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ORIGINAL PAPER

Cyclotron production of technetium radionuclides using a natural metallic molybdenum thick target and consequent preparation of [Tc]-BRIDA as a radio-labelled kit sample

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Abstract. Numerous studies have focused on the use of accelerators for production of ^{99m}Tc, but all of these investigations have been performed at low-level currents. In this research, for the first time, we have constructed a high power level natural Mo target for production of ^{99m}Tc radioisotope using cyclotrons. A high purity natural molybdenum target (130 mg/cm^2), suitable for proton beam power level of several kilowatts, has been constructed using a thermal spray coating method. The target was irradiated in a Cyclone30 accelerator using 160 μA of 25 MeV proton beam energy for 1000 μA-h. The activity of produced ^{99m}Tc was measured as 2.75 Ci. The technetium radionuclides produced were extracted using an MEK organic phase, followed by preparation of Tc-BRIDA as a radio-labelled kit sample. Animal biodistribution studies have been performed in rats. After administration of the radio-labelled Tc-BRIDA in rats, we observed most of the radioactivity accumulated in intestine as expected for IDA derivatives. The results of measurements show a successful production of Tc radionuclides (including ^{99m}Tc) in the bombarded target and subsequent labelling of the kit with Tc. It is anticipated that the developed coating method for the production of high power Mo targets using enriched ^{100}Mo and a proton beam of about 1 mA is capable of producing about 100 Ci of ^{99m}Tc per irradiated target. The developed high power Mo target, if constructed using enriched ^{100}Mo, could be a practical method for a large-scale production of ^{99m}Tc for local applications near cyclotron facilities.

Key words: technetium • molybdenum target • thermal spray method • technetium radiochemical separation • radio--labelling

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Introduction

Technetium is an element that is artificially produced and all its isotopes are radioactive. Several investigations have been performed on the subject of the production of Tc radioisotopes using cyclotrons. Among these radioisotopes, ^{99m}Tc with a half-life of 6.02 h and gamma--ray spectrum with an energy peak at 140.5 keV has a vast application in nuclear medicine. More than 85% of administered radiopharmaceuticals are produced from ^{99m}Tc [5].

So far, ^{99m}Tc used in nuclear medicine has been produced using nuclear reactors with an indirect method (^{99}Mo-^{99m}Tc generator) in which ^{99}Mo is a fission product. ^{99m}Tc could also be produced directly using proton bombardment via the ^{100}Mo(p,2n)^{99m}Tc nuclear reaction [8].

One of the main advantages of the direct production of ^{99m}Tc using cyclotrons, is its low environmental hazards and less waste management difficulties relative to fission-product method, but, on the other hand, due to the relatively short half-life of ^{99m}Tc (6.02 h), the direct production method could only be used for local applications.

Table 1. Reaction channels for ≤ 25MeV protons on 97.46% enriched ^{100}Mo (CIS) target [7, 8]

Mo isotopes	Natural Mo abundance (%)	[a]Enriched ^{100}Mo abundance (%)	^{99m}Tc (6.02 h)	^{96}Tc (4.28 d)	^{95}Tc (20.0 h)	^{94}Tc (293 m)	^{93}Tc (2.75 h)
^{92}Mo	14.84	0.0011					
^{94}Mo	9.25	0.0008					(p,2n) Q = –13.6
^{95}Mo	15.92	0.0016			(p,n) Q = –2.4	(p,n) Q = –5.0	(p,3n) Q = –21.0
^{96}Mo	16.98	0.0020		(p,n) Q = –3.7	(p,2n) Q = –11.6	(p,2n) Q = –12.4	
^{97}Mo	9.55	0.0026		(p,2n) Q = –10.5	(p,3n) Q = –18.5	(p,3n) Q = –21.5	
^{98}Mo	24.13	2.54		(p,3n) Q = –19.2			
^{100}Mo	9.63	97.46	(p,2n) Q = –7.7[b]				

[a] From the Commonwealth of Independent States (CIS).
[b] Reaction Q values in MeV.

