



Use of ^{99m}Tc in The Field of Radiofarmation: A Review

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ABSTRACT

Technetium-99m (^{99m}Tc) has been applied in nuclear medicine as a radiopharmacy for both diagnosis and therapy. ^{99m}Tc is obtained from a $^{99}\text{Mo}/^{99m}\text{Tc}$ (half-life 66 h) generator in the form of sodium pertechnetate ($\text{Na}[^{99m}\text{TcO}_4]$) by decaying to ^{99m}Tc for 6 hours and emitting gamma energy rays ($E_\gamma = 140 \text{ keV}$). This radionuclide has an electron configuration of $4d^5 5s^2$, which will form complexes with different ligands and have oxidation rates from +1 to +7. The coordinated complex of technetium-99m has been utilized in nuclear medicine in tissues and organs (thyroid, red and white blood cells, kidneys, brain, myocardial, and bone). The resulting kit production must have based on Good Manufacturing Practice, which consists of batch planning, washing, sterilization of glassware and stopper, starting material, preparation of large quantities of the solution, sterile filtration, dispensing, crimping, a summary of process control, quarantine, packaging and leaving the production premises.

1. Introduction

In general, radiopharmaceuticals are a medicinal product that is usually given to patients intravenously. Radiopharmaceuticals are a combination of the relationship between 2 elements, carriers, and at least one radioactive atom, which has nuclear, diagnostic, and therapeutic properties. Carriers play a significant role in transporting selective radionuclides to specific biological targets (Figure 1).

Technetium-99m (^{99m}Tc) is a type of medical radionuclide that was widely used for diagnosis in nuclear medicine. ^{99m}Tc radionuclide (half-life of 6 hours) is the decay product of the ^{99}Mo radionuclide, which has a half-life of 66 hours (2). Generally, ^{99m}Tc is obtained from the $^{99}\text{Mo} / ^{99m}\text{Tc}$ generator in sodium

pertechnetate ($\text{Na}[^{99m}\text{TcO}_4]$). ^{99m}Tc decays to ^{99}Tc for 6 hours by emitting gamma energy rays ($E_\gamma = 140 \text{ keV}$) (Hahn *et al.* 2014).

^{99m}Tc labeled radiopharmaceuticals applied in the world of nuclear medicine, including ^{99m}Tc -MDP (methylene diphosphonate) for staging or staging in cancer that will provide bone imaging (4). Also, ^{99m}Tc -DTPA-trastuzumab has been used for assessment in HER2 / neu expressing breast cancer (5). Then ^{99m}Tc -PYP (pyrophosphate) to detect leakage of fluid in the brain (cerebrospinal fluid) (Ponto dan Graham, 2014). ^{99m}Tc -mercaptoacetyl-triglyceride (MAG3) has been used for the diagnosis of kidney function (7). ^{99m}Tc -teboroxime, ^{99m}Tc -sestamibi, and ^{99m}Tc -tetrofosmin have been applied to cardiac perfusion, whereas ^{99m}Tc -exametazime and ^{99m}Tc -bicisate were for brain

perfusion. ^{99m}Tc -mertiatide (detection of renal function), ^{99m}Tc -TRODAT1 (Dopamine reuptake), ^{99m}Tc -depreotide (expression of the somatostatin receptor), and ^{99m}Tc -tilmanocet (lymph node uptake) (8).

The role of radiopharmaceuticals in nuclear medicine is crucial to do as an early preventive measure against cancer before it occurs so that it has expected to help patients before the stage of metastasis.

^{99m}Tc radiation

Technetium has element number 43, which Perrier and Segrè in 1937 in samples of molybdenum irradiated by deuteron (9). ^{99m}Tc has widespread use in nuclear medicine for diagnostic purposes. This metastable isomer decays with a half-life of 6 hours, decomposing to technetium-99m, which has a stable half-life of 2.13×10^5 years, as the decay scheme can be seen in Figure 2.

^{99m}Tc has been widely used in radiopharmaceutical compounds. The metastable state of ^{99m}Tc is 0.1427 MeV in the above-ground state (9). It is then very quickly produced from the primary decay of molybdenum-99 via the compact and portable $^{99}\text{Mo}/^{99m}\text{Tc}$ generator system almost always encountered in nuclear medicine (1).

