The Nucleus ***56****, No. 4 (2019) 163-171*

www.thenucleuspak.org.pk

The Nucleus
ISSN 0029-5698 (Print)
ISSN 2306-6539 (Online)

Technetium-99m Radiopharmaceuticals: A Review on Basic and Applied Aspects

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ARTICLE INFO

Article history:
Received: *03 October, 2019*
Accepted: *28 August, 2020*
Published: *15 September, 2020*

Keywords:
Technetium,
Labelling,
Ligand,
Targeting molecule,
Receptor,
Organ

ABSTRACT

Technetium-99m (^{99m}Tc) usage is increasing worldwide at a rate of 32% per annum. Enriched Uranium-235 is irradiated at nuclear reactor and subsequent process produces Molybdenum-99 (^{99}Mo) which decays to ^{99m}Tc, and ^{99m}Tc converts to ^{99g}Tc. Organic molecules are used as ^{99m}Tc carriers, e.g., ^{99m}Tc-mercaptoactyltriglycine. ^{99m}Tc is excreted from body with feces and urine. It is estimated that 0.22%–38.41% of ^{99m}Tc remains in needles and rest is injected to the patient. Forty generators per week are supplied to medical centers in Pakistan and 1.72 x10^5 Bq/y ^{99g}Tc is returned as radioactive waste. Every used ^{99}Mo/^{99m}Tc generator contains ^{99g}Tc ~ 83.3 Bq. ^{99g}Tc radioactive waste is increasing world-wide, as its global use is ~4.5×10^{14} Bq/week. No satisfactory method exists for ^{99g}Tc immobilization although incorporation of ^{99g}Tc into Fe(III) or Sn(IV) oxide matrix before glass immobilization is suggested. The present review covers all aspect of ^{99m}Tc radiopharmaceutical life-cycle and suggests options for ^{99g}Tc radioactive waste management.

1. Introduction

Diagnostic radiopharmaceuticals are used to diagnose various unhealthy tissues through radioisotope generator system in the hospital. A radioisotope generator system is consisted of a radioisotope and a solid stationary phase which delivers a specific isotope for diagnosis. All radiopharmaceuticals are defined by five major parameters: residence time within the organ, type, rate of radioactive decay, detection characteristics and production factors [1-3]. Based on these parameters many radiopharmaceuticals have been introduced in the market. The strong members of Single Photon Emission Computerized Tomography (SPECT) are Technetium (^{99m}Tc), ^{123}I ($t_{1/2}$ = 13h), and ^{201}Tl ($t_{1/2}$ = 73.5h) [4]. There are other isotopes generator systems including ^{132}Te-^{132}I, ^{87}Sr–^{87}Y, ^{131}Ba-^{131}Cs, ^{68}Ge-^{69}Ga, ^{113}Sn-^{113m}In, and ^{103}Pd-^{103}Rh [1] but ^{99}Mo-^{99m}Tc is used in 85% diagnostic tests worldwide due to numerous reasons. Life-cycle of ^{99m}Tc is summarized in Fig. 1.

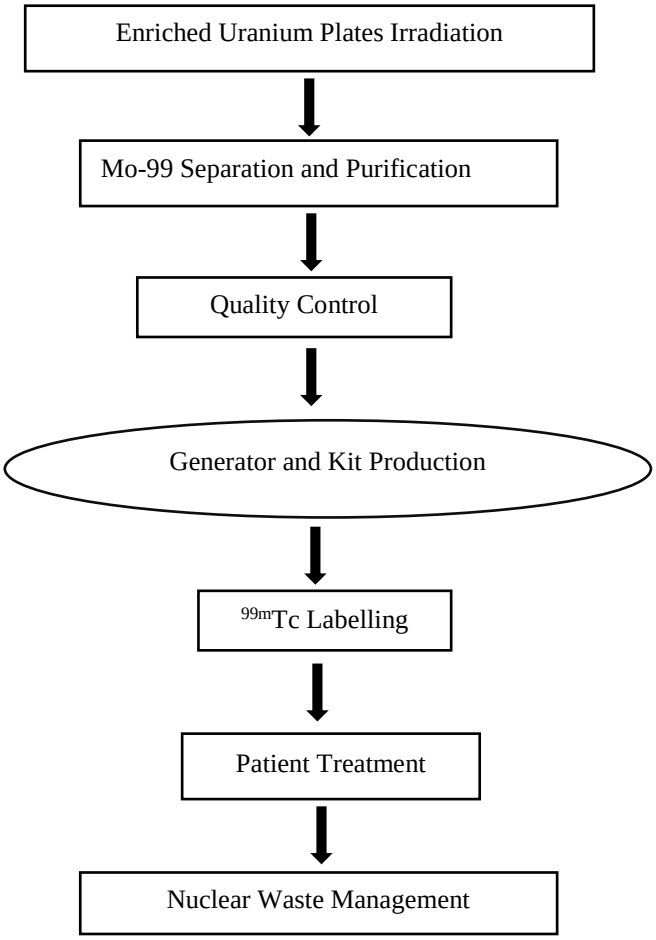

Fig. 1: Life-cycle of ^{99m}Tc radioisotope.

