

Research Article

Influence of the Generator in-Growth Time on the Final Radiochemical Purity and Stability of ^{99m}Tc Radiopharmaceuticals

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At Legnaro laboratories of the Italian National Institute for Nuclear Physics (INFN), a feasibility study has started since 2011 related to accelerated-based direct production of ^{99m}Tc by the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ reaction. Both theoretical investigations and some recent preliminary irradiation tests on ^{100}Mo -enriched samples have pointed out that both the $^{99g}\text{Tc}/^{99m}\text{Tc}$ ratio and the ^{99m}Tc specific activity will be basically different in the final accelerator-produced Tc with respect to generator-produced one, which might affect the radiopharmaceutical procedures. The aim of this work was to evaluate the possible impact of different $^{99g}\text{Tc}/^{99m}\text{Tc}$ isomeric ratios on the preparation of different Tc-labeled pharmaceutical kits. A set of measurements with ^{99m}Tc , eluted from a standard $^{99}\text{Mo}/^{99m}\text{Tc}$ generator, was performed, and results on both radiochemical purity and stability studies (following the standard quality control procedures) are reported for a set of widely used pharmaceuticals (i.e., ^{99m}Tc -Sestamibi, ^{99m}Tc -ECD, ^{99m}Tc -MAG3, ^{99m}Tc -DTPA, ^{99m}Tc -MDP, ^{99m}Tc -HMDP, ^{99m}Tc -nanocolloids, and ^{99m}Tc -DMSA). These pharmaceuticals have been all reconstituted with either the first $[^{99m}\text{TcO}_4]^-$ eluate obtained from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (coming from two different companies) or eluates after 24, 36, 48, and 72 hours from last elution. Results show that the radiochemical purity and stability of these radiopharmaceuticals were not affected up to the value of 11.84 for the $^{99g}\text{Tc}/^{99m}\text{Tc}$ ratio.

1. Introduction

^{99m}Tc , with its peculiar physical-chemical properties, still continues to be the most important radionuclide used in diagnostic nuclear medical procedures. In particular, the developments of technetium chemistry have opened new perspectives in the field of diagnostic imaging [1]. More than 80% of the radiopharmaceuticals are currently labeled with this radionuclide [1] by reconstitution with sodium pertechnetate [2–4] [$\text{Na}^{99m}\text{TcO}_4$] commercial kits containing in lyophilized form the various reagents required for the preparation of each radiopharmaceutical. Its routine applications are ensured by the availability of portable $^{99}\text{Mo}/^{99m}\text{Tc}$ generators in which ^{99}Mo is bound as molybdate anion

to alumina columns. Current global interruptions of ^{99}Mo supply that involved uranium fission of highly enriched ^{235}U targets, aging reactors, and the staggering costs of their maintenance, focused on the search for alternative method of the ^{99m}Tc production [5]. One of the possibilities is to replace the reactors with particle accelerators, aiming at a regional production and distribution. At Legnaro laboratories of the Italian National Institute for Nuclear Physics (INFN), a feasibility study related to accelerated-based direct production of ^{99m}Tc by the $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$ reaction [6, 7] has started since 2011. Theoretical investigations and some recent preliminary irradiation tests on ^{100}Mo -enriched samples point out that both the $^{99g}\text{Tc}/^{99m}\text{Tc}$ ratio and ^{99m}Tc specific

TABLE 1: Radiopharmaceuticals used in the study.

Name	Radiopharmaceutical
Neurolite (Brystol-Myer Squibb)	^{99m}Tc -ECD (^{99m}Tc -Bicisato)
Cardiolite (Brystol-Myer Squibb)	^{99m}Tc -SESTAMIBI
Stamisis (IBA)	^{99m}Tc -SESTAMIBI
Technemibi (Mallinckrodt)	^{99m}Tc -SESTAMIBI
Technescan (Mallinckrodt)	^{99m}Tc -MAG3
Pentaxis (IBA)	^{99m}Tc -DTPA
Medronato II (GE Healthcare)	^{99m}Tc -MDP
Osteocis (IBA)	^{99m}Tc -HMDP
Nanocoll (GE Healthcare)	^{99m}Tc -nanocolloids
Renocis (IBA)	^{99m}Tc -DMSA

