Technetium-99m Radiopharmaceuticals

3

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3.1 Technetium Chemistry

3.1.1 Technetium-99m

The name *technetium* was derived by the scientist Mendeleyev from the Greek word *technetos*, meaning "artificial." Technetium-99m was discovered in 1937 by Perrier and Segre in a sample of naturally occurring ^{98}Mo irradiated by neutrons and deuterons. The first generator as a source for Tc-99m was introduced in 1957 at the *Brookhaven National laboratory*, and the first commercially available ^{99}Mo-^{99m}Tc generator was made available in 1965. Use of Tc-99m really revolutionized nuclear medicine procedures, particularly with the modern gamma cameras coupled to advanced electronics and computing systems. This revolution was not completed until 1970, when the stannous ion reduction method of ^{99m}Tc-diethylene-triaminepentaacetate (DTPA) production as an "instant kit" was described, that simple and convenient "shake-and-bake" preparations for a large number of ^{99m}Tc-labeled radiopharmaceuticals were possible.

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Technetium-99m is a transient metal, exists in many oxidation states, and can combine with a variety of electron-rich compounds. ^{99m}Tc-labeled radiopharmaceuticals are partners of 85% of all nuclear medicine procedures because of the unique properties of ^{99m}Tc, which is considered ideal for the following reasons:

1. It is a gamma emitter with an ideal energy of 140 keV for scintigraphy.
2. The half-life of 6.02 h is suitable for preparations and clinical applications.
3. Radiation burden to the patient is considerably reduced because of the absence of particulate radiation and short half-life.
4. When labeled with a specific chemical substrate, the labeled radiopharmaceutical provides a high ratio of target to nontarget.
5. It is readily available through a weekly delivery of ^{99}Mo-^{99m}Tc generators.
6. Quality control of its radiopharmaceuticals can be achieved rapidly and by routinely available tools in any nuclear medicine department [1].

Technetium can exist in eight oxidation states (i.e., 1− to 7+); the stability of these oxidation states depends on the type of the labeled ligand and the chemical environment. The 7+ and 4+ oxidation states are the most stable. Tc-99 is presented at any ^{99}Mo-^{99m}Tc generator elution due to the decay of Mo^{99} to Tc^{99m}. It represents about 70% of the total technetium concentration in an eluate; however, this percentage may be increased to about 90% for the first eluate and after weekend elutions of generator. Tc-99m and Tc-99 are chemically identical, so they compete for all chemical reactions. In preparations containing only limited Sn^{2+} as a reducing agent (e.g., ^{99m}Tc-HMPAO [hexamethylpropylene amine

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oxime] preparation), only freshly prepared Tc-99m elution is used for obtaining maximum labeling yield [2, 3].

3.1.1.1 ^{99m}Tc Reduction

Generator-produced Tc-99m is available in the form of sodium pertechnetate (^{99m}Tc-NaTcO$_4^-$), which has an oxidation state of 7+ for ^{99m}Tc. TcO_4^- has a configuration of a pyramidal tetrahedron with Tc^{7+} at the center and four oxygen atoms at the apex and corners of the pyramid. TcO_4^- is chemically nonreactive and has no ability to label any compound by direct addition; therefore, reduction of Tc^{7+} to a lower oxidation state is required. The reduction process is obtained using a number of reducing agents (e.g., stannous chloride, stannous citrate, stannous tartarate, etc.), with stannous chloride preferred [4].

The TcO_4^-/stannous chloride ($SnCl_2.2H_2O$) reduction method is described as follows:

$$3\ Sn^{2+} - 6e \rightarrow 3Sn^{4+}$$
$$2TcO_4^- + 16H^+ + 6e \rightarrow 2\ TcO_4^- + 8H_2O$$
$$\text{Overall}, 3\ Sn^{2+} + 2\ TcO_4^- + 16H^+ \rightarrow 3Sn4^+ + 2\ TcO_4^- + 8H_2O$$

Since the amount of ^{99m}Tc in the ^{99m}Tc eluant is very small, only a little Sn^{2+} is required for reduction. However, a 10^6:1 ratio of Sn^{2+} ions to ^{99m}Tc atoms is applied for all ^{99m}Tc-labeled radiopharmaceutical kits to ensure complete reduction of all ^{99m}Tc atoms.

The Tc^{4+} is now in the appropriate chemical form to react with an anion like PYP, Pyrophosphate methylene diphosphonate (MDP), or DTPA. The complex formed is known as a *chelate*; the generic equation is shown as follows:

$$Tc^{4+} + \text{chelating agent}^{n-} \rightarrow Tc - \text{chelate}$$

For example,

$$Tc^{4+} + \text{pyrophosphate}^{4-} \rightarrow Tc - \text{pyrophosphate}$$

Generally, for any ^{99m}Tc-labeled preparation, there are three species that may be present:

- Bound ^{99m}Tc-labeled compound, which is the desired product, and its percentage reflects the yield of preparation
- Free pertechnetate (TcO_4^-), which has not been reduced by tin or produced by the action of oxygen
- Hydrolyzed technetium that did not react with the chelating agent or that was bound to hydrolyzed Sn^{2+}

3.1.1.2 ^{99m}Tc Reduction Problems

Presence of oxygen: The commercially available ^{99m}Tc labeling kits are flushed with N_2 gas to maintain an inert gas atmosphere in it in addition to the implementation of antioxidants (e.g., ascorbic acid). These arrangements are used to prevent the action of oxygen if sneaked into the preparation vial. Oxygen can cause oxidation of the stannous ions present, preventing the reduction to Tc^{7+} and thus increasing the percentage of free TcO_4^- in ^{99m}Tc-labeled radiopharmaceuticals. This problem can also be avoided by using a relatively large quantity of stannous ions.

