beam current was monitored correctly without any problem. Although the reason is still under investigation, there are two potential paths for beam current conduction: (1) the beam itself and the surrounding ionized He atmosphere might conduct the current to the Pt foil and Al chassis; (2) the current might run on the surface of the ceramic with a sputtered Y (suspected from the observation of a stained ceramic, but not confirmed) to Pt and Al.

The target solution recovered from the ceramic was a particulate suspension, and the particles could be observed in the sample even after an extended dissolution time (30 min). Although the ceramic was slightly darkened, it maintained its integrity; thus, we concluded that the particles originated from undissolved Y. The inefficient solubilization can be explained as follows: (a) due to the high reactivity of Y, a fraction of the Y powder acquired surface passivity during storage or irradiation; (b) when Y contacted with HCl at first, because of its vigorous reactivity a portion of the powder might spatter and deposit in areas insufficient exposed to the HCl solution. The undissolved particles resulting from insufficient reaction were then recovered by other solutions with increased volumes.

In the automated system developed in this study, a simple three-way stopcock was used for controlling the target solution. Although common solenoid valves are useful and have low dead volume, they sometimes malfunction when suspended particles are present. The stopcock, in contrast, showed the best performance and durability because of its simple structure. For the same reason, the vented filter placed at the beginning of the processing line was useful for removing the particles; thus, typical solenoid valves placed downstream of this filter maintained their integrity.

CONCLUSION

A newly developed alumina ceramic target in combination with vertical proton beam line (Figure 4, Figure 5) allows us to bombard any kind of chemical forms including salt, powder, liquid or gas, and handle them without complicated robotic system. Direct \(^{99m}\text{Tc}\)-production is considered to be a good application of this target vessel system.
FIG. 4. Beam line and bending magnet for vertical beam line.

FIG. 5. Upright cyclotron; a potential vertical beam provider.
REFERENCE:

ACCELERATOR-BASED ALTERNATIVES TO NON-HEU PRODUCTION OF $^{99}$Mo/$^{99m}$Tc – PROGRESS IN POLAND

R. Mikolajczak et al., Poland

Molybdenum target preparation

1.1. Electroplating of molybdenum from aqueous solution

In order to prepare a Mo target material for its irradiation with protons the preliminary studies on Mo electrodeposition on platinum support from aqueous solutions were performed. For this purpose two-electrode electrochemical system (Pt-Pt) was used. Electrolyte solution in volume of 30 ml contained 1 mM ammonium molybdate and 0.5 M ammonium acetate. The pH of this solution was 8.3. Electrochemical process was carried out at a constant current of 400mA/cm², temperature of 40-45°C and in the argon atmosphere. As result of 60 min process, a multicolor, shining thin film was deposited on the platinum surface. It is supposed, that the deposited layer consists of molybdenum oxides at various oxidation states. Complete coverage of Pt and adherence to it can be observed, however the film was not conductive.

Further work plan: is the application of electrodeposition of molybdenum from molten salts mixture target. The furnace operating up to 1280°C in an atmosphere of inert gases for electroplating Mo from molten salts was purchased via public tender announcement. It was delivered to RC POLATOM in August 2013. Initial experimental works are in progress.

1.2. Preparation of molybdenum pellets

The second method planned to use for manufacturing Mo target is pressing molybdenum powder into pellets and sintering. For this purpose a tantalum and stainless steel plates were used as support. Several pellets using molybdenum powder, particles of 2 µm diameter, were pressed under different values of pressure. The optimized parameters for manufacture molybdenum pellets with various sizes are given in Table 1.

It was found that the pellets did not adhere neither to the tantalum nor stainless steel plates but they conducted electricity very well. Result of tests for stability of pellets is not satisfactory, however it was found that pellets prepared with higher pressure were more mechanically resistant. The hydrogen/inert furnace working up to 1800°C (CTF 18/300, Carbolite) for Mo sintering and hydraulic press were purchased via public tender announcement. They were delivered to RC POLATOM on October 1st 2013.

**TABLE 1. DATA OF PREPARATION OF Mo PELLETS**

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Thickness (mm)</th>
<th>Mass of Mo powder (mg)</th>
<th>Pressure (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.45</td>
<td>170</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>0.46</td>
<td>245</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>0.58</td>
<td>600</td>
<td>15</td>
</tr>
</tbody>
</table>

Further work plan: is to perform the sintering of pressed molybdenum pellets in hydrogen atmosphere and determine the influence of molybdenum powder particle size on mechanical stiffness of molybdenum pellets.

---

2. Electrochemical dissolution of molybdenum foil

Attempts of electrochemical dissolution of metallic molybdenum foil in alkaline solution containing 5M NaOH failed. According to Pourbaix diagram (Fig.1) for molybdenum, with increasing of pH of electrolyte solution, the value of potential of water decomposition is reduced. Therefore in this case the potential not higher than 800mV can be applied, what was not sufficient to oxidize the molybdenum.

![FIG. 1. Potential-pH equilibrium diagram for the system Mo-H₂O at 25 °C](image)

The application of neutral environmental (1M NaCl) for oxidation of molybdenum allowed the use of higher electrochemical potential. It was found, that the use of two-electrode system comprising Mo foils as working electrode and Pt foil as counter electrode under following conditions: constant potential of 1.6V and temperature of electrolyte solution of 45-50°C, during 30 min, the 15% of metallic molybdenum was oxidized and passed into the solution. Increasing the electrochemical potential up to 1.8V and extending the duration of process till 1.5 h resulted in Mo foil dissolution to above 50%. Unfortunately, application of higher electrochemical potentials cases covering the counter electrode with thin film of molybdenum oxides. In order to eliminate of this the electrolytic vessel with two separated chambers was used. In this modified process conducted in 1M NaCl heated to 50°C at potential of 2V maintained for 1 h and then at potential 3 V maintained for 0.5 h, about 65% of metallic molybdenum was electrochemically dissolved. Further improvements of electrochemical dissolution of metallic molybdenum increased its efficiency up to 85% resulting in increasing the sodium hydroxide concentration to 3 M and temperature of this solution to 60°C and extending an electrochemical potential to 4 V.

Further work plan: is to improve the parameters of the process.

3. Chemical dissolution of Mo metal.

In alkaline medium the dissolution obeys the following equations:

\[
\text{Mo} + \text{H}_2\text{O}_2 \rightarrow \text{MoO}_3 + 3 \text{H}_2\text{O}
\]

\[
\text{MoO}_3 + 2 \text{NaOH} \rightarrow \text{Na}_2\text{MoO}_4 + \text{H}_2\text{O}
\]
The Mo metal used for dissolution was in the forms of powder (100 µm) and foil of 1 mm thickness. Mo powder dissolves in 1 M NaOH using twofold excess of the base and 25% excess of H₂O₂ in temperature of 70°C after 30 minutes. Mo as a foil does not dissolve in these conditions. To achieve complete dissolution in 30 minutes it was necessary to use sevenfold excess of H₂O₂.

4. Separation of $^{99m}$Tc from molybdenum

Using RPC-18 (OASIS Plus HLB, 225 mg) column modified with polyethylene glycol PEG-2000 the carrier-free $^{99m}$Tc was adsorbed. After rinsing with 3 M (NH₄)₂CO₃ solution the $^{99m}$Tc was eluted with water in 5 ml fractions (Fig.2).

