Research Article

Research of Potential Production ^{94m}Tc in Medical Cyclotron

German KE^{1*}, Rumyantsev AS^{1,2} and Manukova VA^2

^{1}Frumkin Institute of Physical Chemistry and Electrochemistry RAS, Moscow, Russia
^{2}A.N. Bakulev Scientific Center of Cardiovascular Surgery, Moscow, Russia

Check for updates

🔓 OPEN ACCESS

Abstract

To expand the spectrum of used radiopharmaceuticals, it is proposed to obtain a positron-emitting isotope of technetium ^{94m}Tc. The intention of this work is to research the possibility of producing various technetium isotopes on a medical cyclotron. For this purpose, we carried out a series of irradiations of an aqueous solution of molybdenum of natural isotopic composition with protons of 11 MeV energy. After technetium isolation, results were analyzed on a γ-spectrometer. 511 keV gamma-ray line was obtained.

Introduction

Positron emission tomography combined with computed tomography (PET/CT) is a highly informative diagnostic method in various areas of medicine, such as oncology, and cardiology, as well as in the diagnosis of inflammatory processes. In this regard, it is important to introduce new positron radionuclides for the synthesis of radiopharmaceuticals (RP), which will have a number of advantages over other RP labeled with widely used radionuclides ^{18}F, ^{11}C, and ^{13}N. One of the promising positrons (β+) emitters is the technetium isotope ^{94m}Tc, which has optimal nuclear-physical characteristics for use in PET, such as a positron branching ratio of 72% and a half-life of 52 min, allowing the synthesis of RP. The broad potential of ^{94m}Tc is due to the possibility of using existing commercial kits designed for the manufacture of RP from generator ^{99m}Tc-pertechnetate [1]. For example, ^{94m}Tc-sestamibi can be used as a myocardial perfusion agent [2]. Scientists from the USA conducted comparative research on eight patients with a history of myocardial infarction with radiopharmaceuticals ^{13}N-ammonia and ^{94m}Tc-sestamibi [3] . The authors did not reveal significant differences in the accumulation of RPs in the heart muscle, but the administered dose of ^{94m}Tc-sestamibi is lower than that of ^{13}N-ammonia. In the same way, the technetium isotope ^{94m}Tc can be used for a wide range of radiopharmaceuticals as a radioactive label instead of ^{99m}Tc to obtain PET images. There are many methods to obtain ^{94m}Tc. However, the most suitable method for practical work is to irradiate a stable isotope of molybdenum ^{94}Mo with protons. The reaction ^{94}Mo(p,n)^{94m}Tc gives out a high yield of the target radionuclide and a low content of isotopic impurity ^{94g}Tc about 6% - 10% [4]. In addition, ^{94g}Tc has a short half-life of 293 min

and is itself a partial positron emitter (positron branching ratio 11%), so it will not create excess radiation exposure to patients. However, this method works with proton energy from 8 to 13 MeV only. Scientists from Germany conducted a study and found that above 13 MeV, the probability of a nuclear reaction with releases two neutrons from ^{94}Mo and the formation of isotopes ^{93g,m}Tc begins to increase rapidly, which is shown in the graph in Figure 1 [5]. Accordingly, the production of ^{94m}Tc by the nuclear reaction ^{94}Mo(p,n) ^{94m}Tc is possible only at low-energy accelerators, such as the medical cyclotron Siemens RDS-111 with a proton energy of 11 MeV. It also takes into consideration what is this cyclotron, as well as most other medical cyclotrons, designed for irradiation of liquid and gas target substances only. That's why molybdenum
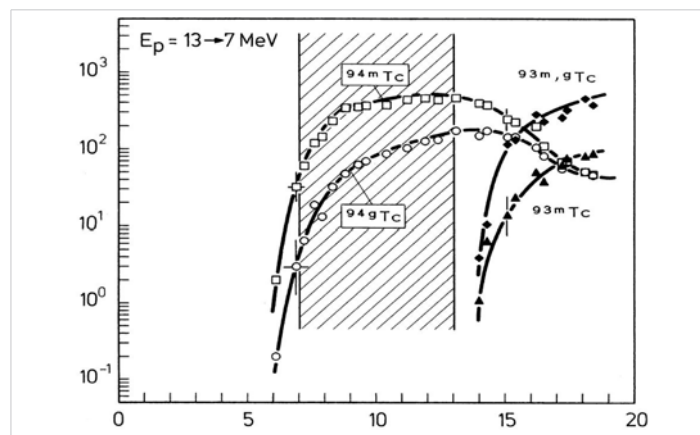

Figure 1: Excitation functions of ^{94}Mo(p,xn)-processes leading to the formation of ^{94m,g}Tc and ^{93m,g}Tc. (Qaim_Syed_M,_2000).

must be used in the form of an aqueous solution. In addition, there are methods for relatively rapid extraction of technetium from the liquid phase [6,7].