activity will be basically different in the final accelerator-produced Tc with respect to generator-produced one, due to the concomitant production of Tc contaminant nuclides, such as ^{99g}Tc , ^{98}Tc , ^{97m}Tc , and ^{97g}Tc . In particular, the amount of the ground-state long-lived β^- emitter ^{99g}Tc , useless for diagnostic procedures, might have a negative effect in the radiopharmaceutical procedures going to compete with ^{99m}Tc for the formation of the corresponding chemically identical radiopharmaceuticals. The presence of an excess of ^{99g}Tc might be responsible for a value of radiochemical purity lower than the standard required for some radiopharmaceutical preparations. In fact, the ^{99g}Tc present in solution could consume reagents of reaction, and in particular the reducing agent (SnCl_2). As a result, unreacted $[\text{}^{99m}\text{TcO}_4]^-$ may remain in the solution, or radioactive by-products not useful for the specific diagnostic procedure may be formed. The quality of ^{99m}Tc is then fundamental for the assurance of radiopharmaceuticals quality [8–10]. The aim of this work was therefore to perform a set of measurements with ^{99m}Tc , eluted from a standard $^{99}\text{Mo}/^{99m}\text{Tc}$ generator, in order to first check possible impact of different $^{99g}\text{Tc}/^{99m}\text{Tc}$ isomeric ratios on the preparation of different Tc-labeled pharmaceutical kits. Results on both radiochemical purity and stability studies (following the standard quality control procedures) are reported for a set of widely used pharmaceuticals (i.e., ^{99m}Tc -Sestamibi, ^{99m}Tc -ECD, ^{99m}Tc -MAG3, ^{99m}Tc -DTPA, ^{99m}Tc -MDP, ^{99m}Tc -HMDP, ^{99m}Tc -nanocolloids, and ^{99m}Tc -DMSA). These pharmaceuticals have been all reconstituted with either the first $[\text{}^{99m}\text{TcO}_4]^-$ eluate obtained from the $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (coming from two different companies) or eluates after 24, 36, 48, and 72 hours from last elution.

2. Materials and Methods

The preparation of radiopharmaceuticals reported in Table 1 was carried out with sodium pertechnetate eluates coming from two different $^{99}\text{Mo}/^{99m}\text{Tc}$ generators: a “dry” DRYTEC generator (GE Healthcare, Via Galeno 36 20126, Milan), and a “wet” Elumatic III generator (IBA-CIS Bio International, Route Nationale 306, Saclay BP 32, 91192 GIF SUR YVETTE, Cedex France).

All generators, with ^{99}Mo calibrated activity of 10 GBq, were eluted with 5 mL of saline solution as indicated by each manufacturer. From each generator, we analyzed and compared the three first elutions, performed just after generator delivery (time elapsed between manufacturing and first use can be estimate in 2–3 days), and 3 elutions were carried out after 36, 48, and 72 hours from the previous elution.

2.1. Quality Control of $^{99}\text{Mo}/^{99m}\text{Tc}$ Generator Eluates. Generator eluates have been subjected to all the tests [11] required by European Pharmacopoeia [14], and Italian Pharmacopoeia, 12th edn., Norme di Buona Preparazione dei Radiofarmaci per Medicina Nucleare, All. A, p.to A.2 “Generatore di $^{99}\text{Mo}/^{99m}\text{Tc}$ (molibdeno/tecnezio)”.

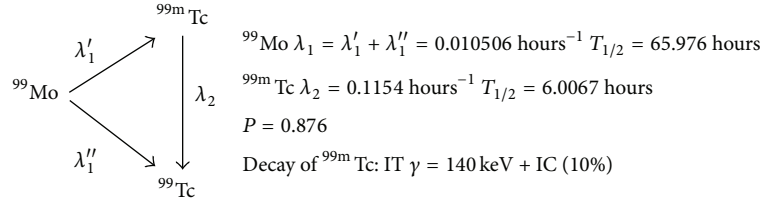
2.1.1. Generator Elution Yield. It was expressed as % of the ratio between the eluate radioactivity measured immediately after elution using a dose calibrator (V_M) and the theoretical radioactivity (V_C) calculated on the basis of the date of calibration and multiplied by the factor 100 [3]. The elution efficiency should be within the range of 90%–110%.

2.1.2. Eluate Visual Inspection. All eluates were visually inspected, pulling the vial from its shielded container. The operation was performed within an adequately shielded cell for radiopharmaceuticals manipulation; the vial containing the pertechnetate eluate was manipulated by operators using a pair of pliers to guarantee an adequate distance from the hands of the operator.