Three different flow rates were used: 0.6; 1.0 and 2 mL/min (Fig.3). The fastest recovery was obtained with 2 mL/min flow rate and it amounted to about 90% in 50 mL volume (Fig.3). When the large excess of Mo carrier to $^{99}$Mo tracer was added, the recovery of $^{99m}$Tc remained at approximately 90% in 50 mL of eluate (Fig 4).

*Further work plan:* more experiments on the $^{99m}$Tc recovery will be carried out.
Institute of Nuclear Chemistry and Technology

5. Separation of $^{99m}$Tc from macro amounts of molybdenum

Several methods for technetium separation from irradiated molybdenum target are available in the literature. Few of them are based on the high volatility of technetium heptaoxide, Tc$_2$O$_7$, others on the wet chemistry. We decided to develop and use a different method, due to the concern on very high specific activity of Tc radiotracers and the necessity to have a radiochemical separation as fast as possible.

Besides the $^{99m}$Tc and $^{99}$Tc radionuclides, irradiation of Mo target with protons induces direct production of Mo, Nb and Zr radionuclides. In the gamma spectra also Y radionuclides obtained from decay of $^{88}$Zr and $^{89}$Zr were identified. For separation of $^{99m}$Tc from irradiated Mo target we tested two precipitation methods. First was elaborated by Bonardi [3] and based on precipitation of MoO$_3$ hydrate, whereas the second was elaborated in our laboratory. In the first method the metallic Mo (25 mg) irradiated in thermal neutron flux was dissolved in 1 ml of nitric acid (from 1 M to 7 M). The bulk of poorly soluble precipitated molybdic acid (MoO$_3$ hydrate) was filtered off and the activity of $^{99}$Mo and $^{99m}$Tc was measured in the filtrate. We found that in 7 M HNO$_3$ only 75 % of molybdenum is present in a solid form and coprecipitation of $^{99m}$Tc is negligible (less than 6%).

The second method based on precipitation of insoluble heteropolyacid - ammonium molybdenum phosphate hydrate (AMP) and obtained results were more promising. The schematic diagram of proposed method is presented on Figure 1.

---

**FIG. 1.** Separation scheme of the process elaborated in the Institute of Nuclear Chemistry and Technology.

In the first step metallic molybdenum target was dissolved in 2 M HNO$_3$. Next, triammonium phosphate was added and Mo was precipitated from the solution according to the reaction:

$$12 \text{MoO}_3 + (\text{NH}_4)_3\text{PO}_4 + 3 \text{H}_2\text{O} \rightarrow (\text{NH}_4)_3\text{P(Mo}_3\text{O}_{10})_4 \cdot 3\text{H}_2\text{O}$$

Different Mo:PO$_4$ substrate ratios were tested to find the optimum separation conditions. The results are presented in Table 1.

<table>
<thead>
<tr>
<th>triammonium phosphate (M)</th>
<th>% of stoichiometry</th>
<th>concentration of Mo in solution (mg/ml)</th>
<th>% Mo in precipitate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>100</td>
<td>4.04</td>
<td>84.0</td>
</tr>
<tr>
<td>0.075</td>
<td>125</td>
<td>1.46</td>
<td>94.1</td>
</tr>
<tr>
<td>0.15</td>
<td>250</td>
<td>1.57</td>
<td>94.0</td>
</tr>
</tbody>
</table>

As shown in Table 1 to effectively precipitate of molybdenum only 25% excess of triammonium phosphate is sufficient. To improve the efficiency of the process we examined the effect of the ammonium nitrate addition on the yield of AMP precipitation.

**TABLE 2. INFLUENCE OF NH$_4$NO$_3$ ADDITION ON Mo SEPARATION FROM SOLUTION**

<table>
<thead>
<tr>
<th>Ammonium nitrate (M)</th>
<th>Concentration of Mo in solution (mg/ml)</th>
<th>% Mo in precipitate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.6</td>
<td>93.6</td>
</tr>
<tr>
<td>0.16</td>
<td>0.64</td>
<td>97.4</td>
</tr>
<tr>
<td>1.56</td>
<td>0.54</td>
<td>97.8</td>
</tr>
<tr>
<td>3.12</td>
<td>0.50</td>
<td>98.0</td>
</tr>
</tbody>
</table>
As can be seen in Table 2, only small addition of ammonium nitrate significantly increased precipitation of AMP. Based on the performed experiments the following parameters of AMP precipitation were selected: F for 25 mg of metallic Mo target dissolved in 1 ml 2 M HNO₃; exactly 0.3 mmol of (NH₄)₃PO₄ and 0.16 mmol of NH₄NO₃ should be added. The precipitate can be separated by filtration or centrifugation after 15 minutes. We studied also possible coprecipitation of ⁹⁹ᵐTc with AMP. After separation process in conditions presented above we found in the filtrate solution 99.6% of total ⁹⁹ᵐTc activity.

From performed studies it can be concluded that the proposed process is promising and allows fast separation of macroamounts of Mo from the solution without co-precipitation of ⁹⁹ᵐTc. For the next year we are planning to use small columns with zirconium oxide for purification of the solution from residues of Mo. Also separation of others radionuclides formed during irradiation process (⁸⁸,⁸⁹Zr, ⁸⁸,⁸⁹Y, ⁹⁰,⁹¹m,⁹⁵mNb) will be studied.

25 mg of metallic Mo target was dissolved in 1 ml two different concentration of HNO₃ (7M and 2M). The lower concentration nitric acid is used the lower amount of Mo is detected in solution. We found that in 2 M HNO₃ 50% of molybdenum is present in a solid form and coprecipitation of ⁹⁹ᵐTc is negligible (about 6%).

We applied three forms of ammonium salts to participate AMP. To obtain the lowest possible level of molybdenum in solution it is necessary to use triammonium phosphate. After that, the next steps was about analyzing the influence of temperature and time on precipitation process. In our case there were also two other parameters to optimize: concentration NH₄NO₃ and (NH₄)₃PO₄*3H₂O. The obtained results are presented as graphs (Fig. 2. and Fig.3.). Microamounts of molybdenum do not noticeably coprecipitate with AMP.

![Graph showing concentration of Mo in solution as a function of concentration of ammonium nitrate.](image)

**FIG.2.** Concentration of Mo in solution as a function of concentration of ammonium nitrate.
We suppose that next steps will be necessary to clean solution from the residue containing Mo. First attempts were made to use ZrO\textsubscript{2} as adsorbent to separate \textsuperscript{99m}Tc from molybdenum. Under acid condition only \textsuperscript{99m}Tc is retained on this sorbent. However, under neutral pH conditions both \textsuperscript{99m}Tc and Mo are not bonded to zirconia oxide.

**Heavy Ion Laboratory, University of Warsaw**

6. **Proton irradiations of the Mo self-supporting targets**

This program is presently in the preparatory phase. The irradiations at 16.5 MeV PETtrace cyclotron will begin shortly after the external irradiation station is constructed. The irradiations at 25 MeV are planned using the cyclotron in National Centre of Nuclear Research, Poland.

7. **Self-supporting target preparation**

The natural Mo target material (99.999) was purchased and the corresponding targets prepared. 5g of \textsuperscript{100}Mo (99.1 \%) was ordered from ISOFLEX/Moscow.