Materials and methods

The essence of the experiment was to produce positron-emitting ^{94m}Tc using the capabilities of a small radiochemical laboratory at the PET center. To achieve this, we faced 4 tasks:

a) Selection of the composition of a molybdenum solution for irradiation on a cyclotron;

b) Selection and programming of the target device;

c) Development of a method for purifying Tc from positron-emitting isotopes in an irradiated solution;

d) Definition of qualitative analysis of the obtained product for the technetium isotope composition.

- **Preparation of liquid target solution**

    In this research, it is irradiated molybdenum of natural isotopic composition (Table 1).

    As a target substance was used, an aqueous solution of potassium molybdate with a molybdenum concentration of about 100 mg/ml, was obtained by dissolving dry molybdenum (VI) oxide in 1M KOH.

- **Cyclotron targets**

    Work on the production of technetium was carried out on the Siemens RDS-111 cyclotron. The target device is a modified standard TCU designed to produce radionuclide nitrogen-13. This allows the entire cycle of obtaining radionuclides to be carried out automatically. The operating principle of this device is shown schematically in Figure 2. The HPLC pump with a capacity of 1.5 ml/min feeds a solution of the target substance into the volume 3 ml aluminum target
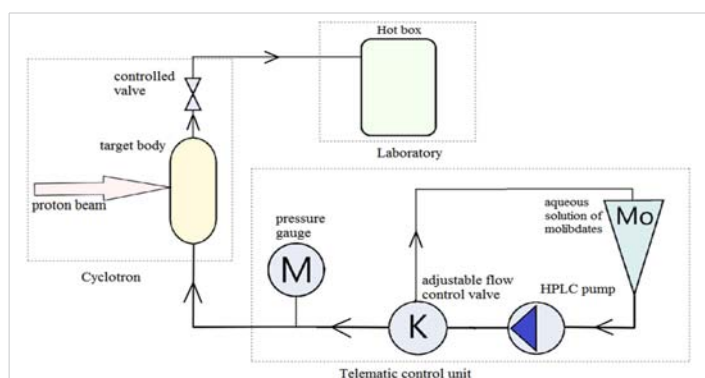
through a mechanical valve set to a system pressure of 300 PSI and the pump constantly supports it during irradiation. After irradiation, a remotely controlled valve opens and the pump flows over the target solution into a hot box in the laboratory.

- **Purification of technetium isotopes from radionuclide impurities**

    The produced technetium is stabilized in the chemical form of an aqueous solution of pertechnetate. The main part of radionuclide impurities to technetium are positron-emitting radionuclides, which are obtained from water by reactions $^{18}O(p;n)^{18}F$ ($T_{1/2}$=110 min) and $^{16}O(p;\alpha)^{13}N$ ($T_{1/2}$=10 min). For this research, the obtained solution is delayed until ^{13}N is fully decayed for at least 2 hours. ^{18}F is formed as fluoride anions and is removed from the solution by precipitation with CaF_2 as an isotopic carrier:

    $$Ca^{2+} + {}^{19}F^- + {}^{18}F^- = Ca^{19}F^{18}F\downarrow; \ (Ca^{2+} + TcO_4^- \neq).$$
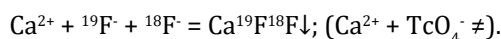
- **Radioisotope measurements by γ-spectroscopy**

A 100 μl sample with an activity of about 1 MBq was added to a 3 ml vial of water and mixed thoroughly. The radionuclide composition was assessed using a γ-spectrometer HPGe with detector GEM30, manufacturer ORTEC. Since positrons annihilate with the emission of γ-quantum with energy 511 keV, then along this line it is possible to identify positron emitters including ^{94m}Tc, which does not have its own unique γ-line. As can be seen from Table 2, other isotopes of technetium have unique γ-energy lines. Shows itself especially well ^{99m}Tc, having a single, separate from other isotopes γ-line 140,45 keV.

