Radiopharmacy: Basics

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2.1 Introduction

A *radiopharmaceutical* is a radioactive compound that has two components, a radionuclide and a pharmaceutical; it is used for the diagnosis and treatment of human diseases. All radiopharmaceuticals are legend drugs and are subject to all regulations that apply to other drugs. The difference between a radiochemical and a radiopharmaceutical is that the former is not administered to humans due to the possible lack of sterility and nonpyrogenicity; any material administered to humans must be sterile and nonpyrogenic. A radiopharmaceutical may be a radioactive element like ^{133}Xe or a labeled compound such as ^{99m}Tc-labeled compounds [1].

In nuclear medicine, about 95% of the radiopharmaceuticals are used for medical diagnosis; only about 5% are used for therapeutic purposes. In designing a radiopharmaceutical, a suitable pharmaceutical is chosen on the basis of its preferential localization in a given organ or its participation in the physiological function of the organ. Then, a suitable radionuclide is tagged onto the chosen pharmaceutical and administered to the patient [2]. The radiation emitted from the organ can be detected by an external radiation detector for assessment of the morphological structure and the physiological function of that organ. Radiopharmaceuticals in most cases have no pharmacological effect as they are mainly administered in tracer amounts. So, they mainly do not show any dose–response relationship. For the therapeutic radiopharmaceuticals, however, the observed biological effect is from the radiation itself and not from the pharmaceutical [3].

Nuclear medicine procedures generally have two classifications; the first is those that depend on single-photon emitters, for which planar and tomographic imaging (single-photon emission computed tomography or SPECT) are the options of image acquisition. The other type is positron emission tomography (PET), for which the detection process relies on positron-electron annihilation and the release of two opposing photons (180° apart). The key component that distinguishes these techniques among other modalities is the diversity and ability of their contrast agents to

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answer a clinical question. The contrast agents in nuclear medicine are radiolabeled compounds or radiopharmaceuticals that, when localized in the region of interest, emit important information about the pathophysiologic status of the tissue involved. Both imaging techniques have high sensitivity in detecting molecular concentrations in the pico or nano range, and their role in functional or molecular imaging is well addressed. SPECT and PET radiopharmaceuticals have a wide acceptance in molecular imaging, biomedical research disciplines, and drug development. However, many SPECT tracers are approved by the U.S. Food and Drug Administration (FDA), widely available, well reviewed in the literature, and relatively cheaper and perform for a significant patient population on a daily basis, whereas this situation is not true for the use of PET compounds.

SPECT radiotracers have a particular position in the matrix of molecular imaging due to their ability to image endogenous ligands such as peptides and antibodies and their ability to measure relatively slow kinetic processes due to the relatively long half-life of the commonly used isotopes (in comparison to PET). In addition, the capability to measure two different photon energies allows SPECT systems to depict two molecular pathways simultaneously by measuring their corresponding photon emissions [4]. In this chapter, we discuss some basic concepts about properties of radiopharmaceuticals, production, and generator systems used in clinical practice.

2.2 An Ideal Radiopharmaceutical

The definition of an ideal radiopharmaceutical in nuclear medicine procedures varies according to its use. The aim of a diagnostic radiopharmaceutical is to provide detectable photons with minimal biological effect to the cells or organ, whereas it is desired to produce a cytotoxic effect in a therapeutic procedure [5]. Generally, an ideal radiopharmaceutical for diagnostic procedures should meet the following characteristics:

Short half-life: Radiopharmaceuticals should have a relatively short effective half-life, which should not exceed the time assigned to complete the study. It provides a smaller radiation dose to the organ and ambient structures together with reduced exposure to workers, family members, and others. However, radiotracers with short lifetimes mandate an injection of a high-activity concentration using fast imaging systems and may also compromise image quality. Thus, an optimal half-life satisfies imaging requirements while maintaining the quality of the scan. Protein synthesis and peptide formation involve a slow kinetic process; thus, single-photon emitters provide an opportunity to study the underlying functional disorders while the tracer still is able to emit a signal [1].

Suitable radionuclide emission: Radiopharmaceuticals emitting γ-radiation by electron capture or isomeric transition (energy between 30 and 300 keV) are commonly used in nuclear medicine diagnostic procedures. For therapeutic purposes, α-, β-, and Auger electron emitters are used because of their high linear energy transfer, which leads to maximum exposure and damage of the target cells. The α-particles and Auger electron emitters are mostly monoenergetic, whereas the β-particles have a continuous energy spectrum up to their maximum energy E_{max}.