2.1.3. Eluate pH. Generator eluate is itself a preparation for injection; ideally it should have a pH as close as possible to the physiological, between 7 and 8. The Pharmacopoeia requires that eluates have pH values within the range of 4–8. Since the molybdenum is adsorbed onto the alumina in an acid environment, the pH values of eluates are slightly acid (4.5–6). It was measured by means of pH usual indicator strip (range 0–14) and checked by electronic pH-meter.

2.1.4. Aluminum Content. It was determined by a semiquantitative procedure employing indicator strips (Tec-Control Biodex Medical, New York, USA) together with standard aluminium solution [12, 13]. A drop of standard solution with a concentration less than $5\text{ }\mu\text{g mL}^{-1}$ of aurointricarboxylic acid was deposited on indicator paper; subsequently, by side a drop of eluate was deposited. If the coloration produced by the latter is lower than the one produced by the standard solution, it can be assumed that the concentration of aluminium in the eluate is less than the maximum acceptable level of $5\text{ }\mu\text{g mL}^{-1}$ provided by Official Pharmacopoeia [14].

2.1.5. Radionuclidic Purity. Radionuclidic purity is the percentage of total radioactivity which may be attributed to the daughter radionuclide. In the case of fission-produced generator, the largest potential source of contamination that could exceed the minimum value detectable can be due to the parent (^{99}Mo) [15]. Trace amount of other fission impurities [16, 17] may be usually present in negligible amounts.

FIGURE 1: Simplified decay scheme of ^{99}Mo to ^{99g}Tc .

The early and quick evaluation of the eluate content of ^{99}Mo was provided by the following procedure, which involved the use of a lead shield of appropriate thickness (0.6 mm of lead) in order to attenuate ^{99m}Tc emission [18]. The activity contained in the unshielded elution vial was measured with a dose calibrator (PET-dose, Comtec, Castalbolognese, Italy); for measuring ^{99}Mo activity, the elution vial was then placed within the lead shield and its activity was recorded. The thickness of the shield was enough to largely attenuate the 140 keV photons [19], and only partly those greater than 700 keV. The measured activity, multiplied by a suitable correction factor which accounts for the attenuation of 740–780 keV photons due to the lead shielding, provides an estimation of the ^{99}Mo activity. This value should not exceed 0.1% of the ^{99m}Tc activity according to the European Pharmacopoeia.

For a more accurate determination of the radionuclidic purity [17, 20], the same eluate sample was examined again (reassayed) after 7–15 days by means of high-resolution gamma spectrometry using a solid-state, high-purity germanium detector [16].

2.1.6. Radiochemical Purity. It was checked by paper chromatography, Whatman no.1 paper strips and saline as mobile phase. According to this procedure, $^{99m}\text{TcO}_4^-$ migrates with the solvent front ($R_f = 1$), whereas reduced hydrolyzed ^{99m}Tc remains at the origin ($R_f = 0$). The radioactivity distribution was measured by a scanning radiochromatography detection system for thin layer chromatography (Cyclone instrument equipped with a phosphor imaging screen and an OptiQuant image analysis software (Packard, Meridien, CT)). Eluate radiochemical purity should be greater than 95%.

2.1.7. ^{99g}Tc to Active ^{99m}Tc Ratio. ^{99}Mo decays to ^{99g}Tc (12.4%) and ^{99m}Tc (87.6%), and the latter, with a physical $T_{1/2}$ of 6.0067 h, decays to ^{99g}Tc ($T_{1/2} = 211,100$ years). Due to this particular branching decay of ^{99}Mo , even fresh elutions from a generator always contain both isotopes (^{99m}Tc and ^{99g}Tc), indistinguishable from the chemical point of view. The amount (μg) of total technetium present in the eluate is directly related to the amount of ^{99}Mo atoms present on the column (i.e., ^{99}Mo activity) and the time that elapsed since the previous elution. The total number of Tc atoms, namely, the sum of ^{99g}Tc and ^{99m}Tc , has been calculated as follows:

$$N_{\text{Tc}(\text{total})} = N_{^{99}\text{Mo}}^0 (1 - e^{-\lambda_1 t}), \quad (1)$$