Results and discussion

Isotopes technetium production

In the work, several irradiations with a current of 30 μA were performed from 5 to 30 minutes. The pressure in the target during irradiation was constantly maintained at 300 PSI. Nuclear reactions with molybdenum isotopes can generate the radionuclides, presented in Table 3.

Table 1: Natural isotopic composition of molybdenum.

^{92}Mo	^{94}Mo	^{95}Mo	^{96}Mo	^{97}Mo	^{98}Mo	^{100}Mo
14,6%	9,2%	15,9%	16,7%	9,6%	24,3%	9,7%

Figure 2: Layout of the target and transfer system for Tc production.

Table 2: γ-energy lines (keV) used for identification of technetium isotopes.

^{99m}Tc	^{95}Tc	β⁺	^{94g}Tc	^{95}Tc	^{96m}Tc	^{96g}Tc	^{94g}Tc	^{94m,g}Tc	^{95}Tc	^{95}Tc
140,45	204,14	511,4	703,3	766,6	779,06	813,4	850,7	872,1	948,8	1075

Table 3: Nuclear reactions for the production of the different Tc isotopes and their specification [8,9].

Reaction	Half-life	Decay
$^{94}Mo(p,n)^{94g}Tc$	293 min	87,9% EC; 11,1% β⁺
$^{94}Mo(p,n)^{94m}Tc$	52 min	29,8% EC; 72,2% β⁺
$^{95}Mo(p,n)^{95}Tc$	1200 min	100% EC
$^{96}Mo(p,n)^{96g}Tc$	6163 min	100% EC
$^{96}Mo(p,n)^{96m}Tc$	52 min	98% IT; 2% IC
$^{100}Mo(p,2n)^{99m}Tc$	360 min	88% IT; 12% IC

Accordingly, if we use isotopically pure Mo, we will obtain the only isotope we need, for example, ^{94m}Tc from ^{94}Mo. This will also ensure high yields of the target radionuclide from irradiation. The only difficulty is the high cost of isotopically pure molybdenum. And since the physical consumption of molybdenum for the production of technetium is very low, it is possible to regenerate molybdenum for its repeated irradiation.

Pertechnetate isolation

2 ml of 0.1 M NaF was pre-added to the vial prepared for collecting the target substance. After unloading the irradiated solution and mixing, 0.5 M CaCl$_2$ was added dropwise to the solution until a white precipitate completely formed. It was then passed through a sterilizing syringe nozzle with 0.22 μm pores, ^{18}F together with precipitate was retained on the filter, and TcO$_4^-$ passed into the filtrate. More effective ^{18}F-fluoride removal is also possible, if the CaCl2 solution is placed in advance, and the isotopic carrier NaF is added after unloading the target substance.

Results of γ-spectroscopy

After cleaning from ^{18}F and a delay of more than 2 hours for decay of ^{13}N, the samples were analyzed on an γ-spectrometer. Spectrum was obtained and deciphered in the form of a diagram in Figure 3. There is a clean line at 140 keV, belonging to the isotope ^{99m}Tc, and line 511 кэВ, belonging to positron emitters. As well as lines belonging to other isotopes

of technetium. It turns out that this method can be used for the production of ^{99m}Tc from stable ^{100}Mo, which has a great advantage, compared to technetium from the generator, in the absence of the long-lived parent radionuclide ^{99}Mo [10].

Dynamic γ-spectroscopy by the line 511 keV

One of the samples was analyzed on an γ-spectrometer every 30 minutes. Based on the obtained data was done graphic representation of the decay rate of positron emitters in the sample (Figure 4). A comparative analysis was carried out with the decay rate of ^{94m}Tc, taking the coinciding points at 30 and 60 minutes as the calculated activity. As can be seen from the graphic, the decay of the sample almost coincides with the decay of ^{94m}Tc, this indirectly confirms that among positron emitters ^{94m}Tc gives the largest share to the line 511 keV. Additionally, a graphic was done of the decay rate of ^{18}F, taking as the calculated value activity the difference between «decay of positron-emitting r/n» and «decay of ^{94m}Tc» in the last point of the graph. The decay rate of ^{13}N is taken as the calculated value activity of the difference between decay graphics in the first point of the graph. As can be seen, these graphics are far from the main one, and therefore their content is at the of small impurities.