Further, the high activity of ^{99m}Tc in the presence of oxygen can cause radiolysis of water-producing hydroxyl (OH), alkoxy (RO), and peroxy (RO_2) free radicals, which can interact with ^{99m}Tc chelates, producing more TcO_4^- in the preparation [5].

Hydrolysis of reduced technetium and tin: In aqueous solutions, ^{99m}Tc may undergo hydrolysis to form many hydrolyzed species of $^{99m}TcO_2$ complexes [6]. Hydrolysis competes with the chelation process of the desired compound, reducing the radiopharmaceutical preparation yield. In addition, these compounds can interfere with the diagnostic test when present in relatively high proportion. Hydrolysis of stannous compounds can also occur in aqueous solutions at pH 6–7, producing insoluble colloids that have the ability to bind to the reduced ^{99m}Tc, resulting in a low labeling yield. An acid is added to the kit to change the pH value of the solution and hence prevent hydrolysis of Sn^{2+} ions. Hydrolysis of reduced technetium and Sn^{2+} can be recovered by adding an excess amount of the chelating agent [7].

3.1.1.3 Technitium-99m Labeling Kit Designation

The kit designation is optimized to ensure that the desired ^{99m}Tc-labeled complex is obtained in its higher yield [8]. Several factors influence the

preparation process; they are primarily the nature and amounts of reducing agents and ligands, pH, and temperature.

An ideal Tc-99m labeling kit should contain the following:

Ligand: For targeting ^{99m}Tc to its desired location (e.g., DTPA, MDP, 2,6-dimethylphenylcarbamoylmethyl iminodiacetic acid [HIDA], and macroaggregated albumin [MAA])

Reductant: For reduction of free pertechnetate (TcO_4^-) (e.g., stannous chloride)

Buffer: To provide a suitable pH environment for the formation of a specific ^{99m}Tc-labeled complex

Antioxidant: To prevent reoxidation of the labeled compounds and hence increase the stability of the radiopharmaceutical (e.g., ascorbic acid, gentisic acid, and p-aminobenzoic acid)

Catalyst: Might be a ligand introduced to form an intermediary coordination complex when the formation of the desired complex is slow relative to formation of hydrolyzed-reduced technetium (e.g., DTPA, gluconate, and citrate)

Accelerators: To increase the radiochemical purity and the rate of complex formation

Surfactants (optional): Required to solubilize lipophilic ^{99m}Tc-labeled complexes (methoxyisobutyl isonitrile, MIBI) and particulate preparations (MAA and microspheres)

Inert fillers: To achieve rapid solubilization of the vial content through the control of particle size during the lyophilization process

3.1.2 Technetium and Technetium-Labeled Compounds

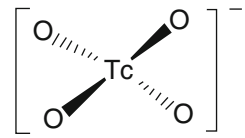
3.1.2.1 ^{99m}Tc-Sodium Pertechnetate

^{99m}Tc-sodium pertechnetate (TcO_4^-) is eluted from the ^{99m}Tc-^{99}Mo generator with sterile isotonic saline. Aseptic conditions should be maintained during the elution and dispensing processes, and the resultant ^{99m}Tc activity concentration depends on the elution volume [9]. Figure 3.1 shows the pertechnetate anion.

^{99m}Tc-sodium pertechnetate is used clinically in the following applications:

- Labeling with different chemical ligands to form ^{99m}Tc-labeled complexes

Fig. 3.1 Pertechnetate anion



- Thyroid scintigraphy
- Salivary gland scintigraphy
- Lachrymal duct scintigraphy
- Meckle's diverticulum scintigraphy

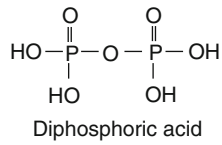
In blood, 70–80% of ^{99m}Tc-pertechnetate is bound to proteins. The unbound fraction is preferentially concentrated in the thyroid gland and other related structures, such as salivary glands, gastric mucosa, choroid plexus, and mammary tissue. ^{99m}Tc-pertechnetate is excreted mainly by the kidneys, but other pathways may be relevant in certain circumstances, such as saliva, sweat, gastric juice, milk, etc [10]. Lactating women secrete 10% of pertechnetate in milk. Pertechnetate can also cross the placental barrier [11].

3.1.2.2 ^{99m}Tc-Labeled Skeletal Imaging Agents

Since phosphonate and phosphate compounds are localized with high concentrations to bony structures, phosphate derivatives were initially labeled with ^{99m}Tc for skeletal imaging in 1972. However, phosphonate compounds are preferable because they are more stable in vivo than phosphate compounds due to the week P–O–P bond of phosphates, which can be easily broken down by phosphatase enzymes, whereas the P–C–P bond in diphosphonate is not affected [12] (Fig. 3.2).

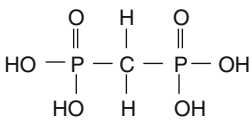
Three commonly used diphosphonate compounds are MDP, hydroxymethylene diphosphonate (HDP), and 1-hydroxyethylidene diphosphonate (HEDP). The first two are shown in Fig. 3.3. ^{99m}Tc-diphosphonate agents are weak chelates and tend to degrade with time in the presence of oxygen and free radicals. Excess tin in the labeling kit can prevent these oxidative reactions while maintaining the optimal value of the tin/chelating agent ratio to avoid the presence of undesired ^{99m}Tc-Sn-colloid.