where $N_{^{99}\text{Mo}}^0$ is the initial ^{99}Mo atoms number present on the column, λ_1 is the decay constant of ^{99}Mo ($0.0105 \text{ hours}^{-1}$), and t is the time that elapsed since the last elution. The number of ^{99m}Tc atoms has been calculated as follows:

$$N_{^{99m}\text{Tc}} = P \frac{\lambda_1}{\lambda_2 - \lambda_1} N_{^{99}\text{Mo}}^0 (e^{-\lambda_1 t} - e^{-\lambda_2 t}), \quad (2)$$

where λ_2 is the decay constant of ^{99m}Tc ($0.1149 \text{ hours}^{-1}$) and P is the decay probability ($P = 0.876$). A simplified decay scheme of ^{99}Mo to ^{99g}Tc is shown in Figure 1. From the above equations the number of ^{99g}Tc atoms can be easily calculated as follows:

$$N_{^{99g}\text{Tc}} = N_{\text{Total Tc}} - N_{^{99m}\text{Tc}} \quad (3)$$

and thus the ^{99g}Tc to active ^{99m}Tc ratio can be estimated.

The determination of the ^{99g}Tc content in a fresh eluate requires an immediate measurement after the elution of the ^{99m}Tc activity and a later measurement of the total activity of ^{99g}Tc (in a few months almost all the ^{99}Mo and ^{99m}Tc atoms decay into ^{99g}Tc). The evaluation of ^{99m}Tc activity in the sample has been performed by using a dose calibrator (PET-dose, Comtec, Castalbolognese, Italy), while the evaluation of ^{99g}Tc activity has been performed using the TRI-CARB 2810TR liquid scintillation analyzer (Perkin Elmer Inc., Monza, Italy). The samples for ^{99g}Tc activity measurements were prepared taking an aliquot of 0.8 mL from an eluate decayed for 60 days (total volume of the eluate: 5 mL) and adding 5.4 mL of liquid scintillator (Ultima Gold LLT cocktail, Perkin Elmer Inc., Monza, Italy). The measurement of ^{99g}Tc activity was performed using the 0–295 keV energy window.

2.2. Radiopharmaceuticals Labeling. The elutions were used to label different commercial kits (Table 1). Kits reconstitution was performed according to the methods described in the package included within the commercial kits. The radiochemical purity (RCP) of radiopharmaceuticals was evaluated immediately after preparation ($t = 0$) and at the end of the stability period indicated by the manufacturer. The radiochemical purity and stability were measured using methods specified by manufacturer, with the exception of TechneScan (Mallinckrodt) for which the following chromatographic system was used [21]: mobile phase, 54/45/1 (physiological/methanol/glacial acetic acid) and stationary phase, RP-18 (Merck). Thin-layer chromatography plates were analyzed with a Cyclone instrument equipped with a

TABLE 2: pH, ^{99}Mo , ^{103}Ru , and ^{131}I amounts and radiochemical purities (mean \pm standard deviation) of the evaluated generators' elutions.

Type of generator	Type of elution	pH	^{99}Mo %	^{103}Ru %	^{131}I %	RCP %
Drytec-GE	1° eluate	6.0 \pm 0.3	(2.1 \pm 0.2) $\times 10^{-2}$	(1.9 \pm 0.2) $\times 10^{-6}$	(1.4 \pm 0.4) $\times 10^{-7}$	99.8 \pm 0.3
	36 h	6.0 \pm 0.4	(3.9 \pm 0.5) $\times 10^{-2}$	—	—	99.7 \pm 0.3
	48 h	6.1 \pm 0.3	(3.7 \pm 0.4) $\times 10^{-2}$	—	—	99.8 \pm 0.2
	72 h	6.0 \pm 0.2	(3.1 \pm 0.2) $\times 10^{-2}$	—	—	99.7 \pm 0.3
Elumatic III	1° eluate	6.2 \pm 0.1	(2.7 \pm 0.3) $\times 10^{-2}$	(1.7 \pm 0.5) $\times 10^{-7}$	(2.2 \pm 0.3) $\times 10^{-7}$	99.8 \pm 0.1
	36 h	6.2 \pm 0.3	(2.5 \pm 0.5) $\times 10^{-2}$	—	—	99.8 \pm 0.3
	48 h	6.2 \pm 0.4	(2.5 \pm 0.1) $\times 10^{-2}$	—	—	99.6 \pm 0.2
	72 h	6.1 \pm 0.2	(2.5 \pm 0.3) $\times 10^{-2}$	—	—	99.4 \pm 0.1
E.P.		4.8–8.0	<0.1%	<5 $\times 10^{-3}$	<5 $\times 10^{-3}$	≥ 95.0

E.P.: European pharmacopoeia; 36, 48, and 72 h indicate the time from the previous elution; the amount of ^{99}Mo represents the % of total radioactivity in the generators' eluates determined with "rapid method"; ^{103}Ru (0.497 MeV) and ^{131}I (0.365 MeV) are the most common gamma radionuclide detectable by gamma spectrometry, and in the table are reported the % of total radioactivity in the generators' eluates.

