

Title A Solvent-Extraction Module for Cyclotron Production of High-Purity Technetium-99m

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Abstract

The design and fabrication of a fully-automated, remotely controlled module for the extraction and purification of technetium-99m (Tc-99m), produced by proton bombardment of enriched Mo-100 molybdenum metallic targets in a low-energy medical cyclotron, is here described. After dissolution of the irradiated solid target in hydrogen peroxide, Tc-99m was obtained under the chemical form of $[^{99m}\text{Tc}][\text{TcO}_4]^-$, in high radionuclidic and radiochemical purity, by simple solvent extraction with methyl ethyl ketone (MEK). The extraction process was accomplished inside a glass column-shaped vial especially designed to allow for an easy automation of the whole procedure. Recovery yields were always > 90% of the loaded activity. The final pertechnetate saline solution $\text{Na}[^{99m}\text{Tc}][\text{TcO}_4]^-$, purified using the automated module here described, is within the Pharmacopoeia quality control parameters and is therefore a valid alternative to generator-produced ^{99m}Tc . The resulting automated module is cost-effective and easily replicable for in-house production of high-purity Tc-99m by cyclotrons.

Keywords Technetium-99m; Molybdenum-100; Cyclotrons; Pertechnetate; Solvent Extraction; Methyl Ethyl Ketone (MEK); Automated Module.

Manuscript category Radiochemistry and Radionuclide Applications

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Dear Editor,

I'm submitting the paper entitled 'A Solvent-Extraction Module for Cyclotron Production of High-Purity Technetium-99m' by Martini, P., et al., to be considered for publication on Applied Radiation and Isotopes as a full article.

This paper describes the design and construction of a new automated module for the efficient separation and purification of Tc-99m produced by proton irradiation of highly enriched Mo-100 targets. We believe that the main value of this work lies in its simplicity and easy functioning achieved through the introduction of a few original solutions. In principle, this module that could be easily replicated in house using commercially available modular components and accessories, and an easy-to-make glass column.

We hope this work could be of interest for your journal.

Thank you for your consideration of this request.

Sincerely,

Petra Martini

A Solvent-Extraction Module for Cyclotron Production of High-Purity Technetium-99m

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Keywords: Technetium-99m; Molybdenum-100; Cyclotrons; Pertechnetate; Solvent Extraction; Methyl Ethyl Ketone (MEK); Automated Module.

ABSTRACT

The design and fabrication of a fully-automated, remotely controlled module for the extraction and purification of technetium-99m (Tc-99m), produced by proton bombardment of enriched Mo-100 molybdenum metallic targets in a low-energy medical cyclotron, is here described. After dissolution of the irradiated solid target in hydrogen peroxide, Tc-99m was obtained under the chemical form of $[^{99m}\text{Tc}][\text{TcO}_4]^-$, in high radionuclidic and radiochemical purity, by simple solvent extraction with methyl ethyl ketone (MEK). The extraction process was accomplished inside a glass column-shaped vial especially designed to allow for an easy automation of the whole procedure. Recovery yields were always $> 90\%$ of the loaded activity. The final pertechnetate saline solution $\text{Na}[^{99m}\text{Tc}][\text{TcO}_4]^-$, purified using the automated module here described, is within the Pharmacopoeia quality control parameters and is therefore a valid alternative to generator-produced ^{99m}Tc . The resulting automated module is cost-effective and easily replicable for in-house production of high-purity Tc-99m by cyclotrons.

1. Introduction

Technetium-99m ($t_{1/2} = 6$ h, $E_\gamma = 140$ keV) is the most important gamma-emitting medical radionuclide as it is employed in nearly 85% of all diagnostic nuclear medicine procedures carried out every year around the world. Tc-99m is usually supplied to hospitals through a portable $^{99}\text{Mo}/^{99m}\text{Tc}$ generator where it is generated from the β decay of the parent nuclide Mo-99 ($t_{1/2} = 66$ h), which in turn is produced in nuclear reactors *via* neutron fission on Highly Enriched Uranium Weapon-Grade (HEU-WG) material (Boyd, 1982, 1987; Molinski, 1982; Van, 2014; Arano, 2002; Uccelli et al., 2013). The dramatic shortage of the global supply chain of reactor-produced Mo-99, due to the unplanned, relatively long term, shut down for some of the few reactors authorized, occurred in 2009–2010, has forced the scientific community to investigate alternative production routes for Tc-99m. One of the most attractive solution was, to consider the direct, cyclotron-based methods as potential replacement of reactor-based technology.

Since the cyclotron production of Mo-99 having comparable specific activity was soon ruled out, because of the lack of favorable proton-induced nuclear reactions, the direct production of Tc-99m finally emerged as the most worthwhile approach (Hou et al., 2016; Celler et al., 2011). In particular, our group has extensively contributed, both theoretically and experimentally in the framework of research projects funded by the Italian National Institute for Nuclear Physics research (INFN). (Esposito et al., 2013; Manenti et al., 2014; Pupillo et al., 2014), to identify the nuclear reaction $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ as the most favorable for setting up a routine production of Tc-99m using a conventional medical cyclotron. This conclusion mostly relies on results of accurate calculations and measurements of the cross section of the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ reaction. Actually, data convincingly showed that the optimal proton energy for yielding Tc-99m, in enough amounts and with a radionuclidic purity level suitable for clinical applications, falls in the range 15–20 MeV. Since this energy range is easily accessible by a conventional medical cyclotron, this prompted us to suggest that in-house cyclotron-produced Tc-99m could become a convenient replacement of generator-based Tc-99m, even in the event of another supply crisis. It should be noted that the rationale behind the in-house approach to the cyclotron production of Tc-99m is exactly antipodal

to that underlying the proposal of a centralized production carried out in a professional radiopharmacy, which would require a less conventional, high-current cyclotron to ensure a daily production of Tc-99m in amounts sufficient able to meet the clinical demand of a metropolitan area (Ruth, 2009, 2014; Pillai et al., 2013; Bénard et al., 2014).

