TECHNETIUM-99m IN PRODUCTION AND USE

by

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Several types of generators have been developed for the production of ^{99m}Tc. Due to its excelent performances, the chromatographic type, based on the fission-produced ^{99}Mo sorbed in alumina, is predominant. Technetium-99m is obtained in the form of sodium pertechnetate-^{99m}Tc. However, due to the known disadvantages of the production of (n, f)^{99}Mo, attempts are made to avoid uranium fission. The technologies based on (n, γ)^{99}Mo (sublimation, extraction, gel) are, with the exception of the gel generator, of limited importance. Certain nuclear reactions in cyclotrons can produce ^{99}Mo (or directly ^{99m}Tc) but the obtained results are still not satisfying. Technetium-99m is used in the form of radiopharmaceuticals which are prepared by addition of ^{99m}Tc-eluate to the inactive components comprised in the "cold" kits. The chromatographic (n, f)^{99}Mo/^{99m}Tc generator and several ^{99m}Tc-radiopharmaceuticals have been developed and are regularly produced in the Vinča Institute of Nuclear Sciences (Laboratory for Radioisotopes).

Key words: technetium-99m, molybdenum-99, technetium-99m-generator, technetium-99m-radiopharmaceuticals

INTRODUCTION

Nuclear medicine is a medical modality which uses nuclear properties of radionuclides to diagnose diseases.The best suited ones are γ-emitters. It is essential that a given radionuclide is concentrated in the adequate area in the organism. Usually, this is achieved by attaching it to a chemical which is selectively sorbed by specific organs or tissues. After a certain time after its introduction into the body, it is accumulated in the desired spot. The emitted radiation penetrates the tissues and is finally detected by an external counting device. The obtained scintigram provides the information needed for diagnostics (the size, shape, function of the given organ). The chemical with the attached radionuclide is usually denoted as a radiopharmaceutical.

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Beside on physical properties (the type and energy of radiation emitted, half life), the routine application of a given radionuclide depends also on its availability in sufficient activities, quality and price. The development of adequate chemistry is needed for the production of radiopharmaceuticals. An elaborated production procedure on the regular basis should be established, including the necessary facilities. The shorter-lived radionuclides should be available either from generators or from an efficient central distribution supply [1-3].

For years, the most often used radionuclide in diagnostics has been ^{99m}Tc. Excellent physical and chemical properties made it applicable in a large variety of indications. Technetium-99m fulfils all other criteria required for a broad use: reliable production at the appropriate price, easy and regular availability, and known chemistry. The chromatographic ^{99}Mo/^{99m}Tc generators based on the parent ^{99}Mo obtained from uranium fission have become the common and very reliable source of large activities of ^{99m}Tc of high quality meeting all criteria prescribed by Pharmacopoeia. Uranium fission ensures large activities of ^{99}Mo needed for the regular generator production.

The paper presents a short review covering some important aspects of the production of ^{99m}Tc and its parent radionuclide ^{99}Mo. The radiopharmaceuticals labeled with ^{99m}Tc are widely investigated. The main

preparations, indications for their use and the recommended ^{99m}Tc-activities are given.

PRODUCTION OF MOLYBDENUM-99

Molybdenum-99 is routinely produced in nuclear reactors. Two nuclear reactions are employed. The first one is the direct neutron activation of the stable ^{98}Mo which gives the so-called (n, γ)^{99}Mo. The second route is uranium fission induced by neutrons. By separation from other fission products, molybdenum-99, usually denoted as (n, f)^{99}Mo, is obtained [4].

The advantage of the production of (n, γ)^{99}Mo is that it is relatively simple and cheap. Large quantities of the target material (molybdenum trioxide, with ^{98}Mo in natural abundance or enriched in ^{98}Mo), can be easily irradiated with the minimal need for the post-irradiation processing. Only small quantities of low-activity radioactive waste are produced. By the proper choice of the target, the content of the radionuclidic impurities can be reduced to minimum. The main disadvantage is the low specific activity of ^{99}Mo (less than 400 GBq/g Mo). Also, high flux nuclear reactors are not always at the disposal.

The neutron-induced fission of ^{235}U is currently the main source of commercial (n, f)^{99}Mo. The target contains ^{235}U in natural abundance (0.7%) or enriched ^{235}U up to almost 100%. The fission yield is about 6%. The advantages of this technology are high activities and very high specific activities of the produced ^{99}Mo [5]. However, there are some principal disadvantages that have to be carefully considered. They are: economical (high capital and running costs), complex separation of ^{99}Mo including the recovery of the non-reacted uranium, ecological (the generation of large quantities of high-activity waste), and political (target material has the potential for the clandestine use in nuclear weapons).