TABLE 3: RCP of radiopharmaceuticals at $t = 0$, prepared with generator DRYTEC GE Healthcare eluates at time superior to 24 h from the last elution.

Commercial name	Radiopharmaceuticals	RCP ₃₆	RCP ₄₈	RCP ₇₂	RCP requirements
Neurolite	$^{99\text{m}}\text{Tc}$ -ECD	98.57 \pm 0.45	99.41 \pm 1.51	98.73 \pm 1.85	$\geq 90\%$
Cardiolite	$^{99\text{m}}\text{Tc}$ -Sestamibi	97.91 \pm 0.38	98.35 \pm 1.02	99.40 \pm 1.23	$\geq 94\%$
Stamicis	$^{99\text{m}}\text{Tc}$ -Sestamibi	97.88 \pm 0.28	97.90 \pm 0.15	98.16 \pm 0.11	$\geq 94\%$
Technemibi	$^{99\text{m}}\text{Tc}$ -Sestamibi	98.18 \pm 0.23	97.77 \pm 0.33	98.53 \pm 0.27	$\geq 94\%$
TechneScan	$^{99\text{m}}\text{Tc}$ -MAG3	98.89 \pm 0.64	99.10 \pm 0.44	99.31 \pm 0.14	$\geq 95\%$
Pentacis	$^{99\text{m}}\text{Tc}$ -DTPA	98.84 \pm 1.01	98.91 \pm 0.24	99.12 \pm 0.33	$\geq 95\%$
Medronato II	$^{99\text{m}}\text{Tc}$ -MDP	99.01 \pm 0.24	98.44 \pm 0.16	99.63 \pm 0.64	$\geq 95\%$
Osteocis	$^{99\text{m}}\text{Tc}$ -HMDP	99.22 \pm 0.14	98.01 \pm 0.52	99.13 \pm 0.11	$\geq 95\%$
Nanocoll (PRC = 40 min)	$^{99\text{m}}\text{Tc}$ -nanocolloids	99.34 \pm 0.09	99.38 \pm 0.16	98.94 \pm 0.41	$\geq 95\%$
Renocis	$^{99\text{m}}\text{Tc}$ -DMSA	99.55 \pm 0.08	99.22 \pm 0.77	99.11 \pm 0.03	$\geq 95\%$

RCP_{36,48,72} indicate the radiochemical purity carried out with eluates obtained 36, 48 and 72 hours after the previous elution.

phosphor imaging screen and an OptiQuant image analysis software (Packard, Meriden, CT).

2.3. Imaging Studies. Three $^{99\text{m}}\text{Tc}$ eluates produced by $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator with different $^{99\text{g}}\text{Tc}/^{99\text{m}}\text{Tc}$ ratio R were used for imaging studies; the R values were 4.16, 9.51, and 15.2, respectively. Each tomographic acquisition has been performed by filling a NEMA phantom NU 4-2008 with 74 MBq of $^{99\text{m}}\text{Tc}$ -pertechnetate solution, and the data have been acquired with the YAP-(S)PET small animal scanner prototype [22] and reconstructed by using an EM-ML algorithm.

3. Results and Discussion

The results of the quality control (Table 2) performed on all eluates obtained from two different generator (DRYTEC GE Healthcare and Elumatic III IBA) are consistent with the European Pharmacopoeia requirements [12]. For simplicity, data of visual inspection, yield of elution, and the aluminum content in eluates are not reported, because they fell within European Pharmacopoeia requirements.