Several investigations have been performed for research scale production of ^{99m}Tc by low current proton beam bombardment of molybdenum targets in accelerators using direct and indirect methods. So far, molybdenum targets for ^{99m}Tc production in accelerators have been produced using thin layer coating, metallic foil preparation, molybdenum oxide precipitation and pills made from molybdenum powder or its compounds [1, 2, 4, 7–9, 11–14] but due to the low heat transfer characteristics of these targets, which cannot withstand high currents, production of ^{99m}Tc on a large scale had not yet been achieved [1]. In this work, we have used natural molybdenum as target material to produce thick targets withstanding high proton beam currents.

Natural molybdenum consists of several isotopes including ^{92}Mo, ^{94}Mo, ^{95}Mo, ^{96}Mo, ^{97}Mo, ^{98}Mo, and ^{100}Mo. During proton bombardment of natural Mo, depending on proton energy, several reaction channels may be present to produce various isotopes of technetium mainly ^{99m}Tc, ^{96}Tc, ^{95}Tc, and ^{94}Tc. Abundances of various molybdenum isotopes in natural Mo and enriched ^{100}Mo (from the Commonwealth of Independent States, CIS; 97.46%) mainly contributing in reaction channels with related Q-values are given in Table 1 [7, 8]. The excitation functions for each of these reaction channels are compiled and/or measured by Lagunas-Solar in Ref. [7].

In Ref. [7] Lagunas-Solar has also predicted (from extrapolation of thin target-low current data) that if a thick target of enriched ^{100}Mo (CIS; 97.46%) could withstand high proton beam currents, a large amount of ^{99m}Tc activity could be produced with a very low level of other Tc impurities. He predicted that 1 mA of proton beam bombarding an enriched ^{100}Mo (CIS; 97.46%) thick target for 6 h will produce 99.6 Ci of activity of ^{99m}Tc at EOB. It should be emphasized that this value of thick target-high current yield has been determined by extrapolation of the data from thin target and low proton current (< 1 μA) measurements.

It should be mentioned that the unavailability of measured thick target-high current ^{99m}Tc yield is due to the technical difficulties in producing thick Mo targets capable of withstanding high currents. In this work, we have overcome these difficulties and we achieved to prepare a thick metallic natural molybdenum target with high thermal conductivity to produce ^{99m}Tc using high current proton beams. It should also be mentioned that the use of Mo target enriched in ^{100}Mo instead of natural Mo and choosing a suitable proton energy and high current will result in a much higher activity of ^{99m}Tc and a very low amount of by-product impurities [7].

In order to investigate the performance of the designed high power molybdenum target, proton bombardment of the constructed natural molybdenum target has been performed at 160 μA (the highest achievable current in our cyclotron at the date of experiment). Technetium radionuclides were then extracted and purified successfully for preliminary radio-labelled kit tests in rats.

All the above mentioned investigations have been performed to find out the efficacy of our designed and constructed high power Mo target to produce ^{99m}Tc on a large scale with the capability of its labelling with Tc kits.

Materials and methods

Materials

All chemicals were purchased from Sigma-Aldrich Chemical Co, UK. Radio-chromatography has been performed by counting of polymer-backed silica gel paper thin layer sheets using a thin-layer chromatography scanner, Bioscan AR2000, Paris, France. All calculations and RTLC counting were based on the ^{99m}Tc 140.5 keV peak. All values are expressed as mean ± standard deviation and the data were compared using the Student t-test. Statistical significance was defined as $P < 0.05$. Animal studies have been performed in accordance with the United Kingdom Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations, 2nd edition.

Targetry

Natural molybdenum containing ^{92}Mo(14.8%), ^{94}Mo(9.3%), ^{95}Mo(15.9%), ^{96}Mo(16.7%), ^{97}Mo(9.6%), ^{98}Mo(24.1%) and ^{100}Mo(9.6%) isotopes with an approximate thickness of 130 mg/cm^2 (about 130 μm) coated as metallic layer on copper backing on an area of 20.5 cm^2 using the thermal spray coating method [10]. Due to the formation of molybdenum-copper junction with a strong metal-metal interaction, heat produced during bombardment is effectively transferred to the copper backing and finally to the cooling water running at the back of the target. The front and the back surfaces of the molybdenum target used in this study are shown in Figs. 1 and 2, respectively.

