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Radioisotopic purity of sodium pertechnetate ^{99m}Tc produced with a medium-energy cyclotron: implications for internal radiation dose, image quality, and release specifications

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ABSTRACT

Cyclotron production of technetium-99m (^{99m}Tc) is a promising route to supply ^{99m}Tc-radiopharmaceuticals. Higher ^{99m}Tc yields can be obtained with medium-energy cyclotrons in comparison to those dedicated to PET isotopes production. To take advantage of this capability, evaluation of radioisotopic purity of ^{99m}Tc produced at medium energy (20-24 MeV) and its impact on image quality and dosimetry was required. **Methods:** Thick ^{100}Mo (99.03% and 99.815%) targets were irradiated with incident energy of 20, 22, and 24 MeV for 2 or 6 h. The targets were processed to recover an effective thickness corresponding to ~5 MeV energy loss and the resulting sodium pertechnetate ^{99m}Tc was assayed for chemical, radiochemical, and radionuclidic purity. Radioisotopic content in final formulation was quantified using gamma-ray spectrometry. Internal radiation dose for ^{99m}Tc-pertechnetate was calculated based on experimentally measured values and biokinetic data in humans. Planar and SPECT imaging was performed using thin capillary and water filled Jaszczak phantoms. **Results:** Extracted sodium pertechnetate ^{99m}Tc met all provisional quality standards. The formulated solution for injection had pH 5.0–5.5, contained >98% of radioactivity in the form of pertechnetate ion, and was stable for at least 24 h after formulation. Radioisotopic purity of ^{99m}Tc produced with 99.03% enriched ^{100}Mo was >99.0% decay corrected (d.c.) to the end of bombardment (EOB). Radioisotopic purity of ^{99m}Tc produced with 99.815% enriched ^{100}Mo was ≥99.98% (d.c. EOB). Estimated dose increase relative to ^{99m}Tc without any radionuclidic impurities was below 10% for sodium pertechnetate ^{99m}Tc produced from 99.03% ^{100}Mo if injected up to 6 h post-EOB. For 99.815% ^{100}Mo, the increase in effective dose would be <2% at 6 h post-EOB and <4% at 15 h post-EOB when the target is irradiated at E_{in}=24 MeV. Image spatial resolution and contrast with cyclotron-produced ^{99m}Tc were equivalent to that obtained with ^{99m}Tc eluted

from a conventional generator. **Conclusion:** Clinical grade sodium pertechnetate ^{99m}Tc was produced with a cyclotron at medium energies. Quality control procedures and release specifications were drafted as part of a clinical trial application that received approval from Health Canada. The results of this work are intended to contribute to establishing a regulatory framework for using cyclotron-produced ^{99m}Tc in routine clinical practice.

Keywords: ^{99m}Tc-pertechnetate, cyclotron, radionuclidic and radioisotopic purity, dosimetry, imaging

INTRODUCTION

Technetium-99m (^{99m}Tc) remains an indispensable radioisotope in nuclear imaging. ^{99m}Tc is usually obtained from generators containing the mother-isotope ^{99}Mo, which in turn, is made from highly-enriched ^{235}U (≥20%, typically 93%) in nuclear reactors. ^{99m}Tc is eluted in the form of sodium pertechnetate and can be used as is or as the starting material for other ^{99m}Tc-radiopharmaceuticals used in a variety of diagnostic applications. Cyclotron production of ^{99m}Tc could be a viable alternative or a complement to the current supply chain of ^{99m}Tc-radiopharmaceuticals. The amount of ^{99m}Tc produced using a conventional medical cyclotron operating at 16–18 MeV can be sufficient to support local demand (*1*,*2*). Higher ^{99m}Tc yields can be obtained with medium-energy cyclotrons capable of accelerating protons up to 24 MeV. It was shown previously in theory (*3*) and empirically (*4*) that the yield doubles when incident energy increases from 16 MeV to 24 MeV. To take advantage of higher production capacity of medium-energy cyclotrons, the quality of ^{99m}Tc manufactured at higher energies and, in particular, its radioisotopic purity required detailed evaluation.

^{99m}Tc is formed by irradiation of ^{100}Mo targets via the ^{100}Mo(p,2n)^{99m}Tc nuclear reaction. When thick targets are used, as in this work, the incident beam is significantly degraded in energy traversing the target material (*5*). Therefore, nuclear reactions occur over a range of energies starting with the incident energy (E_{in}) of the proton and down to the outgoing energy (E_{out}) when the particle exits the target. Other radionuclides are co-produced as a result of (p,pn), (p,α) and (p,αn) reactions, namely Mo and Nb isotopes, and are easily separated from ^{99m}Tc during target processing. Inherent isotopic contaminants in the ^{100}Mo starting material also undergo nuclear transformations via (p,n), (p,2n), (p,3n) into corresponding radionuclides giving rise to $^{93m+g}$Tc, $^{94m+g}$Tc, $^{95m+g}$Tc, $^{96m+g}$Tc, $^{97m+g}$Tc,

^{98}Tc, and ^{99g}Tc isotopes. All Tc isotopes are chemically identical and cannot be separated during target chemical processing. As a result, the final formulation of the cyclotron-produced sodium pertechnetate ^{99m}Tc will contain traces of other Tc isotopes, which may contribute to an increase in patient dose and potentially affect image quality. Theoretical calculations on the extent of ^{99m}Tc radioisotopic purity and experimental evaluation of cross sections on thin foils made of enriched molybdenum were conducted previously by others (*3*,*4*). This work was dedicated to the evaluation of the quality of sodium pertechnetate ^{99m}Tc produced with cyclotron starting from thick (0.58, 0.72, and 0.88 g/cm^2) ^{100}Mo targets. We present here experimental results of the irradiations at 20–24 MeV, including chemical, radiochemical, and radionuclidic purity of produced sodium pertechnetate ^{99m}Tc, its imaging efficacy and explain initial grounds for proposed release specifications.