High target-to-nontarget ratio: In all diagnostic procedures, it is well known that the agent with better target uptake is a superior imaging agent since the activity from the nontarget areas can interfere with the structural details of the organ imaged. Therefore, the target-to-nontarget activity ratio should be as large as possible.

Target uptake rate: The rate at which an organ takes up the administrated radiopharmaceutical is also considered a key characteristic of an ideal radiopharmaceutical because it influences the period after which imaging acquisition is done. It is preferable to get images as early as possible for patient convenience. For example, ^{99m}Tc-pertechnetate is preferable to ^{123}I-NaI because the thyroid-imaging procedure can be performed after 20 min of dose administration, while with ^{123}I-NaI it takes 4–6 h to launch the imaging session.

Tracer excretion: The most common excretion route is renal clearance, which is rapid and can reduce exposure to the blood, whole body, and marrow. In contrast, the gastrointestinal tract (GIT) and hepatobiliary excretion is slow and leads to higher GIT and whole-body exposures. With GIT excretion, reabsorption into the blood also occurs. Since organ visualization is better when the background tissues have less uptake than the target organ, the radiopharmaceutical must be cleared from the blood and background tissue to achieve better image contrast.

Availability: The ideal radiopharmaceutical should be cost effective, inexpensive, and readily available in any nuclear medicine facility. This feature also characterizes the spread and diffusion of gamma emitters compared to PET-based compounds.

2.3 Production of Radionuclides

Naturally occurring radionuclides cannot be employed for medical diagnosis because of their long half-lives, which warrant the need for production of other radionuclides that can be safely used for medical applications. Most of the radionuclides for medical use are produced in nuclear reactors or cyclotrons. Some of the radionuclides are eluted from the generators in which the parent radionuclide is produced from a reactor or a cyclotron [2].

The process of all radionuclide production can be described by the general equation

$$X(\text{``}BP\text{''}, \text{``}EP\text{''})Y$$

where

X is the target element.
Y is the product element.
BP is the bombarding particle (projectile).
EP is the emitted product.

Pure metals are the best targets to use because of their high ability to sustain the high temperature in cyclotron and reactor systems.

2.3.1 Reactor-Produced Radionuclides

The two major principles of a nuclear reactor are that the neutrons induce fission in the fissile material constructing the fuel rods (e.g., U^{235}, P^{239}) of the reactor and the number of neutrons released in that fission reaction is about two or three neutrons with a mean energy of 1.5 MeV.

$$U^{235} + n \rightarrow \text{ fission products} + \upsilon n$$

These new neutrons are used to produce fission in other nuclei, resulting in the release of new neutrons that initiate the chain reaction. This chain reaction must be controlled to avoid the possible *meltdown* situation in the reactor using special neutron moderators (low molecular weight materials such as water, heavy water, and graphite, which are distributed in the spaces between the fuel rods), and neutron absorbers (e.g., cadmium rods placed in the fuel core) are used to thermalize and reduce the energy of the emitted neutrons to 0.025 eV to maintain equilibrium [1].

From the medical usefulness point of view, there are two types of nuclear reactions used to produce radioisotopes of interest 2 types: thermal neutron reactions and fission (n, f) reactions.

2.3.1.1 Thermal Neutron Reactions

The thermal neutrons around the core of the nuclear reactor can induce the following types of nuclear reactions:

$$A_Z^Y + n \rightarrow A_Z^{Y+1} + \gamma$$

$$A_Z^Y + n \rightarrow A_{Z-1}^Y + p$$

In the first type of reaction, the target atom A captures a neutron and emits gamma rays (γ), also written as an (n, γ) reaction.

For example:

$$^{98}Mo\ (n,\gamma)\ ^{99}Mo$$

$$^{50}Cr\ (n,\gamma)\ ^{51}Cr$$

In the second type of reactions, a proton is emitted after absorption of the neutron, resulting in a new element with different atomic number (Z).

For example:

$$^{14}N(n,p)\ ^{14}C$$

$$^{3}He(n,p)\ ^{3}H$$

Although the (n, γ) reaction produces a radioisotope from a stable one with a low specific activity product that are not carrier free, no sophisticated chemical separation procedures are required.