The generator system is an effortless piece of equipment consisting of an alumina column, where ^{99}Mo is absorbed in the chemical form of molybdate $[\text{MoO}_4]^{2-}$. The decay of ^{99}Mo to ^{99m}Tc leads to the formation of pertechnetate $[\text{TcO}_4]^{-}$, which is less tightly bonded to the alumina column because the negative charge is single compared to the double negative charge on the molybdate. $[\text{TcO}_4]^{-}$ can be eluted easily from the column using saline solution resulting in a reduction caused by the under-vacuum vial when introduced to the pertechnetate collecting area (Figure 3). The ^{99m}Tc -pertechnetate sodium obtained is readily available for injection or other radiopharmaceutical preparation (1).

Chemical Basic Properties of Tc

Technetium has an electron configuration of $4d^5$

$5s^2$, where it will undergo the formation of complexes with different ligands, and the oxidation state changes from +1 to +7. The level of oxidation is the main parameter in determining the chemical properties of complex compounds. Technetium can form chemical bonds consisting of sigma and pi electrons. Sigma bonds are of a colligative and coordinative type when there are a spin replacement and an electron pair donation (10).

The structure of the technetium complex is characterized by a coordination number (N) varying from 4 to 7 so that it is possible to form a tetrahedral ($N = 4$), a tetragonal pyramid ($N = 5$), an octahedral ($N = 6$) and a pentagonal bipyramidal geometry ($N = 7$). Technetium also has an electric charge (Z) consisting of anionic ($Z = -1$), neutral ($Z = 0$) and cationic ($Z = +1$). Table 1 presents the various types of complexing centers and their oxidation state parameters, coordination number, and electrical charge (10).

The technetium compound used for clinical use is ^{99m}Tc -sodium pertechnetate for brain and thyroid imaging, while colloidal ^{99m}Tc -sulfur for imaging the liver, spleen, and bone marrow (9). The advantages of using ^{99m}Tc for imaging purposes are :

1. Low radiation dose because it has a short half-life and no beta radiation.
2. The resulting photons were very high (89%) from 140 keV gamma; excellent network penetration, and easily collimated and detected efficiently by a gamma camera.
3. Availability of generators for local use.
4. They were quickly combined into various other chemical forms.

^{99m}Tc Radiopharmaceutical Generation

The radiopharmaceutical generation from ^{99m}Tc can be divided into two generations, namely :

- a. When the first generation of technetium was produced, it was necessary to ensure reduction. This is because technetium has a very short physical half-life, so marking on the spot is required. The kit formulation has provided freeze-

drying ligands compatible with Sn(II)-chloride as a reducing agent. The results were carried out by a one vial marking system. The kit was dissolved by injecting pertechnetate (eluate generator) into the freeze-dried product under aseptic conditions. The earliest technetium radiopharmaceuticals were ^{99m}Tc -gluconate and ^{99m}Tc -glucoheptonate, but no experimental evidence of the pentacoordinate geometry was found. Although this complex is hydrophilic, it shows high plasma protein bonds (50–70%) (10).

Therefore, both glomerular filtration and tubular excretion by the kidneys occur by very slow pharmacokinetics. This is why ^{99m}Tc -gluconate and ^{99m}Tc -glucoheptonate are no longer used in kidney studies because they have low stability for red cell marking and as ligand exchange pairs for tagging other molecules. Another radiopharmaceutical with hydrophilic properties is ^{99m}Tc -DTPA. However, only 10% of the ^{99m}Tc -DTPA is bound to plasma proteins, and glomerular excretion occurs in the kidneys. The pharmacokinetics of ^{99m}Tc -DTPA is much faster than ^{99m}Tc -gluconate.

In an alkaline medium ($\geq \text{pH } 8$), all -SH free groups of dimercaptosuccinic acid (DMSA) will react with technetium to form a penta coordinated biscomplex, ^{99m}Tc -DMSA (V). This biscomplex accumulates both in the kidneys and in soft tissue tumors such as medullary carcinoma. If the pH is not more than 9, the compound has suitable stability and can be injected. When the DMSA marking is carried out in an acidic medium, a hexacoordinated asymmetric biscomplex is formed where one molecule is attached to the technetium through the 2 -S- and 1 -O- bridges, while the other is attached to the 1 -S- and 2 -O- and 1 -SH bridges, which remains free. Renal scintigraphy uses ^{99m}Tc -DMSA (III), which provides quantitative information about each kidney's functional mass since renal uptake is proportional to the available group.