Currently, over 95% of ^{99}Mo is produced by using highly enriched uranium (HEU) targets. This production is carried out in a limited number of industrial companies and national centers. They, collectively, are able to cover the world's demand for ^{99}Mo, but any disturbance in the production could have high negative impact on the routine supply of medical centers with ^{99m}Tc.

Several attempts have been made to avoid fission. Attractive and competitive alternative to reactors may be cyclotrons. Several nuclear reactions considered for an eventual production of ^{99}Mo (or directly ^{99m}Tc) are listed in tab. 1.

The production of ^{99}Mo by the nuclear reaction ^{100}Mo(γ, n)^{99}Mo followed by the separation of ^{99m}Tc by sublimation is promising [6]. The reaction ^{100}Mo(p, 2n)^{99m}Tc proceeds with an acceptable yield under condition that highly enriched target material is used [7]. However, both nuclear reactions produce activities which are too low to cover the needs. Therefore, it could be concluded that the existing options still can not compete with the uranium fission.

Table 1. Candidate nuclear reactions for production of ^{99}Mo and ^{99m}Tc by accelerators [6, 7]

Projectiles	Nuclear reaction
Protons (neutrons produced by spallation)	^{98}Mo(n, γ)^{99}Mo
Protons (neutrons produced by spallation)	^{100}Mo(n, 2n)^{99}Mo
Protons (neutrons produced by spallation)	^{235}U(n, f)^{99}Mo
Protons	^{100}Mo(p, pn)^{99,99m}Nb(β^-)^{99}Mo
Protons	^{100}Mo(p, pn)^{99}Mo
Electrons (γ-rays produced by bremsstrahlung)	^{100}Mo(γ, n)^{99}Mo
Deuterons	^{98}Mo(d, p)^{99}Mo
Protons	^{98}Mo(d, γ)^{99m}Tc
Protons	^{100}Mo(p, 2n)^{99mo}Tc

TECHNETIUM-99m AND TECHNETIUM-99m RADIOPHARMACEUTICALS

Technetium-99m is the main radionuclide for *in vivo* diagnostics in nuclear medicine. Its drawback, however, is a relatively short half-life of six hours, so that distant users can not be supplied without heavy losses in activity. This logistic problem is solved with the development of ^{99}Mo/^{99m}Tc generators. The principle of the generator is based on the radioactive parent ^{99}Mo ($T_{1/2}$ = 66 hours), which decays to the daughter radionuclide ^{99m}Tc ($T_{1/2}$ = 6 hours). So, instead of the short-lived ^{99m}Tc, the longer-lived ^{99}Mo, bound to an appropriate matrix, is shipped and ^{99m}Tc is separated by the end user. Molybdenum-99 then, by decay, generates a new supply of the daughter so that the separation can be repeated. The generators are usually calibrated a few days in advance so that they can be transported to places very distant from the production site. Normally, a generator is used for 14 days after calibration. After that, its activity is already too low and it is shipped back to the producer where it is disposed of.

Table 2 reveals the main generator types in dependence on the technology of the separation of ^{99m}Tc from ^{99}Mo.

The best one is the chromatographic (n, f)^{99}Mo/^{99m}Tc generator. Fission-produced ^{99}Mo can be, due to its very high specific activity, sorbed in a small volume of sorbent (most often alumina). Therefore, the column usually contains up to 1 g of alumina only. For the elution, the small volumes of eluence are needed, which results in a high specific activity product. The generator is simple, portable and easy to use.

Table 2. Methods of separation of ^{99m}Tc from ^{99}Mo, characteristics of the generators operation and their perspectives

Separation of ^{99}Mo and ^{99m}Tc	^{99}Mo	Separation efficiency of ^{99m}Tc [%]	Ease of generator operation	Prospect
Chromatography	(n, f)	80-95	Simple, portable	Yes
Chromatography	(n, γ)	80-95	Simple, portable	No
Extraction	(n, γ)	50-75	Complex, fixed	No
Sublimation				
– High temperature	(n, γ)	30	Complex, fixed	No
– Low temperature	(n, γ)	50	Complex, portable	Yes
Gel	(n, γ)	80-95	Simple, portable	Yes

The reason why (n, γ)^{99}Mo can not be used for the production of the chromatographic generators is its low specific activity. The sorption capacity of alumina for molybdate anions is only about 0.2 wt.%. So, for the sorption of higher activities of (n, γ)^{99}Mo large columns are needed (about 20 g of alumina). High elution volumes result in low specific activity ^{99m}Tc. Even by using targets highly enriched in ^{98}Mo, the obtained ^{99}Mo would enable the production of the chromatographic generators of the activities of up to about 2 GBq of ^{99m}Tc. For the modern nuclear medicine this is insufficient. For comparison, most often used are the generators of the activities between 12-20 GBq. For some specific applications, activities of up to 37 GBq are needed. This can be achieved only by using (n, f)^{99}Mo.