Clearly, an accelerator technology, grounded on the $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$ nuclear reaction, will always require the application of an effective separation technique to allow recycling of the costly Mo-100 enriched targets and ensuring the economy of the whole production process. Several separation techniques have been previously investigated for the isolation of Tc-99m from bulky molybdenum and these have been nicely reviewed recently (Dash et al., 2013). Among them, the solvent extraction (SE) method with methyl ethyl ketone (MEK) has been proven to be one of the most efficient techniques (Novak and Fajgelj, 1983; Taskaev et al., 1995, Chattopadhyay et al., 2010; Zykov et al., 2001; Skuridin and Chibisov, 2010; Tachimori et al., 1971; Noronha, 1986; Dallali et al., 2007). The purpose of this work was to develop a fully automated, remotely controlled module for the fast and efficient extraction and purification of Tc-99m from an irradiated Mo-100 enriched molybdenum metallic target by exploiting the high efficiency of the SE technique. There are two key advantages in using an automated procedure for Tc-99m purification. Primarily, this will sharply decrease the radiation exposure of operators in handling high radioactive materials and, secondly, will definitely contribute to make the whole process much more reproducible and traceable. That is indeed a key pre-requisite for attaining a clinical-grade quality for the recovered Tc-99m. In turn, this may strongly favor a possible approval by regulatory authorities for its use in patients.

When this work was underway, another research group published similar results on the development of an automated module for the separation of Tc-99m from a bulk of low-activity Mo-99 produced in a nuclear reactor by neutron irradiation of natural molybdenum (Chattopadhyay et al., 2012). Albeit not intended for this purpose, in principle, the described procedure could be applied to the extraction of Tc-99m from a Mo-100 after some initial chemical treatment necessary to dissolve the metallic target. The automated module here described was fully designed for being a single component of a more comprehensive technology capable of handling all the steps in the chain starting with the irradiation of the target, its transfer to the extraction module and collection of the final Tc-99m product in physiological solution inside a sterile vial. For this purpose, the module was conceived as a cost-effective and easy-to-make device that can be easily assembled from commercially available mechanical and electronic building blocks. To achieve this result some key differences had to be introduced in comparison with the published module. The description of this alternative apparatus is reported in the present work.

2. Experimental

2.1. Materials

All chemicals and reagents were of analytical grade unless otherwise specified. Hydrogen peroxide (35% w/w) and sodium hydroxide pellets were purchased from Sigma-Aldrich (Milan, Italy). Methyl ethyl ketone (MEK) was obtained from Carlo Erba (Milan, Italy). Sodium chloride was received from Fresenius Kabi (Verona, Italy).

Silica and acidic alumina SepPak cartridges were obtained from Waters Corporation (Milford, MA, USA).

Technetium-99m, as $\text{Na}^{[99\text{mTc}]\text{TcO}_4$ in physiological solution, was obtained from a Drytec $^{99}\text{Mo}/^{99\text{mTc}}$ generator (GE Healthcare, UK).

Mo-100 enriched molybdenum powder was purchased from Isoflex (San Francisco, USA) (Isoflex, 2012). The isotopic composition of the batch of the enriched material was: ^{100}Mo (99.05%), ^{98}Mo (0.54%), ^{97}Mo (0.07%), ^{96}Mo (0.11%), ^{95}Mo (0.10%), ^{94}Mo (0.05%), and ^{92}Mo (0.08%).

2.2. Module assembly

A schematic representation of the module setup is illustrated in Fig. 1. The prototype was constructed by assembling six prepackaged modular units (Modular-Lab Standard, Eckert & Ziegler, Berlin, Germany) comprising a flow controller module, a heater reactor module (air-cooled), a vial holder module and three connector modules containing two- and three-way switching valves and tubing for fluid and gas transfer. A control unit, equipped with Modular-Lab Software 4.3.2.0 (Eckert & Ziegler), remotely controlled the various modules. This assembly was customized by adding to the vial holder module a dedicated, handmade glass column (length = 10 cm, \varnothing = 1 cm) specifically designed to accommodate the solvent extraction step with the highest separation efficiency (Fig. 1). All consumable and accessories, including PEEK™ tubing for fluid transfer, PTFE tubing for gas transfer, PEEK™ or Teflon connectors flange-type fitting plugs, PEEK™ vial heads for 4 connectors (1/4"-28), glass vials for reagents, pressure sensors (250 bar) and activity detectors, were purchased from Radius, Bologna, Italy.

2.3. Separation procedure

A representative description of the whole process and the various steps accomplished by the automated module are reported below.