^{99m}Tc-diphosphonate complexes are used for multipurpose bone imaging, whereas ^{99m}Tc-pyrophosphate

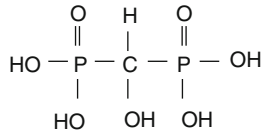


Diphosphoric acid

Fig. 3.2 Diphosphonic acid



Methlene diphosphonic acid



Hydroxymethylene diphosphonic acid

Fig. 3.3 MDP and HDP

compounds are used in red blood cell (RBC) labeling for gated blood pool and gastrointestinal tract (GIT) bleeding procedures.

Many mechanisms of tracer uptake by the skeleton have been proposed, and many factors play a role. The most common and applicable principle states that the calcium and phosphate on mature bone are presented as hydroxyapatite (HAB; sheets of calcium and hydroxyl ions with phosphate bridges linking them), which constructs any bony structure. In immature HAB, in which the calcium-to-phosphorus molar ratio is low, phosphate groups of the tracer can be obtained in this reactive new bone formulation phase. This idea has been evidenced by the higher uptake of these tracers in the joint and active areas of bone formulation in children. It is not well known if the technetium molecule can liberate itself from this bony structure or if it remains [13].

About 40–50% of ^{99m}Tc-HDPs accumulate in the skeleton following intravenous injection, while the rest is excreted mostly with urine.

Maximum bone accumulation occurs after 1 h and remains constant for 72 h. Cumulative activity excretion percentage varies according to the diphosphonate agent; however, it has been observed that about 75–80% of the activity is excreted through urine in the first 24 h.

^{99m}Tc-MDP, ^{99m}Tc-HDP, and ^{99m}Tc-HEDP have almost the same diagnostic efficiency, especially in detection of bone metastasis, trauma, infection, and vascular and metabolic diseases [14, 15].

3.1.2.3 ^{99m}Tc-Labeled Renal Imaging Agents

Diethylenetriaminepentaacetate (DTPA)

DTPA is produced commercially as a pentasodium or calcium salts in the presence of an appropriate amount of stannous chloride for reduction of the added free technetium [16]. The structural formula is shown in Fig. 3.4. The exact oxidation state of the ^{99m}Tc-DTPA complex is not known, although several valency states have been suggested (III–V).

The ^{99m}Tc-DTPA complex is used successfully in

- Renal studies and glomerular filtration rate (GFR) determination
- Cerebral scintigraphy when a blood-brain barrier (BBB) leak is expected
- Lung ventilation studies when used as an aerosol
- Localization of inflammatory bowel disease

The ^{99m}Tc-DTPA complex should undergo extensive quality control testing when used for GFR determination and pyrogenicity testing when used as a cerebral imaging agent since the brain is sensitive to pyrogens. After intravenous injection, ^{99m}Tc-DTPA penetrates the capillary walls to enter the extravascular space within 4 min. Because of its hydrophilicity and negative charge, it is eliminated from cells to the extracellular space. ^{99m}Tc-DTPA is removed from the circulation exclusively by the kidneys. ^{99m}Tc-DTPA cannot pass through the BBB unless there is a structural defect that permits diffusion of the tracer and hence is used for detection of vascular and neoplastic brain lesions. As an aerosol, diffusion of 0.5-μm diameter particles is to the lung periphery and alveolar retention, whereas larger particles ($\geq$1 μm) tend to diffuse to the trachea and upper bronchial tree [17].

Dimercaptosuccinic Acid (DMSA)

The kit contains an isomeric mixture of dimercaptosuccinic acid (DMSA) as a mesoisomer (>90%) in addition to D- and L-isomers (<10%). The structural formula of DMSA is shown in Fig. 3.5. Precaution should be taken with The ^{99m}Tc-DMSA labeling procedure because of the high sensitivity of the formulated complex to oxygen and light. In an acidic medium, the ^{99m}Tc(III)-DMSA complex (renal agent)

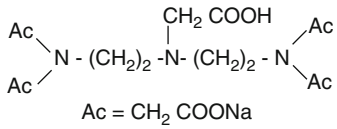


Fig. 3.4 Pentetate

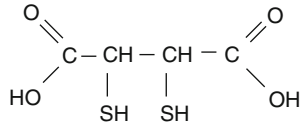


Fig. 3.5 Dimercaptosuccinic acid

is formed with high yield (95%). On the other hand, with elevated pH up to 7.5–8.0, the pentavalent ^{99m}Tc (V)-DMSA complex is produced.

After intravenous injection, the ^{99m}Tc(III)-DMSA complex is taken up in the renal parenchyma [18]. After 1 h, approximately 25% of the injected dose is found in the proximal tubules, 30% in the plasma, and 10% in the urine. The main uses of ^{99m}Tc-DMSA are to diagnose renal infection in children and in morphological studies of the renal cortex. Pentavalent ^{99m}Tc (V)-DMSA is used to detect medullary thyroid cancer cells and their soft tissue and bone metastases [19].