The following equipment was ordered via public tender announcement:

* Rolling mill; * Pressing mould allowing powder outgassing during pellet production + finished pellet form (the \textsuperscript{100}Mo will be supplied in form of metal powder and for rollable bead formation needs to be melted); * Hydraulic press;

Studies of gamma spectra are planned to be performed for two energy ranges of protons: 25-16 MeV and 18 – 8 MeV. It requires targets with various thicknesses to assure appropriate energy loss. Targets for the first tests were produced using powder pressing technique. For this purpose pressing tool with hydraulic press was used (Fig.6). The mould construction allows simultaneous air removal during powder pressing what improves the tablet stability under the beam.
Molybdenum self-supporting targets prepared using pressing tool are shown in Fig. 7.

Unfortunately, due to major problems with functioning of cyclotron delivering protons with energy of 28 MeV located at National Centre of Nuclear Research in Poland, the tests were not made.

8. Construction of the external, well cooled, target holder for the PETtrace cyclotron

The external target system design is almost finished. This system presented in Fig.8 is connected to the cyclotron PETtrace through a short drift tube. At the end of the drift tube a diagnostic box is located.
FIG 8. The target holder system for the PETtrace cyclotron

The diagnostic box is equipped with remotely movable, water cooled Faraday cup, low and high vacuum gauges, a vacuum turbo molecular pump system and a vacuum window. The vacuum window resistance is strengthened by the helium gas cooling system. A target body is directly connected to the vacuum window. In order to release an irradiated target material the target body is movable by means of actuator presented on the right side of this slide. The target body, same as Faraday cup, is cooled with demineralized and deionized water. The whole system is fixed to the dedicated support.

The target holder accepts the power dissipation of about 300 W, as the first step. Calculations of thermal condition of the Faraday cup and the target body we have done. The manufacturing of mechanical components is completed in the HIL workshop:
- the drift tube,
- the vacuum window with helium cooling system,
- the Faraday cup with its actuator,
- the target body with its actuator and
- the support

The diagnostic chamber is at the stage of manufacturing and should be ready soon. All vacuum components have been purchased via tender procedure. We expect to start assembling the target station in next two-three weeks. The design of the helium cooling system is also completed. The tender procedure for a computer control system was successfully completed. The delivery of computer for remotely controlled system purposes should arrive in next two weeks. In a meantime, construction of the helium cooling system of the target station will start.

The target sandwich will be placed on the beam line in a special holder made of aluminium (see Fig. 8).
ACCELERATOR-BASED ALTERNATIVES TO NON-HEU PRODUCTION OF $^{99}$Mo- $^{99m}$Tc

Ibrahimm Al Jammaz, Saudi Arabia

1. Introduction

Nuclear medicine applications of the cyclotron produced radiopharmaceuticals are being increasingly utilized for both research and routine clinical diagnosis and therapy of an extensive variety of diseases. Numbers of medium energy cyclotrons world-wide have rapidly increased specially after the introduction of Positron Emission Tomography (PET) and this number is expected to grow in the future. Due to the major shortage supply of the molybdenum-99 ($^{99}$Mo) caused by the prolonged shutdown of various reactors, the need to explore alternative methods of producing technetium-99m ($^{99m}$Tc) isotope using medium energy cyclotron is well justified to allow continued use of all existing radiopharmaceuticals designed for $^{99m}$Tc in nuclear medicine.

Recently, numbers of member states have embarked on research programs to investigate the use of accelerators for the production of $^{99}$Mo or $^{99m}$Tc directly. These approaches make use of the $^{100}$Mo($\gamma$,n)$^{99}$Mo and $^{100}$Mo(p,2n)$^{99m}$Tc reactions, respectively. Early indications have shown that the cyclotron approach holds promise for at least being able to supplement generator availability with production rate of 17 mCi/µAh. At this rate it is possible for the existing cyclotrons with proton energies of 16-19 MeV and beam current ranging from 60-100 µA to produce significant amounts of $^{99m}$Tc for local use on a daily basis.

Therefore, as member of the International Atomic Energy Agency’s co-ordinated meeting entitled “Accelerator-based Alternatives to Non-HEU production of Mo-99 /Tc-99m”, we will be focusing on the electroplating method of $^{100}$Mo, targetry design, production $^{99m}$Tc from proton bombardment of enriched $^{100}$Mo using $^{100}$Mo(p,2n)$^{99m}$Tc nuclear reaction, fast and efficient separation of $^{99m}$Tc from enriched $^{100}$Mo as well as resourceful recovery of enriched $^{100}$Mo. In addition, quality control parameters for $^{99m}$Tc pertechnetate and its radiopharmaceuticals prepared will be fully investigated.

Design of Solid Targets System

The crucial part of designing a solid target is associated with heat transfer problem that need to be removed continuously as the beam bombarding the target surface. Because the density of solids is typically higher than that of liquids or gases, the path length of the beam is shorter, and the target somewhat smaller. The energy lost when charged particles pass through the target medium is dissipated in the form of heat. The following items were found to play role in affecting yield:

- Target inclination (Beam to target angle)
- Sufficient cooling system (water and helium)
- Beam current
- Beam energy and
- Beam sweeping method

Therefore, the target is designed to be cooled by both water and helium channels and the beam aligned to be perpendicular to the target (90°). Fig 1 displays the developed solid target for $^{100}$Mo and its control system which remotely controls the target from the cyclotron room. This target is a modified target of the recently developed solid target for I-124 and Cu-64.
Beam Monitoring and Control Systems

In order to ensure that the beam is spread over the target area; beam diagnostic tool such as collimator system can be used. Collimators are usually designed to be slightly smaller than the target opening or window. This ensures the size of the beam is limited to the size of the target opening and, therefore, the beam current that is read on the target is an accurate indication of the beam hitting the target. Moreover, it prevents the front flange of the target from becoming activated and therefore lowers the radiation dose to the operator when maintenance is required. Fig 2 elucidates the developed four fingers collimator system at the research centre in King Faisal Specialist Hospital (FSHRC). In such a system beam current is adjusted until measured on the four figures indicating that the beam is wide enough and covering the whole area. For beam to be spreaded, other tools are used to defocus it on the collimator: a magnetic focusing element (quadruples) and steering magnet.

Target Preparation

While the use of a $^{99m}$Mo foil is the simplest target design employed for $^{94m}$Tc production, thick foils of enriched $^{100}$Mo are not readily available. Therefore, several alternative strategies for target preparation using different forms of $^{100}$Mo have been investigated previously to overcome this limitation. In addition, our initial attempt to electroplate enriched $^{100}$Mo on aluminum target plate did not proceed well. Since one of the most common methods for thick target preparation is the pressing of an enriched MoO$_3$ pellet into aluminum or platinum cavity target, circular copper and aluminum target plates to fit the remotely controlled target were fabricated utilizing our well-equipped precision
machine shop. The diameter of target plate is 25 mm, thickness is 2 mm and the cavity depth in the center of the target is 1.25 mm with diameter of 10 mm (Fig 3).