For the separation of ^{99m}Tc from (n, γ)^{99}Mo other methods, rather than the chromatography, have been used (tab. 2). The differences in the volatilities of oxides of ^{99m}Tc and ^{99}Mo are exploited in the sublimation generators. Technetium-99m can also be isolated by solvent extraction, mainly by using methyl ethyl ketone (extraction generators). The gel generator combines the excellent performances of the chromatographic generator and the use of (n, γ)^{99}Mo. Instead with alumina, the generator column is filled with the irradiated powder of zirconium or titanium molybdate. Thus, the content of molybdenum in the column is raised up to 40 wt.%, thus providing higher activities of ^{99m}Tc. Further data on the performances of these generators can be found in literature [8].

The common comment to these, sometimes named the alternative generator technologies, can be summarized as follows. Extraction and sublimation generators are complex devices in which the quality of ^{99m}Tc depends also on the skill of the operator. Probably the best perspective is offered by the gel generator. However, all three types, without some essential innovation, can not compete with the chromatographic generator based on (n, f)^{99}Mo. It should be mentioned that these types of generators have been developed and used mainly in the countries which, due to the economical or geographical reasons, do not have access to (n, f)^{99}Mo.

The chromatographic (n, f)^{99}Mo/^{99m}Tc generators have been developed in several countries. A feature common to them all is a glass or plastic column filled with alumina onto which (n, f)^{99}Mo is sorbed. Technetium-99m is eluted by sucking the eluence saline (0.9% NaCl) through the column by vacuum. The predominant type is the "dry" type in which the column is dry between two successive elutions. In the "wet" type the column remains filed with saline. The column is incorporated in a closed elution system, thus minimizing the risk of microbial contamination and situated in a protective lead shielding. The whole assembly is in a plastic container.

Many countries run the generator production by using their own technology and the imported (n, f)^{99}Mo, thus avoiding the expensive plants for the irradiation and separation of (n, f)^{99}Mo. This solution has also been applied in Serbia. Nowadays, only a few suppliers of fission ^{99}Mo in the world exist.

The development of the chromatographic (n, f)^{99}Mo/^{99m}Tc generator in the Vinča Institute of Nuclear Sciences, Laboratory for Radioisotopes, started more than thirty years ago. It was first reported in 1982 [9] and the first paper appeared in 1983 [10]. The plastic column contains two layers: pure alumina covered by alumina modified by the addition of divalent copper in which (n, f)^{99}Mo is sorbed. The elution is carried out by passing home-made saline (0.9% NaCl) through the column by vacuum. After elution, the column is additionally dried (the "dry" type of the generator). The fast and simple elution procedure, carried out at room temperature, is completed in less than a minute. After the connection of the vacuum vial, the presence of the operator is not even necessary. The generator column is placed in the protective lead container (d = 41 mm Pb). The technology has been developed in the Laboratory for Radioisotopes and the only imported component is (n, f)^{99}Mo. The routine large scale production started in 1982 [11].

The development and the regular generator production in the Laboratory have been accompanied by the investigations of several aspects of the generator system. The summary of the results is reviewed in ref.

[12]. One of the most important is the maintenance of the high and stable ^{99m}Tc elution yield. The cause of low yield, *i. e*., the retention of ^{99m}Tc on the column, was found to be the reduction of heptavalent technetium by hydrated electrons formed by radiolysis of water. The remedy applied was the introduction of divalent copper as the radical scavenger into the column [12, 13]. An important feature is the radionuclidic purity of ^{99m}Tc eluates as well. Several radioisotopes (^{103}Ru, ^{106}Ru, ^{125}Sb, ^{131}I), originating from (n, f)^{99}Mo, were detected [14]. However, the prescribed criterion of the radionuclidic purity is fulfilled in all cases. With regards to the safe storage of the spent generators, the main long-lived contaminants in the columns were determined [15].