For further scientific work in this direction, it is necessary first of all refine the separation methodology pertechnetate anions not only from fluoride but also from ^{13}N in anionic form. After which, to synthesize the radiopharmaceuticals, it will be necessary to construct a new or redesign already existing
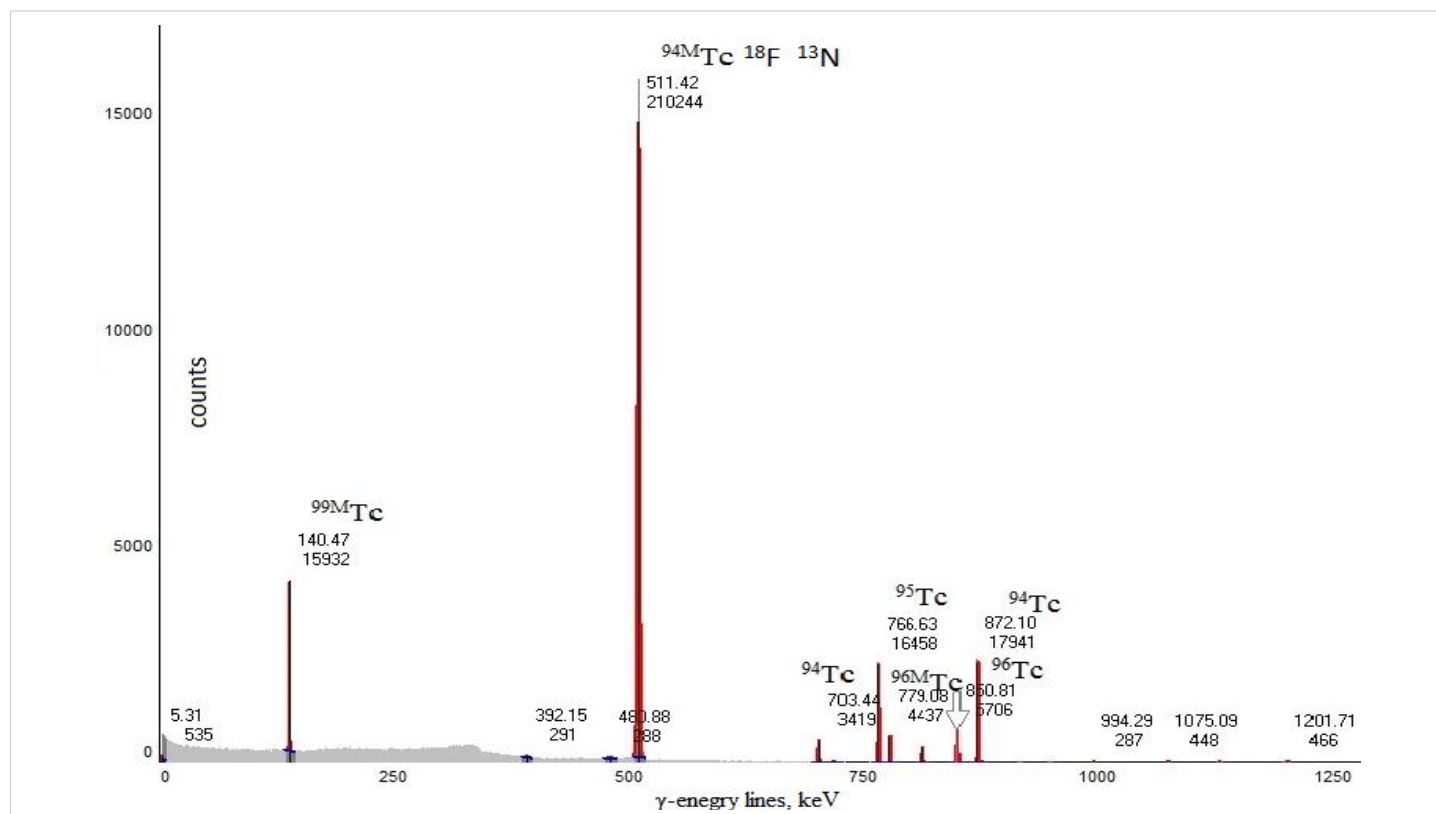

Figure 3: Spectrum of the sample with decoding.