MATERIALS AND METHODS

All commercially available reagents and solvents were used as received. High-purity water (Optima LC/MS, UHPLC-UV grade, 0.03 μm filtered, Fisher Scientific) was used to prepare all buffer solutions. Generator-eluted ^{99m}Tc was supplied in bulk vials by Lantheus Medical Imaging. Radioactivity measurements were performed in an ionization chamber (CRC-25PET, Capintec) on ^{99m}Tc setting to control process efficiency and by gamma-ray spectrometry with a calibrated high-purity germanium detector (GMX HPGe, ORTEC) for analytical quantitation. Electron microscopy was carried out at the Materials Characterization Centre of the Université de Sherbrooke.

Target Fabrication

Coin-shaped targets were prepared using two batches (Batch A and Batch B) of ^{100}Mo (ISOFLEX USA) with different enrichment and isotopic composition (Table 1). Interaction depth (target "thickness" in g/cm^2) providing required proton beam attenuation was calculated using SRIM software (*6*). Mass of ^{100}Mo powder for each target was determined from the calculated target thickness and pellet geometry. The ^{100}Mo metal powder was pressed into a grove of ∅ 6.35 mm in the middle of a coin-shaped aluminum backing measuring 24 mm in diameter and 2 mm thick. Pressing protocol was standardized as much as possible to produce a consistent density pellet. The ^{100}Mo packing density in pressed targets is different from crystal density for molybdenum (used in SRIM), but as long as target thickness in units of g/cm^2 remains unchanged, energy attenuation will be the same. Targets were prepared at the Laboratory of Materials Preparation and Characterization of the Brockhouse Institute for Materials Research, McMaster University, ON, Canada, according to the specifications provided above.

Irradiation Conditions

Targets (n ≥ 3 per condition) were irradiated facing a perpendicular proton beam in a solid target holder mounted to a target selector installed directly on a TR-24 cyclotron (Advanced Cyclotron Systems Inc.). Irradiations were performed at incident energies (E_{in}) of 20, 22, and 24 MeV. Collimated proton beam was 10 mm in diameter. Target current of 15 μA was applied during 2 h irradiations, while 6 h runs were performed with 5 μA to achieve comparable integrated current. Batch A targets reached the integrated current of 1882±28 μA·min, 1811±10 μA·min, and 1727±29 μA·min at E_{in} of 20, 22, and 24 MeV, respectively. Batch B targets reached 1898±70 μA·min at E_{in} of 24 MeV.

Target Processing and ^{99m}Tc-Pertechnetate Purification

Processing of the target solute was performed following a published procedure (*7*) with some modifications. Instead of sodium hydroxide, ammonia carbonate solution (2.5M) was used to load the separation column and sodium carbonate (1M) to rinse it. In addition, load/elution flow direction was not reversed. The detailed description can be found in the Supplemental Data.

Relative isolated radiochemical yield (^{99m}Tc radioactivity as a fraction of all radioactivity originally present) was calculated based on the total radioactivity recovered after processing. Recovered radioactivity in this case is the sum of measurements of all post-processing radioactive materials, e.g. product vial with sodium pertechnetate ^{99m}Tc, target solute containing Mo-99, Nb-96, Nb-97 as well as potentially non-trapped Tc isotopes, and cartridges with resins as measured in an ionization chamber on ^{99m}Tc setting.

Process efficiency was calculated as fraction of ^{99m}Tc radioactivity in the product vial to total recovered ^{99m}Tc radioactivity post-processing, e.g. product vial with sodium pertechnetate ^{99m}Tc, cartridges with resins, and waste vial.

Analytical Procedures

Chemical purity in the final formulation was evaluated semi-quantitatively by using commercially available indicator strips to measure trace amounts of aluminum (Tec-Control, Biodex, detection limit 10 µg/ml), molybdenum (EM Quant Molybdenum Test, EMD, detection limit 5 µg/mL), ammonia (Quantofix Ammonium, Macherey-Nagel, detection limit 10 µg/mL), and hydrogen peroxide (Quantofix Peroxide, Macherey-Nagel, detection limit 0.5 µg/mL).

Radiochemical identity and purity of the final product were determined by thin-layer chromatography (TLC). TLC plates with silica gel matrix (4×8 cm, polyethylene terephthalate support, Fluka) were developed in acetone (Sigma-Aldrich). Radioactivity

was quantified using InstantImager A2024 digital autoradiograph (Canberra Packard) or AR-2000 scanner (Bioscan).

Radiochemical stability was evaluated in sterile pyrogen-free vials in upright and inverted position up to 24 h after the formulation. For this, determination of radiochemical identity and purity was performed according to the TLC procedure described above.

Radionuclidic identity was confirmed by gamma-ray spectrometry (the most prominent gamma-ray of ^{99m}Tc has energy of 140.5 keV) and by measuring product's radioactivity half-life in an ionization chamber. For the half-life, the radioactivity of the sample was measured after completion of the formulation (arbitrary time t_0, 3–4 h post-EOB), and re-measured again at another time-point t (at least 36 min, which is 10% of the ^{99m}Tc half-life and up to 30 h).

Quantitative Determination of Radionuclidic/Radioisotopic Impurities

Radionuclidic/radioisotopic purity was determined using gamma-ray spectrometry and decay corrected to EOB. The procedure is described in detail in Supplemental Data. Test samples originated from formulated sodium pertechnetate as well as from target solute before and after pertechnetate extraction. A test sample of formulated sodium pertechnetate was assayed at 3, 6, 9, 12, and 24 h after EOB and decay corrected measured values were averaged. The samples were also assayed at approximately 1, 2, and 4 weeks after production to quantify long-lived isotopes (e.g. ^{95m}Tc and ^{97m}Tc). For target solute, additional corrections were applied to the counts registered at 140.5 keV as described elsewhere (*8*,*9*).