Technetium belong to transient metals group VIIb. Perrier and Segré [3] discovered ground state Technetium (^{99g}Tc), the name came from technetos, meaning artificial. Tc as pertechnetate (TcO_4^-) chemically behaves like ReO_4^- while its biological behavior resembles to I, as both accumulate in thyroid gland. Among 21 isotopes of Tc, ^{110}Tc has the shortest half-life (0.86 sec) and ^{97}Tc has the longest half-life (2.6× 10^6 y) while ^{99m}Tc is metastable state of ^{99}Tc. Technetium forms organic complexes in eight oxidation states (-1 to +7) [5]. Ligands and the chemical environment determine the oxidation state of the ion in a complex. Tc in lower states (-1 to +3) can be stabilized by complex formation. Technetium exist as Tc(V) and Tc(VI) in radiopharma-

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ceuticals complexes and it disproportionate to +4 and +7 states, when Tc(VII) is reduced with Sn(II) or any other reducing agent in the absence of strong ligand [6, 7]. Technetium octet is completed in TcO_4^- as it is the most stable form in aqueous solution. ^{99m}Tc is commercially available as $Na^{99m}Tc(VII)O_4$ as it is produced from ^{99}Mo, as shown in eq. (1) [4].

$$^{99}Mo = {}^{99m}Tc(87.2\%) + {}^{99g}Tc(12.8\%) + \beta^- + v_e \quad (1)$$

^{99m}Tc is radionuclide of choice in diagnostic industry because it has 6 hours half-life, no beta radiation and an ideal gamma-ray energy of 140 keV [2]. First ^{99m}Tc commercially available generator was supplied in 1965 [1, 2]. Technetium-99m emits three photons of 0.0022, 0.1405, and 0.1427 MeV. The 0.1405 MeV photon has 89.1% abundance [8].

Technetium (^{99g}Tc) is a daughter product of ^{99}Mo and has a half-life of 2.13×10^5 years; therefore, its waste management is required. The reactions are shown in eqs. (2) and (3) [2].

$$1\ mCi\ {}^{99m}Tc = 3.3\ pCi\ {}^{99g}Tc \quad (2)$$

$$1\ mCi\ {}^{99}Mo = 0.3\ pCi\ {}^{99g}Tc \quad (3)$$

2. Reactor Production

Molybdenum-99 (^{99}Mo) is produced by two methods: ^{235}U fission process ($_0n^1$, f) and bombardment of ^{98}Mo by thermal neutrons ($_0n^1$, γ)[a] in a nuclear reactor [4]. Cross section of ($_0n^1$, γ) reaction is only 0.13 barns (b), despite high radionuclide purity and low specific activity than fission process [1, 2, 4, 9, 10].

Fission, $_0n^1$ flux ~ $10^{13}{}_0n^1/cm^2/sec$, σ ~ 584 b

$$^{235}U\ (100mg) + {}_0n^1 = {}^{99}Mo\ (2.2\ Ci); \quad (4)$$

Thermal neutron σ ~ 0.13b, $_0n^1$ flux ~ $10^{13}{}_0n^1/cm^2/sec$

$$^{98}Mo\ (1g) + {}_0n^1 = {}^{99}Mo\ (200\ mCi) + \gamma \quad (5)$$

Enriched ^{235}U as uranium-aluminum alloys or UO_2 is used in fission process ($^0n_1$, *f*) for production of ^{99m}Tc [4]. After fission, irradiated ^{235}U fuel assemblies are transferred to processing cells. Next step is to dissolve ^{235}U plates into HNO_3. During acidic condition $^{99}MoO_4^{-2}$ adsorbs on alumina (Al_2O_3) column (^{132}Tl also adsorbs on alumina which gives ^{132}I). Later column is washed with HNO_3 to remove U and other fission product cations. These fission products consist of Sr(II), Cs(I), In, and many others. The $^{99}MoO_4^{-2}$ is eluted with NH_4OH, and ^{132}Tl can be recovered by elution with NaOH from alumina column. Alternatively, basic dissolution can also be applied to recover ^{99}Mo from ^{235}U plates.

Further $^{99}MoO_4^{-2}$ solution is loaded on Dowex 1x8 anion exchange resin; purification can be achieved by washing to remove trace impurities. The final product $^{99}MoO_4^{-2}$ is eluted with 1.2 N HCl solutions. The $^{99}MoO_4^{-2}$ in 1.2 N HCl is loaded on alumina column (which is called generator together with other accessories), and later on $^{99m}TcO_4^-$ (produced from $^{99}MoO_4^{-2}$ decay) is milked with 0.9% NaCl (0.15 M NaCl) [4] saline solution in hospital's radio-pharmacies [1].