All ^{99m}Tc -phosphonates with ligands such as MDP, HMDP, and HEDP can be characterized by the general formula $\text{H}_2\text{O}_3\text{P-X-PO}_3\text{H}_2$, where $\text{X} = -\text{CH}_2, -$

$\text{CH}(\text{OH})-$ and $-\text{C}(\text{OH})(\text{CH}_3)-$. This is because it does not depend on its substituents, where phosphonates show a tendency to form oligomers, which can be prevented by adding antioxidants such as ascorbic acid before freeze-drying products and applied to bone scintigraphy. After all, technetium phosphonates are extracted from normal bone and bone lesions by chemisorption, followed by an exchange of hydroxyapatite (inorganic matrix of bone). Pyrophosphate can be used for in-vitro marking on red blood cells. Cold lyophilizate, Sn(II)-phosphate, can be injected after reconstitution in a solution containing salts, where this non-radioactive compound accumulates in red blood cells. Free pertechnetate is injecting into the patient 20 minutes after injection of Sn(II)-phosphate, resulting in red cell marking in in-vivo conditions (this is the first example of a targeting technique).

^{99m}Tc colloid sulfur is prepared from sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3$) in an acidic atmosphere (4.6 M HCl) or sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$) in neutral conditions by reducing technetium at high temperatures (88–100 °C). It can also contain more fine particles when prepared from Sn(II)-fluoride, which reacts with pertechnetate. ^{99m}Tc rhenium-sulfide colloid with a particle size of 10–80 nm can also be used for bone marrow scintigraphy, lymphoscintigraphy, and inflammation detection. Also, technetium-99m macroaggregate (particle size 10–45 μm) can be obtained from human serum albumin when the alkaline human serum albumin solution is neutralized at pH 5.2, and ^{99m}Tc microspheres (particle size: 5–75 μm) can be obtained when the treated human serum albumin alkaline solution is heated thus denaturing. Technetium-99m macroaggregate is used for pulmonary perfusion scintigraphy because lung accumulation is proportional to blood flow (10).

- b. After the success of the first generation of technetium radiopharmaceuticals, conventional radionuclides such as ^{51}Cr , ^{131}I , ^{197}Hg were regulated with technetium. Although difficult,

various small organic molecules giving neutral, lipophilic, or positively charged complexity are synthesized and tagged with technetium. These efforts resulted in the radiopharmaceutical technology being used today to study the brain and myocardial performance and investigate and quantify renal tubular function. Thus, as a cost-effective alternative to non-technological radiopharmaceuticals, second-generation products are of great clinical importance. Technetium-99m-MAG3 (mercaptoacetyltriglycine) was developed as an alternative to o-radioiodo-hippurate in complete renal function radiopharmaceuticals high tubular secretion is required. The tubular secretion of a compound is facilitated enzymatically by using a special geometry consisting of three atomic oxygen molecules (10).

If a hydrogen atom replaces a para-position amino acid, and when the same radioiodine is inserting into the ortho position, the resulting o-radioiodo-hippurate molecule shows a renal tubular excretion of about 85%. Simultaneously, the clinical use of radioiodo-hippuran daily is minimal, as the ^{125}I and ^{131}I are not suitable for gamma camera renography, and the ^{123}I is very expensive in some countries. On the other hand, the three oxygen atoms' ideal geometry is the -COOH terminal and the adjacent carbonyl group of a tripeptide such as triglycerine. In comparison, three nitrogen atoms can take part in the complexation with technetium. To ensure a stable complex with a coordination number of 5, a mercaptoacetyl group binds to the nitrogen terminal triglyline to give the N_3S complex (MAG3) (10).