Assessment of Internal Radiation Dose

Estimation of internal dose was based on the experimentally measured radioisotopic composition of each Tc isotope at a certain time (EOB and potential injection time of 3, 4,

5, 6, 9, 12, 15, 18, and 24 h post-EOB). Biokinetic model for [^{99m}Tc]$NaTcO_4$ in humans (intravenous administration, no blocking agent) described in ICRP Publication 53 (*10*) was used to calculate effective dose for ^{99m}Tc. Published time-integrated activity coefficients ($\tilde{a}$) for other Tc isotopes in form of pertechnetate (*11*) were applied to calculate internal dose that would result from each Tc isotope if injected individually. The dose for each isotope was multiplied by its fraction in the solution of sodium pertechnetate at a tentative time of injection and partial doses due to each isotope were added together. The calculations were performed using OLINDA/EXM software (*12*).

Phantom Imaging

Phantom imaging of sodium pertechnetate ^{99m}Tc was performed using cyclotron-produced ^{99m}Tc (E_{in} = 24 MeV, 2 h irradiation, 99.815% ^{100}Mo) and commercially available ^{99m}Tc from a generator up to 18 h after the end of production/elution. Planar and SPECT images were acquired on a Discovery NM/CT 670 SPECT/CT camera (General Electric) equipped with low energy high resolution collimators. The energy window was 140.5 keV ± 7.5%. SPECT acquisition with capillary phantom was performed with constant rotation radius of 23 cm, 120 projections, 18 sec/projection, angular step 3°, and reconstructed using filtered back-projection algorithm (128×128 matrix, ramp filter). Capillary phantom (Capilets glass capillary micro-haematocrit tube, DADE) was used for planar and SPECT imaging. The Jaszczak phantom filled with water (Jaszczak Flangeless Deluxe SPECT Phantom, Biodex, cold rod diameters: 4.8, 6.4, 7.9, 9.5, 11.1 and 12.7 mm; cylinder interior dimensions: ∅ 20.4 cm × 18.6 cm) was used for planar imaging only. The phantom was positioned vertically on top of the camera collimator. The images with ^{99m}Tc eluted from a generator (730 MBq, n=2) or ^{99m}Tc produced using a cyclotron (620−746 MBq, at 5, 7.5, 9, 11, 13, 15, 17 h post-EOB, n=1 at each time point) were acquired for 4-5

minutes to reach comparable total number of counts. Image contrast and contrast-to-noise ratio (*CNR*) were calculated using the following equations:

$$Contrast = \frac{R_{hot} - R_{cold}}{R_{cold}}$$

$$CNR = \frac{\frac{R_{hot} - R_{cold}}{R_{cold}}}{\sqrt{(\frac{\sigma_{hot}}{R_{hot}})^2 + (\frac{\sigma_{cold}}{R_{cold}})^2}}$$

where R_i are expressed in counts per second per pixel and σ_i are standard deviations. The R_{cold} values were determined by averaging the background count rates in the largest (12.7 mm) cold spots, while the R_{hot} values were estimated in a large region-of-interest surrounding the cold spots.

RESULTS

Target Fabrication

Calculated and actual ^{100}Mo targets parameters are shown in Table 2. Due to a slightly higher Mo mass than required for targets prepared for an energy drop of 22→10 MeV, actual attenuation was to 9.1±0.2 MeV.

Target Dissolution and ^{99m}Tc-Pertechnetate Purification

Irradiation conditions and target radioactivity measured at retrieval (approximately 1 h post-EOB) are described in Table 3. Radioactivity measurement of the target before and after processing (80–90 min time difference, not d.c.) showed that some 50–65% of the radioactivity did not dissolve and remained on the target, which was also confirmed by measuring non-dissolved target mass after decay (Table 3). The measured values are arbitrary, since a range of other radionuclides (Tc, Nb, and Mo isotopes) are present in an irradiated target and produce a different response of the ionization chamber detector.

Relative isolated radiochemical yield (the efficiency of separation from other radionuclides) of sodium pertechnetate was in a range of 66–86% and depended on proton incident energy (Table 3). Four to seven percent of the radioactivity was distributed between cartridges and washing effluent. The remaining radioactivity (10-30%, overestimated due to the fact that radionuclides with higher γ-ray energies than ^{99m}Tc produce a higher reading in an ionization chamber on ^{99m}Tc setting) was found in the vial with processed target solute, which contained a mixture of ^{99}Mo, ^{96}Nb, and ^{97}Nb. Although these values are arbitrary, they give the ability to follow the radioactivity flow during the separation process. Of total ^{99m}Tc radioactivity, 93±2% was found in the product vial, 3.1±0.9% remained trapped on the separation column, 2.1±0.8% was lost to the purification resins and <1% was found in the waste vial.

Quality Control

Solutions of sodium pertechnetate ^{99m}Tc formulated for injection had pH 5.0–5.5 and contained >98% of radioactivity in the form of pertechnetate ion. The product was stable for at least 24 h after its formulation. Half-life measured up to 24 h post-EOB was in a range 5.87–6.09 h (^{99m}Tc half-life is 6.015 h (*13*)). Concentration of the aluminum, molybdenum, and ammonium were below the detection limit of the employed commercial test kits, e.g. <10 μg/ml for aluminum, <5 μg/ml for molybdenum, and <10 μg/ml for ammonium. Hydrogen peroxide was detected in some batches at concentration between 0.5–2 μg/ml with detection limit being 0.5 μg/ml.

Determination of Radioisotopic and Radionuclidic Purity

Radionuclidic composition of the target solute for Batch A of ^{100}Mo at different irradiation conditions measured by gamma-spectrometry is shown in Table 4. An increase

in efficiency of ^{100}Mo(p,pn)^{99}Mo reaction was notable when shifting to higher irradiation energy.