2.1 ^{99m}Tc Production from $^1H_1$ and γ Irradiation

^{99}Mo can also be produced by proton irradiation and gamma irradiation of ^{100}Mo, as shown in eqs. (6) and (7); however, these processes are not commercially viable till date.

$$^{100}Mo_{42} + {}^1H_1 = {}^{99m}Tc_{43} + 2\ {}_0n^1 \quad (6)$$

$$^{100}Mo_{42} + \gamma = {}^{99}Mo_{42} + {}_0n^1 \quad (7)$$

2.2 Separation Mechanism

^{99m}Tc can be separated by column chromatography using acidic alumina [5], solvent extraction using methyl ethyl ketone [8], sublimation of Tc oxides from Molybdenum compounds [8] and elution from zirconium molybdate gel columns [11]. Activated alumina is commercially used as stationary phase; it is acidified and MoO_4^{-2} polymerizes as $Al[Mo_6O_{24}]^{9-}$ on the alumina column [5, 12, 13]. ^{99m}Tc labelling is achieved by injecting ^{99m}Tc eluate into the freeze-dried vial under aseptic conditions. ^{99m}Tc is milked from ^{99}Mo generator with 0.9% NaCl saline solution and generator is ready to milk again at full capacity after 23 hours, hence it is called cow [11].

3. Generator and Kit Production

3.1 ^{99m}Tc Generator

^{99m}Tc generator contains glass column which contain alumina, Molybdedate (MoO_4^{2-}) is adsorbed on it in acidic pH range [5, 12, 13]. Its daughter $^{99m}TcO_4^{-1}$ adsorbs as negative ion and it is eluted with NaCl (0.9% w/v) due to single charge and less adsorption than MoO_4^{-2}. There are two types of methods used to extract ^{99m}Tc from generator, wet and dry. In dry extraction, the residual saline is drawn out with evacuated vial, without adding additional saline. Dry extraction is recommended because radiation produces electrons that can reduce ^{99m}Tc, as shown in eq. (8) and ultimately labeling yield is decreased [9].

$$e^- + TcO_4^- = TcO_4^{2-} \quad (8)$$

3.2 Kit

Kits consist of coordinating ligands, reducing agent and adjuvant, for example, ancillary chelating agents, buffers and antioxidants [14]. Mostly ^{99m}Tc radiolabeling reactions occur at pH 4-6 [14]. Higher ligand concentration is used to avoid hydrolysis of ^{99m}Tc as well as to overcome ^{99m}Tc-Sn side reaction with ligand [14]. Ancillary chelating agents are added to avoid ^{99m}Tc and Sn hydrolysis, when reaction with ligand is slow, ancillary chelating agent (also known as transfer ligand) forms temporary complex with ^{99m}Tc and later this exchange/transfer ligand is replaced with coordinating ligand. Sodium tartarte, sodium gluconate and sodium citrate are used as transfer ligands in mertiatide, tetrofosmin and sestamibi kits, respectively [15].

[a] MoO_3 is used in this ($_0n^1$, γ) reaction

$^{99m}TcO_4^-$ is reduced to appropriate oxidation state using suitable reducing agents. Tl(III), Cr(II) and Cu(I) is avoided due to complex formation while oxalates, formats, hydroxylamine and hydrazine are also avoided due to complex formation with ^{99m}Tc. Sn(II) is suitable but Khan et al. [6] found that Sn(II) also form hetero complexes with Re and possible with ^{99m}Tc as well [4, 7, 16]. $SnCl_2$ to $^{99m}TcO_4^-$ molar ratio is as high as 10^8 to 10^9 and most of Sn(II) is oxidized by oxygen as shown in eq. (9).

$$2Sn^{2+} + 4H^+ + O_2 = 2H_2O + 2Sn^{4+} \quad (9)$$

Ligand is also kept higher than Sn(II) to avoid Sn-Tc colloid formation. DTPA ligand to Sn(II) molar ratio is ≥ 33 in ^{99m}Tc radiopharmaceuticals commercial kits, [9]. Free radicals oxide labeled complexes, so anti-oxidants are part of kits to avoid oxidation of ^{99m}Tc in ^{99m}Tc-Ligand. Sodium thiosulfate, ascorbic acid, methylene blue, sodium methabisulfite and sodium bisulfate provide H to free-radicals to convert ROO to ROOH. These free radicals are produced by radiation exposure (at rate of 33×10^{-5} µg mCi^{-1} h^{-1}) in $^{99m}TcO_4^-$ solution [17]. Kits are sterilized and pyrogen free, dried by lyophilization and stored under nitrogen.

3.3 Labelling

Labelling is a process of binding metal (^{99m}Tc) to a biologically active chelator. Biologically active molecule is a ligand which has two functions, link to metal and incorporate complex to targeting vector. There are three methods of labeling: bifunctional chelator approach, direct labeling approach and integrated approach [15, 18]. In the bifunctional chelator approach, a ligand binds to metal at one side, while other side is covalently linked to targeting molecule/vector. In direct labeling approach, the labeling biomolecule is an integral part of the biomolecule. Thiols, thioether groups and aliphatic or aromatic amines are binding sites. In this method, labeling yield is not enough, hence purification is required. The reducing agent Sn(II) forms colloids and forms functionalities on the antibodies; therefore, dithiothreitol (DDT) is employed with Sn(II). In this approach $[Tc(CO)_3]^+$ moiety is used for direct labeling of antibodies. The incorporation of ^{99m}Tc in receptor targeting molecule without bioactive molecule as vector is called on integrated approach.