Technetium-99m-HMPAO (hexamethyl propylene amine oxime) is the first neutral lipophilic technetium compound that can cross the brain's blood barrier. Brain uptake of the d and l (trans) isomers is high (up to 4% of the injected dose), whereas the meso (syn) isomer does not show acceptable accumulation of brain tissue. The corresponding concentration of trans isomers in the brain is constant from 2 to 4 minutes post-injection. The trans isomers are transformed intracellularly

into hydrophilic compounds and captured in brain cells. The brain uptake of $^{99\text{m}}\text{Tc}$ -HMPAO is proportional to tissue perfusion. Also, technetium-99m-MIBI (methoxyisobutylisonitrile), or $^{99\text{m}}\text{Tc}$ -sestamibi is a lipophilic complex with a positive charge often used clinically. To confirm the positive charge of the complex, the technetium atom in the low oxidation state (+1) is reacted with the isonitrile monodentate ligand to obtain $[\text{Tc}(-\text{C} = \text{NR})_6]^+$ with a hexacoordinated (octahedral) structure (10).

Tc Labeling

In current decays, the marking vector's targeting has become a significant object of modern radiopharmaceutical research. Technetium is a transition metal, which has a disadvantage when combined with other radionuclides, namely biologically active molecules. For example, $^{99\text{m}}\text{Tc}$ cannot replace carbon or hydrogen atoms in a targeting molecule, such as marking with ^{11}C , ^{18}F , and ^{123}I . The metallic fragments shown in figure 4 show a combination with a well-coordinated set of atoms, which provides an effective strategy for tethering biologically active parts to the technetium-99m complex. The metal fragment strategy involves a two-component system consisting of radioactive metal fragments and a suitable chelating group that will then bind to the selected bioactive molecule via the spacer group.

The high affinity of the precursor metal fragments for the bioactive ligand's specific binding site makes it possible to obtain the conjugate complexes produced from the selected molecular block building (figure 5).

1. $^{99\text{m}}\text{Tc(V)}$ -Oxo Core

$^{99\text{m}}\text{Tc(V)}$ -Oxo Core is a widely used metal fragment. These complexes are based on cores, generally pentacoordinated, which adopt a square pyramidal geometry with π bonds of oxo groups at the apical position. The effect of the strong transposition of the oxo group makes the six oxo-coordinated technetium compounds relatively uncommon. The oxo core is stabilizing by donating atoms σ - and π - derived from amino, amido, and thiolate ligands as tetradentate

ligands of class N_4-xSx .

This ligand is very efficient in forming ^{99m}Tc -oxo complexes, which are more stable than those derived from bidentate ligands. This compound can be prepared by direct reduction of the ^{99m}Tc -pertechnetate anion in the presence of tin chloride, which is the first step in the preparation of conventional ^{99m}Tc radiopharmaceuticals or through the ligand exchange reaction with $[\text{}^{99m}\text{Tc}]\text{Tc}$ -glucoheptonate (figure 6).

l,l - $[\text{}^{99m}\text{Tc}]\text{Tc}$ -ECD as a perfusion imaging agent in the brain with the market name Neurolite®. This complex compound is neutral and is forming by many $\text{Tc}=\text{O}$ coordination bonds of the tetradentate ligand with the two donor atoms of nitrogen and sulfur whose arrangement is square or pyramidal. This excellent symmetry makes the complex hydrophobic due to lipophilicity, which crosses the blood-brain barrier.

2. $^{99m}\text{Tc(V)}$ -Hydrazido Metal Fragment

Metalorganohydrazine chemistry is an alternative approach to radiopharmaceutical design based on the stable and inert state of the ^{99m}Tc fragment substitution. The ^{99m}Tc -hydrazido metal fragment is forming by a technetium-HYNIC (HYNIC = 6-hydrazinonicotinamide) core consisting of metal in the V oxidation state and one or two ligand positions at the coordination site. The bioactive molecules labeled with HYNIC are undoubtedly the most investigated, such as the somatostatin derivative for imaging neuroendocrine tumors. Most of the published data concern the commercially available ^{99m}Tc -[HYNIC, Tyr(3)]octreotide (Figure 7) prepared in a two-vial kit formulation containing EDDA as a co-ligand.