No breakthrough of co-produced ^{99}Mo, ^{96}Nb or ^{97}Nb was detected in the purified sodium pertechnetate across all the experiments. We did not detect metastable ^{93m}Tc and ^{94m}Tc as predicted by theoretical calculations, probably because of their very low content and short half-life (Supplemental Table 1). Quantification of ^{96m}Tc was not possible because of its short half-life, low gamma-ray intensity, as well as the overlapping gamma-ray signature with its ground-state counterpart ^{96}Tc. Therefore, all counts at 812.5 keV were assigned to ^{96}Tc. Technetium isotopes, namely ^{93}Tc, ^{94}Tc, ^{95}Tc, ^{95m}Tc, ^{96}Tc, and ^{97m}Tc, were detected along with ^{99m}Tc when produced from Batch A molybdenum targets. Radioisotopic purity of ^{99m}Tc exceeded 99.0% (range 99.1–99.5%, d.c. EOB) (Figure 1). The quantity of radioisotopic contaminants was dependent on irradiation energy and irradiation time (Figure 2). For Batch B ^{100}Mo targets irradiated at E_{in} = 24 MeV for 2 h, only trace amounts of ^{95m}Tc (<0.00001%), ^{96}Tc (~0.01%), and ^{97m}Tc (<0.001%) were detected, resulting in an apparent radioisotopic purity of ^{99m}Tc ≥99.98% (d.c. EOB) (Table 5). Due to low trace levels, detection of longer-lived ^{95m}Tc and ^{97m}Tc was possible only by measuring full product vial after complete decay of ^{99m}Tc and partial decay of ^{96}Tc (at least 2 weeks after EOB).

Assessment of Internal Radiation Dose

Figure 3 shows estimated radiation dose increase for sodium pertechnetate ^{99m}Tc produced from both batches of molybdenum under different irradiation conditions relative to pure ^{99m}Tc (without any radionuclidic impurities) and how it changes depending on the time of injection post-EOB. The internal dose to target organs is exemplified for tentative injection time of 6 h after EOB (Table 6).

Phantom Imaging

For a capillary phantom filled with sodium pertechnetate ^{99m}Tc eluted from a generator, planar image resolution at full width half-maximum (FWHM) was 4.15±0.05 mm at 0 cm and 6.82±0.04 mm at 10 cm from the gamma-camera collimator. The resolution of images with cyclotron-produced ^{99m}Tc (E_{in} = 24 MeV, 2 h irradiation, 99.815% ^{100}Mo) was 4.21±0.06 mm when the capillary was positioned at 0 cm from the collimator and 6.83±0.09 mm at 10 cm. In both cases, the resolution remained stable in time, within measurement error (Figure 4). In SPECT, FWHM for capillary filled with generator sodium pertechnetate ^{99m}Tc was 14.47 mm at 0 cm and 14.39 mm at 9 cm from the center of rotation (single measurements). The resolution of images with cyclotron-produced ^{99m}Tc was the same (14.45±0.12 mm) when the capillary was positioned at 0 cm from the center of rotation, and insignificantly degraded to 14.55±0.12 mm at 9 cm.

Planar images acquired using the Jaszczak phantom were of comparable quality without significant loss in spatial resolution (Figure 5). On average, the contrast of images acquired using cyclotron-produced ^{99m}Tc (E_{in} = 24 MeV, 2 h irradiation, 99.815% ^{100}Mo) up to 17 h post-EOB (n=7) was 1.16±0.02 with contrast-to-noise ratio (*CNR*) of 10.47±0.26, which compares favorably to the best of two values obtained for generator-eluted ^{99m}Tc: 1.14 (contrast) and 10.28 (*CNR*).

DISCUSSION

The main distinguishing difference between cyclotron-produced ^{99m}Tc and generator-eluted ^{99m}Tc is that cyclotron-produced ^{99m}Tc is contaminated with other Tc isotopes (Table 4). This may contribute to additional radiation dose to patients and affect image resolution and contrast. Before direct manufacturing of ^{99m}Tc using cyclotrons becomes

routine, there is a necessity to acquire sufficient supporting data about the quality of the cyclotron-produced sodium pertechnetate ^{99m}Tc and establish a regulatory framework for its use in clinical practice. Since absolute production yields increase with higher energies, it would be advantageous to use the highest practical energy (24 MeV with TR-24 cyclotron). This would make the manufacturing process shorter and more cost-effective per hour of manufacturing time. Therefore, we evaluated the quality of the sodium pertechnetate ^{99m}Tc produced with a cyclotron at medium energies (E_{in} = 20–24 MeV), including its radioisotopic purity, and assessed the results with respect to internal radiation dose and image quality.

A limitation of the current study is that the irradiated target material did not dissolve completely. Low surface area of the reaction and relatively high metrical thickness seem to be the main reasons. To investigate the extent of dissolution, after ~10 months decay, the targets were taken apart (Supplemental Fig. 2) and the remaining ^{100}Mo pellets were weighed (Table 3) and inspected under electron microscope. Since the erosion depth of the remaining target material is rather uniform (Supplemental Fig. 3), we assume that the dissolved target thickness is also uniform. Based on the cross-sections for ^{99m}Tc and co-produced radionuclides (*3*) and analyzing potential dose from each Tc isotope if injected individually (Supplemental Table 2), it can be demonstrated that the results presented in this work are a conservative estimation of the radioisotopic purity. One could observe that ^{94}Tc, ^{95m}Tc, ^{95}Tc, ^{96}Tc, and ^{97m}Tc contribute the most to the effective dose. ^{94}Tc, ^{95m}Tc and ^{95g}Tc are produced from $^{94–97}$Mo, each of which represent <0.003% of the initial target composition of high purity ^{100}Mo (Batch B) material, resulting in a very low amount of ^{94}Tc, ^{95m}Tc and ^{95}Tc in the final product that can be considered negligible (Table 5). Technetium-97m content is also rather low since reaction channels leading to this isotope