![FIG 3. Circular copper and aluminum target plates.](image)

Several natural Mo ($^{nat}$Mo) targets in metallic form were prepared by hydraulically pressing $^{nat}$Mo metallic powder (300-400 mg) into the circular cavity aluminum target plates at 5000 psi, this was followed by heating in a furnace at 450°C for four hours. For quality control, each target was examined microscopically to ensure its smoothness and homogeneity (Fig 4).

![FIG 4. Normal and microscopic image of metallic $^{nat}$Mo targets.](image)

Similarly, enriched Mo ($^{100}$Mo, 99.05%) targets in oxides form were prepared by hydraulically pressing $^{100}$Mo oxides powder (150-200 mg) into the circular cavity aluminum target plates at 7000 psi, this was followed by heating in a furnace at 400°C for four hours. For quality control, each target was examined microscopically to ensure its smoothness and homogeneity. In initial experiments, when hydraulically pressing was 5000 psi and temperature was increased to insure the adhesion of Mo-oxide to the aluminum plate, however, cracks and ununiformed shape was observed and target material flakes during irradiation (Fig 5)

![FIG 5. Normal and microscopic image of oxide $^{100}$Mo targets.](image)
**Target Irradiation**

To insure stability against high energy and current, $^{99m}$Mo targets in metallic form were irradiated and the isotopic composition measured using Multi Channel Analyzer (MCA, Ge-Li detector). The results are summarized in table 1.

Tc-$^{99m}$ was produced by the bombardment of enriched Mo-100 targets with variable energies (15-23 MeV) protons from the CS-30 Cyclotron external beam using the $^{100}$Mo(p,2n) $^{99m}$Tc nuclear reaction. The proton current was 1 $\mu$A and the irradiation time was 10 minutes. The irradiated targets were measured using MCA to determine the isotopic composition of the recovered $^{99m}$Tc. As shown in table 2, the yield of $^{99m}$Tc has increased dramatically when increasing the energy from 15 to 23 MeV. However, the amount of $^{99}$Mo increased from 0.38 to 6.44% when increasing energy from 15 to 23 MeV. These results may suggest that the optimum energy for the production of $^{99m}$Tc is between 17-19 MeV.

**TABLE 1. ISOTOPIC COMPOSITION OF THE IRRADIATED $^{nat}$Mo TARGETS.**

<table>
<thead>
<tr>
<th>Energy MeV</th>
<th>$^{99m}$Tc %</th>
<th>$^{93m}$Tc %</th>
<th>$^{94}$Tc %</th>
<th>$^{95m}$Tc %</th>
<th>$^{96g}$Tc %</th>
<th>$^{96m}$Tc %</th>
<th>$^{90}$Nb %</th>
<th>$^{90g}$Nb %</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>1.168</td>
<td>0.0</td>
<td>1.577</td>
<td>93.138</td>
<td>2.072</td>
<td>0.758</td>
<td>0.0</td>
<td>0.994</td>
</tr>
<tr>
<td>17</td>
<td>2.976</td>
<td>0.0</td>
<td>5.721</td>
<td>82.273</td>
<td>4.738</td>
<td>1.480</td>
<td>0.092</td>
<td>2.499</td>
</tr>
<tr>
<td>19</td>
<td>2.784</td>
<td>3.536</td>
<td>6.748</td>
<td>78.465</td>
<td>3.547</td>
<td>1.0222</td>
<td>0.159</td>
<td>2.839</td>
</tr>
</tbody>
</table>

**TABLE 2. ISOTOPIC COMPOSITION OF THE IRRADIATED ENRICHED $^{100}$Mo TARGETS.**

<table>
<thead>
<tr>
<th>Energy MeV</th>
<th>$^{99m}$Tc %</th>
<th>$^{99}$Mo %</th>
<th>Irradiation time (min)</th>
<th>Current $\mu$A</th>
<th>$^{99m}$Tc Yield mCi/$\mu$A-hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>99.62</td>
<td>0.38</td>
<td>10</td>
<td>1</td>
<td>41.98</td>
</tr>
<tr>
<td>17</td>
<td>99.27</td>
<td>0.73</td>
<td>10</td>
<td>1</td>
<td>44.46</td>
</tr>
<tr>
<td>19</td>
<td>98.39</td>
<td>1.61</td>
<td>10</td>
<td>1</td>
<td>46.96</td>
</tr>
<tr>
<td>23</td>
<td>93.56</td>
<td>6.44</td>
<td>10</td>
<td>1</td>
<td>102.1</td>
</tr>
</tbody>
</table>
4. Looking ahead

Protocols for the recovery of $^{99m}$Tc as well as enriched $^{100}$Mo will be developed using either liquid or solid phase extraction. In addition to the process of recycling the $^{100}$Mo, the impact of using recycled enriched $^{100}$Mo on the quality of the extracted $^{99m}$Tc will also be investigated. Because of contaminants profile of cyclotron-produced pertechnetate may have a direct impact on the labeling efficiency of $^{99m}$Tc-radiopharmaceuticals. The quality control of any contaminants and their effect, if any, on labeling efficiency will be characterized. Efficient and safe incorporation of cyclotron-produced pertechnetate into all $^{99m}$Tc-radiopharmaceutical kits will be achieved. To ensure safe $^{99m}$Tc-radiopharmaceuticals for human use prepared using this method rigorous quality control protocols for the final products will be developed.
Acknowledgment

The research team would like to acknowledge the International Atomic Energy Agency (IAEA) and King Faisal Specialist Hospital and Research Center (KFSH&RC) for their support.
PRODUCTION OF Tc-99m FOR MEDICAL APPLICATIONS USING CYCLOTRON

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Abstract. Multiple methods and experiences have been carried out to perform a suitable target for high current proton beam for $^{99m}$Tc production. Different electroplating bathes have been used for target support electroplating. The quality of the different electroplated Mo layer on copper substrate was not suitable for high current proton beam and high activity $^{99m}$Tc production. The thickness obtained by different electroplating procedure do not exceed 2-3 micrometer having a total surface of 10 cm$^2$. After these dissatisfying electroplating experiences, testes on pressed then sintered of molybdenum oxide method in order to prepare a molybdenum target had been achieved. Another method for the production of $^{99m}$Tc based on liquid target has been explored. A related method for the separation of $^{99m}$Tc and recovery of enriched molybdenum has been tested.

Introduction

The global shortage of $^{99}$Mo production and the increasing demands on $^{99m}$Tc in nuclear medicine, have led to look for other routes for production of $^{99m}$Tc. Several reactions were investigated for the production of $^{99m}$Tc directly or indirectly via production of $^{99}$Mo. In this study we will focus our research on the direct production of $^{99m}$Tc by proton bombardment of enriched molybdenum. High activity of $^{99m}$Tc will be produced based on $^{100}$Mo(p,2n) $^{99m}$Tc reaction. To make this production route feasible using 30MeV cyclotron, proton energy will be adjusted on different energies between 18 and 24 MeV. Targets irradiated on different energies, at the same irradiation time, (18, 20, 22, 24 MeV) will be treated in order to determine the impurities and results will be compared with theoretical calculations.

The successful key of this work is to prepare a robust target which can resist to more than 150 micro ampere of proton beam. This step will take more time than the other step of production. Method for separation and purification will be investigated. The ion exchange chromatography technique will be applied for Tc-99m separation to meet the requirement of high specific activity and purity.