Laminated enriched molybdenum circular metal foils (\varnothing = 0.9 cm) were routinely produced at the Legnaro National Laboratories (LNL) target laboratory, starting from Mo-100 enriched molybdenum metal powder melted under an argon-gas atmosphere and temperature-controlled conditions. Five foils per each irradiation test were packed together (total thickness = 143 μm , total mass = 124.5 mg) and mounted in a copper target holder.

The stack-foil target was then irradiated for 90 min at 16.5 MeV proton beam and 20 μA current in a medical cyclotron (PETtrace, GE Healthcare, USA) located at the Department of Nuclear medicine of St. Orsola Hospital, Bologna.

After irradiation, the target holder was pneumatically transported into a dedicated hot cell through a solid-target transfer system and the five irradiated foils transferred into the reactor vial (1 in Fig. 1) afterwards. Dissolution of the metallic foils was obtained by addition of 1.5 mL of H_2O_2 (35%) followed by heating at 90°C for 5 min. After cooling to 50°C, 5.0 mL of NaOH (6 M) were added to the resulting solution, which was further cooled to 30°C. After transferring the alkaline aqueous solution to the separation column (2 in Fig. 1), the reactor vial was washed with 4.0 mL of MEK. The organic solvent was then injected slowly from the bottom into the separation column and the resulting mixture vigorously shaken by bubbling helium gas, at a flow rate of 60 mL/min, for

7.0 min in order to maximize the contact between the two phases. Keeping the mixture at rest for 4.0 min resulted in a marked phase separation, the organic solution containing ^{99m}Tc -pertechnetate lying at the top of the column. The organic phase was collected from the separation column, and then passed through a silica SepPak cartridge (3 in Fig. 1) and subsequently through an alumina SepPak cartridge (4 in Fig. 1), which immobilized Tc-99m activity. The residual MEK was then sent into the waste vial (5 in Fig. 1). To maximize the extraction yield, 3.0 mL of MEK were further added to the aqueous phase still present at the bottom of the separation column, and the procedure was repeated. After completing the waste recovery of the second organic fraction, the silica column was washed with 1.5 mL of pure MEK, which was then passed through the alumina column before reaching the waste. Finally, the alumina column was washed with 10.0 mL of deionized water followed by 6.0 mL of saline, thus causing the removal of the adsorbed $[\text{}^{99m}\text{Tc}]\text{TcO}_4^-$. The final activity was collected in a sterile vial (6 in Fig. 1) and the process was completed. The total time to complete the automated procedure was approximately 70 min starting from the introduction of the irradiated foils into the module.

Before starting a new run, the automated module was finally washed by passing 20 mL of deionized water through the system after removal of the cartridges and of the residual liquid fraction in the reactor. The recovered aqueous waste (washing fraction) was measured for radioactivity by gamma spectroscopy as detailed below.

2.4. Quality Control

Radiochemical purity (RCP) of $[\text{}^{99m}\text{Tc}]\text{TcO}_4^-$ was determined by paper chromatography on Whatman 1 strips using either a mixture methanol/water (8:2 v/v) or saline as mobile phases. Activity on each strip was detected using a Cyclone Plus Storage Phosphor System equipped with OptiquantTM software.

The molybdenum content was assessed using the kit Merckoquant Molibdeno 5-250 MG/L purchased from Merck (Darmstadt, Germany). Similarly, the aluminum content was measured with a Tec-Control Aluminium Breakthru kit from Biodex (Shirley, New York, USA).

Radionuclidic purity was investigated by gamma spectrometry using a high-purity germanium (HPGe) detector and data were decay corrected at the End-Of-Bombardment (EOB). Radionuclides were identified from their acquired spectra using the Genie 2000 software (Canberra, Meriden, USA). Efficiency calibration was carried out in the range 59–1836 keV using a multiplex certified source (LEA SEARCH, Areva, France). Calibration was performed according to IEC 61452 standard (IEC, 1995) using the same Genie 2000 software and has been routinely verified on the day before the experiment.

A Capintec CRC-15R dose calibrator (Ramsey, NJ, USA) was used for activity measurements. To fix the geometry, radioactive samples and solutions were introduced in a FalconTM conical test tube (50 mL, BD Bioscience, Bedford, MA, USA) before measurement.

The MEK content in the final ^{99m}Tc -pertechnetate solution was measured by gas chromatography (GC) performed with a GC 6850 Series II Network gas chromatograph equipped with a Pal G6500-CTC injector, a mass selective detector 5973 Network and a J&W DB-624 UI 20m 0.18mm 1.00u column (Agilent Technologies Italia, Milan, Italy). The operating conditions were: carrier gas, He; pressure, 0.97 bar; constant flow rate, 0.7 mL/min; incubation time, 50 min;

incubation temperature, 80 °C, injection volume, 500 µL. Fluorobenzene (51411 analytical standard, Sigma-Aldrich) was used as reference standard.