Mercaptoacetyltriglycine (DMSA)

The ^{99m}Tc-labeled mercaptoacetyltriglycine (MAG_3), ^{99m}Tc-MAG_3 (^{99m}Tc-Mertiatide) (Fig. 3.6), is the radiopharmaceutical of choice for renal tubular function assessment, particularly in renal transplants, replacing ^{123}I- and ^{131}I-hippuran (orthoiodohippurate, OIH) because of the unique characteristics of ^{99m}Tc for diagnostic purposes.

^{99m}Tc-Mertiatide is obtained by adding $^{99m}TcO_4$ to the kit vial and heating in a water bath (100°C for 10 min) followed by cooling for 15 min [20, 21]. Heating is required because at room temperature, formation of the ^{99m}Tc-MAG_3 is slow (52% in 2 h).

Generally, labeling should be performed with the highest possible specific concentration, although there are two recommended methods:

1. Use 3 ml of fresh eluate with an activity up to 30 mCi and dilute to 10 ml, then add $^{99m}TcO_4$ to the vial and heat for 10 min in a water bath. The 10 ml of complex volume is stable for 4 h.

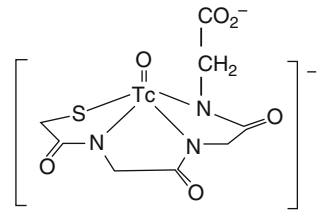


Fig. 3.6 ^{99m}Tc(V)-MAG_3 (mercaptoacetyltriglycine) complex

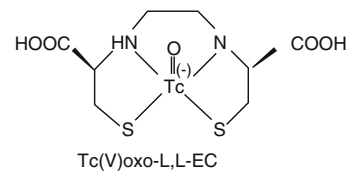


Fig. 3.7 Tc-99m-labeled ethylene dicysteine

2. Use 1 ml fresh eluate with maximum activity of 25 mCi and dilute to 4 ml to obtain a higher activity concentration. A complex stable for only 1 h will be obtained.

After intravenous injection, ^{99m}Tc-MAG_3 is rapidly distributed in the extracellular fluid and excreted by the renal system. The maximum renal accumulation occurs after 3–4 min injection. ^{99m}Tc-MAG_3 is used to evaluate renal dynamic function in obstructive uropathy, renovascular hypertension, and complications of transplant. It is also used to evaluate renal function as a presurgical assessment for donors admitted for kidney transplant [22].

Ethylene Dicysteine (EC)

The ethylene dicysteine (EC) kit consists of three vials: A, B, and C. The labeling procedure is achieved by adding $^{99m}TcO_4$ to vial A containing the EC active ingredient. Then, the dissolved contents of vial B (stannous chloride as a reducing agent) are added to vial A to react for 15 min. Finally, the contents of vial C (ascorbic acid in a buffer solution as a stabilizer) are dissolved and injected in vial A [23].

The ^{99m}Tc-EC complex (Fig. 3.7) has been used successfully since 1992 as a renal agent for the determination of the tubular extraction rate and examination of renal function in patients with transplanted kidneys, but it is not widely used because of its long and complicated preparation procedure in comparison

to MAG_3. It has similar clinical applications as MAG_3 [24].

Many other radiopharmaceuticals have been introduced for renal scan purposes, as ^{99m}Tc-p-aminohippuric acid (^{99m}Tc-PAH) and ^{99m}Tc-DACH, diaminocyclohexane but they have possessed inferior diagnostic and biokinetic features [25].

3.1.2.4 ^{99m}Tc-Labeled Myocardial Perfusion Agents

Methoxyisobutyl Isonitrile

^{99m}Tc-sestamibi was introduced initially under the brand name Cardiolite as a technetium-based radiopharmaceutical to replace Tl-201 in myocardial perfusion imaging.

The Cardiolite kit contains a lyophilized mixture of the MIBI chelating agent in the form of copper salt to facilitate labeling with ligand exchange at elevated temperature [26].

Labeling is achieved by addition of 1–3 ml of ^{99m}Tc-pertechnetate (25–150 mCi) to the reaction vial and shaking vigorously. Figure 3.8 shows the Tc-99m-labeled sestamibi complex. As with all other types of preparations that need heat, vial pressure normalization is essential in ^{99m}Tc-sestamibi preparation procedures. Heating in a water bath (100°C for 10 min) or in a microwave oven for 10 s is required to complete the formulation procedure [27].

^{99m}Tc-sestamibi is used for

1. Myocardial perfusion studies; diagnosis of ischemic heart disease, diagnosis and localization of myocardial infarctions, and assessment of global ventricular function
2. Diagnosis of parathyroid hyperfunctioning adenoma
3. Tumor (breast, bone and soft tissue, lymphoma, and brain) imaging

^{99m}Tc-sestamibi accumulates in the viable myocardial tissue according to blood flow like thallous chloride but is not dependent on the functional capability of the Na/K pump. Elimination of the complex from blood is fast, and the hepatobiliary tract is the main clearance pathway of the complex [28].