3.4 Patient Administration

Labelled ^{99m}Tc is injected through veins by a trained personal. A typical injection of 10–30 mCi is administered and it gives dose of 10 mSv, equivalent to 500 chest X-rays [19, 20]. The 140 keV γ-rays are measured and organ is imaged through scintigraphy or emission tomographic process. The camera moves around patient, coinciding the organ being scanned. Tl-activated NaI single crystal is used as detector, whose image resolution depends on distance between collimator and object [21].

4. Quality Control

Stability of the kits [14, 22, 23] is an important quality measure, which depends on reducing agent, residual moisture and the freeze-drying process. Loss of tin leads to incomplete reduction of the $^{99m}TcO_4^-$; therefore, estimation of the Sn(II) is important and can be conducted by iodometery or polarography [5].

4.1 Sterility Testing

Endotoxins are determined using Limulus amebocyte lysate (LAL) [14] while the purity is determined by paper, thin layer and HPL chromatography [14, 23, 24].

4.2 Impurities Limits

Many fission fragments and trans-uranic elements are produced in fission process; therefore, European pharmacopeia has set limits to these radionuclides in the generator elutes. These radionuclides per mCi of ^{99m}Tc should be as follows: 1 µCi ^{99}Mo, 50 nCi ^{103}Ru, and 50 nCi ^{131}I, 100 nCi all γ emitters, 0.6 nCi ^{89}Sr, 0.06 nCi ^{90}Sr, and 1 pCi all α-emitters. These limits have been calculated, supposing ^{99m}Tc is injected within 12 h of elution [4, 24–26].

5. ^{99m}Tc Radiopharmaceutical Generations

The ^{99m}Tc radiopharmaceuticals can be broadly placed into 2 categories: technetium-essential and technetium non-essential. Technetium essential are first generation radiopharmaceuticals in which ^{99m}Tc is integral part of the molecule. ^{99m}Tc tagged radiopharmaceuticals are those in which bioactive molecule is labeled directly or via bifunctional chelate with ^{99m}Tc. Most of the current ^{99m}Tc radiopharmaceuticals are essential and kit contains readymade ligand, reducing agent usually Sn(II), an antioxidant and solubilizing as well as stabilizing agent [9, 11, 27].

5.1 First and Second Generation Radiopharmaceuticals

First generation ^{99m}Tc radiopharmaceuticals were developed using ^{99g}Tc precursor (17 mCi/g). Initial studies developed brain and myocardial perfusion agents [27, 28]. These radiopharmaceutical reach within tumor based on diffusion principal.

Second generation radiopharmaceuticals have bifunctional chelating agents which are organ specific [9, 11, 18, 29-31]. Complex formation core should be far away from bio-specific part of the molecules. The labelled species should possess high specific activity as binding sites are limited in living tissues [32-34].

Research is ongoing for 3rd generation radiopharmaceuticals; in this category, target molecule is bonded with receptor after that receptor should be blocked [5]. A detail list of 1st, 2nd and 3rd generation radiopharmaceuticals are given in Table 1, while oxidation state of numerous radiopharmaceuticals are given in Table 2.

5.2 Organ Specific Radiopharmaceuticals

Most of the current commercial radiopharmaceuticals (Table 1) are essential and first generation. For specific organ base radiopharmaceuticals synthesis (2nd and 3rd generation), knowledge of molecular structure and organ receptors is necessary [18]. A famous TRODAT-1 crosses blood-brain

Table 1: Common commercial radiopharmaceuticals of 1st, 2nd and 3rd generation.