Technetium-99m in the generator eluate is in the form of ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$). The eluate is the sterile, pyrogen-free and isotonic radiopharmaceucal which can be used, for example, for brain imaging. However, ^{99m}Tc is mainly used for labeling compounds for which it has been established that they perform the affinity toward certain organs or tissues. These radiopharmaceuticals are most often formulated in the form of so called "cold" (technetium-99m-free) kits. The inactive components of a preparation are in lyophilized form contained in a glass vial usually in vacuum or in an inert atmosphere. To such a pre-sterile and validated commercial kit, the user should only add a certain volume of ^{99m}Tc eluate containing the needed ^{99m}Tc activity. This simple "shake, mix or even heat" radiopharmaceutical preparation is performed in the "hot" laboratories in the nuclear medical centers.The "cold" kits, designed to have a long-term shelf-life, can be transported at the room temperature and then stored by the user in a refrigerator to ensure their stability.

Research in the field of radiochemistry has been carried out in the Laboratory for Radioisotopes for several decades [16]. The obtained results together with the investigations in chemistry, physical chemistry, biochemistry, and radiopharmacy have formed the basis for the production of radionuclides (^{32}P, ^{35}S, ^{51}Cr, ^{131}I, ^{198}Au, *etc.*) and radiopharmaceuticals for medical use [17]. In the early seventies of the past century, ^{99m}Tc and its complex compounds prevailed in medicine. A large number of ^{99m}Tc-radiopharmaceuticals were investigated and developed in the Laboratory for the use in diagnostic in nuclear medicine. The complex research in physical, analytical and coordination chemistry of technetium resulted also in a number of papers. The review of the results on ^{99m}Tc in the first two decades is given in the literature [18, 19]. The investigations covered several topics. For example, it is important to establish the factors which influence the conditions of the complex formation, affect radiochemical purity of the product, *etc.* [20-25]. The stability of the "cold" preparation, the effect of some chemical additives, like ascorbic or gentisic acid [26, 27], *etc.,* is also of interest. The comprehensive survey of technetium complexes, their structure, modes of preparation, *etc.*, can be found in ref. [28].

Table 3 presents a list of ^{99m}Tc radiopharmaceuticals, indications for their use and the recommended ^{99m}Tc activities [3, 12, 29].

Together with the development of production of radionuclides and radiopharmaceuticals, the comprehensive methodology of physical, chemical, and pharmaceutical control procedures should also be established. Beside the standard controls of radioactive substances, several specific regulations for the radiopharmaceuticals are introduced as these preparations are used in medicine *in vivo* and are considered as drugs. They are subjected to the law regulations and to the requirements of Pharmacopoeia. The quality control tests include the determination of: radiochemical purity checked by different chromatographic methods, radionuclidic purity checked by γ-spectrometry, biologic selectivity checked by the assessment of biodistribution in experimental animals as well as sterility and apyrogenicity checked by microbiologic methods. Chemical purity tests and the determination of pH and isotonicity with human blood are also prescribed.

The Laboratory for Radioisotopes organizes the routine quality control, both for ^{99m}Tc eluates and ^{99m}Tc-radiopharmaceuticals. All the tests are performed according to Pharmacopoeia [30].

The Laboratory is accredited for the investigations of radiopharmaceuticals for *in vivo* and *in vitro* applications and particularly for ^{99}Mo/^{99m}Tc generators and ^{99m}Tc eluates.

CONCLUSIONS

Technetium-99m has very suitable physical properties for *in vivo* diagnostics in nuclear medicine. Almost pure γ-radiation, with the energy of 140 keV is convenient for the commonly used detection equipment. The problem of the transportation due to its short half-life is solved with the development of ^{99}Mo/^{99m}Tc generators. In combination with its versatile chemistry, ^{99m}Tc became far the most important radionuclide in the diagnostics in nuclear medicine.