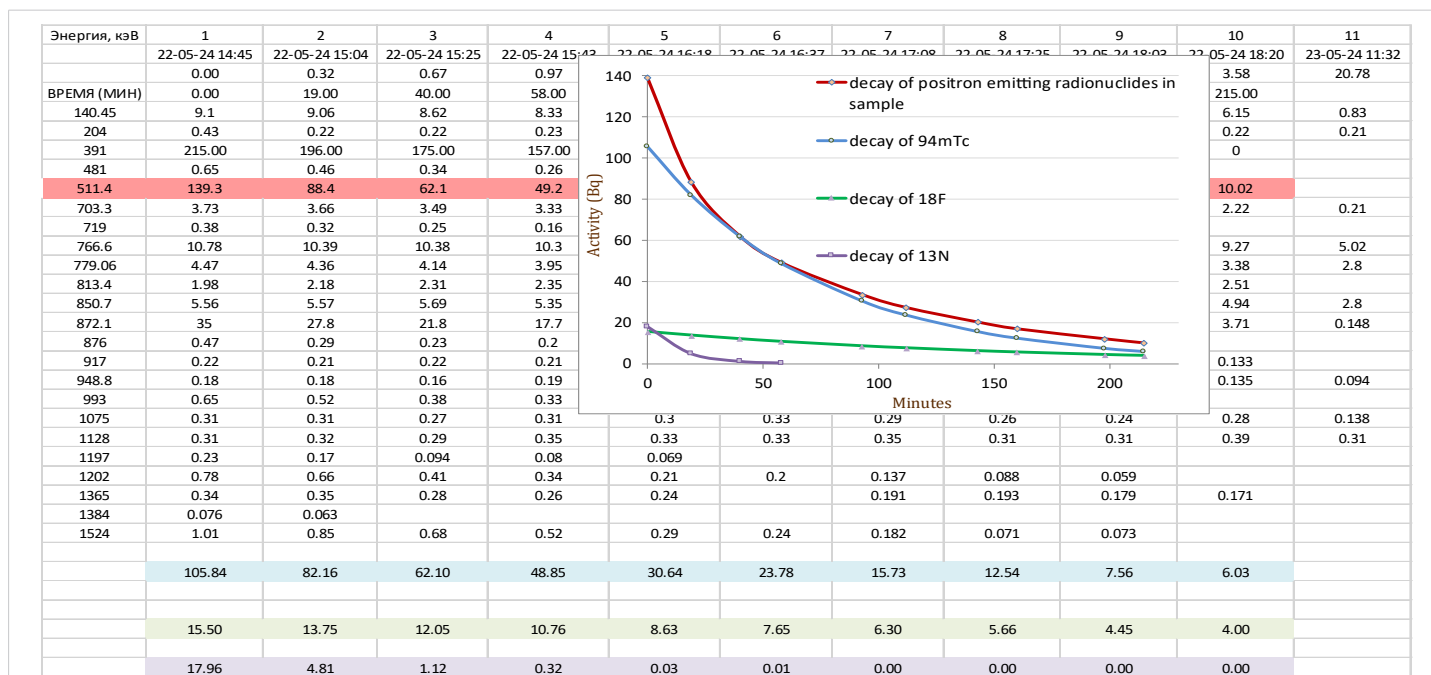| Энергия, кэВ	1	2	3	4	5	6	7	8	9	10	11
	22-05-24 14:45	22-05-24 15:04	22-05-24 15:25	22-05-24 15:43	22-05-24 16:18	22-05-24 16:37	22-05-24 17:08	22-05-24 17:25	22-05-24 18:03	22-05-24 18:20	23-05-24 11:32
	0.00	0.32	0.67	0.97						3.58	20.78
ВРЕМЯ (МИН)	0.00	19.00	40.00	58.00						215.00	
140.45	9.1	9.06	8.62	8.33						6.15	0.83
204	0.43	0.22	0.22	0.23						0.22	0.21
391	215.00	196.00	175.00	157.00						0	
481	0.65	0.46	0.34	0.26							
511.4	139.3	88.4	62.1	49.2						10.02	
703.3	3.73	3.66	3.49	3.33						2.22	0.21
719	0.38	0.32	0.25	0.16							
766.6	10.78	10.39	10.38	10.3						9.27	5.02
779.06	4.47	4.36	4.14	3.95						3.38	2.8
813.4	1.98	2.18	2.31	2.35						2.51	
850.7	5.56	5.57	5.69	5.35						4.94	2.8
872.1	35	27.8	21.8	17.7						3.71	0.148
876	0.47	0.29	0.23	0.2							
917	0.22	0.21	0.22	0.21						0.133	
948.8	0.18	0.18	0.16	0.19						0.135	0.094
993	0.65	0.52	0.38	0.33							
1075	0.31	0.31	0.27	0.31	0.3	0.33	0.29	0.26	0.24	0.28	0.138
1128	0.31	0.32	0.29	0.35	0.33	0.33	0.35	0.31	0.31	0.39	0.31
1197	0.23	0.17	0.094	0.08	0.069						
1202	0.78	0.66	0.41	0.34	0.21	0.2	0.137	0.088	0.059		
1365	0.34	0.35	0.28	0.26	0.24		0.191	0.193	0.179	0.171	
1384	0.076	0.063									
1524	1.01	0.85	0.68	0.52	0.29	0.24	0.182	0.071	0.073		
	105.84	82.16	62.10	48.85	30.64	23.78	15.73	12.54	7.56	6.03	
	15.50	13.75	12.05	10.76	8.63	7.65	6.30	5.66	4.45	4.00	
	17.96	4.81	1.12	0.32	0.03	0.01	0.00	0.00	0.00	0.00	