2.5. Evaluation of the recovery yield

For process optimization, preliminary tests were performed using non-radioactive natural molybdenum to prepare metal foils having a shape identical to those obtained from enriched Mo-100 material. Ten tests were carried out in order to evaluate the performance of the separation module and the recovery yield. In each test run, five foils (total mass = 125 mg) were loaded manually into the reactor module and spiked with a few drops of ^{99m}Tc -pertechnetate eluted from a commercial $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (Tc-99m loads were in the range 0.02–0.5 GBq). Then the module was allowed to operate in the automated mode to perform the dissolution, the extraction and purification cycle using the same solvent mixture and following exactly the same procedure as described above for Mo-100 enriched foils. The activity in the final solution was assayed using a dose calibrator and corrected for the decay. Recovery yield was expressed as percentage fraction of the total Tc-99m activity measured in the reactor load solution (Table 1). Residual activities remaining in other relevant components of the module after withdrawal of the final $[\text{}^{99m}\text{Tc}]\text{TcO}_4^-$ solution were also similarly determined as reported in Table 1.

Since transfer and processing of the irradiated Mo-100 targets was fully automated, to estimate the initial activity at the end of bombardment (EOB) and recovery yield a similar procedure was applied. In particular, activity in the irradiated target was inferred by adding activities, measured by gamma spectrometry after completion of the extraction/purification procedure in four main compartments of the module (*i.e.*, cartridges, aqueous phase, waste, washing fraction), to the activity detected in the resulting $[\text{}^{9x}\text{Tc}]\text{TcO}_4^-$ solution. All these values were decay corrected to give a reasonable estimate of radioactivity produced at EOB. Analysis of the radionuclidic content of the purified $[\text{}^{9x}\text{Tc}]\text{TcO}_4^-$ solution (Table 2, 3) and of the various compartments (Table 4) was carried out by gamma spectroscopy.

3. Results

Operation of the automated module for the separation of $[\text{}^{9x}\text{Tc}]\text{TcO}_4^-$ from proton-irradiated ^{100}Mo -enriched metallic targets was basically of four main steps: (1) dissolution of the irradiated target in $\text{H}_2\text{O}_2/\text{NaOH}$, (2) double solvent extraction of ^{99m}Tc -pertechnetate from the aqueous alkaline into the MEK organic phase, (3) chromatographic purification of the extracted ^{99m}Tc -pertechnetate onto silica and alumina columns, (4) collection of $[\text{}^{9x}\text{Tc}]\text{TcO}_4^-$ from the alumina column by elution with a physiological solution (Martini, 2014). The entire process lasted for approximately 70 min distributed as follows: step 1, 30 min, step 2, 30 min, and steps 3–4, 10 min.

Purification onto a silica column was intended to remove residual traces of molybdenum ions, whereas passage through the alumina column was added to wash out MEK by trapping $[\text{}^{9x}\text{Tc}]\text{TcO}_4^-$ onto the column. The absorbed activity was finally recovered with saline.

The performance of recovery of the overall separation procedure was assessed by carrying out a number of test runs using natural molybdenum metal foils and adding some amount of generator-produced $[\text{}^{99m}\text{Tc}]\text{TcO}_4^-$. Observed recovery yield, calculated over ten runs as percent ratio between

decay-corrected Tc-99m activity collected in the final vial and the activity loaded in the reactor solution, were $93 \pm 2.8\%$ (Table 1). As a control, the percentage of activity stuck onto the major compartments of the module was also determined (Table 1).

Recovery yields were also evaluated when the automated module was employed for processing irradiated Mo-100 enriched targets. To overcome the problem of measuring the activity at EOB without interrupting the automated process, its value was inferred by combining the activities detected in the final ^{99m}Tc -solution, in the aqueous phase and SepPak cartridges after separation, in the waste container and in the washing aqueous fraction used to clean the module. The estimated activity at EOB was approximately 3.15 ± 0.05 GBq under the irradiation conditions described in this work. This value was in close agreement with that predicted by numerical simulations (Esposito et al., 2013). Observed recovery yields from the irradiated targets were $> 90\%$.

The aqueous phase was always preserved for the recycling of the enriched target material, but this issue was not addressed in the present work.

Values of radionuclidic (RNP), chemical (CP) and radiochemical (RCP) purities, determined on the final ^{99m}Tc -pertechnetate solutions, are reported in Table 2. In particular, RNP was found to be always $> 99\%$ and the residual MEK content, measured by gas-chromatography, was $\leq 0.0004\%$ v/v (Table 2).

Gamma spectrometric measurements revealed trace amounts of a number of technetium radioisotopes which are anyway coproduced. The cumulative activity of these radioisotopes is however $< 1\%$ of the total activity (Table 2). A more detailed determination of the amount of technetium radionuclides is reported in Table 3. Other radioactive contaminants, expected to originate in the course of the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ reaction, were below the detectable limit in the final purified solution (Table 2). However, their presence was found in the aqueous solution left over after removal of the organic phase and in the washing fraction (Table 4).

4. Discussion

The basic principles underlying the design of the extraction module for the separation of Tc-99m from bulky molybdenum described in this work are identical with those employed by other authors involved in the development of a similar device (Chattopadhyay et al., 2012). In particular, solvent extraction with MEK was proposed decades ago and largely employed for the separation of Tc-99m from low specific-activity Mo-99 in a special class of $^{99}\text{Mo}/^{99m}\text{Tc}$ generators (Dash et al., 2013; Osso et al., 2012; Moore, 1984). In the present design, however, there are a few original solutions that could add some crucial advantages over previous prototypes.