Commercial Name	Complex/ Radiopharmaceutical	Organ/ Function	Generation	Ref.
Ceretec	^{99m}Tc-D,L-HM-PAO	Brain, regional blood perfusion, cerebral stroke, ischemia, epilepsy, tumors	1st	[4, 60]
Neurolite	^{99m}Tc- L,L-ECD	Brain, regional blood perfusion, trauma, cerebral stroke, focal epilepsy	1st	[4, 60]
	^{99m}TcCl-$(DMG)_3$2MP	Brain, regional blood perfusion	1st	[4]
Cardiotec	^{99m}Tc-teboroxime	Myocardial & brain imaging agent	-	[5]
	^{99m}Tc-3,3-diphosphono-1,2-propanedicarboxylic acid (DPD)	Bone metastases from prostate cancer	1st	[40]
	Teboroxime	Myocardial perfusion	-	[15]
Cardiolite	^{99m}Tc-2-methoxyisobutylisonitrile (^{99m}Tc-sestamibi)	Myocardial imaging, parathyroid, breast	2nd	[9, 15, 40, 61]
Myoview	^{99m}Tc-1,2-bis[bis(2-ethoxyethyl)phosphino]ethane (^{99m}Tc-tetrofosmin)	Heart	2nd	[4, 9, 61, 60]
	^{99m}Tc-hexamibi	Heart	2nd	[4]
	^{99m}Tc-CDO-MeB	Heart	2nd	[4]
TechneScan Q12	^{99m}Tc-furifosmin	Heart	2nd	[61]
	^{99m}Tc-pentetate (^{99m}Tc-DTPA)	Renal Function agents	2nd	[5, 9]
	^{99m}Tc-DTP	Renal Function agents	2nd	[5]
Technescan	^{99m}Tc-mertiatide (^{99m}Tc-MAG3)	Renal Function agents	2nd	[5, 61]
	^{99m}Tc-mercaptoacetyltriglycine (MAG-3)	Renal scintigraphy	2nd	[40]
	^{99m}Tc-succimer (^{99m}Tc-DMSA)	Renal Cortical	1st	[4, 9]
	^{99m}Tc-dimercaptosuccinic acid (DMSA)	Renal defects	1st	[40]
	^{99m}Tc-methylenediphosphonic acid (^{99m}Tc-MDP)	Bone	1st	[4, 40]
	^{99m}Tc-hydroxymethylenediphosphonic acid (^{99m}Tc-HMDP)	Bone scanning	1st	[40]
	^{99m}Tc-Diphosphonate	Bone	1st	[15]
	[^{99m}Tc]-BMS-181321	Hypoxia Tissue Marker	2nd	[60]
	[^{99m}Tc]-BMS-194796	Hypoxia Tissue Marker	2nd	[60]
	[^{99m}Tc]-3+1-pyridinium analogue	Hypoxia tissue markers	2nd	[60]
	[^{99m}Tc]-3+1-dihydropyridine analogue	Hypoxia tissue markers	2nd	[60]
	^{99m}Tc-PnAO (BMS181321)	Hypoxia Imaging	2nd	[5]
AcuTect®P280	^{99m}Tc-apticide	Clot detection	2nd	[60]
	^{99m}Tc-TRODATI	Early detection of Parkinson's disease	2nd	[9]
	^{99m}Tc-NGA	Hepatoma, cirrhosis, Liver and liver metastases.	2nd	[4]
	^{99m}Tc-DISIDA	Biliary	1st	[15]
	^{99m}Tc-DTPA	Renal dynamics, brain, lung ventilation	1st	[15]
	^{99m}Tc-Glycoheptonate	Brain/Kidney ,Renal Dynamics	1st	[15]
	^{99m}Tc-HMPAO	Brain Perfusion	1st	[15]
	^{99m}Tc-HMPAO-WBC	Infection	2nd	[15]
	^{99m}Tc-HMPAO-RBC	GI blood loss, cardiac function, hepatic hemangioma	2nd	[15]
	^{99m}Tc-MAA	Lung perfusion, leveen shunt patency, intraarterial liver	2nd	[15]
Choletec [Bracco]	^{99m}Tc-Mebrofenin	Biliary	2nd	[9]
	Pertechnetate ($^{99m}TcO_4^-$)	Thyroid, salivary glands, meckel diverticulum, testicular	1st	[40]
	^{99m}Tc-S colloids	Liver, spleen, red bone marrow, esophageal transit, gastric emptying	1st	[40]
	^{99m}Tc-PPi or ^{99m}Tc-PYP (^{99m}Tc-pyrophosphate)	Bone imaging agent/Transthyretin cardiac amyloidosis	1st	[9]
	^{99m}Tc-HYNIC-Tyr^3-octreotide (Tektrotyde)	Neuroendocrine tumours	3rd	[40]

Table 2: Oxidation state of Tc in various radiopharmaceuticals [27].

Oxidation state	Chemical form
Tc(VII)	$^{99m}TcO_4^-$, ^{99m}Tc-S colloid
Tc(V)	Gluceptate, gluconate, HMPAO, MAG3, tetrofosmin, DMSA (high pH) , ECD, citrate
Tc(IV)	DTPA, HDP, MDP, PPi(PYP), $TcO_2.H_2O$
Tc(III)	DMSA (low pH), HIDA analogues, furifosmin, teboroxime,
Tc(I)	Sestamibi

barrier (BBB) and binds to dopamine presynaptic transporter through tropane [9, 35]. Famous ^{99m}Tc-tricarbonyl, ^{99m}Tc-4+1, ^{99m}Tc-N-PNP cores bind to receptors, whose one end is linked to metals and other end is bonded to specific set of donor atoms. This method of scanning gives more specific information that is needed for diagnostic [9, 15] and can be used in gynecological cancers [36]. ^{99m}Tc-galactosyl-neoglycoalbumin (^{99m}Tc-NGA) is used to monitor liver diseases like hepatoma, cirrhosis and liver metastases [4, 18].