The radiochemical purity (RCP) values of all radiopharmaceuticals labeled with each eluate are reported in Tables 3 and 4. Results refer to the RCP evaluated immediately after the preparation ($t = 0$). For simplicity, data at the end of the stability period specified by the manufacturer are not reported, because they fell within the specifications required by the manufacturer. Tables 5 and 6 report the RCP data obtained from reconstitution of the kits with the first eluate. The values refer to the checks carried out immediately after the preparation ($t = 0$) and at the end of the stability period specified by the manufacturer in the package insert of each radiopharmaceutical. The values of radiochemical purity are always superior to the standards required by the manufacturer. The results show that the total amount of technetium ($^{99\text{g}}\text{Tc} + ^{99\text{m}}\text{Tc}$) present in the first eluate and in the eluates obtained at longer intervals, from 24 h up to 72 h, did not affect the radiochemical purity of the final products. Table 7 shows an estimation of the total amount of technetium present in an eluate obtained from a $^{99\text{m}}\text{Tc}$ generator with ^{99}Mo calibrated activity of 10 GBq. The ratios R of three $^{99\text{m}}\text{Tc}$ eluates at 24 hours and two $^{99\text{m}}\text{Tc}$ first eluates at 48 hours have been measured, and the results have been $R_{24\text{h}} = 3.23 \pm 0.15$ and $R_{48\text{h}} = 6.68 \pm 0.31$, respectively. While

TABLE 4: RCP of radiopharmaceuticals at $t = 0$, prepared with generator Elumatic III (IBA) eluates at time superior to 24 h from the last elution.

Commercial name	Radiopharmaceutical	RCP ₃₆	RCP ₄₈	RCP ₇₂	RCP requirements
Neurolite	^{99m} Tc-ECD	98.77 ± 0.89	99.21 ± 0.71	98.68 ± 0.95	≥90%
Cardiolite	^{99m} Tc-Sestamibi	97.88 ± 0.78	98.83 ± 0.92	99.13 ± 0.63	≥94%
Stamcis	^{99m} Tc-Sestamibi	98.78 ± 0.23	98.90 ± 0.20	98.00 ± 0.19	≥94%
Technemibi	^{99m} Tc-Sestamibi	98.45 ± 0.09	98.17 ± 0.23	98.11 ± 0.06	≥94%
TechneScan	^{99m} Tc-MAG3	99.79 ± 0.64	98.10 ± 0.44	99.44 ± 0.14	≥95%
Pentacis	^{99m} Tc-DTPA	99.14 ± 0.12	98.88 ± 0.15	98.12 ± 1.03	≥95%
Medronato II	^{99m} Tc-MDP	99.11 ± 0.33	99.44 ± 0.15	99.11 ± 0.43	≥95%
Osteocis	^{99m} Tc-HMDP	99.01 ± 0.24	98.44 ± 0.16	99.63 ± 0.64	≥95%
Nanocoll (PRC = 40 min)	^{99m} Tc-nanocolloids	98.99 ± 0.03	99.18 ± 0.49	98.11 ± 0.11	≥95%
Renocis	^{99m} Tc-DMSA	99.35 ± 0.22	98.67 ± 0.17	99.03 ± 0.29	≥95%

RCP_{36,48,72} indicate the radiochemical purity carried out with eluates obtained 36, 48 and 72 hours after the previous elution.

TABLE 5: RCP of radiopharmaceuticals at $t = 0$ and at the expired time specified by the manufacturer, prepared with the first eluate obtained from DRYTEC GE Healthcare generator.

Commercial name	Radiopharmaceutical	RCP ($t = 0$)	RCP _{ex}	RCP requirements
Neurolite	^{99m} Tc-ECD	99.17 ± 0.25	99.13 ± 0.21	≥90%
Cardiolite	^{99m} Tc-Sestamibi	97.67 ± 1.24	97.71 ± 1.13	≥94%
Stamcis	^{99m} Tc-Sestamibi	98.65 ± 0.40	98.57 ± 0.57	≥94%
Technemibi	^{99m} Tc-Sestamibi	98.15 ± 0.11	98.01 ± 0.04	≥94%
TechneScan	^{99m} Tc-MAG3	98.79 ± 0.02	98.11 ± 0.15	≥95%
Pentacis	^{99m} Tc-DTPA	99.03 ± 0.24	99.88 ± 0.11	≥95%
Medronato II	^{99m} Tc-MDP	98.10 ± 0.13	98.02 ± 0.15	≥95%
Osteocis	^{99m} Tc-HMDP	99.23 ± 0.18	98.15 ± 0.16	≥95%
Nanocoll (PRC = 40 min)	^{99m} Tc-nanocolloids	98.22 ± 0.13	98.33 ± 0.39	≥95%
Renocis	^{99m} Tc-DMSA	99.28 ± 0.07	98.55 ± 0.21	≥95%

RCP_{ex} indicates the radiochemical purity at the end of the expired time.