Technetium production cross-sections via proton interaction with molybdenum predicted by ALICE computer code and also those reported in experimental measurements [7] suggests that the best proton energy range for the ^{100}Mo(p,2n)^{99}Tc reaction is 25–12 MeV. Therefore, the target has been made thick enough to reduce the proton energy from 25 MeV to about 12 MeV. SRIM computer program [15] was applied to determine the best target thickness for this energy range. The prepared target was irradiated with 160 μA protons beam of 25 MeV for 1000 μA-h in a Cyclone30 machine (installed in Agriculture, Medical and Industrial Research School (AMIRS)) at a glancing angle of 6 degrees to achieve higher production yield. At this angle, the effective thickness of the target is about 10 times of the actual thickness (i.e. 1300 mg/cm^2 approx.).

Fig. 1. Natural molybdenum coated as a metallic layer on copper backing (front surface of the molybdenum target).

Fig. 2. Grooved copper backing of the molybdenum target proved to enhance cooling during irradiation (back surface of the molybdenum target).

Extraction of TcO_4^- in normal saline for kit radio--labelling

The rapid dissolution of the molybdenum target layer was performed using a mixture of warm HNO_3 and HCl, (6.7 and 13.3 ml, respectively). After dissolution, the mixture was made basic with NaOH and the radioactive TcO_4^- was extracted into an equivolume of methyl ethyl ketone (MEK) [6]. Successive washings with fresh 10 N NaOH (20 ml) reduced molybdenum content. After four solvent extractions, the technetium bearing MEK fraction was blown dry in a nitrogen stream at 100°C and taken up in 1 ml of 0.9% physiological saline. This activity (pH = 7) proved to be > 99% TcO_4^- as shown by thin-layer chromatography (TLC) (silica gel, MEK R_f = 0.9) and high-performance liquid chromatography (HPLC). In addition to careful attention, a good laboratory technique had been practised up to this point, the TcO_4^- solution was next passed through a sterile, 0.22 μm filter (Millipore, Millex GV) prior to introduction into any commercial kit preparation.

Radionuclide assays

The activities of various technetium radionuclides produced in the target have been measured 12 h after EOB using gamma spectroscopy system with an HPGe detector of 38.5% relative efficiency. Calibration of energy and efficiency of this detector has been performed with a mixed-radionuclide (^{133}Ba, ^{241}Am, ^{137}Cs, ^{60}Co and ^{152}Eu) reference source. The detector was coupled to an MCA Plug-In Card, and the card was connected to an IBM compatible PC-AT. Peak area analysis has been performed using Maestro II and Omnigam MCA emulation software. In order to avoid dead time problems, we used a dilute sample of the dissolved target coating such that the counting dead time was less than 3%.

Similar measurements have been also performed for assaying the purity of TcO_4^- (extracted in normal saline using methyl ethyl ketone) of the irradiated molybdenum target.

Preparation of [Tc]-BRIDA as a model radio-labelled kit

[Tc]-BRIDA is a neutral, lipophillic compound which can penetrate into liver cells through perfusion; however its structure changes due to the metabolism in hepatocytes. Figure 3 shows the chemical structure

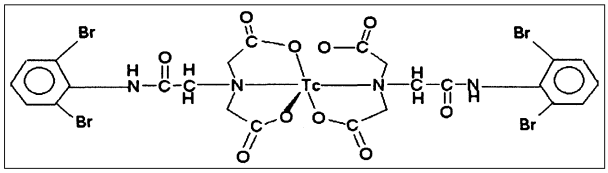

Fig. 3. Chemical structure formula for [^{99m}Tc]-BRIDA.

of [Tc]-BRIDA. BRIDA kits (Kavoshyar Co, Tehran, Iran) were obtained commercially. Typically, 20–30 mCi (about 1 GBq) of TcO_4^- prepared in 1 ml of 0.9% physiologic saline was introduced into the BRIDA kit, shaken and kept at room temperature for 30 min. At the end of labelling, radiochemical purity in excess of 97% was shown by both standard TLCs (Whatman no. 2, mobile phases of saline and silica gel using MEK as eluent).