have limited physical thick target yields (*4*). Therefore, ^{96}Tc is the primary isotope responsible for the dose increase and potentially harmful to image quality due to its energetic gamma-rays. The main production route for ^{96}Tc in Batch B targets is ^{98}Mo(p,3n)^{96}Tc nuclear reaction, which starts to occur at >20 MeV proton beam. The dissolved top layer of the target surface will contain the higher proportion of ^{96}Tc relative to ^{99m}Tc than the rest of the target, where proton energy degraded to <20 MeV and this reaction does not happen anymore, which is exemplified by Figure 6. For batch B targets irradiated at E_{in} = 24 MeV, actual E_{out} for the dissolved fraction was 19±1 MeV as estimated from the dissolved target mass. It means that our current data overestimate relative ^{96}Tc content compared to fully dissolved target (Figure 6). In addition, accordingly to previously published calculations (*3*), the individual ratios of contaminants to ^{99m}Tc are the most advantageous below the threshold of 19 MeV. Therefore, the results reported here represent the less favorable for ^{99m}Tc production 24→19 MeV energy region and can serve as a reasonable "worst case" approximation.

ABEC resin was selected for separation as it is known to retain pertechnetate from industrial alkaline waste (*14*) and was reported for separation of medical ^{99m}Tc (*15*). A range of other resins of the same nature, namely Tentagel and ChemMatrix product lines, were tested recently by others and showed similar results (*16*,*17*). We speculate that any resin with high enough PEG load (≥2000) will perform sufficiently well.

Quality control of the formulated sodium pertechnetate ^{99m}Tc confirmed that it's chemical and radiochemical purity conformed to the limits set by European and US Pharmacopeias for the generator-eluted pertechnetate (Table 7). Among raw materials (aluminum, molybdenum, ammonium, and hydrogen peroxide), only hydrogen peroxide was above the detection limit in some batches (≤2 μg/ml) if tested at EOS. Tests were

negative when repeated after a few hours. All above mentioned chemicals are biogenic and do not pose a toxic or pharmacologic hazard at low trace levels. Therefore, these tests, while performed as part of the process validation, may not be needed for daily quality control procedure.

Isotopic content of starting ^{100}Mo is crucial for obtaining high isotopic purity ^{99m}Tc. It was shown previously that irradiation of ^{100}Mo with higher enrichment resulted in product with lower radioisotopic purity compared to irradiation of lower enriched ^{100}Mo having less ^{92}Mo-^{97}Mo (*11*). Another factor responsible for the radionuclidic purity of cyclotron-produced ^{99m}Tc is irradiation energy and time. The amount of produced isotopes depends on each radioisotope cross-section and can be controlled by irradiation parameters as evidenced by Figure 2. Therefore, specifications for the target material based solely on ^{100}Mo enrichment are not sufficient. Control of the isotopic composition of the starting material together with irradiation parameters is mandatory to guarantee radioisotopic purity of the final product.

For high purity ^{100}Mo (Batch B) irradiated at 24 MeV for 2 h, virtually no radioisotopic impurities were found with ^{99m}Tc being ≥99.98% pure at EOB and ≥99.95% during tentative product shelf-life of 12 h after formulation. Current US Pharmacopeia requires ^{99m}Tc from a generator (fission) to be at least 99.96% pure as a radionuclide, while European Pharmacopeia expects 99.88% radioactivity due to ^{99m}Tc. Depending on ^{99}Mo production method, both Pharmacopeias allow trace amounts of ^{131}I, ^{103}Ru, ^{89}Sr, ^{90}Sr, as well as ^{99}Mo to be present in sodium pertechnetate ^{99m}Tc, in addition to some other gamma-emitting radionuclidic impurities.

Since each isotope delivers different radiation dose and its relative content in final formulation changes with time, we decided to devise specifications for radioisotopic purity

based on potential radiation dose increase comparing to pure ^{99m}Tc. The calculations were performed for several time points after EOB to reflect various "injection times". It is postulated, conservatively, that maximum 10% dose increase would be acceptable to nuclear medicine practitioners. Based on this assumption, one could select appropriate irradiation conditions for a given batch of enriched ^{100}Mo target material to fulfill this requirement. The shelf-life of the final product can also be adjusted based on the radioisotopic purity of the final formulation. For example, according to our dosimetry assessment (Figure 3), Batch A of Mo-100 must be irradiated at ≤20 MeV to produce acceptable quality product with a shelf-life of 12 h post-synthesis, while Batch B can be used at any irradiation energy up to 24 MeV (inclusive) with a shelf-life potentially exceeding 24 h. Alternatively, Batch A can be irradiated at higher energy, including 24 MeV, but the shelf-life of the product must be reduced accordingly, so that the radiation dose will not increase by more than 10%. As can be seen from Figure 3, sodium pertechnetate ^{99m}Tc produced from Batch A at 24 MeV, 2 h irradiation (empty triangles) could be used up to 12 h post-irradiation (which is approximately 9 h after formulation). Correlation of the variation of radioisotopic impurities in time with corresponding increase in effective dose for sodium pertechnetate (Figure 3) allowed us to suggest that at least 99.4% of total radioactivity of the radiopharmaceutical drug product must be due to ^{99m}Tc to remain inside the 10% limit for dose increase. However, this value will be different for other ^{99m}Tc radiopharmaceuticals since biological half-life as well as residence time in various organs differ among compounds, thus influencing absorbed dose.

The results of capillary phantom imaging with sodium pertechnetate ^{99m}Tc produced from high-purity ^{100}Mo (Batch B) at 24 MeV for 2 h showed that the degradation of spatial resolution that may be due to scattering of high energy gamma-rays originating from

isotopic impurities in cyclotron-produced ^{99m}Tc is insignificant (Figure 4) and is not expected to have an impact on image definition and contrast. This was confirmed by the Jaszczak phantom studies, when the contrast and contrast-to-noise ratio of images acquired using cyclotron-produced ^{99m}Tc compared favorably to the best of two values obtained for generator-eluted ^{99m}Tc. Visually, two side-by-side images produced with ^{99m}Tc from generator and cyclotron were found equivalent by several experienced readers (Figure 5).