3. $[\text{}^{99m}\text{Tc(N)PNP}]^{2+}$ Metal Fragment

The mixed ligand complex of technetium nitride $[\text{}^{99m}\text{Tc}][\text{Tc(N)(PNP)Cl}_2]$ provides a further example for metal fragments, where the Tc (N) group has coordinated to a diphosphate chelating ligand of the PNP type, and two chloride atoms saturate the pentacoordinated geometry. These atoms can easily be replaced by bidentate (Y~Z) ligands, which have many electrophilic properties in the electron structure of the

molecular atoms (Y, Z), which are highly reactive to the metal block $[\text{}^{99m}\text{Tc(N)(PNP)}]^{2+}$ to obtain complexes asymmetrical $[\text{}^{99m}\text{Tc(N)(PNP)(Y~Z)}]^{0/+}$. The most representative myocardial tracers showed high effectiveness from this asymmetric complex, including ^{99m}Tc -N-DBODC and ^{99m}Tc -N-MPO (Figure 8).

4. $[\text{}^{99m}\text{Tc}][\text{Tc(CO)}_3]^+$ Metal Fragment

Core $[\text{}^{99m}\text{Tc}][\text{Tc(CO)}_3]^+$ is a powerful organometallic component formed chemically by technetium in oxidation state 1 in coordination with three carbonyl groups. The precursor $[\text{}^{99m}\text{Tc}][\text{Tc(CO)}_3(\text{H}_2\text{O})_3]^+$ can easily be prepared from pertechnetate eluted with the generator under reduced conditions (1).

GMP for KIT Production

The production of kits for the ^{99m}Tc radiopharmaceutical formulation is considered sterile medicinal products based on GMP (Good Manufacture Practice). Therefore, special requirements are needed to minimize the risk of the particle, microbiological and pyrogen contamination. Minimizing this risk depends on the skills, training, and attitudes of the personnel involved. Quality assurance is of utmost importance, and this type of manufacture must follow carefully defined and validated preparation methods and procedures. Personnel involved in the aseptic process of producing kits for the ^{99m}Tc marking must strictly follow the hygiene standards set out in the general GMP introduction.

This process shall be documented in the batch processing record. It is important that these notes are filled in during the process, not after completion. All forms must be written and confirmed with a signature, and identification of the person who wrote them must be made. If necessary, another staff member or supervisor should carry out a record check. Any deviations from the routine should also be noted, and the potential impact on product quality evaluated.

Completed batch processing should be recording and stored for at least three years after product expiration to trace the history of the product and process and the starting material used for its

manufacture. General procedures for radiopharmaceutical kit production include batch planning, washing, sterilization of glassware and stoppers, starting materials, preparing large quantities

of solutions, sterile filtration, dispensing, crimping, and summary controls processes, quarantine, packaging, and leaving the production premises (10).

Table 1. Characterization of the various technetium complexes (10)

Coordination number	Oxidation state	Electric charge	Tc complexing center		Compound	Organ/tissue-specific
			Sigma bond	Pi bond		
4	+7	-1	-	(= O) ₄	Pertechnetate	Thyroid
5	+5	-1	O ₄	= O	Gluconate	Red blood cell marking
			N ₃ S	= O	MAG ₃	Kidney
			N ₂ S ₂	= O	EC	Kidney
			S ₄	= O	DMSA (V)	Soft tissue tumor
5	+5	0	N ₄	= O	HMPAO	Brain, white blood cells
			N ₂ S ₂	= O	ECD	Brain
			S ₄	= N	NOET	Myocardium
6	+1	+1	C ₆	-	MIBI	Myocardium
	+1	+1	C ₃ N ₃ , C ₃ N ₂ O	-	Tricarbonyl	Few
	+3	+1	N ₂ O ₂ P ₂	-	Q 12	Myocardium
	+5	+1	P ₄	(= O) ₂	Tetrofosmin	Myocardium
6	+4	-	N ₃ O ₃	-	DTPA	Kidney
	+3	-1	S ₃ O ₃	-	DMSA(III)	Kidney
	-1	-	N ₂ O ₄	-	HIDA derivatives	The hepatobiliary system
	+4	-1	O ₆	-	Phosphonate	Bone
7	+3	0	N ₆ Cl	-	Tebroxime	Myocardial flow
7	+5	-1	N ₂ O ₄	= O	EDTA, DTPA, HIDA derivatives	Kidney, hepatobiliary system