Tc-99m-Labeled Tetrofosmin

With the brand name Myoview, tetrofosmin was introduced as a myocardial imaging agent with the advantage that heating is not required. The ^{99m}Tc-tetrofosmin complex (Fig. 3.9) is formulated by adding up to 240 mCi of free technetium in a 4- to 8-ml volume with a specific concentration not greater than 30 mCi/ml to the reaction vial and shaking gently. Although the complex formation could be enhanced by heating, it is formed rapidly at room temperature in high yield. Tetrofosmin is sensitive to the preparation variables, especially the age of the eluate (less than 6 h) and the time interval from the last elution [29]. ^{99m}Tc-tetrofosmin is used in the diagnosis of myocardial perfusion abnormalities in patients with coronary artery

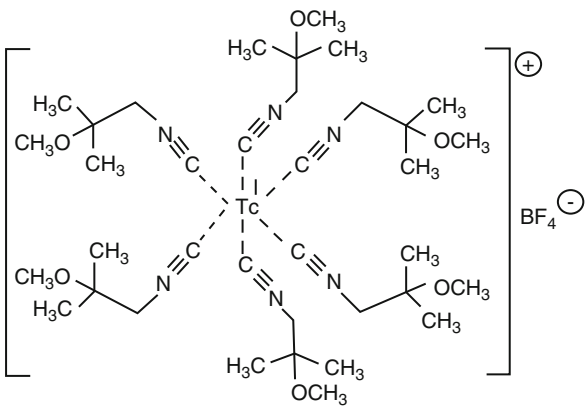


Fig. 3.8 ^{99m}Tc(I) sestamibi complex

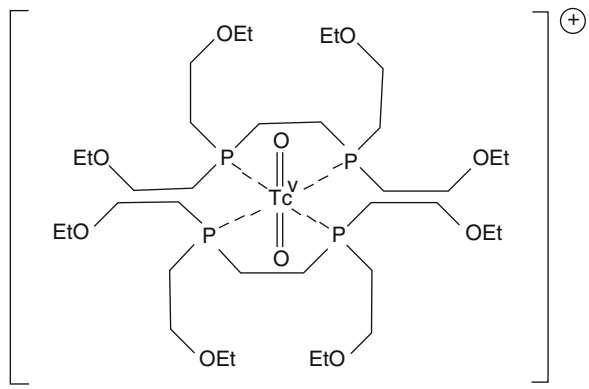


Fig. 3.9 ^{99m}Tc(V)-tetrofosmin complex

disease [30–32]. ^{99m}Tc-tetrofosmin is diffused to the viable myocardial tissue proportional to blood flow. After 5 min of intravenous injection, myocardial uptake is 1.2% at rest and 1.3% during stress and remains constant for at least 4 h. Elimination from blood is fast, and the major pathway of tetrofosmin clearance is the hepatobiliary tract.

3.1.2.5 ^{99m}Tc-Labeled Brain Perfusion Agents

Hexamethylpropylene Amine Oxime (HMPAO)

Use of ^{99m}Tc-HMPAO (exametazime) (Fig. 3.10) as a brain perfusion agent is based on its ability to cross the BBB as a lipophilic complex. The complex is obtained by adding up to 30 mCi of $^{99m}TcO_4$ to the reaction vial and inverting gently for 10 s. The ^{99m}Tc-HMPAO complex (primary complex) is initially unstable and tends with time to convert to a less-lipophilic form (secondary complex) that has less ability to cross the BBB [33]. Hence, it should be used within 30 min postpreparation after labeling to obtain radiochemical purity more than 85%. Instability of the complex has been attributed to the following three main factors:

1. High (9–9.8) pH
2. Radiolysis by hydroxy free radicals
3. Excess stannous ions

Stabilization of the ^{99m}Tc-HMPAO primary complex for up to 6 h could be achieved by adding stabilizers like methylene blue in phosphate buffer or cobalt (II)-Chloride to the reaction vials [34].

As mentioned, ^{99m}Tc-HMPAO is primarily used in brain perfusion imaging, although it is used for leukocyte labeling substituting ^{111}In-oxine. Methylene blue and phosphate buffer should not be used when the complex formulation is designed for labeling of leukocytes.

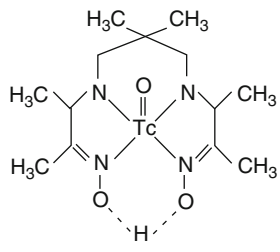


Fig. 3.10 ^{99m}Tc(V)-D,L-HMPAO (hexamethylpropylene amine oxime) complex

Neutral lipophilic molecules may cross the BBB by diffusion or active transport depending on the molecular size and structural configuration. The lipophilic ^{99m}Tc-HMPAO complex can cross the BBB and be extracted from blood with high efficiency. Cerebral extraction is about 5% of the total injected radioactivity. In vivo, the primary complex decomposes rapidly to a charged, less-lipophilic complex and then is trapped in the brain [35, 36].

After injection, 50% of the radioactivity is eliminated from blood within 2–3 min. After 5 min when the lipophilic complex has disappeared from blood and brain, the persisting image of the brain due to the trapped activity will be stable for 24 h.

Ethyl Cysteinate Dimer (ECD)

Ethyl cysteinate dimer (ECD) is also called Neurolite and contains two vials, A and B. The ^{99m}Tc-ECD (bicisate) complex (Fig. 3.11) is obtained as follows:

1. Add 3 ml saline to vial A, which contains the active ingredients, and then invert the vial to dissolve the kit contents.
2. Add 2 ml of $^{99m}TcO_4$ (25–100 mCi) aseptically to vial B, which contains 1 ml phosphate buffer.
3. Withdraw 1 ml of vial A contents, add to vial B, and allow the reaction to take place for 30 min at room temperature. The produced ^{99m}Tc-bicisate complex shows high in vitro stability.