Quality control of the cyclotron-produced pertechnetate will be investigated. Voltampprometric method will be use to measure the presence of any contaminant.

Radionuclidic impurities will be determined by gamma spectrometry.

Labelling efficiency of different kits and image quality of Tc-radiopharmaceuticals using cyclotron-produced $^{99m}$Tc will be investigated.

Possible parameters of consideration with regards to target design include the molybdenum deposition technique, the selection of target support plate material (e.g. with regards to thermal properties, machinability, mechanical strength, chemical inertness, cost, activation products, etc.), the beam power density, and the target cooling system.

While several strategies for metallic molybdenum deposition have been tested, further development into these and/or other methods is warranted. Examples of molybdenum deposition strategies which have been tested for this application include both sintering and electroplating. Sintering has been used to prepare dense (100 µm) metallic molybdenum targets. The conditions for sintering, the lower-limit of thickness that can be achieved, and the development of a simple technique for bonding of the enriched molybdenum pellet to a suitable backing plate require further evaluation. Electroplating molybdenum directly from a molybdate solution onto a suitable target plate can be achieved to make thin (<5 µm) metallic coatings, however accelerator targets need to be substantially thicker. Research into the plating conditions and electrolyte composition can be carried out to develop a technique that promotes thick, adherent, metallic molybdenum deposits for irradiation.
We think that improving pressed then sintered metal powder target will be the suitable method that can be used for preparation from new metallic and recovered material of Mo metallic powder. A new method for the production of $^{99m}$Tc has been explored based on liquid target. The activity production yield should be studied in more details. As well as the quality of the separated and purified pertechnetate need confirmation for direct medical uses.

**Results and discussion:**

**Target support electroplating method:**

The electrolyte bath for electroplating consists of 100 grams of potassium fluoride dehydrate, KF$_2$H$_2$O: 10 to 15 cc. of 48% aqueous hydrofluoric acid, HF: 50 to 130 cc. of water: and 5 grams of molybdic anhydride, MoO$_2$.

The current density used is from 0.25 to 0.35 ampere per square centimeter. The temperature is preferably maintained between 30°C. and 50°C.

When the temperature rises above than 65°C, dark non-adherent deposits are obtained. With our process as above described, we have been able to obtain smooth, bright, adherent deposits of molybdenum in five minutes. The deposited metal is resistant to acid such as cold hydrochloric and sulfuric and resistant to strong alkalis, but is soluble in nitric acid.

The accent used process in our laboratory as following:
- 5 g molybdic anhydride
- 100 g. KF$_2$H$_2$O
- 13.5 cc. HF (48%)
- 50 ml water

The optimum conditions for obtaining deposition of molybdenum from this bath are cathode current density 0.3 ampere per square centimeter (the used current is about: 240 mA ); temperature 30°C to 50°C (used temperature is about : 45°C). dark, non-adherent deposits are obtained in five minutes. The weight of the average deposit (two targets) is 0.0075 g. on an area of 10 square centimeters of cathode surface, the used anode is a conducting material which not be attacked by the reaction products such as carbon.

Figure 1 shows the electroplated target and target surface.

*Fig.1 Copper target support electroplated with Mo.*
Pressing and Sintering method:

Natural molybdenum oxide has been pressed in a disc form. Then this disc is sintered at 650°C for the duration of 24 hours in air atmosphere. The disc became harder and more resistant to shocks. When the surface has been analyzed by Scanning Electron Microscopy (SEM), the particle consisting the disc appeared to be not well bounded. This means the heat conductance of sintered material will be not good.

Figure 2 shows the surface by SEM before and after pressing and sintering experiments.

Scanning electron microscopy (SEM) of the pressed non-

Scanning electron microscopy (SEM) of the pressed and sintered MoO$_3$ (650°C, 24h)
Another experiment has been carried out in order to see the effect of the temperature on the sintered materials. We found that at 750°C crystals of sintered molybdenum oxide is formed on the surface of the disc. Figure 3 shows the surface of the sintered MO₃ at 750°C.

![Pressed and Sintered MoO₃ (750°C)](image1)

On the other side we use a modified IBA solid target which we think can be an ideal effective system for cooling point of view.

Fig. 2 shows a modified IBA blank target before pressing Mo inside the engraved central region of this support.

![Fig. 2 modified engraved at the center of IBA blank target.](image2)
Then on the engraved area we pressed Mo metal powder on the center of the target (surface 1 cm$^2$). Figure 3 shows the prepared target. The thickness of the pressed mater is about 50 μm.

**FIG.3 The prepared target. The pressed Mo material is inside the engraved circular area.**

At this time a sintering condition for molybdenum powder metal (temperature and heating atmosphere will be optimized. We hope that this target can resist to more than 150 μA proton beam current. For our future work we can enlarge engraved central area (may be can be an oval shape) where we can put more Mo metal powder.

**Irradiation of Molybdenum in liquid target**

Sodium molybdate solution has been prepared by the dissolution of 0.5 g of Na$_2$MoO$_4$.2H$_2$O/1 ml deionized water (solubility 0.56 g/ml, 0°C)

**Irradiation conditions:**
- Irradiated Liquid Volume: 0.85 ml
- Niobium target used for $^{18}$F production
- Target Window: Havar
- Irradiation current: 30 Micro Amperes
- Target pressure: 35 Bars
- Irradiation time: 30 min
- Irradiated Mo weight: 0.16 g

After the bombardment, the irradiated liquid has been loaded on the separation column containing Acidic Alumina resin which has been preconditioned by HNO$_3$ 3M. The column has been rinsed by 2ml of HNO$_3$ 3M. Then radioactive molybdenum is eluted by 5ml of 0.9% NaCl. Then the recovery of molybdenum was performed by passing 30 ml of NH$_4$OH 1M. All these solutions were analyzed by gamma spectrometry.
Column elution profile
Gamma ray spectra of the first rinsed solution by HNO$_3$

Gamma ray spectra of the eluted radioactive technetium
Gamma ray spectra of the eluted radioactive technetium

Gamma ray spectra of the recovered Molybdenum
Gamma ray spectra of the recovered Molybdenum

Gamma ray spectra of the separation column confirm no molybdenum, good recovery
Gamma ray spectra of the separation column confirm no molybdenum, good recovery

Acknowledgements

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CYCLOTRON PRODUCTION OF $^{99m}$Tc AT WASHINGTON UNIVERSITY

Vernal Richards, Suzanne E. Lapi, USA

Abstract. $^{99m}$Tc is the most commonly used isotope in diagnostic nuclear medicine with over 16 million scans using this isotope performed annually in the United States and over 40 million scans performed annually worldwide. Common procedures using this isotope include bone scans, heart studies and more recently, targeted molecular imaging in oncology using agents such as $^{99m}$Tc octreotide analogues. This project aims to address the current urgent problem of availability of $^{99m}$Tc. Currently $^{99m}$Tc is mainly produced via nuclear fission using highly enriched uranium (HEU) which is a concern due to nuclear proliferation risks.