The chromatographic (n, f)^{99}Mo/^{99m}Tc generators are nowadays the main source of ^{99m}Tc. By elution, these generators provide large activities of high quality ^{99m}Tc. Due to the inherent disadvantages of the production of (n, f)^{99}Mo, attempts are made to avoid uranium fission either by using (n, γ)^{99}Mo or by transferring the production of ^{99}Mo (or directly ^{99m}Tc) from reactors to cyclotrons. Extraction, sublimation, and gel generators based on (n, γ)^{99}Mo are, despite some advantages, at the present stage of development, not capable of replacing (n, f)^{99}Mo chromatography. Nuclear reactions in cyclotrons seem promising but, due

Table 3. Indications for the application of some technetium-99m radiopharmaceuticals, their chemical forms and recommended maximum activity per test [3, 12, 29]

Indication	Chemical form of the radiopharmaceutical	Maximum activity per test [MBq]
Brain imaging (static)	Pertechnetate (TcO_4^-)	500
Brain imaging (SPECT)	TcO_4^-, DTPA, gluconate, glucoheptonate HM-PAO	500
Cerebral brain flow	HM-PAO	800
Thyroid imaging	TcO_4^-	200
Radionuclide ventriculography	Labeled red blood cells	1110
Myocardial imaging (SPECT)	Isonitriles	300
First pass blood flow studies	DTPA, TcO_4^-	800
Blood pool imaging	Human albumin complex	40
Lung ventilation imaging	DTPA-aerosol	80
Lung perfusion imaging (with venography)	Human albumine (macroaggregates or microspheres)	160
Lung imaging (SPECT)	Macroaggregated albumin (MAA)	200
Liver and spleen imaging	Labeled colloid	80
Functional biliary system imaging	Iminodiacetates and equivalent agents	150
Spleen imaging	Labeled denaturated red blood cells	100
Liver imaging (SPECT)	Labeled colloid	200
Renal imaging (static)	DMSA	160
Renal imaging/renography	DTPA, gluconate, glucoheptonate, PAH, MAG_3	350
Bone imaging (planar)	Phosphate (PyP) and phosphonate compounds (MDP, DPD, *etc.*)	600
Bone imaging (SPECT)	Phosphate (PyP) and phosphonate compounds (MDP, DPD, *etc.*)	800
Detection of inflammatory bowel diseases	Sucralphate	200
Salivary gland imaging	TcO_4^-	40
Gastrointestinal bleeding	Labeled colloid	400
Oesophagal transit and reflux	Labeled colloid	40
Localization of bacterial infection	Ciprofloxacin	555
Tumor imaging	DMSA(V)	400

SPECT – single photon emission computerized tomography; DTPA – diethylenetriamine pentaacetic acid, HM-PAO – hexamethyl propyleneamine oxime, MAA – macroaggregated albumin, DMSA – dimercaptosuccinic acid, PAH – p-aminohippurate, MAG_3 – mercaptoacetyl triglycine, PyP – pyrophosphate; MDP – methylene diphosphonate; DPD – dicarboxypropane diphosphonate

to the insufficient yields, still can not compete with uranium fission.

The chromatographic $^{99}Mo/^{99m}Tc$ generators, based on the domestic technology and the imported (n, f)^{99}Mo, are routinely produced in the Vinča Institute of Nuclear Sciences, Laboratory for Radioisotopes as well.

Technetium-99m finds its use in the form of ^{99m}Tc-radiopharmaceuticals. Beside ^{99m}Tc-pertechnetate obtained in the generator eluate, a considerable number of these preparations, developed in the "cold" kit form, are routinely produced in the Laboratory.

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Јурај ВУЧИНА, Надежда НИКОЛИЋ, Ђокица ПЕТРОВИЋ

ПРОИЗВОДЊА И ПРИМЕНА ТЕХНЕЦИЈУМА-99м

За добијање ^{99m}Tc развијено је више типова генератора, а доминантан је хроматографски у коме је ^{99}Mo, добијен фисијом ^{235}U, сорбован на Al_2O_3. Технецијум-99m се добија у облику натријумпертехнетата-^{99m}Tc. Међутим, због познатих недостатака које прате добијање (n, f)^{99}Mo, чине се покушаји да се избегне фисија уранијума. Технологије засноване на (n,)^{99}Mo (сублимација, екстракција, гел), са изузетком гел генератора, од ограниченог су значаја. Молибден-99 или директно ^{99m}Tc могу се добити коришћењем неких нуклеарних реакција у циклотрону али, за сада, добијени резултати не задовољавају. Технецијум-99m користи се у облику ^{99m}Tc-радиофармацеутика који се добијају додавањем ^{99m}Tc-елуата у неактивни ("хладни") прибор. Хроматографски (n, f) ^{99}Mo/^{99m}Tc генератор и више ^{99m}Tc-радиофармацеутика развијено је и редовно се производе у Лабораторији за радиоизотопе Института за нуклеарне науке "Винча".

Кључне речи: технецијум-99т, молибден-99, технецијум-99т генератор, технецијум-99т радиофармацеутици