Taking results together, we found the quality of sodium pertechnetate ^{99m}Tc produced with a cyclotron at medium energies satisfactory and suitable for use in humans. All prepared batches were tested, met provisional release specifications (Table 7), and complied with standard requirements for parenteral injections.

CONCLUSION

We showed that the quality of ^{99m}Tc produced with a cyclotron at medium energy can be fully adequate for clinical use provided that the isotopic composition of the starting molybdenum together with its irradiation parameters (energy, time) are selected appropriately. Analysis of the collected data allowed for drafting quality control protocols and release specifications as part of a clinical trial application. Clinical trial (ClinicalTrials.gov identifier: NCT02307175, health authority: Health Canada) is ongoing; the outcome will be reported in due course. The results of this work are intended to contribute to establishing a regulatory framework for using cyclotron-produced ^{99m}Tc in routine clinical practice.

DISCLOSURE

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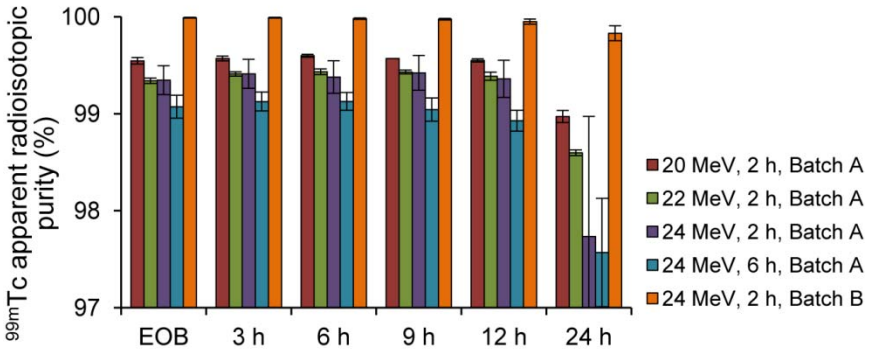

FIGURE 1. Apparent radioisotopic purity of sodium pertechnetate ^{99m}Tc produced at different irradiation parameters as a function of time post-EOB.

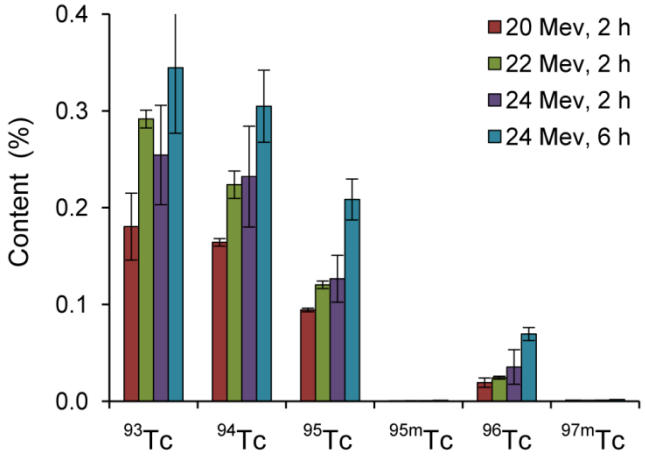

FIGURE 2. Profile of radioisotopic impurities in sodium pertechnetate ^{99m}Tc from Batch A ^{100}Mo targets as a function of irradiation energy and irradiation time. The content is expressed as percentage of radioactivity due to a given isotope to total radioactivity in the sample.

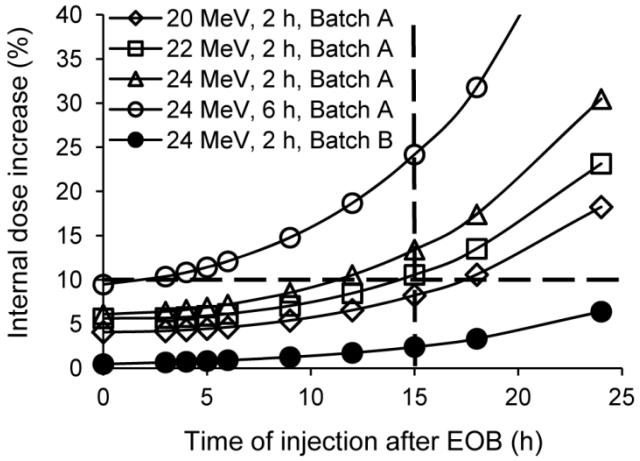

FIGURE 3. Estimated internal dose increase comparing to pure ^{99m}Tc. Horizontal dashed line is a tentative 10% cut off for potentially accepted dose increase. Vertical dashed line is a tentative shelf-life for the sodium pertechnetate ^{99m}Tc injection after end of synthesis (12 h EOS = 15 h EOB).

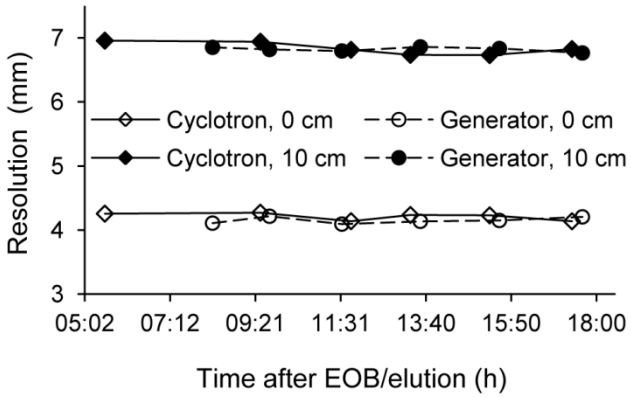

FIGURE 4. FWHM resolution of planar capillary images with cyclotron and generator produced sodium pertechnetate ^{99m}Tc.