Biodistribution of [Tc]-BRIDA in normal rats

[Tc]-BRIDA was administered to three separate normal rat groups. A volume (50 μl) of [Tc]-BRIDA solutions containing 80±2 μCi radioactivity was injected intravenously to rats via their tail veins. The animals were sacrificed at exact time intervals (30, 60 and 120 min), and the ID/g% of different organs was determined as percentage of injected dose (based on area under the curve of 140.5 keV ^{99m}Tc gamma line) per gram by gamma spectroscopy using the HPGe detector.

Results and discussion

After bombardment of the constructed natural molybdenum target at 160 μA of 25 MeV proton beam for 1000 μA-h, technetium radionuclides were extracted from the irradiated target as mentioned in the previous section.

To extract technetium from the bombarded molybdenum target, it was dissolved by acid and then neutralized by NaOH.

Due to the use of natural Mo target, in addition to ^{99m}Tc several other technetium radioisotopes have been also produced as by-products of ^{99m}Tc. We assayed them as ^{99m}Tc (6.02 h), ^{96}Tc (104.4 h), ^{95m}Tc (1464 h), ^{95}Tc (20.0 h), ^{94}Tc (4.8 h) and ^{93}Tc (2.75 h) using gamma spectroscopy. The γ-ray spectrum of the dilute sample of Tc radionuclides, 12 h after the end of bombardment (EOB), is shown in Fig. 4. In this figure the gamma lines of the Tc radionuclides including ^{99m}Tc, ^{96}Tc, ^{95}Tc, ^{94}Tc and ^{93}Tc have been shown. The different radionuclides produced in the target and the energy of γ-ray lines to radioassay the dilute sample of main radioactive solution (target dissolved molybdenum layer) is given in Table 2 showing the production of 2.75 Ci of ^{99m}Tc at EOB.

As stated in the introduction section, from investigations performed by Lagunas-Solar [7] extrapolated from a thin target and μA proton beams it is anticipated that

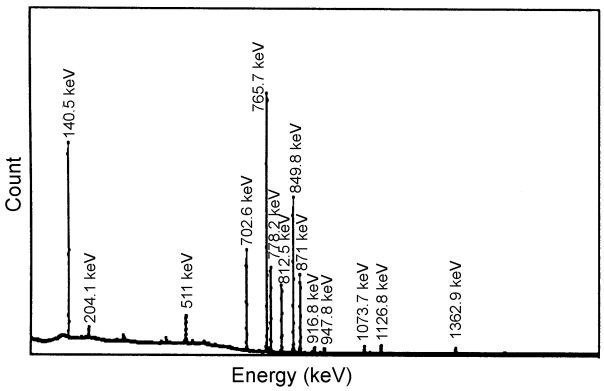

Fig. 4. Gamma-ray spectrum of a sample of molybdenum target irradiated with 25 MeV proton beam measured 12 h after EOB.

in the case of using enriched ^{100}Mo instead of ^{nat}Mo and by using higher proton beam of 1 mA, about 100 Ci of ^{99m}Tc could be produced. This is in agreement with the yield obtained using 160 μA proton beam with our natural Mo thick target normalized to 1 mA for enriched ^{100}Mo.

The legitimacy of our extrapolation from ^{nat}Mo to enriched ^{100}Mo is obvious due to the presence of just one single ^{99m}Tc production channel via the ^{100}Mo(p,2n)^{99m}Tc reaction in the desired proton energy range. However, 100% enriched ^{100}Mo is not available, so reactions leading to the formation of radionuclide impurities such as ^{93}Tc, ^{94}Tc, ^{95}Tc and ^{96}Tc (see Tables 1 and 2) are of high concern for the production of high purity ^{99m}Tc from enriched ^{100}Mo targets. The presence of these by-products could be minimized to acceptable limits using a high quality enriched material such as ^{100}Mo (CIS; 97.46%).