During the first half of the CRP, we have conducted a study of the $^{100}$Mo(p,2n)$^{99m}$Tc reaction on a medical cyclotron using $^{100}$Mo$_2$C. This is the first report of this compound being used as a target for this reaction. $^{100}$Mo$_2$C, a refractory carbide with high thermal conductivity, properties which underscore its use on a cyclotron, was synthesized using $^{100}$MoO$_3$. Its ease of oxidation back to $^{100}$MoO$_3$ under air at elevated temperatures facilitates the use of thermo-chromatography, a high temperature gas phase separation technique for the separation and isolation of $^{99m}$Tc. Activity yields for $^{99m}$Tc averaged 84% of the calculated theoretical yields. Additionally, the percent recovery of MoO$_3$, the precursor for Mo$_2$C, was consistently high at 85% ensuring a good life cycle for this target material.

1. Introduction

$^{99m}$Tc is the most commonly used isotope in diagnostic nuclear medicine with over 16 million scans using this isotope performed annually in the United States(1) and over 40 million scans performed annually worldwide(2). Common procedures using this isotope include bone scans, heart studies and more recently, targeted molecular imaging in oncology using agents such as $^{99m}$Tc octreotide analogues(3).

$^{99m}$Tc is commonly available in a generator form. In this system, the parent radionuclide $^{99}$Mo ($t_{1/2} = 2.75$ d) is bound to a solid phase column and the daughter isotope, $^{99m}$Tc, is continuously ‘milked’ off the column with a saline eluant and incorporated into an appropriate radiopharmaceutical. In this manner hospital nuclear medicine departments can have a generator delivered approximately once a week for ongoing maintenance of $^{99m}$Tc supplies for diagnostic patient procedures. Presently, the majority of the United States supply of $^{99}$Mo is generated by Canadian reactors. These reactors are ageing and have become unreliable with several recent unexpected shutdowns. Over the last few years the $^{99m}$Tc isotope supply has been drastically reduced due to issues with the Canadian reactors and with other suppliers in the world.

In addition to this vulnerability in supply due to the reactors’ age, these reactors run using highly enriched (weapons grade) uranium fuel (HEU) for the production of $^{99}$Mo. HEU is a proliferation risk and thus there are significant security issues associated with the current route of production. The American Medical Isotopes Production Act(2) (introduced in 2009) would also halt United States export of highly enriched uranium in seven to ten years thus making fuel availability for these reactors uncertain. AECL currently runs the (130 MW) NRU reactor with low enriched uranium (LEU) fuel and HEU targets. Substantial radioactive waste (also classified as HEU) is also generated in processing. HEU ($> 19.7\%$ $^{235}$U) is currently supplied to Canada by the US. As HEU has significant security issues, the future of $^{99}$Mo/$^{99m}$Tc production will require alternative routes of production.

Direct production of $^{99m}$Tc

The direct production of $^{99m}$Tc using lower energy medical accelerators via the $^{100}$Mo(p,2n) reaction has several advantages, several of which are listed below:

1. Cyclotrons already in operation could be used to produce $^{99m}$Tc, thus alleviating the problem without having to invest in new infrastructure.
2. The ability to produce these isotopes onsite at hospitals will result in less shipping, thus reducing costs and loss of the radionuclide due to decay.
3. This method is an alternative to using HEU and thus solves the proliferation risk associated with current methods of production.

Overall this is a straightforward solution to the current isotope crisis which also addresses the proliferation issues associated with the current method of production. The sharing of this technology with institutes in developing nations will enhance the supply, utilization and hence the reliability of these important radiotracers.

2. Research Plan

2.1 Progress during this Period

This progress period we have focused on production of $^{99m}$Tc via the $^{100}$Mo (p,2n)$^{99m}$Tc reaction, using a $^{100}$Mo target material of Mo$_2$C(4). Previous work at Washington University used $^{94}$Mo$_3$O$_7$ to produce $^{94m}$Tc via the $^{94}$Mo(p,n)$^{94m}$Tc reaction and the highly efficient thermo-chromatographic method to separate the $^{94m}$Tc from the $^{94}$Mo target material(5). Mo$_3$O$_7$ has a lower melting point and low thermal conductivity. Thus we chose to use $^{100}$Mo$_2$C as an alternative target material. This compound has been synthesized from $^{100}$Mo$_3$O$_7$ and has ideal properties that make it suitable for use on a cyclotron. Its melting point is 50 °C below that of Molybdenum metal, and being an interstitial carbide it maintains metal-metal bonds(6), which along with other factors gives it a high degree of thermal conductivity. Pressing into well compacted powdered targets can be achieved at room temperature. In addition, it lends itself to be processed by the well-established and efficient thermo-chromatographic technique, as it re-oxidizes to the oxide at temperatures above 500 °C facilitating easy separation of the $^{99m}$Tc and collection of the $^{100}$Mo$_3$O$_7$ starting material.

Materials and methods

Synthesis of Ammonium heptamolybdate(7)

Enriched $^{100}$Mo$_3$O$_7$ was used as the molybdenum source for the synthesis of ammonium molybdate. The full isotopic composition of the material as given by the supplier was $^{92}$Mo (0.09%), $^{94}$Mo (0.06%), $^{95}$Mo (0.10%), $^{96}$Mo (0.11%), $^{97}$Mo (0.08%), $^{98}$Mo (0.55%) and $^{100}$Mo (99.01%). 1.00 g of $^{100}$Mo$_3$O$_7$ was dissolved in 10 ml of 28% aqueous ammonia (NH$_3$.H$_2$O) solution while stirring. The resulting clear solution was evaporated slowly to dryness at 40 °C.

Synthesis of Ammonium heptamolybdate –HMT complex and Molybdenum carbide(8)

$\text{(NH}_4\text{)}_6\text{Mo}_7\text{O}_{24}\cdot4\text{H}_2\text{O} + \text{excess (CH}_3\text{)}_4\text{N}_4 \rightarrow \text{(NH}_4\text{)}_4\text{(HMT)}_2\text{Mo}_7\text{O}_{24}\cdot4\text{H}_2\text{O}$

0.800 g of ammonium molybdate and 0.900 g of hexamethyldiamine (HMT) were dissolved in 20 ml of 28% NH$_3$ solution while stirring. The solution was allowed to evaporate to dryness under air at room temperature after which the resulting solid was subjected to drying under vacuum at 40 °C for 3 hours. The solid obtained (1.550 g) was crushed to a fine powder using a mortar and pestle, after which it was loaded in a quartz boat and placed inside a quartz tube of a horizontal furnace. Heating was carried out under argon flow.

$\text{(NH}_4\text{)}_4\text{(HMT)}_2\text{Mo}_7\text{O}_{24} \rightarrow 7/2 \text{ Mo}_2\text{C}(s) + 17/2 \text{ CO}(g) + 7/2 \text{ H}_2\text{O}(g) + 3\text{NH}_3(g) + 9/2\text{N}_2(g)$

The temperature of the furnace was increased by step by step heating at a rate of 10 °C per minute until a temperature of 700°C was reached. Heating was maintained at this temperature for 2 hours after which it was increased to 900°C and heating continued for an additional 2 hours. On cooling the powder was removed, ground with a mortar pestle and stored in air at room temperature for further use.
Target preparation and irradiation

A platinum disc target holder was used for the cyclotron bombardment of $^{100}$Mo$_2$C. Approximately 50 mg of $^{100}$Mo$_2$C was transferred to the cylindrical dimple located in the centre of the platinum disc. The powder was pressed at 5000 psi for 30 seconds to secure it in place, after which the target was mounted into the cyclotron for bombardment. Proton irradiations were carried out using the CS-15 at Washington University. Production runs were conducted in the 15→ 10 MeV energy window determined by SRIM software(9, 10), and at 3, 4 and 5 µA currents. For each µA, the total µAhr was varied from 1 to 3 in successive runs.