5.2.1 Heart

Many positive ions (K^+, Na^+, Rb^+ and Cs^+) accumulate in the myocardium (heart tissues) through Na^+/K^+-ATPase, therefore it is thought that many myocardium radiopharmaceuticals carry net positive charge and follow Na^+/K^+-ATPase but ^{99m}Tc-hexa-MIBI does not obey Na^+/K^+-ATPase. ^{99m}Tc-CDO-MeB washes out rapidly from the heart, therefore possibility of Na^+/K^+–ATPase cannot be ignored [4]. Lipophilicity also play role for uptake in the heart, with logP > 5, the agents may bind to blood protein [4]. ^{99m}Tc tertiary butyl isonitrile (TBI) showed realistic myocardial uptake, however liver and lung activities were high and prolonged leading to high background activity. Among Isonitriles series, ^{99m}Tc-hexakis-2-methoxy-2-isobutylisonitrile (MIBI) shows good properties for myocardial imaging. It's uptake is not repressed to any observable limit with metabolic inhibitors, hence myocardial uptake is thought to be independent of Na^+/K^+-ATPase pump [5].

5.2.2 Cerebral blood flow agents

The cerebral blood agents should be stable in-vivo and should be high uptake to brain after passively passing the BBB. Blood-brain barrier is effectively crossed when molecule is less than 500 Da and logP should be 0.5-2.5, while the logP is distribution coefficient between octanol and water [5, 32].

5.2.3 Renal function agents

Function and morphology of kidneys are studied by ^{99m}Tc radiopharmaceuticals. Originally Na[^{99m}TcO4] was used as kidney agent but it is excreted rapidly through liver. Later on ^{99m}Tc-DTPA and ^{99m}Tc-DMSA (dimercaptosuccinic acid) were discovered with required physicochemical properties. The structure of ^{99m}Tc-DTPA is still unknown. ^{99m}Tc-MAG_3 is also renal function agent with 5^+ oxidation state. ^{99m}Tc-MAG_3 structure is well known with $[TcO]^{3+}$ cor which is reduced from Tc(VII) by $SnCl_2$. The excess $SnCl_2$ is destroyed by air ventilation of the kit [5]. ^{99m}Tc-MAG_3 is also produced in Pakistan, while it is produced in USA with TechneScan®, as commercial name. Renal mass is measured by other agents; for example, ^{99m}Tc(V)-DMSA (dimecapto-succinic acid) and TcO(glucoheptonate). Ethylene -dicysteine (^{99m}Tc(V)-ECD)$^{2-}$ have 40% higher clearance than ^{99m}Tc-MAG_3 and it is excreted through renal tubes. ^{131}I-hippuran was replaced with ^{99m}Tc-MAG_3 [11]. Attempts to modify MAG_3 ligand by replacing glycine or introducing a chiral center have yielded modified ligands, such as ^{99m}Tc-D-MAMAG [11].

5.2.4 Brain perfusion agents

Blood-brain barrier is crossed by active transport or passive diffusion routes. Other essential nutrients enter the brain by active transport. Neutral lipophilic compounds of lower molecular weight less than 500 Dalton and partition coefficient of 0.9–2.5 for lipids, enter via passive diffusion.

Propylene amine oxime (PnAO) makes neutral lipophilic complexes with ^{99m}Tc, e.g., ^{99m}TcO-d,l-HM-PAO, ^{99m}TcCl $(DMG)_3$2MP, ^{99m}TcO-L, L-ECD go through BBB due to neutral and lipophilic character [4, 5]. Most of the current brain perfusion agents reach brain through diffusion are called first generation, while future research activities may lead to prepare complexes which can metabolize in the brain and may stay longer [4]. ^{99m}Tc-d, l-hexamethyl propylene amine oxime (HMPAO) shows such features but have limited stability. ^{99m}Tc-ECD have relatively more stability and fast clearance from the blood into the renal system [5].

5.2.5 Infection and inflammation agents

^{99m}Tc-citrate and ^{99m}Tc-glutathione accumulate in inflammatory lesions. ^{99m}Tc-human hlgG is effective for detection of inflammation. The main development for imaging infection involves the use of the antibiotic ciprofloxacin. ^{99m}Tc-labeled antimicrobial peptide ubiquicidin [37] ^{99m}Tc-HNE and ^{99m}Tc-antigranulocyte MoAb and ^{99m}Tc-labeling sulfadiazine are important infection imaging agents [38].

5.2.6 Tumour imaging

There are limited ^{99m}Tc complexes for imaging tumors. ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are used for imaging breast cancer lesions and metastatic thyroid cancer. ^{99m}Tc(V)-DMSA is used for medullary thyroid carcinoma. ^{99m}Tc-TBI is used for metastatic thyroid carcinoma and ^{99m}Tc-d,I-HMPAO is used for brain tumors.

5.2.7 Hypoxia imaging

Hypoxic tissues are resistant to radiotherapeutics and chemotherapeutic agents. However, ^{99m}Tc complexes of nicotinamide and pyridinium derivatives of monodentate thiols have been discovered for hypoxia imaging [5].

5.2.8 Colloids

Since, the start of ^{99m}Tc radiopharmaceuticals diagnostic applications, ^{99m}Tc-S and $^{99m}Tc_2S_7$ colloids are being used for liver, spleen and bone marrow imaging [8].