A first improvement was brought about by the possibility to fully integrate into the module the dissolution process of the irradiated Mo-100 enriched metallic target. Assuming an optimized setup, where the radioactive solid target will be always transported into the module through a pneumatic solid transfer system, this option can dramatically decrease operator's exposure to potentially huge amounts of radioactivity. In this work, the key parameters of the dissolution process (solvent's volume, temperature and time) were carefully adjusted considering the mass of the enriched Mo-100 target). However, in principle, a wide range of different target's weights and configurations could be easily accommodated.

Presumably, the most original solution was introduced in handling the solvent extraction step, which constitutes the core of the purification process. As described above, ^{99m}Tc -pertechnetate was extracted by mixing MEK with the aqueous alkaline solution resulting from the preceding dissolution step. To enhance the efficiency of the extraction process, surface contacts between the aqueous and organic phases should be maximized. Thus, vigorous bubbling was introduced by passing a helium stream through the mixture. To accomplish all these procedures in a single compartment, a special glass column, 10 cm in length and 1 cm in diameter, was designed and handmade. This simple device allowed a continuous mixing of the two immiscible phases by flushing the He gas from the bottom of the column and let it bubbling until reaching the top. The dimensions of the glass column were carefully studied to contain the required volume of each phases and to ensure the most efficient gas diffusion through the liquids. Most importantly, this arrangement was nicely fitting into the modular apparatus and, thus, easily automated.

Quality controls were carried out routinely to ascertain whether the final $^{99m}\text{Tc}[\text{TcO}_4]^-$ solution met all pharmaceutical requirements described in monographs published by European Pharmacopoeia and other equivalent institutions (European Pharmacopoeia, 2016a, 2016b; Lebeda et al., 2012). Observed values of RNP, CP and RCP were constantly well below the maximum allowed limits dictated for generator-produced ^{99m}Tc -pertechnetate solutions and, thus suggesting that the purified, cyclotron-produced $^{99m}\text{Tc}[\text{TcO}_4]^-$ could be potentially suitable for human studies. The almost negligible amount of other technetium radioisotopes, such as Tc-93, Tc-94, Tc-95 and Tc-96 (Table 3), are unavoidable by-products of the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ nuclear reaction. Therefore, they will necessarily follow the same extraction route as Tc-99m since isotopes of the same element cannot be chemically separated. Conversely, the radionuclidic impurities corresponding to various molybdenum (^{9x}Mo) and niobium (^{9x}Nb) contaminant isotopes, along with other minor impurities, again co-produced during the proton irradiation of the Mo-100 enriched target, were quantitatively retained into the aqueous phase and, as a result, they were not detectable in the final $^{99m}\text{Tc}[\text{TcO}_4]^-$ solution (Table 4).

Gas chromatographic analysis revealed that contamination by residual organic solvent MEK into the final $^{99m}\text{Tc}[\text{TcO}_4]^-$ solution was well below the maximum limit set up by pharmaceutical standards (European Pharmacopoeia, 2016c).

As expected, the separation efficiency of the water/MEK solvent system was superior in comparison with other separation technologies due to the well-known high affinity of $^{99m}\text{Tc}[\text{TcO}_4]^-$ for this organic phase. In particular, using aqueous biphasic extraction chromatography (ABEC) or Dowex SPE chromatography, the recovery yield of $^{99m}\text{Tc}[\text{TcO}_4]^-$ were 69.8 ± 6.0 and 89.8 ± 4.7 , respectively (Morley et al., 2012), whereas with a Chemmatrix resin was 78 ± 8 (Schaffer et al., 2015). With the method described here the recovery yield was 93.0 ± 2.8 , thus significantly higher than other reported procedures and comparable with results obtained with a similar separation module based on the MEK solvent extraction technique (Chattopadhyay et al., 2012). Finally, it is worth noting that the automated module described here has been set up using commercially available, pre-assembled modular components. In principle, therefore, it could be easily replicated by other laboratories, at relatively reduced costs, and conveniently used for conducting assessment studies with generator-produced Tc-99m.

5. Conclusion

The cyclotron-production of ^{99m}Tc through the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ nuclear reaction could become a convenient route to current reactor-based technology for providing an alternative source of this important diagnostic radionuclide in the event of future unexpected shortages in the global production chain. In the perspective to stimulate a local routine production of sodium ^{99m}Tc -pertechnetate by in-house low-energy and low-current medical cyclotrons, it was reported here the development of an easy-to-make and cost-effective automated module for the extraction of Tc-99m from proton-irradiated Mo-100 enriched metallic targets. According to pharmaceutical standards, the quality of the resulting $[^{99m}\text{Tc}]\text{TcO}_4^-$ was fully adequate for clinical applications. However, it should be considered that, because of its particularly simple and adjustable structure, the automated module described here could be easily adapted to process targets with different conformations and increased Mo-100 enrichment, from 99.05% used in the present work up to 99.86%, which is already commercially available. This will presumably allow to obtain cyclotron-produced $[^{99m}\text{Tc}]\text{TcO}_4^-$ with a quality approaching that of current generator-produced Tc-99m.

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Table 1

Tc-99m recovery efficiency* of the automated separation procedure

Component	% of initial ^{99m} Tc-activity
Final solution	93.0 ± 2.8
Aqueous phase	5.3 ± 3.0
Waste	0.7 ± 0.9
Silica column	0.6 ± 0.8
Alumina column	0.4 ± 0.1

*Expressed as percent of the initial activity of generator-produced [^{99m}Tc]TcO₄⁻ loaded into the reactor module.