Figure 4: Comparison of decays +¦+-emitting radionuclides at a frequency of 511 keV.

automated radiochemistry synthesizer. The synthesis itself is hypothetically ordinary – useful RPs, labeled with the isotope ^{99m}Tc, and methods of their analysis are used everywhere. To obtain ^{94m}Tc without other isotopes of technetium expensive isotopically pure ^{94}Mo is required. And the main problem is allocation with minimal losses of molybdenum from irradiated solution. Without this, the research direction will not be economically justified.

Conclusion

This paper demonstrates the possibility of obtaining various technetium isotopes in a liquid target device of a low-energy proton accelerator. Particular attention should be paid to the positron-emitting isotope ^{94m}Tc. The optimal half-life of 52 minutes allows chemistry reactions with ^{94m}Tc to obtain radiopharmaceuticals in PET diagnostics. In the future, if the irradiation parameters are optimized and isotopically pure ^{94}Mo is used in the target substance, it will be possible to obtain high yields of the target radionuclide.

References

1. Kovács Z. Technetium-99m pharmaceuticals: preparation and quality control in nuclear medicine. Berlin: Springer; 2006:151-3.

2. Szajek LP, Der M, Dive J, Huang BX, Plascjak P, Eckelman WC. Production and radioassay of Tc-94m for PET studies. Radiochim Acta. 2003;91:613-6. Available from: https://doi.org/10.1002/jlcr.25804401269

3. Stone CK, Christian BT. Technetium 94m-labeled methoxyisobutyl isonitrile: dosimetry and resting cardiac imaging with positron emission tomography. J Nucl Cardiol. 1994;1(5):425-33. Available from: https://doi.org/10.1007/bf02961596

4. Qaim SM. Production of high purity 94mTc for positron emission tomography studies. Nucl Med Biol. 2000;27:323-8. Available from: https://doi.org/10.1016/s0969-8051(00)00104-9

5. Rosch F, Qaim SM. Nuclear data relevant to the production of the positron emitting technetium isotope 94mTc via the 94Mo(p,n)-reaction. Radiochim Acta. 1993;62:115-121. Available from: https://doi.org/10.1524/ract.1993.62.3.115

6. Hoehr C, Morley T, Buckley K, Trinczek M, Hanemaayer V, Schaffer P, et al. Radiometals from liquid targets: 94mTc production using a standard water target on a 13 MeV cyclotron. Appl Radiat Isot. 2012;70:2308-12. Available from: https://doi.org/10.1016/j.apradiso.2012.06.004

7. Harper R, Morim DR, Mehta D, Rosecker V, Archibald SJ, Southworth R, et al. Optimised production of technetium-94m for PET imaging by proton-irradiation of phosphomolybdic acid in cyclotron liquid target. Appl Radiat Isot. 2024;210:111381. Available from: https://doi.org/10.1016/j.apradiso.2024.111381

8. Lamere E, Couder M, Beard M, Simon A, Simonetti A, Skulski M, et al. Proton-induced reactions on molybdenum. Phys Rev C. 2019;100:034614. Available from: https://doi.org/10.1103/PhysRevC.100.034614

9. Sun H, Han R, Liu B, Chen Z, Yang B, Zhang X, et al. Thick target yields of proton-induced reactions on natural molybdenum. Appl Radiat Isot. 2022;190:110474. Available from: https://doi.org/10.1016/j.apradiso.2022.110474

10. Martini P, Boschi A, Cicoria G, Corazza A, Zagni F, Uccelli L, et al. In-house cyclotron production of high-purity Tc-99m and Tc-99m radiopharmaceuticals. Appl Radiat Isot. 2018;139:325-31. Available from: https://doi.org/10.1016/j.apradiso.2018.05.033