TABLE 6: RCP of radiopharmaceuticals at $t = 0$ and at the expired time specified by the manufacturer, prepared with the first eluate obtained from Elumatic III (IBA) generator.

Commercial name	Radiopharmaceuticals	RCP ($t = 0$) ($n = 3$)	RCP _{ex} ($n = 3$)	RCP requirements
Neurolite	^{99m} Tc-ECD	98.38 ± 0.54	98.74 ± 0.25	≥90%
Cardiolite	^{99m} Tc-Sestamibi	97.68 ± 0.56	97.77 ± 0.88	≥94%
Stamcis	^{99m} Tc-Sestamibi	98.42 ± 1.02	99.03 ± 0.48	≥94%
Technemibi	^{99m} Tc-Sestamibi	97.99 ± 0.11	98.15 ± 0.14	≥94%
TechneScan	^{99m} Tc-MAG3	98.11 ± 0.62	98.43 ± 0.29	≥95%
Pentacis	^{99m} Tc-DTPA	99.16 ± 0.32	99.19 ± 0.11	≥95%
Medronato II	^{99m} Tc-MDP	99.13 ± 0.04	98.77 ± 0.08	≥95%
Osteocis	^{99m} Tc-HMDP	99.17 ± 0.12	98.76 ± 0.29	≥95%
Nanocoll (PRC = 40 min)	^{99m} Tc-nanocolloids	98.79 ± 0.16	98.92 ± 0.59	≥95%
Renocis	^{99m} Tc-DMSA	99.11 ± 0.35	99.01 ± 0.32	≥95%

RCP_{ex} indicates the radiochemical purity at the end of the expired time.

TABLE 7: Evaluation of total technetium amount in ^{99m}Tc eluates coming from a generator with ⁹⁹Mo calibrated activity of 10 GBq, at different times by previous elution.

Time by the previous elution	Amount of total Tc calculated	^{99g} Tc/ ^{99m} Tc ratio calculated	Amount of total Tc found	^{99g} Tc/ ^{99m} Tc ratio found
72 h	0.30 µg	11.84		
48 h	0.22 µg	6.50	0.22 ± 0.01	6.68 ± 0.31
36 h	0.18 µg	4.34		
24 h	0.13 µg	2.54	0.12 ± 0.01	3.23 ± 0.15

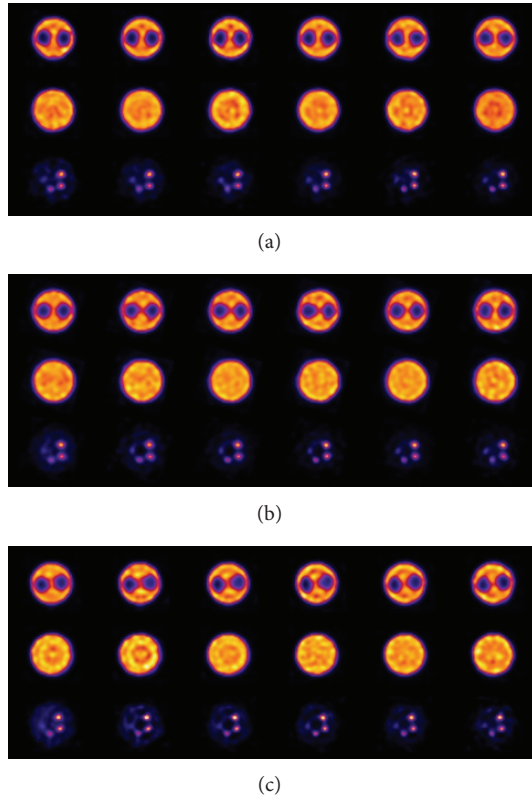


FIGURE 2: Reconstructed SPECT trans-axial slices of NEMA NU 4-2008 filled with ^{99m}Tc -pertechnetate solution. Top images (a) have $R = 4.16$, middle images (b) have $R = 9.51$, and bottom images (c) have $R = 15.2$.