After extraction of TcO_4^- in normal saline for kit radio-labelling, we prepared [Tc]-BRIDA as a model radio-labelled kit. At the end of labelling, radiochemical purity in excess of 97% was shown by both standard TLCs (Whatman no. 2, mobile phases of saline and silica gel using MEK as eluent). In TLC studies of pertechnetate (Fig. 5) we observed that uncomplexed TcO_4^- migrated to higher R_fs (0.9) while colloidal Tc fractions, correlate to smaller R_fs (R_f = 0.0–0.1) using MEK as eluent. It was shown that the colloidal Tc was less than 2% in all cases. Using the same eluent, the [Tc]-BRIDA complex remains at the base R_f (R_f = 0.0). In all radio-labelling runs (n = 9), the integral ratio of the two peaks was constant (97:3), showing the high radiochemical purity and consistency of the labelling method except that there is a 3% colloidal compound overlapped by the radio-labelled compound.

Table 2. Nuclear decay data for radionuclides produced in the irradiated natural Mo target and activities measured by γ-ray spectrometry 12 h after EOB

Radionuclide	γ-Emissions[(a)] (keV)	γ-Intensity[(a)] (%)	$T_{1/2}$[(a)] (s)	Measured[(b)] activity of the dilute sample (μCi)	Measured[(b)] activity of the target (Ci)
Tc-99m	140.51	89.06	21,636	14.4	2.75
Tc-96	778.22	99.79	369,792	5.2	0.99
Tc-95	765.789	93.8	72,000	24.3	4.64
Tc-94	702.67	99.6	17,580	37.1	7.08
Tc-93	1362.94	66.2	9900	11.4	2.17

[(a)] Data taken from [3].
[(b)] Activities at EOB.

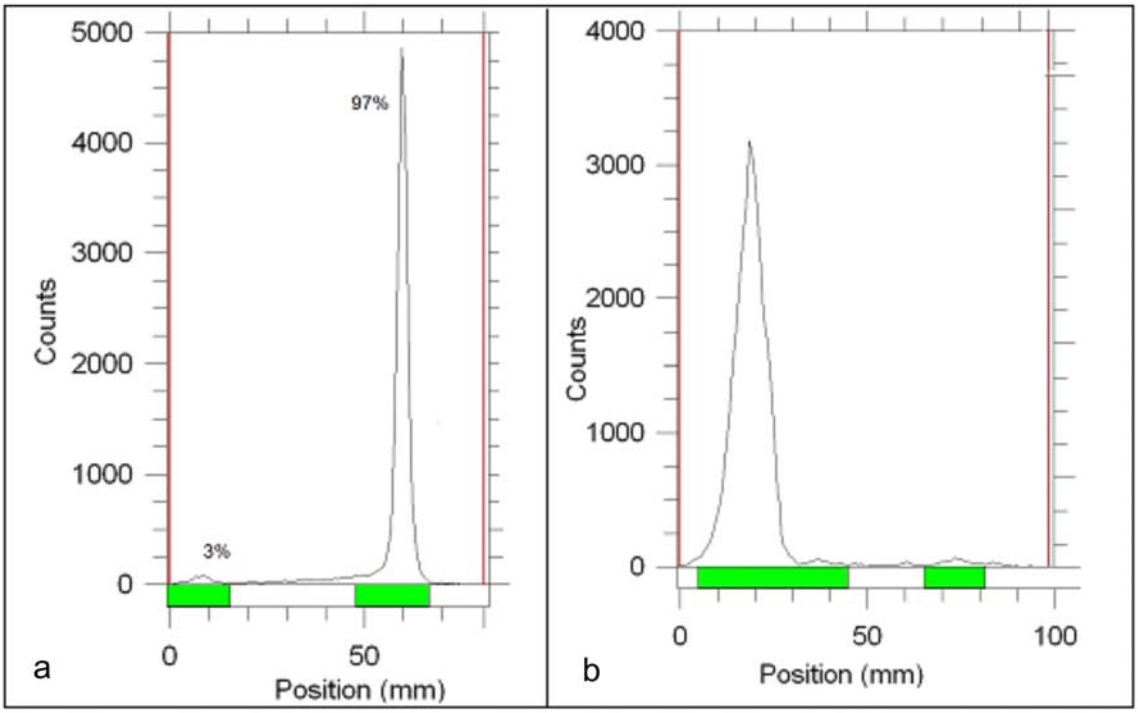

Fig. 5. RTLC of the starting [Tc]-TcO_4^- (a) and [Tc]-BRIDA (b).