Table 2Estimated quality parameters for ^{99m}Tc-pertechnetate solutions

Parameter	Found	Reference values*	
RNP	^{9x} Nb [¶]	< MDA [§]	
	^{9x} Mo [¶]	< MDA [§]	
	^{9x} Tc [¶]	< 1%	
CP	pH	4.5–5	4–8
	Mo	< 5 ppm	
	Al	< 5ppm	< 5ppm
	MEK	< 0.0004% (v/v)	< 0.5% (v/v)
RCP	^{99m} TcO ₄ ⁻	> 99%	≥ 95%

* European Pharmacopoeia, 2016a, 2016b, 2016c.

[¶] Expressed as percent of the total activity.

[§] MDA = minimum detectable activity.

Table 3

Technetium radioisotopes contaminants

Radionuclide	T _{1/2}	Activity (Bq)	%Activity*	Uncertainty (Bq)
Tc-93g	2.8 h	2.76×10^5	0.012%	2.82×10^4
Tc-94g	4.9 h	2.08×10^6	0.094%	4.87×10^4
Tc-95g	20 h	2.43×10^6	0.110%	7.39×10^4
Tc-95m	61 d	1.32×10^4	0.001%	9.74×10^2
Tc-96g	4.3 d	6.63×10^5	0.031%	1.22×10^4
Tc-99m	6.01 h	2.20×10^9	99.758%	4.66×10^7

* Expressed as percent of the activity at the end of the separation process (decay corrected).

Table 4

Isotope recovery in the various modular compartments*

	^{99m} Tc	⁹⁹ Mo	^{99m} Nb
Final solution	93.22 ± 0.05	ND	ND
Aqueous phase	5.75 ± 0.02	97.96 ± 0.04	98.31 ± 0.03
Waste	0.03 ± 0.01	ND	ND
Washing fraction	0.55 ± 0.01	2.04 ± 0.04	1.69 ± 0.05
Silica column	0.22 ± 0.01	ND	ND
Alumina column	0.23 ± 0.01	ND	ND

* Expressed as percent of the initial activity (decay corrected).

ND = not detectable.