the experimental value of first eluates at 48 hours is in good agreement with the theoretical value of 6.5, the experimental value of eluates at 24 hours shows a large difference with respect to the theoretical value of 2.55. This discrepancy could be explained by taking into account the elution efficiency $\varepsilon = 0.91$ of ^{99}Mo generators used in our work. Indeed, the recalculated ratio R at 24 hours is included in the range (2.78–3.38) and depends on temporal sequence of previous elutions. The reconstructed SPECT images of NEMA phantom, for the different $^{99g}\text{Tc}/^{99m}\text{Tc}$ ratios R used, are shown in Figure 2. The average reconstructed activity along the phantom axis, for the three values of R , is shown in Figure 3. The visual inspection on the images doesn't show significant difference in image quality and radioactivity distribution. Currently, CERETEC is the only commercial product for which the use of a fresh eluate, obtained from a generator eluted for not more than 24 hours, is required. This exception is linked to the low amount of tin chloride dehydrate in its formulation ($7.6\ \mu\text{g}$), which makes its radiochemical purity strongly influenced by the amount of ^{99g}Tc present in the eluate. All formulations studied possess significantly higher amount of tin. A further limitation to the use of eluates characterized by greater amount of ^{99g}Tc (elution intervals $> 24\ \text{h}$) could be due to radioprotection reasons related to the physical characteristics of ^{99g}Tc ($t_{1/2} = 2 \times 10^5\ \text{y}$, $\beta_{\text{max}} = 292\ \text{keV}$). However

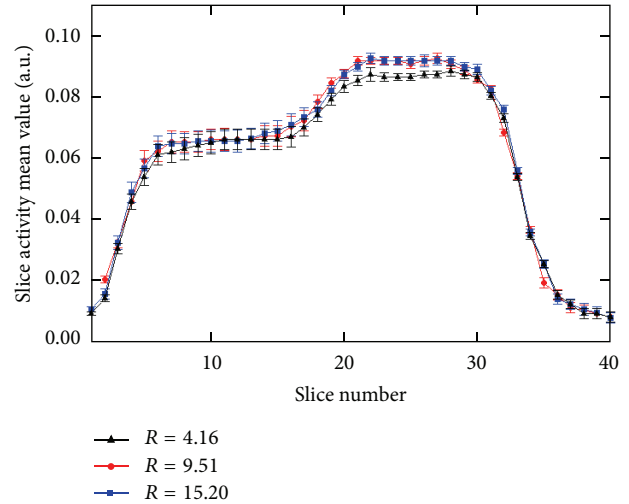


FIGURE 3: The average activity for reconstructed 40 slices of NEMA NU 4-2008 phantom filled with ^{99m}Tc -pertechnetate solution having $R = 4.16$, $R = 9.51$, and $R = 15.2$.

the amount of radioactivity associated with the mass value is very low (e.g., $1\ \mu\text{g}$ of ^{99g}Tc corresponds to 630 Bq).

4. Conclusion

In order to first check the possible impact of different $^{99g}\text{Tc}/^{99m}\text{Tc}$ isomeric ratios on the preparation of different Tc-labeled pharmaceutical kits, the radiochemical purity and stability of ^{99m}Tc -Sestamibi, ^{99m}Tc -ECD, ^{99m}Tc -MAG3, ^{99m}Tc -DTPA, ^{99m}Tc -MDP, ^{99m}Tc -HMDP, ^{99m}Tc -nanocolloids, and ^{99m}Tc -DMSA were studied by using ^{99m}Tc eluates coming from $^{99}\text{Mo}/^{99m}\text{Tc}$ generator eluted at different times from the previous elution. The results prove that radiochemical purity and stability of these radiopharmaceuticals are not affected up to $^{99g}\text{Tc}/^{99m}\text{Tc}$ ratio of 11.84.

A future goal will be to repeat the experiments with ^{99m}Tc eluates coming from generators with ^{99}Mo calibrated activity higher than 10 GBq, in order to check the possible impact of ^{99g}Tc in higher ^{99m}Tc activities solutions at different $^{99g}\text{Tc}/^{99m}\text{Tc}$ ratio.

Another future goal will be to study the impact of accelerated-based ^{99g}Tc and other Tc-isotopes on the image quality and determine the allowed limit for ^{99g}Tc and other Tc-isotopes in the final accelerator-produced Tc.

Conflict of Interests

The authors declare that they have no conflict of interests.

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