^{99m}Tc-ECD is indicated for brain scintigraphy for diagnosis of acute cerebral ischemia, epilepsy, head trauma, and dementia [37]. After intravenous injection, ^{99m}Tc-ECD is distributed in the normal brain proportional to blood flow. The lipophilic complex crosses the BBB with a percentage of 6.5% of the total injected activity after 5 min. After 1 h, less than 5% of the radioactivity is present, mainly as the non-lipophilic complex. Excretion of ^{99m}Tc-ECD from the body is primarily by the kidneys, approximately 50% during the first 2 h [38].

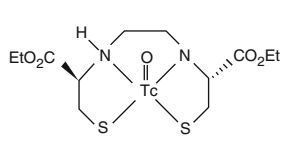


Fig. 3.11 ^{99m}Tc(V)O-L,L-ECD (ethyl cysteinate dimer)

3.1.2.6 ^{99m}Tc-Labeled Hepatobiliary Agents

Iminodiacetic Acid Derivatives (IDA)

Since the first iminodiacetic acid (IDA) derivative, HIDA, was developed, several N-substituted IDA derivatives have been prepared: 2,6-diethyl (DIDA or etilfenin), paraisopropyl (PIPIDA or iprofenin), para-butyl (BIDA or butilfenin), diisopropyl (DISIDA or disofenin), and bromotrimethyl (mebrofenin) (Fig. 3.12) [39].

^{99m}Tc-IDA complexes are formed by mixing 1–5 ml of $^{99m}TcO_4$ (8–40 mCi) with the vial contents and allowing the reaction to be completed in 15 min. ^{99m}Tc-IDA complexes are formed easily with reduced technetium at room temperature. Yield, radiochemical purity, and stability are not affected by the size of the substituents attached to the phenyl ring [40].

^{99m}Tc-IDA derivatives are used to

- Evaluate hepatocyte function
- Rule out or prove acute cholecystitis
- Demonstrate common bile duct partial or complete obstruction
- Verify hepatic bile duct atresia in infants

After intravenous injection, the ^{99m}Tc-IDA complex is bound to the plasma protein (mainly albumin) and carried to the liver; maximum liver uptake is measured at 10 min. Whole activity is seen in biliary trees and the gall bladder in 15–25 min and in the intestines in 45–60 min. Hepatobiliary excretion of ^{99m}Tc-IDA complexes is governed by molecular size and affected by the type of the substituents attached to the phenyl ring.

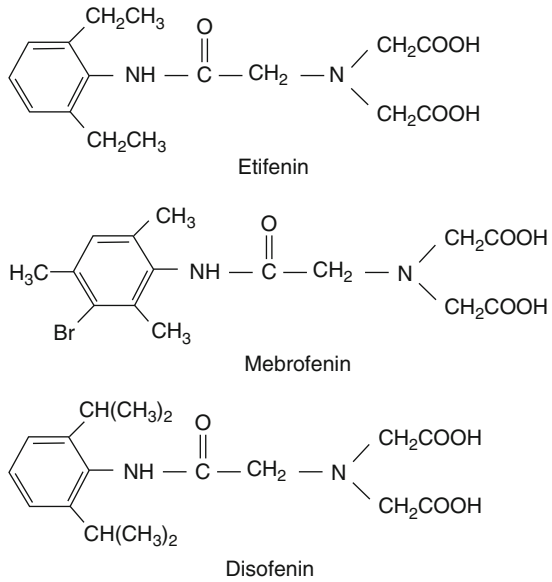


Fig. 3.12 Iminodiacetic derivatives

3.1.2.7 ^{99m}Tc-Labeled Human Serum Albumin

Human Serum Albumin (HSA)

^{99m}Tc-labeled albumin is a product derived from human serum albumin (HSA), which is a natural constituent of human blood. The labeling of a kit containing HSA and Sn^{+2} is carried out by adding up to 60 mCi of $^{99m}TcO_4$ in a volume of 1–8 ml to the kit vial; labeling efficiency should be greater than 90%. The contents of the vial should be thoroughly mixed before drawing the patient dosage. The oxidation state of technetium in ^{99m}Tc-HSA is not known but has been postulated to be 5^+ [41]. ^{99m}Tc-HSA is used for cardiac blood pool imaging and first-pass and gated equilibrium ventriculography [42].

Macroaggregated Human Serum Albumin

MAA is obtained by aggregation of HSA at acidic pH. The number of particles varies from 1 to 12 million particles per milligram of aggregated albumin. The shape of the particles is irregular, and the size ranges between 10 and 90 μm, with no particles larger than 150 μm.

Preparation of ^{99m}Tc-MAA is carried out by adding 2–10 ml of ^{99m}Tc-pertechnetate with activity up to 100 mCi aseptically to the reaction vial; the complete reaction time is from 5 to 20 min. Prior to injection and dosage administration, the contents of the vial should be agitated gently to make a homogeneous suspension. Similarly, the contents of the syringe also should be thoroughly mixed before administration [43].