Target Processing

After bombardment, the target was allowed to decay for two hours before being processed in order to allow short lived isotopes ($^{100}$Tc, $^{96m}$Tc) to decay. To extract the $^{99m}$Tc from the irradiated target material, a sublimation method described by Vleck et al.(11, 12) was employed. Custom quartz glassware based on the design put forward by Roesch et al.(13) was used for the separation. The individual pieces and the complete arrangement of the apparatus are shown in Figure 1. The assembled glassware with the target in the location was inserted into a preheated furnace at 850°C. Moist air was pumped into the apparatus, via the spout- like opening on tube B. Moist air was obtained by pumping air through a water-filled bubbling tube. Heating under these conditions continued for 20 minutes and the $^{99m}$Tc and $^{100}$Mo compounds were deposited in tubes D (~ 250 °C) and C respectively. The deposition is temperature dependent, thus $^{100}$Mo deposits lower down in tube C at a higher temperature zone (~500 ºC). Heating under these conditions converts the $^{100}$Mo$_2$C to $^{100}$MoO$_3$. After the processing, Tube D was washed with 8 ml of hot 1.0 x 10$^{-4}$ M NaOH.

Radionuclidic and Radiochemical purity analysis

10 µL of the resulting solution was diluted to 1000 µL using Millipore water and analyzed on a high purity Ge gamma spectrometer 5 minutes after obtaining the NaOH solution. Using the peak areas and peak efficiencies, radioactivity quantities were subsequently determined and back calculated to end of bombardment (EOB). To determine the identities and quantities of long lived radionuclidic impurities, the solution was allowed to decay for a minimum of 72 hours after which the analysis was repeated where peak data was collected for 6 h.

Radiochemical purity of the $^{99m}$TcO$_4^-$ in NaOH was determined by instant radio-thin layer chromatography (ITLC) using Alumina oxide TLC plates and acetone as the developing solvent. Sep-Pak Light alumina N cartridges were used to purify and concentrate the $^{99m}$TcO$_4^-$ for radiochemistry. The column was first conditioned with 8 ml of acidified Millipore water (pH 2). The water was acidified with 2 M HCl by drop wise addition until the desired pH was reached. After
conditioning, 8 ml of NaOH containing \( ^{99m} \text{TcO}_4^- \) was then slowly passed through the column, followed by elution with 400 µL of saline solution resulting in the final purified product. Radiochemical purity of the final product was also determined by radio-ITLC.

In order to examine the efficiency of recovery of \( ^{99m} \text{Tc} \) through the sublimation process, a separate target was bombarded under identical conditions as those processed and entirely dissolved in 10 ml of 30% H₂O₂. 10 µL of this raw target peroxide solution was then subjected to the same dilution and Ge gamma spectrometer analysis as performed above.

Results

Target Synthesis

Enriched \( ^{100} \text{Mo}_2 \text{C} \) was synthesized from enriched \( ^{100} \text{MoO}_3 \) using a 3 step thermal carburization method. The initial step involved the conversion of \( ^{100} \text{MoO}_3 \) to ammonium heptamolybdate tetrahydrate ((NH₄)₆Mo₇O₂₄.4H₂O) with 28% NH₃(aq). (NH₄)₆MoO₂₄.4H₂O yield was consistently averaged at 99% ± 0.7%. The second step involved the conversion of (NH₄)₆MoO₂₄.4H₂O to a HMT-molybdate complex ((NH₄)₄(HMT)₂MoO₂₄.4H₂O) by its reaction in 28% NH₃(aq) with hexamethylenetramine (HMT). The third step involved heating the dried HMT-molybdate complex in argon atmosphere to give \( ^{100} \text{Mo}_2 \text{C} \) with an average yield of 96% for this step. The process was repeated starting with recycled \( ^{100} \text{MoO}_3 \) (from previous irradiation and sublimation separation) resulting in a yield of 93. Elemental analysis showed the following composition Mo – 87%, C – 7.2%. Theoretical composition was calculated to yield, Mo – 93%, C – 6.2%. The X-ray diffraction (XRD) pattern is shown in Figure 2. The major component is Mo₂C, and matched ICDD card 04-008-1889.

FIG.2. XRD pattern for Mo₂C sample. Overlay of purple spectra indicates Mo₂C reference standard

Target preparation, bombardment and processing

Using Pt as the target holder, \( ^{100} \text{Mo}_2 \text{C} \) powder targets were pressed at 5000 psi for bombardment. The integrity of the powder was preserved during bombardment period. While processing the target by thermal chromatography using moist air, hot \( ^{100} \text{MoO}_3 \) (yellowish) is deposited below the constriction in tube C, and \( ^{99m} \text{Tc} \) as pertechnetate (\( ^{99m} \text{TcO}_4^- \)) was deposited in tube D. Confirmation of the yield of \( ^{99m} \text{Tc} \) deposited in tube D was confirmed post thermo-chromatography by using a dose calibrator. The depth to which the thermo-chromatography apparatus was lowered into the vertical furnace was 15 cm as indicated in Figure 1. This ensured maximum deposition of \( ^{99m} \text{Tc} \) in tube D and washing tube D with hot (~ 100 °C) NaOH resulted in near quantitative recovery of \( ^{99m} \text{Tc} \). The total processing time typically less than 45 minutes, with 20 minutes required for the thermal chromatography process. Complete dissolution of targets irradiated under identical conditions using 30% H₂O₂ after bombardment was employed and the activities obtained were compared to recovered values obtained via thermo-chromatography, in order to evaluate the recovery efficiency of the chromatography process. Calculated activities for H₂O₂ processed targets show good agreement with activities for thermal chromatography processed targets indicating near quantitative recovery.
**Purification**

Radio-ITLC analysis performed on the recovered $^{99m}$Tc revealed that a small amount of $^{99m}$TcO$_3$ (5%) was present along with $^{99m}$TcO$_4$. Purification of the wash with a Sep-Pak light alumina N cartridge conditioned by acidified Millipore water (pH 2) resulted in only pertechnetate. Eluting this cartridge with 400µL saline solution was effective in releasing the pertechnetate with a 71% to 75% activity recovery.

**Analysis of radionuclidic impurities**

The gamma–ray spectrum in Figure 3A shows the characteristic 140 keV peak for $^{99m}$Tc. Table 1 lists the calculated activities corrected to EOB along with the percent recovery for the various parameter settings employed. Radionuclidic impurities were identified following a 6 hour scan on samples where $^{99m}$Tc was allowed to decay for 72 hours post irradiation. A gamma-ray spectrum of an analysis for long-lived impurities is shown in Figure 3B. In addition to the peak at 140 keV other peaks at various energies became more conspicuous. Based on their energies peaks were assigned to $^{95}$Tc and $^{96}$Tc. Those associated with $^{95}$Tc occurred at the following energies, 204 keV and 765 keV, with branching ratios of 63% and 94% respectively. Peaks at 778 keV, 812 keV, 850 keV and 1127 keV were assigned to $^{96}$Tc, with branching ratios of 99%, 82%, 97% and 15% respectively. The percentages of these impurities expressed relative to $^{99m}$Tc are shown in Table 1.