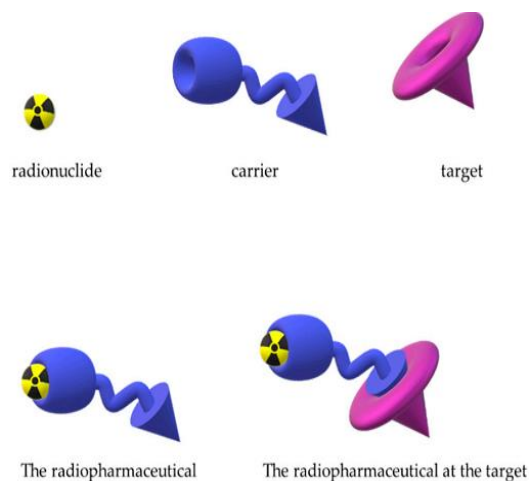


Figure 1. Schematic representation of the linkage between a carrier and radioactive atoms to form radiopharmaceuticals where interactions with specific biological targets (1)

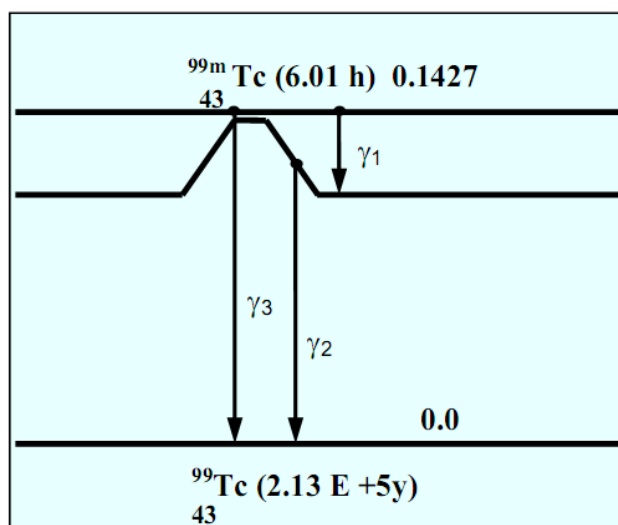


Figure 2. Schematic of the decay for technetium-99m (9)

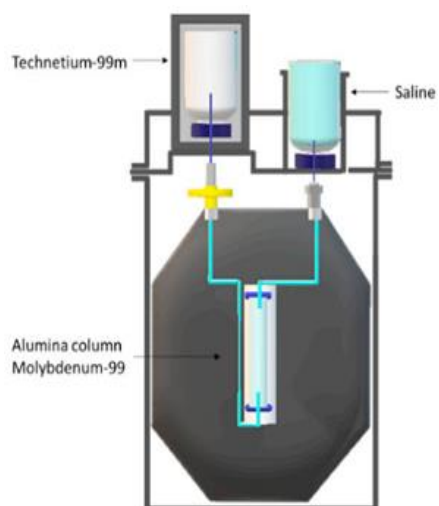


Figure 3. Schematic overview of the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator system (1)

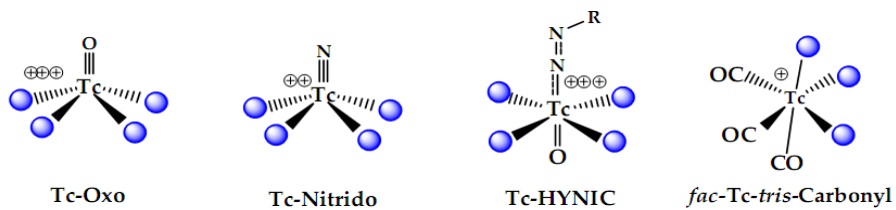


Figure 4. Inorganic Tc functional group for tagging bioactive molecules (1)

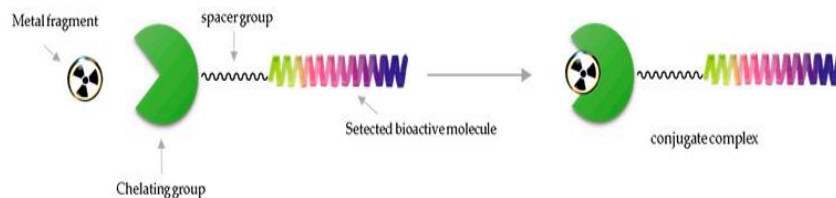


Figure 5. Schematic representation of metal fragment strategies for labeling bioactive molecules (1)