5.2.9 Bone scan

^{99m}Tc-MDP and ^{99m}Tc-HMDP are well-established radiopharmaceutical for skeletal imaging. ^{99m}Tc complexes of lidocaine derivatives, i.e., acetanilido iminodiacetic acid (IDA), include IDA, HIDA, BIDA, EHIDA, DISIDA, PIPIDA and LIDA are also used for bone scan. Subramanian et al. [4, 11] discovered ^{99m}Tc-tri-polyphosphate for bone tumors. ^{99m}Tc-polyphosphate, ^{99m}Tc-pyrophosphate (PYP), diphosphonates [1-hydroxyethylidene diphosphonate (HEDP), methylene diphosphonate (MDP), ^{99m}Tc-glucarate and hydroxymethylene diphosphonate (HMDP)] have been synthesized. These complexes accumulate in bone because of their affinity with calcium in actively growing bones.

6. ^{99g}Tc Radioactive Waste

When ^{99m}Tc is injected to patients, a significant portion remains in injection vials and decays to ^{99g}Tc. ^{99m}Tc residual activity in injection vials after patient injection can vary from 1% [39] to 50% [10], depending upon whether tracer is lipophilic or hydrophilic, syringe material and tracer time in the vial. ^{99m}Tc residual activity of 0.22-38.41%, with an average value of 13.07% has been recently reported [40]. The average value is calculated from 1837 measurement over a period of one year [40]. Usually 90% of the ^{99m}Tc is eluted with 5 ml of saline solution, and residual activity is just 10%, as revealed during an interview of molybdenum experts at PINSTECH.

One mCi of ^{99m}Tc is equal to 3.3 pCi of ^{99g}Tc, as shown in eq. (2). As time passes ^{99g}Tc mole fraction increases in the generator than ^{99m}Tc [39, 40]. Milking of generator within 12 hours is advisable, otherwise the share of ^{99g}Tc is increased (Table 3). Sometime patients do not reach hospital on the day of appointment or plant may produces ^{99}Mo generators more than demand. In this case ^{99m}Tc is not milked from the ^{99m}Tc generator, ^{99}Mo decays to ^{99g}Tc, and a sizeable waste of ^{99g}Tc is generated which needs proper waste management.

Table 3: Mole fraction of ^{99m}Tc/^{99g}Tc on generator with time after complete elution.

Time since elution (hour)	Mole fraction ^{99m}Tc/Tc$_{total}$	Mole fraction ^{99g}Tc/Tc$_{total}$	^{99g}Tc/^{99m}Tc
3	0.73	0.27	0.4
6	0.62	0.38	0.6
12	0.46	0.54	1.2
24	0.28	0.72	2.6
48	0.13	0.87	6.6
72	0.077	0.923	12.1

^{99g}Tc is mobile in ^{99g}Tc(VII)O_4^- anionic form, however low valent mineral phase of ^{99g}Tc, i.e., $^{99g}TcO_2.2H_2O$, is stable [41]. ^{99g}Tc water solubility is 3.08×10^{-9} M (~190 Bq/L) in mineral form and this value is higher than maximum permissible drinking level concentration of 5.3×10^{-10} M (~33 Bq/L). ^{99g}Tc(IV) is less soluble in TcS_2 and Tc_2S_7, so reducing ^{99g}Tc(VII)O_4^- to ^{99g}Tc-S further hinders remobilizations [42].

^{99g}Tc radioactive waste is a challenge from spent fuel and radiopharmaceutical perspective. A huge stockpile of ^{99g}Tc in low radioactivity waste is present worldwide due to partially used/unused ^{99m}Tc generators and medical centers' syringes [43]. ^{99g}Tc is redox sensitive and volatile radionuclide, so it is not captured in glass due to low temperature volatility of $^{99g}TcO_4^-$ [44]. Currently it is suggested to immobilize ^{99g}Tc by lattice incorporation into stable mineral oxide of other minerals. The immobilization strategies evolved during past two decades for ^{99g}Tc radioactive waste have been summarized in Table 4. Currently zeolites, titanates, silicotitanates and hexacyanoferrates are available as commercial sorbents for ^{99g}Tc immobilization. However, inorganic materials that are highly selective for anionic radionuclides have been tested for their sorption properties for technetium, including tin dioxide [45] and Iron [46]. Few authors have reported antimony-doped SnO_2 as sorption based material for ^{99g}Tc. Risto [7] has reported up to 40% doping of Sb (as surrogate of ^{99m}Tc) into SnO_2 does not changed SnO_2 structure [45]. Khan et al. [6.] suggested Re-doped SnO_2 (Re as surrogate of ^{99g}Tc) for ^{99g}Tc immobilization. They argued up to 50% doping of Re into SnO_2 does not change SnO_2 structure [6, 7]. SnO_2 is one option to chemically modify ^{99g}Tc into inorganic oxides,

Table 4: Evolution of ^{99g}Tc waste forms.