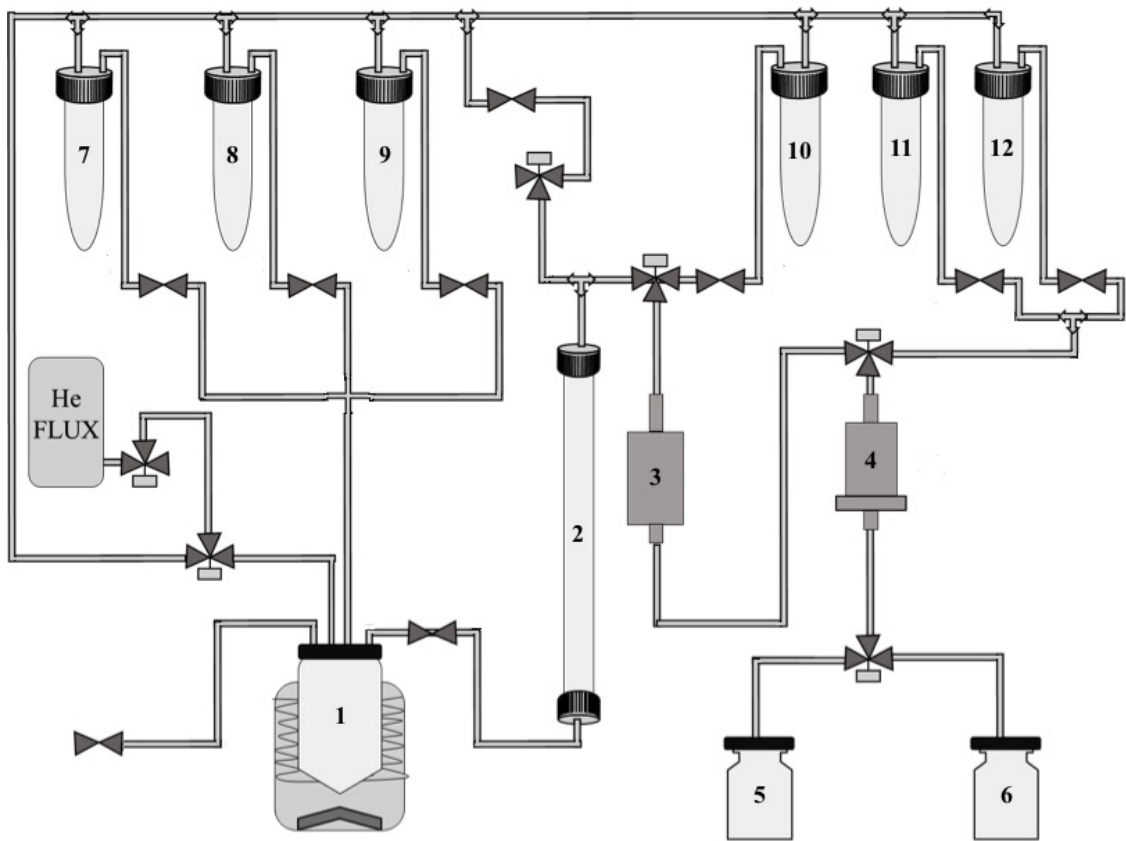


Fig. 1

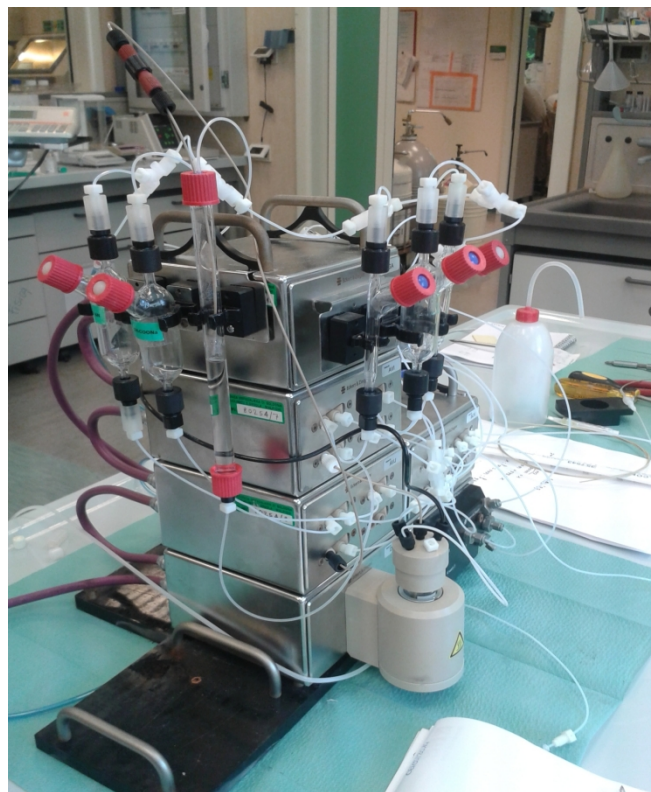
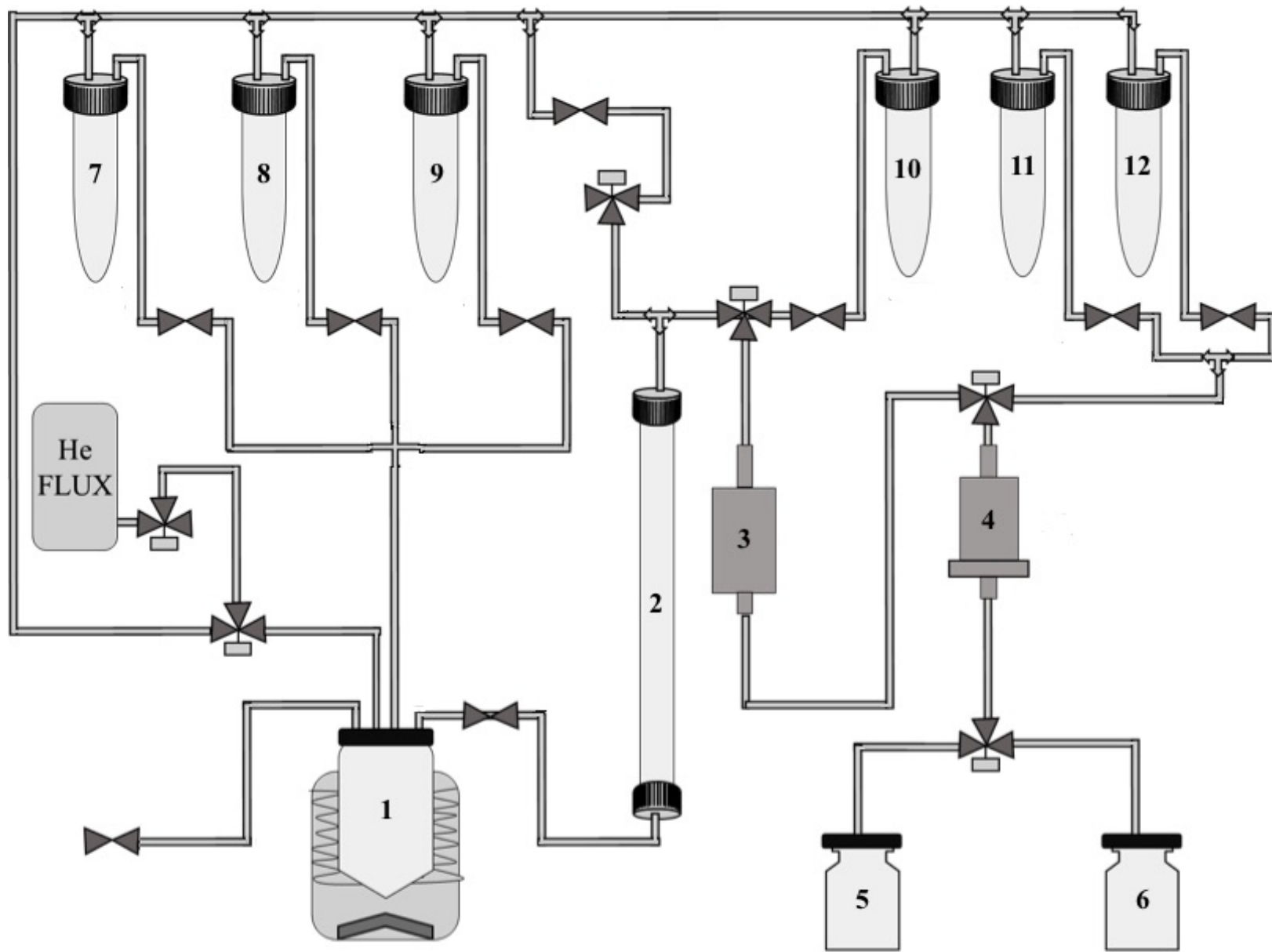