Following intravenous injection, more than 90% of the ^{99m}Tc-MAA is localized in lung capillaries and arterioles. Organ selectivity is directly related to particle size, small particles (<8 μm) pass the capillaries and retained in the reticuloendothelial system while relatively larger particles (>15 μm) accumulate in the lung capillaries [44]. ^{99m}Tc-MAA is the

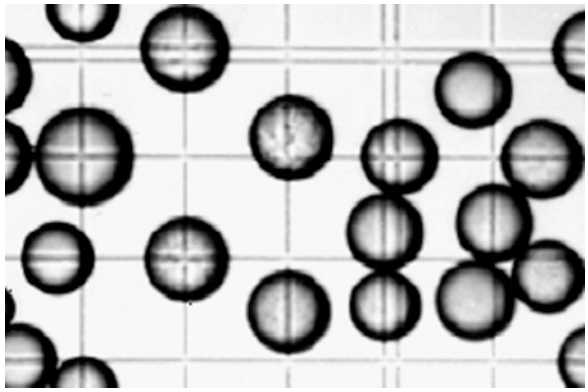


Fig. 3.13 Albumin microspheres (40 μm) (small square 50 × 50 μm, 150 fold), From [7] with permission from Springer+Business Media.

radiopharmaceutical of choice for lung perfusion scan with ventilation scan to exclude pulmonary embolism. In addition it is also used for radionuclide venography for detection of deep vein thrombosis (DVT).

Human Serum Albumin Microspheres (HSAM)

Human serum albumin microspheres (HSAM; Fig. 3.13) are produced by heat denaturation of HSA in vegetable oil [45]. A particle size between 12 and 45 μm is regularly obtained from the commercial kit. The commercial kit may contain 10 mg of microspheres, corresponding to 800,000–1,600,000 microspheres per vial. Complex preparation is obtained when 5–150 mCi of ^{99m}Tc-pertechnetate in 2–10 ml is added to the reaction vial followed by labeling time at room temperature for 15 min. Clinically, ^{99m}Tc-HSAM is used for pulmonary perfusion scintigraphy and determination of right-to-left shunts [46].

3.1.2.8 ^{99m}Tc-Labeled Colloids

Sulfur Colloid (SC)

^{99m}Tc-sulfur colloid (SC) complex is obtained by mixing $^{99m}TcO_4$ and the kit contents of sodium thiosulfate in an acidic medium and then heating at 95-100°C in a water bath for 5–10 min. The pH of the mixture is adjusted from 6 to 7 with a suitable buffer. Kits of ^{99m}Tc-SC available from commercial manufacturers, in addition to the basic ingredients of thiosulfate and an acid, may contain gelatin as a protective colloid and ethylenediaminetetraacetic acid (EDTA) to remove by chelation any aluminum ion present in the $_{99m}$Tc-eluate [47]. The particle size ranges from 0.1 to 1 μm, with a mean size of 0.3 μm, and the size distribution can vary from preparation to preparation and from kit to kit.

The ^{99m}Tc-SC complex formation procedure is a two-step procedure:

Step 1: The acid reacts with sodium thiosulfate in the presence of $^{99m}TcO_4$ and forms colloidal $^{99m}Tc_2S_7$:

$$2Na^{99m}TcO_4 + 7Na_2S_2O_3 + 2HCl \rightarrow {}^{99m}Tc_2S_7 + 7Na_2SO_4 + H_2O + 2NaCl$$

Step 2: Colloidal sulfur is precipitated as

$$Na_2S_2O_3 + 2HCl \rightarrow H_2SO_3 + S + 2NaCl$$

Certain precautions should be taken to eliminate large colloidal particles and to avoid usage of ^{99m}Tc-pertechnetate with eluate containing an alumina concentration above 10 μg aluminum/ml [48].

^{99m}Tc-SC may be useful for the following diagnostic applications:

- Determination of GIT bleeding sites
- Gastric-emptying scan
- Bone marrow imaging
- Liver-spleen scintigraphy

Tin Colloid (TC)

^{99m}Tc-tin colloid (TC) is now considered the agent of choice for liver-spleen scintigraphy since it does not need special labeling conditions (heating or pH adjustment). The complex is formed simply by adding up to 100 mCi of ^{99m}Tc-pertechnetate to the reaction vial. Labeling occurs with high efficiency after 20 min at room temperature. ^{99m}Tc-tin colloid shows a particle size distribution between 0.2 and 0.8 μm [49]. Biodistribution of colloids is typically dependent on the particle size. With a particle size of 0.3–0.6 μm, 80–90% of the radioactivity accumulates in the liver, with 5–10% in the spleen and 5–9% in the bone marrow [50]. Larger particles tend to localize in the spleen and

smaller ones in the bone marrow. Colloids are rapidly removed from blood by phagocytosis, mainly in the liver. It has similar application as those of sulfur colloid and is more commonly used because of its easier preparation, which avoids the need for boiling.

Albumin Nanocolloid

The commercial nanocolloid kit contains the HSA colloid and stannous dihydrate and is characterized by small size particles (almost 95% of the particles are less than 0.08 mm with a mean size of 0.03 mm). Complex labeling is obtained when proper $^{99m}TcO_4$ activity (up to 150 mCi) in a small volume is added aseptically to the vial and the reaction is continued for 10 min at room temperature [51]. Because of the smaller size of the particles, more nanocolloid localizes in the bone marrow (≈15%) relative to ^{99m}Tc-SC (2–5%).

^{99m}Tc-albumin nanocolloid is used in

- Sentinel lymph node (SLN) scintigraphy [52]
- Lymphoscintigraphy
- Bone marrow scintigraphy
- Inflammation scintigraphy

Biodistribution of ^{99m}Tc-albumin nanocolloid was discussed in regard to a small size colloidal particle.