Immobilization strategy	Year
Low-temperature phosphate ceramic waste forms development	1997 [62]
Magnesium potassium phosphate (MKP) ceramics of ^{99g}Tc	2006 [63]
Antimony-doped SnO_2 as sorption based material for ^{99g}Tc	2010 [64]
Borosilicate nuclear waste Glass	2012 [65]
Iron oxide waste form	2012 [66]
Iron phosphate glass for immobilization of ^{99g}Tc	2013 [67]
99-Tc(IV) incorporation in Magnetite	2014 [68]
Layered double hydroxide $Mg_6Al_2(OH)_{17}TcO_4$, sodalite $Na_8(AlSiO_4)_6(TcO_4)_2$, pyrochlore $Cd_2Tc_2O_7$, spinel Mg_2TcO_4, perovskite $SrTcO_3$, rutile $TiO.6TcO.4O_2$, and goethite FeO(OH)	2015 [69]
Magnetite waste form doped with first row transition metal can significantly enhance ^{99g}Tc retention in magnetite in the order Co>Zn>Ni.	2016 [70]
99-Tc(IV) immobilization using graphene modified nanoscale zero-valent iron particles	2016 [71]
Mineral incorporation: zeolites, titanates, silicotitanates, hexacyanoferrates, mackinawite (FeS) forms	2016 [46]
Ceramic immobilization options for technetium	2017 [72]
Mineral incorporation:c-precipitation of ^{99g}Tc with Sn(II) as SnO_2 phase	2018 [7]
Cement waste form	2018 [73]
^{99}Tc immobilization from off-gas waste streams using nickel-doped iron spinel	2019 [74]
Immobilization of solidified ceramic forms with magnesium phosphate cement	2019 [75]
99-Tc(IV) in Magnetite	2020 [76]

while others include magnetite (Fe_3O_4) and mackinawite (FeS) [47], layered double hydroxide $Mg_6Al_2(OH)_{17}TcO_4$, sodalite $Na_8(AlSiO_4)_6(TcO_4)_2$, pyrochlore $Cd_2Tc_2O_7$, spinel Mg_2TcO_4, perovskite $SrTcO_3$, rutile $Ti_{0.6}Tc_{0.4}O_2$ and goethite FeO(OH) [44].

5. Conclusions

^{99m}Tc is important candidate of future diagnostic options including SPECT and SPECT/CT. It is cheaper than PET and can be a possible competing method of diagnosis. In order to expand its basis, a fundamental research is needed to explore ^{99m}Tc redox chemistry and ^{99m}Tc-ligand coordination chemistry [48]. A detailed analysis of ^{99m}Tc radiopharmaceutical literature gives impression that ^{99m}Tc radiopharmaceuticals industry is changing in three major areas in future: these are ^{99}Mo/^{99m}Tc production methodology, generator design and drug delivery in the organ. Beaver and Hupfh [49] proposed cyclotron based production of ^{99}Mo in 1971 but it was not method of choice because of low specific activity and low cross section. Neutron based method is still considered to be a non-efficient method. Proton irradiation of enriched molybdenum [^{100}Mo(p,2n)^{99m}Tc] target can be an effective method in the future. Accurate calculation suggests proton must have energy 15-20 MeV for optimum yield, sufficient activity and purity [9]. This energy proton can be produced by medical synchrotron. The excitation function (^{100}Mo(p,2n)^{99g}Tc) is 4 times higher for ^{99g}Tc than ^{99m}Tc in the same energy; however, the ratio of ^{99m}Tc/$^{99m+99g}$Tc is same as 24-h life ^{99m}Tc generator. ^{98}Tc can be minimized by keeping energy below 17 MeV. The ^{99m}Tc yield is 5-14 Ci using 99.05% ^{100}Mo with 20 MeV proton beam for irradiation time of 1-3 hour [9, 50–58]. Currently ^{99m}Tc is milked from ^{99}Mo using alumina column; however, other methods can be tried to get ^{99m}Tc. High capacity sorbents like poly zirconium, poly titanium oxychloride and synthetic alumina functionalized with sulfate moiety are future sorbent materials. Multicolumn selectivity inversion generator (MSIG) and supported liquid membrane can be future design [59–61]. Current commercial alumina column based ^{99m}Tc generators are most sophisticated [59] but research is ongoing for better technology. Time required to prepare existing alumina column generator is less than 5 minutes, its high specific activity is greater than 37 TBq, 95% ^{99m}Tc is eluted in less than 4 mL saline and ^{99}Mo to ^{99}Tc breakthrough is ~10^{-4}. The 3rd avenue is receptor specific labelled radiopharmaceuticals and there is large space for biochemists and organometallic chemists to work together in this field to produce high quality 3rd generation radiopharmaceuticals.

Acknowledgement

Authors are thankful to Dr. Muhammad Khalid (Head IPD), Mr. Masood Mahmood, Mr. Khalil Ahmad, Mr. Rashid Khan, Mr. Babar Hussain, Mr. Irshad Ullah, and Mr. Munib Shafique for support in this work. The authors are highly thankful to Head HPD (Mr. Khalid Mehmood), Director S & S (Mr. M. Rafiq Sheikh) and former DG PINSTECH (Engineer Iqbal Husain Khan) for support and encouragement. The authors are thankful to Dr. Khalid Khan (Head Radioactive Waste Management Facility), Bashar Khan (former head generator production group), Dr. Abdul Jabbar (Head Environmental Monitoring Group) and Dr. Muhammad Adnan Iqbal for fruitful discussions related to this review article.

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