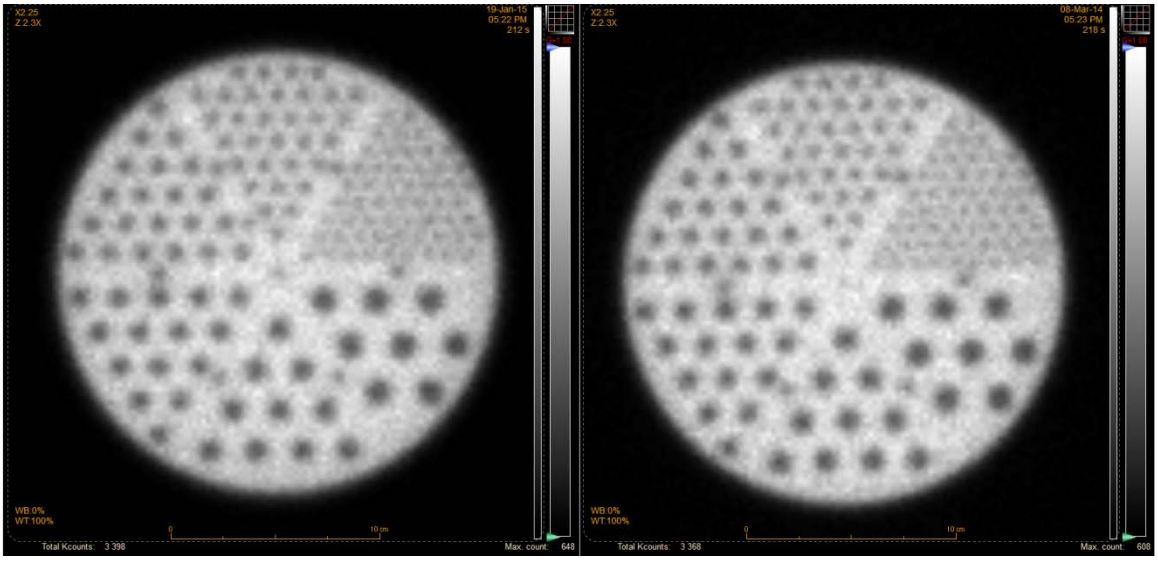

FIGURE 5. Images of Jaszczak phantom filled with a solution of sodium pertechnetate ^{99m}Tc. Left panel – eluted from a generator; Right panel – cyclotron-produced. Images are on linear gray scale with white being equal to maximum intensity. Cold rods are 4.8, 6.4, 7.9, 9.5, 11.1 and 12.7 mm in diameter.

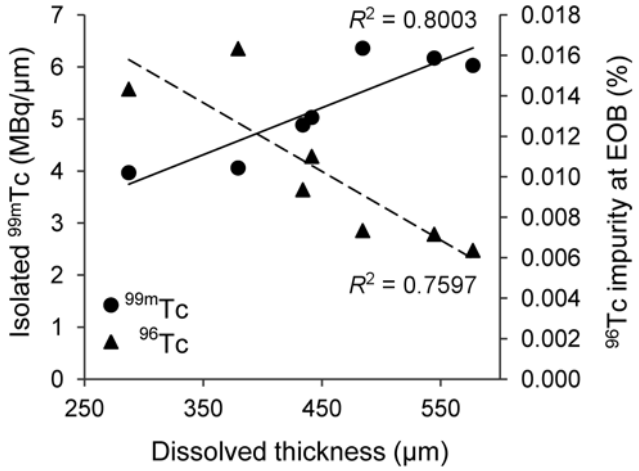

FIGURE 6. For the energy attenuation of 24→19±1 MeV, the relative isolated yield of ^{99m}Tc increases with dissolved target depth. The content of ^{96m}Tc, on contrary, is decreasing.

TABLE 1. Isotopic composition of Mo-100 targets.

	Mo-100	**Mo-98**	**Mo-97**	**Mo-96**	**Mo-95**	**Mo-94**	**Mo-92**
Batch A	99.03	0.54	0.08	0.11	0.09	0.07	0.08
Batch B	99.815	0.17	0.003	0.003	0.003	0.003	0.003

TABLE 2. Mo-100 targets characteristics.

Energy drop (MeV)	**Mo crystal density (g/cm^3)**	**Thickness of Mo layer at crystal density (mm)**	**Calculated thickness of Mo layer (g/cm^2)**	**Calculated Mo mass (mg)**	**Actual Mo mass (mg)**	**Calculated E_{out} (MeV)**
20→10	10.206	0.564	0.58	182.2	179.9±0.6	10.2±0.1
22→10	10.206	0.709	0.72	229.0	241.2±3.2	9.1±0.2
24→10	10.206	0.865	0.88	279.4	280.7±2.2	9.9±0.2

TABLE 3. Target irradiation conditions and processing results.

E_{in} (MeV)	Calculated E_{out} (MeV)	Irrad. Time (min)	Integrated current (μA·min)	Mo enrich-ment (%)	Target activity at retrieval (~1 h post-EOB) (GBq)	Dissolved fraction (by mass) (%)	E_{out} based on dissolved fraction (MeV)	^{99m}Tc relative isolated yield* (%)
20	10.2±0.1	133±13	1882±28	99.03	9.2±0.2	51.9±0.5	15.50±0.04	84.5±1.8
22	9.1±0.2	123±2	1811±10	99.03	10.2±0.4	35±6	18±1	77.0±4.7
24	9.7±0.1	121±1	1709±32	99.03	9.7±1.1	42±6	18±2	71.9±5.8
24	9.8±0.1	361±2	1744±13	99.03	7.85±0.05	38±11	20±1	67.8±1.7
24	10.04±0.06	122±5	1946±141	99.815	9.8±0.8	43±9	19±1	70.2±3.7

* Based on the dissolved and recovered radioactivity at the end of synthesis (EOS); not to be mistaken for the absolute yield of a nuclear reaction.