As shown in Fig. 6, the ID/g% of different organs determined using 140.5 keV gamma line of ^{99m}Tc it is observed that due to lipophilicity of the [Tc]-BRIDA it is rapidly washed out from the blood stream while easily penetrates into hepatocytes and rapidly from there into the intestine. The compound has a slight liver uptake which is almost common with iminodiacetic acids. Interestingly, the tracer is highly accumulated in the lungs after 120 min. The results of measurements are in agreement with the expected time behaviour of the kit in different organs, showing a successful labelling of the kit with Tc (including ^{99m}Tc) produced from the bombarded Mo thick target.

Conclusion

The production of technetium radioisotopes has been reported in several investigations in low proton current (less than 1 μA), but in this research we have investigated the production of ^{99m}Tc and other technetium radioisotopes on an industrial scale by high level proton currents.

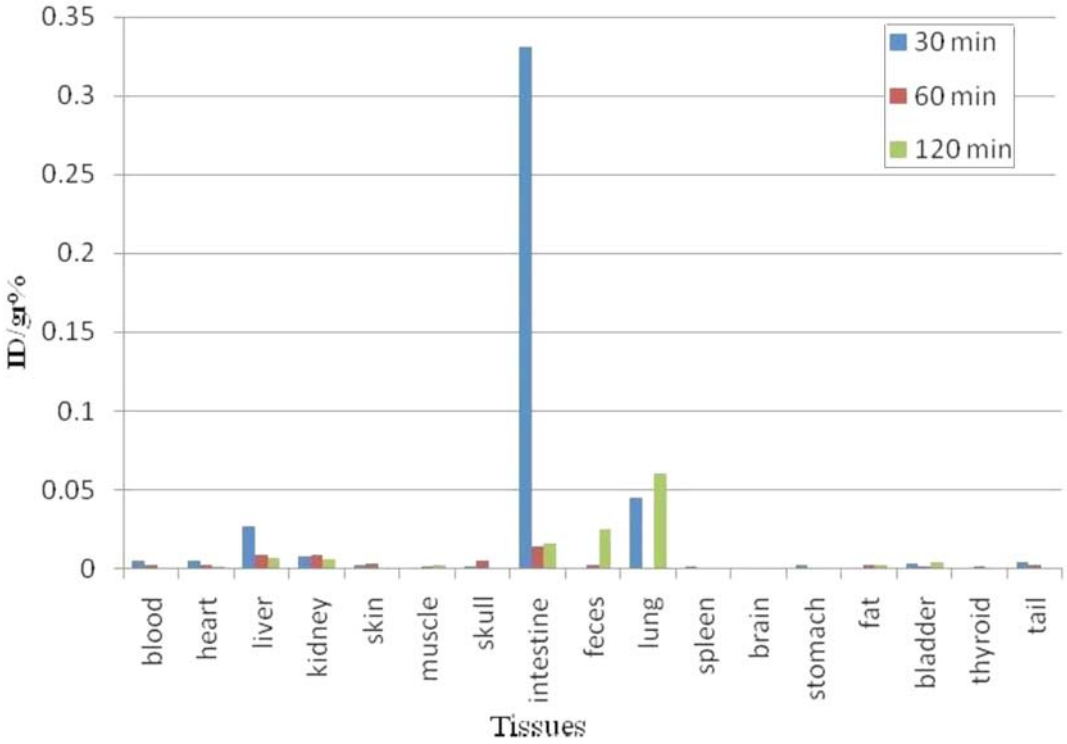

Fig. 6. Calculated ID/g% of the [Tc]-BRIDA after 30, 60, and 120 min post I.V. injection in normal rats.

In this study, a high power metallic natural molybdenum target has been designed and constructed. Then, the target was bombarded by 160 μA protons of a 25 MeV proton beam optimized for the production of ^{99m}Tc using the Cyclone30 cyclotron. The activity of ^{99m}Tc of the target at EOB has been measured as 2.75 Ci for 1000 μA-h of irradiation. To extract technetium from the bombarded molybdenum target, it was dissolved in acid and then neutralized with NaOH.