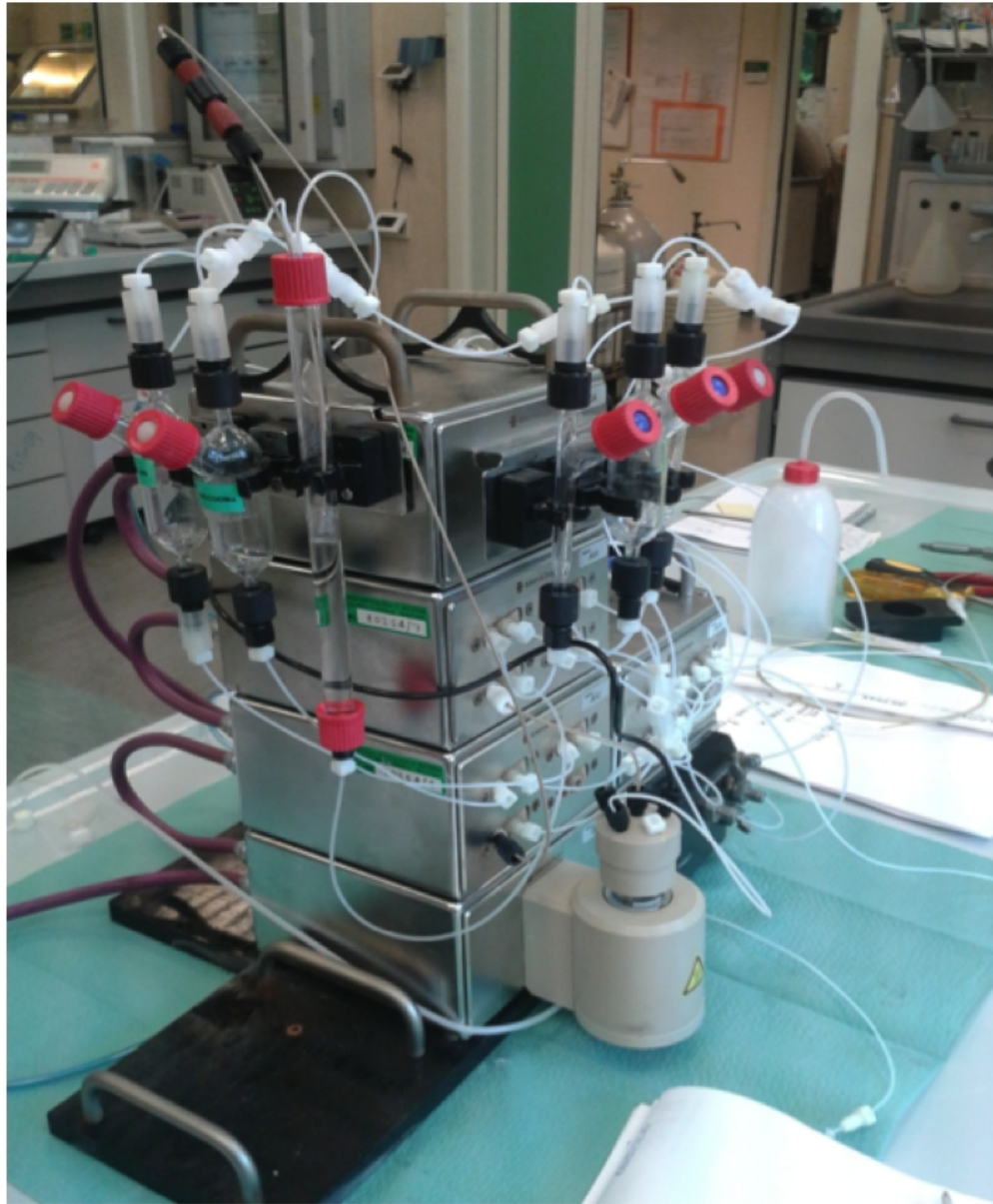
Fig. 2

CAPTIONS TO FIGURES

Fig. 1. A schematic drawing of the extraction process. **1** dissolution reactor, **2** solvent-extraction column, **3** silica column, **4** alumina column, **5** waste, **6** final Tc-99m solution, **7** H₂O₂, **8** NaOH, **9/10** MEK, **11** H₂O, **12** saline.

Fig. 2. View of the automated solvent-extraction module..





HIGHLIGHTS

- Cyclotron production of Tc-99m carried out through the $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$ nuclear reaction.
- Solvent extraction of Tc-99m was accomplished by assembling an easy-to-make, cost-effective automated separation module.
- Purification of the final $^{99\text{m}}\text{Tc}$ -pertechnetate was achieved in *ca.* 70 min with recovery yields > 90%.
- Quality parameters of final Tc-99m solution were well within the limits established by international pharmaceutical standards.