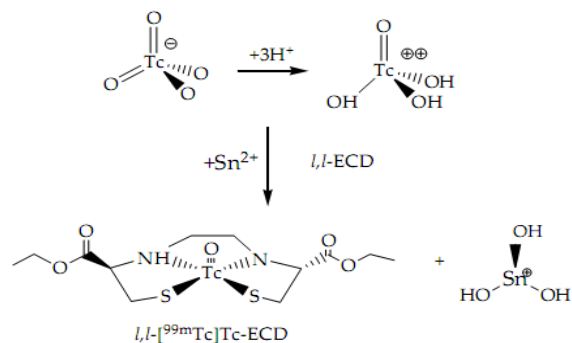


Figure 6. Reaction scheme of ^{99m}Tc N, N-1,2-ethylene diylbis-L-cysteine diethyl ester dihydrochloride of ^{99m}Tc pertechnetate (1)

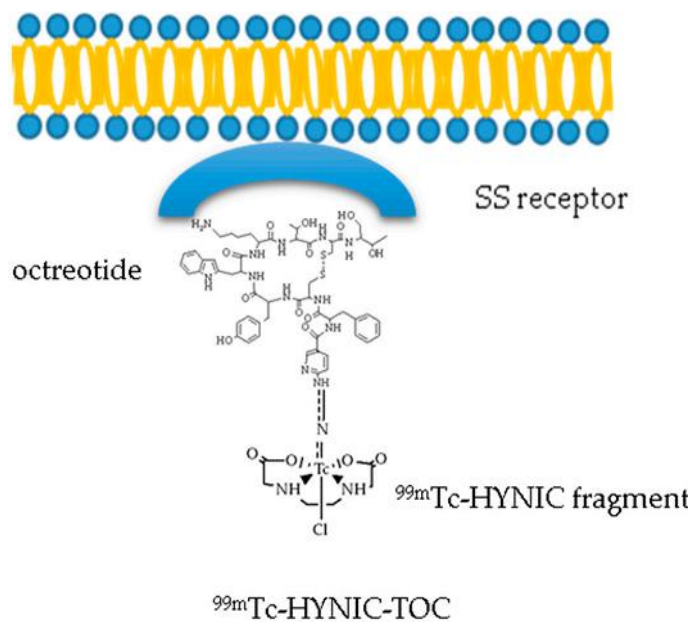


Figure 7. Illustration of the chemical structure of the ^{99m}Tc -HYNIC-TOC complex as an imaging agent for neuroendocrine tumors (1)

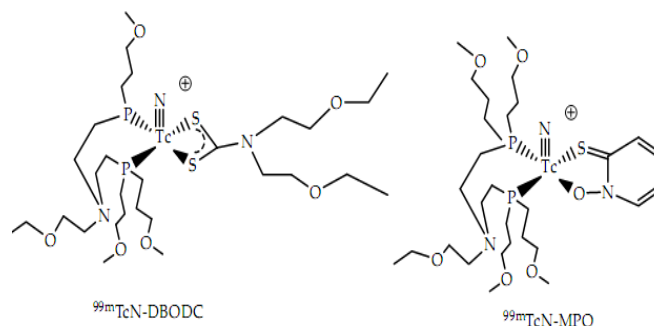


Figure 8. Chemical structure of two non-commercial imaging agents for myocardial perfusion, namely ^{99m}Tc -NDBODC and ^{99m}Tc -N-MPO (1)

2. Conclusion

Technetium has an electron configuration of $4d^5 5s^2$, which forms complexes with different ligands and has an oxidation state of +1 to +7. The use of ^{99m}Tc in nuclear medicine is very diverse in tissues and organs for diagnosis and therapy, ranging from the thyroid, red and white blood cells, kidneys, brain, myocardial, and bone. ^{99m}Tc is made from a generator, which is straightforward equipment consisting of an alumina column, where ^{99}Mo is absorbed in the chemical form of molybdate $[\text{Mo}]\text{MoO}_4^{2-}$ and decays from ^{99}Mo to ^{99m}Tc leads to the formation of pertechnetate $[\text{Mo}]\text{TcO}_4^-$. Thus, ^{99m}Tc becomes a radiopharmaceutical for use in nuclear medicine. This radiopharmaceutical kit's production is based on Good Manufacturing Practice with special requirements in mind to minimize the risk of contamination from particles, microbiology, and pyrogens.

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