![Gamma Spectroscopy plot](image)

**FIG.3. A. Gamma Spectroscopy plot for $^{99m}$Tc sample at 4 hours post EOB. B. Gamma Spectrometer plot of $^{99m}$Tc, $^{96}$Tc and $^{95}$Tc at 85 hours post EOB. Scan time was 6 hours.**

**TABLE 1. AVERAGE ISOTOPIC IMPURITIES AT EOB. VALUES EXPRESSED AS A PERCENTAGE RELATIVE TO $^{99m}$Tc**

<table>
<thead>
<tr>
<th></th>
<th>$^{99m}$Tc</th>
<th>$^{96}$Tc</th>
<th>$^{95}$Tc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
<td>0.08%</td>
<td>8.6*10^-6%</td>
</tr>
</tbody>
</table>

**Target Recycling**

As the thermal chromatography process results in a conversion of the $^{100}$Mo$_2$C target material to $^{100}$MoO$_3$ we aimed to develop a life cycle recycling process. This is illustrated in Figure 4. Tube B was washed with 28% NH$_3$(aq) to dissolve the material and this ammonia solution was stored for further use in the synthesis of (NH$_4$)$_6$Mo$_7$O$_{24}$.4H$_2$O. MoO$_3$ was converted to Mo$_2$C as described above with an average efficiency of 85%. In the synthesis of (NH$_4$)$_6$Mo$_7$O$_{24}$.4H$_2$O using recovered $^{100}$MoO$_3$,
Heating to 50 °C was necessary for complete dissolution. On using $^{100}\text{Mo}_2\text{C}$ obtained from recycled $^{100}\text{MoO}_3$, activities were identical to those obtained using fresh $^{100}\text{MoO}_3$.

**FIG.4. Life cycle of MoO$_3$ in the $^{109}\text{Mo}(p,2n)^{99m}\text{Tc}$ reaction production method**

**Discussion**

Use of the material $^{100}\text{MoO}_3$ for the sustainable cyclotron production of $^{99m}\text{Tc}$ was not considered ideal for a number of reasons. The first and foremost issue is that the low thermal conductivity of MoO$_3$ means that heat dissipation upon bombardment would be low. At room temperature MoO$_3$ is an insulator due to its fixed ions in its ionic lattice. As temperature rises, thermal conductivity in insulators fall leading to local thermal hotspots, which in the case of MoO$_3$ would facilitate sublimation of the oxide. Additionally, if the target holder being used is not sufficiently inert, such hotspots could possibly be the starting points for a chemical reaction between the MoO$_3$ and the target holder. The third and perhaps most important issue is one of stoichiometry. Each unit of MoO$_3$ has one in every four atoms being $^{100}\text{Mo}$, thus the percentage of target atoms is considerably lower than that of other materials.

Ideally, one would want to use elemental metal $^{100}\text{Mo}$ as the target material for the cyclotron production of $^{99m}\text{Tc}$. $^{100}\text{Mo}$ has a high melting point of 2850 °C and has a high thermal conductivity. Additionally this target material contains 100% $^{100}\text{Mo}$ nuclei. Whereas one can readily obtain $^{100}\text{Mo}$ powder for cyclotron bombardment, pretreatment of this starting material by sintering and melting are necessary for maximum adherence to a metallic backing and also for a sufficiently dense structure(14, 15). The wet chemical processing techniques that are used are multi-chemical, multi-step(14, 15) and at times multi-column operations to a purified pertechnetate. Similarly, the recovery of the target material entails a multi-step high temperature hydrogen reduction(14). The production of $^{94m}\text{TcO}_4^-$ using $^{94}\text{MoO}_3$ piqued our interest because of its simplicity in arriving at the purified pertechnetate solution and recovery of the starting material(5).

Mo$_2$C was seen as a viable alternative to MoO$_3$ because of its unique properties. These include its high melting point of 2800 °C, which compares favorably with elemental Mo. Also the high degree of chemical stability of Mo$_2$C means that handling at ambient conditions is possible. The high thermal conductivity also aid with heat dissipation during bombardment. Unlike insulators where thermal conductivity decreases with temperature, Mo$_2$C as an interstitial carbide experiences an increase in thermal conductivity caused by strong scattering of electrons and phonons by the carbon vacancies(16). Unlike MoO$_3$ where only 25% of the nuclei are Mo, Mo$_2$C has a much higher percentage of Mo nuclei, 66.66%.

Thermo-chromatographic separation has proven itself as an efficient method for the separation of Mo and Tc species (5, 11-13, 17) . Dash et al. list the high radio-nuclidic purity of $^{99m}\text{Tc}$ attained, the
repeated use of the same set up and the ready recycling of target material as some of the strengths of using this separation method(17). Under these conditions, Mo₂C undergoes oxidation to MoO₃ which then readily sublimes at a lower temperature than Mo₂C would, thus enhancing the feasibility of this process. It should be noted that under these processing conditions platinum was an ideal target holder material due to its inert nature and high melting point.

Technetium was recovered by rinsing the glassware with 0.1mM NaOH. Radio-ITLC analysis of the recovered ⁹⁹ᵐTc revealed that a small amount of ⁹⁹ᵐTcO₃ (5%(13, 18) was present along with ⁹⁹ᵐTeO₄. Purification of the wash with Sep-Pak light alumina N cartridge conditioned by acidified Millipore water (pH 2) resulted in only the TcO₄⁻ species.

The cross section values for, Scholten(19), Takas(20) and Khandaker(21) were used in the determination of the theoretical yields. Actual yields for this study were determined to be an average of 84% for the various currents employed. These high yields indicate that Mo₂C is an effective target material for the ¹⁰⁰Mo (p, 2n) ⁹⁹ᵐTc reaction. In addition to the high yields, the radionuclidic impurities produced in this reaction, ⁹⁵Tc and ⁹⁶Tc were relatively low.

2.2 Future Work

Expand irradiation parameters and production yields using Mo₂C target material

Thus far we have been conducting proof of principle experiments using the Mo₂C target material at relatively low beam currents and irradiation times. We aim to increase the irradiation current and length of bombardment to increase yields and investigate the properties of our material under these conditions. With the installation of the ACS TR19 scheduled for November 2013 at Washington University, we also plan to run targets at variable proton incident energies (14-19 MeV) to investigate yields and contaminants produced at various energies.

Design of an automated system for the distillation separation of ⁹⁹ᵐTc from ¹⁰⁰Mo target material

As we scale up cyclotron production of ⁹⁹ᵐTc the use of automated systems will be necessary to decrease dose to personnel. During the next CRP period we propose to design an automated system for the distillation separation procedure.

3. Project Summary

The overarching goal of this project is for Washington University to develop the in house capability to routinely produce ⁹⁹ᵐTc for nuclear medicine patient procedures and to translate this capability to other nuclear medicine departments. Overall the proposal introduces a straightforward solution to the current crisis while also addressing the proliferation issues associated with the current method of production. This project has the potential to substantially alleviate the current major problem of the diagnostic SPECT isotope, ⁹⁹ᵐTc, availability in the United States.

4. References


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