3.1.2.9 ^{99m}Tc-Labeled Monoclonal Antibodies

Arcitumomab (CEA Scan)

Carcinoembryonic antigen (CEA) (CEA Scan kit introduced by Mallinckrodt Medical) as a single-dosage kit contains the active ingredient Fab^- fragment of arcitumomab, a murine monoclonal antibody IMMU-4. ^{99m}Tc-CEA labeling is carried out by adding 1 ml of $^{99m}TcO_4$ (20–30 mCi) to the reaction vial and incubating the mixture for 5 min at room temperature. The labeling yield should be more than 90%. The complex is stable for 4 h after labeling. CEA is expressed in a variety of carcinomas, particularly of the GIT, and can be detected in the serum. IMMU-4 is specific for the classical 200,000-Da CEA, which is found predominantly on the cell membrane. ^{99m}Tc-CEA Scan complexes the circulating CEA and binds to CEA on the cell surface. The Fab^- fragment of arcitumomab is cleared rapidly by the urinary tract and plasma clearance due to its small particle size [53].

The IMMU-4 antibody is targeted against the CEAs of colorectal tumors; therefore, ^{99m}Tc-CEA Scan is used for the detection of recurrence or metastatic carcinomas of the colon or rectum, particularly when high levels of CEA are detected [54]. However, it is an uncommon procedure following positron emission tomographic/computed tomographic (PET/CT) scan.

Sulesomab (LeukoScan)

The kit vial for LeukoScan contains the active ingredient Fab^- fragment, called sulesomab, obtained from the murine monoclonal antigranulocyte antibody IMMU-MN3. It is a single-dose kit introduced by Immunomedics Europe in 1997. Labeling is carried out by adding 0.5 ml of isotonic saline and swirling the content for 30 s; immediately after dissolution, 1 ml of $^{99m}TcO_4$, corresponding to an activity of 30 mCi, is added to the vial. The reaction is allowed for 10 min, and the labeling yield should be more than 90%. After intravenous injection, elimination of ^{99m}Tc-LeukoScan from the blood is indicated by 34% of the baseline activity after 1 h. The route of excretion is essentially renal, with 41% of the activity excreted in urine over the first 24 h [55]. ^{99m}Tc-sulesomab targets the granulocytes and therefore is primarily used to detect infection and inflammation, particularly in patients with osteomyelitis, joint infection involving implants, inflammatory bowel disease, and foot ulcers of diabetics [56].

3.1.2.10 ^{99m}Tc-Labeled Peptides and proteins

Depreotide (NeoSpect)

The depreotide (NeoSpect) kit vial contains a lyophilized mixture of depreotide, sodium glucoheptonate, stannous chloride, and sodium EDTA. Labeling of the depreotide (cyclic decapeptide) with ^{99m}Tc is performed by ligand exchange of intermediary ^{99m}Tc-glucoheptonate. The ^{99m}Tc-NeoSpect complex is obtained by aseptically adding up to 50 mCi ^{99m}Tc-pertechnetate in a volume of 1 ml to the vial. After normalizing the pressure, the vial should be agitated carefully for 10 s and then placed in a water bath for

10 min; when the labeling procedure is completed, the vial should be left for cooling at room temperature for 15 min (running water should not be used for cooling) [57]. Depreotide is a synthetic peptide that binds with high affinity to somatostatin receptors (SSTRs) in normal as well as abnormal tissues. This agent is used to detect SSTR-bearing pulmonary masses in patients proven or suspected to have pulmonary lesions by CT or chest x-ray. Negative results with ^{99m}Tc-depreotide can exclude regional lymph node metastasis with a high degree of probability [58].

Some reports showed that ^{99m}Tc-depreotide was accumulated in pulmonary nodules 1.5–2 h following the intravenous injection [58, 59]. ^{99m}Tc-depreotide can be also seen in the spine, sternum, and rib ends [60]. The main route of elimination of the compound is the renal system. This is an uncommon procedure when PET/CT is available that can show lesions as small as 5 mm.

Apcitide (AcuTect)

^{99m}Tc-apcitide was introduced under the brand name of AcuTect as a single-dosage kit. The kit vial contains bibapcitide, which consists of two apcitide monomers, stannous chloride and sodium glucoheptonate. Labeling is performed by adding up to 50 mCi of $^{99m}TcO_4$ to the kit vial and heating for 15 min in a boiling water bath. The labeling yield should be greater than 90%. ^{99m}Tc-apticide binds to the GP glycoprotein IIb/IIIa receptors on activated platelets that are responsible for aggregation in forming the thrombi and therefore is used for the detection of acute DVT in lower extremities [40].

Annexin V (Apomate)

Annexin V (Apomate) is a human protein with a molecular weight of 36 kDa, has a high affinity for cell membranes with bound phosphatidyl serine (PS) [61]. In vitro assays have been developed that use annexin V to detect apoptosis in hematopoietic cells, neurons, fibroblasts, endothelial cells, smooth muscle cells, carcinomas, and lymphomas. ^{99m}Tc-annexin V has also been suggested as an imaging agent to detect thrombi in vivo because activated platelets express large amounts of PS on their surface [62]. The radiopharmaceutical is prepared by adding about 1,000 MBq ^{99m}Tc-pertechnetate to 1 mg freeze-dried (n-1-imino-4-mercaptobutyl)-annexin V (Mallinckrodt, Petten, The Netherlands). This mixture is incubated for 2 h at room temperature [63].

^{99m}Tc-Annexin strongly accumulates, with a biological half-life of 62 h, in the kidneys (21%) and the liver (12.8%) after 4 h of injection. Accumulation in myocardium and colon is limited, and excretion is obtained exclusively by urine (75%) and feces (25%) [63].

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