Then, [Tc]-BRIDA was prepared using the extracted TcO_4^- as a model radio-labelled kit and administered to normal rats by intravenously injection via their tail veins. Due to lipophilicity of the [Tc]-BRIDA, it is rapidly washed out from the blood stream while easily penetrates into hepatocytes and rapidly from there into the intestine which is in agreement with the expected time behaviour of the kit in different organs. This shows a successful labelling of the kit with produced Tc (including ^{99m}Tc).

It is also anticipated that the developed coating method for the production of high power Mo targets using enriched ^{100}Mo instead of natural Mo, is capable of producing about 100 Ci of ^{99m}Tc using a proton beam of about 1 mA. It should also be mentioned that although the reactions leading to the formation of impurities are important for natural Mo targets, but with selecting a high quality enriched target material and matching its thickness with suitable proton energy range, the amount of impurities in the production of ^{99m}Tc could be minimized to acceptable values.

Finally, it can be concluded that the direct method of production of ^{99m}Tc, using high proton beams and our constructed high-current thick target, is promising for a large-scale local production of ^{99m}Tc as an alternative to ^{99}Mo-^{99m}Tc generators based on reactor-produced fission fragments.

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References

1. Beaver JE, Hupf HB (1971) Production of ^{99m}Tc on a medical cyclotron. J Nucl Med 12;11:739–741
2. Bonardi M, Birattari C, Groppi F, Sabbioni E (2002) Thin-target excitation functions, cross-section and optimized thick-target yields for ^{nat}Mo(p,*x*n)$^{94g,95m,95g,96(m+g)}$Tc nuclear reactions induced by protons from threshold up to 44 MeV, no-carrier-added radiochemical separation and quality control. Appl Radiat Isot 57:617–635
3. Brookhaven National Laboratory (1998) Nuchart, version 4.0.0. National Nuclear Data Center, BNL
4. Challana MB, Comsana MNH, Abou-Zeidb MA (2007) Thin target yields and MPIRE-II predictions on the accelerator production of technetium-99m. J Nucl Radiat Phys 2;1:1–12
5. Eckelman WC (2009) Unparalleled contribution of technetium-99m to medicine over 5 decades. J Am Coll Cardiol Img 2:364–368
6. IAEA (1995) Alternative technologies for ^{99m}Tc generators. IAEA-TECDOC-852. International Atomic Energy Agency, Vienna
7. IAEA (1999) Production technologies for molybdenum-99 and technetium-99m. IAEA-TECDOC-1065. International Atomic Energy Agency, Vienna
8. Khandaker MU, Uddin MS, Kim KS, Lee YS, Kim GN (2007) Measurement of cross-sections for the (p,*x*n) reactions in natural molybdenum. Nucl Instrum Methods Phys Res B 262:171–181
9. Lagunas-Solar MC, Kiefer PM, Carvacho OF, Lagunas CA, Ya Po Cha (1991) Cyclotron production of NCA ^{99m}Tc and ^{99}Mo, an alternative non-reactor supply source of instant ^{99m}Tc and ^{99}Mo → ^{99m}Tc generators. Appl Radiat Isot 42;7:643–657
10. Pawlowski L (1995) Engineering of thermal spray coatings. John Wiley & Sons, Inc., New York
11. Rosch F, Qaim SM (1993) Nuclear data relevant to the production of the positron emitting technetium isotope Tc-94m via the Mo-94(p,n) reaction. Radiochim Acta 62:115–121
12. Takacs S, Szucs Z, Tarkanyi F, Hermanne A, Sonck M (2003) Evaluation of proton induced reactions on ^{100}Mo new cross-sections for production of ^{99m}Tc and ^{99}Mo. J Radioanal Nucl Chem 257;1:195–201
13. Takacs S, Tarkanyi F, Sonck M, Hermanne A (2002) Investigation of the ^{nat}Mo(p,*x*n)^{96mg}Tc nuclear reaction to monitor proton beam: new measurements and consequences on the earlier reported data. Nucl Instrum Methods Phys Res B 198:183–196
14. Uddin MS, Hagiwara M, Tarkanyi F, Ditroi F, Baba M (2004) Experimental studies on the proton-induced activation reactions of molybdenum in the energy range 22–67 MeV. Appl Radiat Isot 60:911–920
15. Ziegler JF, Biersack JP (2003) SRIM 2003.20, http://www.SRIM.org