TABLE 4. Radionuclidic composition (%) of target solute as a function of irradiation energy.[#]

Nuclide	20 MeV	22 MeV	24 MeV
^{99m}Tc	90.2±0.8	87.23±0.02	86±2
^{97m}Tc	0.0011±0.0003	0.0010±0.0002	0.0011±0.0009
^{96}Tc	0.063±0.001	0.13±0.01	0.14±0.05
^{95}Tc	0.087±0.001	0.108±0.006	0.2±0.2
^{95m}Tc	0.00049±0.00002	0.0005±0.0001	0.0006±0.0001
^{94}Tc	0.147±0.001	0.201±0.005	0.19±0.02
^{93}Tc	0.18±0.03	0.26±0.02	0.2±0.1
^{99}Mo	2.7±0.2	4.7±0.4	5±1
^{97}Nb	6.3±0.5	6.6±0.2	6.6±0.6
^{96}Nb	0.32±0.05	0.78±0.09	0.8±0.3

[#] Gamma-spectrometry measurements (d.c. EOB) for Batch A ^{100}Mo targets irradiated for 2 h.

TABLE 5. Radioisotopic composition (%) of cyclotron-produced[⊥] sodium pertechnetate.

Nuclide	^{100}Mo Batch A (n=4)	^{100}Mo Batch B (n=7)
^{99m}Tc	99.35±0.15	99.9896±0.0035
^{97m}Tc	0.0011±0.0009	0.00060±0.00008
^{96}Tc	0.035±0.017	0.0098±0.0035
^{95}Tc	0.127±0.024	< DL[§]
^{95m}Tc	0.00059±0.00007	0.0000067±0.0000007
^{94}Tc	0.23±0.05	< DL
^{93}Tc	0.25±0.05	< DL

[⊥] Irradiation conditions: 24 MeV, 2 h; d.c. EOB.
[§] DL: detection limit

TABLE 6. Internal dose (mSv/MBq) to organs assuming injection time of 6 h post-EOB.[⊥]

Organ/Tissue	**[^{99m}Tc]$NaTcO_4$ from ^{100}Mo[⊥] Batch A (99.03%)**	**[^{99m}Tc]$NaTcO_4$ from ^{100}Mo[⊥] Batch B (99.815%)**	**[^{99m}Tc]$NaTcO_4$ without any radionuclidic impurities**
Adrenals	3.59E-03	3.32E-03	3.28E-03
Brain	2.10E-03	1.95E-03	1.93E-03
Breasts	1.83E-03	1.68E-03	1.66E-03
Gallbladder Wall	6.38E-03	5.93E-03	5.87E-03
Lower Large Intestine Wall	2.20E-02	2.06E-02	2.04E-02
Small Intestine	1.64E-02	1.56E-02	1.55E-02
Stomach Wall	1.18E-02	1.13E-02	1.12E-02
Upper Large Intestine Wall	2.88E-02	2.75E-02	2.73E-02
Heart Wall	3.12E-03	2.89E-03	2.85E-03
Kidneys	4.05E-03	3.74E-03	3.70E-03
Liver	3.61E-03	3.33E-03	3.29E-03
Lungs	2.62E-03	2.43E-03	2.40E-03
Muscle	3.22E-03	2.97E-03	2.93E-03
Ovaries	9.66E-03	8.84E-03	8.72E-03
Pancreas	5.01E-03	4.66E-03	4.61E-03
Red Marrow	3.57E-03	3.26E-03	3.22E-03
Osteogenic Cells	7.47E-03	7.20E-03	7.16E-03
Skin	1.86E-03	1.71E-03	1.69E-03
Spleen	3.96E-03	3.67E-03	3.63E-03
Testes	2.99E-03	2.74E-03	2.70E-03
Thymus	2.56E-03	2.36E-03	2.33E-03
Thyroid	2.23E-02	2.17E-02	2.16E-02
Urinary Bladder Wall	1.76E-02	1.66E-02	1.65E-02
Uterus	8.19E-03	7.58E-03	7.50E-03
Total Body	3.57E-03	3.31E-03	3.27E-03
Effective Dose Equivalent	**1.01E-02**	**9.51E-03**	**9.42E-03**
Effective Dose	**9.93E-03**	**9.34E-03**	**9.26E-03**

[⊥] Irradiation conditions: 24 MeV, 2 h.

TABLE 7. Provisional release specifications for sodium pertechnetate ^{99m}Tc injection manufactured with a cyclotron.

Parameter/Trace	Test method	Provisional specifications	Validation batches (n=5)	Eur.Ph.	USP
Appearance	visual	clear, colorless	conform	clear, colorless	–
pH	pH test strip	4.0–8.0	5.0–5.5	4.0–8.0	4.5–7.5
Radiochemical identity	TLC	R_f > 0.7[a]	0.8–0.9	R_f ~0.6	R_f ~0.9±10%
Radiochemical purity	TLC	≥95%	>98%	≥95%	≥95%
Radionuclidic identity	gamma spectrometry	γ-ray at 141 keV	141 keV	140 keV	140 keV
Radioisotopic purity	gamma spectrometry	>99.4%	>99.98%	>99.88%	>99.935%
Other nuclides (not Tc)	gamma spectrometry	undetectable γ-ray at 569, 658, 740 keV[b]	conform	≤0.12%[c]	≤0.065%[c]

[a] Validated for silica-gel / acetone system; R_f for sodium pertechnetate in other systems may be different.
[b] Gamma-ray peaks correspond to ^{96}Nb (569 keV), ^{97}Nb (658 keV), and ^{99}Mo (740 keV).
[c] Trace amounts of ^{99}Mo, as well as other non-Tc radionuclides, are permitted in ^{99m}Tc eluate.