The (n, p) reaction produces an isotope with a different atomic number (element), enabling the

production of high specific activity and carrier-free radioisotopes. *Specific activity* can be defined as the amount of activity per unit mass of a radionuclide or a labeled compound.

Products of (n, γ) reactions include parent isotopes, which are commonly used in nuclear generators to produce daughter radionuclides, which are the isotopes of interest; these are usually separated from their parents by column chromatography procedures.

For example:

$$^{98}\mathrm{Mo(n,\gamma)}\,^{99}\mathrm{Mo} \xrightarrow{t1/2=67\,\mathrm{h}} {}^{99\mathrm{m}}\mathrm{Tc}$$

$$^{124}\mathrm{Xe}(n,\gamma)\,^{125}\mathrm{Xe} \xrightarrow{t1/2=67\,\mathrm{h}} {}^{125}\mathrm{I}$$

2.3.1.2 Fission or (n, f) Reactions

Fission is a process of breaking up a heavy nucleus (e.g., ^{235}U, ^{239}Pu, ^{232}Th) and any other material with an atomic number greater than 90 into two fragments (by-products).

For example:

$$U_{92}^{235} + \mathrm{n} \rightarrow U_{92}^{236} \rightarrow Kr_{36}^{89} + Ba_{56}^{144} + 3\mathrm{n}$$

$$U_{92}^{235} + \mathrm{n} \rightarrow U_{92}^{236} \rightarrow I_{53}^{131} + Y_{39}^{102} + 3\mathrm{n}$$

$$U_{92}^{235} + \mathrm{n} \rightarrow U_{92}^{236} \rightarrow Mo_{42}^{99} + Sn_{50}^{135} + 2\mathrm{n}$$

The neutron interacts with the ^{235}U nucleus to form unstable uranium atom ^{236}U, which breaks into two different smaller atoms and a number of neutrons. The isotopes produced may be employed in nuclear medicine (^{99}M, ^{131}I, ^{133}Xe); the greatest portion of these radioisotopes is not useful in nuclear medicine as they tend to decay by β^- emission. Unlike the radioisotopes formed from (n, γ) reactions, fission products can be chemically treated to produce carrier-free radionuclides. But, the major problem is how to separate them from the other products to obtain the highest level of radiochemical purity of the end product. The radioisotopes are mainly separated by appropriate chemical procedures that may involve precipitation, solvent extraction, ion exchange, distillation, and chromatography. Two of the most common isotopes are discussed as examples:

Molybdenum-99: For ^{99}Mo separation, the irradiated uranium target is dissolved in nitric acid, and the solution is adsorbed on an alumina (Al_2O_3) column. The column is then washed with nitric acid to remove uranium and other fission products.

Iodine-131: For chemical separation of ^{131}I from ^{235}U, the latter is dissolved in 18% sodium hydroxide (NaOH) by heating, and hydroxides of many metal ions are then precipitated by cooling. The supernatant containing sodium iodide is acidified with sulfuric acid. Iodide is oxidized to iodine by the effect of the acid, and iodine is collected in a NaOH by distillation.

2.3.2 Cyclotron-Produced Radionuclides

Cyclotron systems, which were invented in 1930, have an obvious role in the production of a wide range of nuclear medicine radiopharmaceuticals, especially those with short half-lives.

The basic principle of their operation is the acceleration of charged particles such as protons, deuterons, and α-particles in a spiral path inside two semicircular, flat, evacuated metallic cylinders called "dees." The dees are placed between the two poles of a magnet (see Fig. 2.1) so that the ion beam is constrained within a circular path inside the dees. At the gap between the dees, the ions experience acceleration due to the imposition of the potential difference. The beam particles originate at the ion source at the center of the cyclotron, and as they spiral outward in the dees, they acquire increasing energy for each passage across the gap of the dees. Eventually, the high-energy particles reach the periphery of the dees, where they are directed toward a target for bombardment [6].

Fixed-frequency cyclotrons can accelerate positively charged ions up to only 50 MeV for protons due to the relativistic increase in the mass of the accelerated particle, while for linear accelerators, particle acceleration can occur up to several hundreds of mega-electron-volts because of the ability of the accelerator to compensate for the increase in mass of high-energy particles. Advanced techniques have been developed to use cyclotrons to accelerate particles to much higher energies [7].

The majority of cyclotrons built prior to 1980 accelerated positively charged ions (i.e., H^+); medical

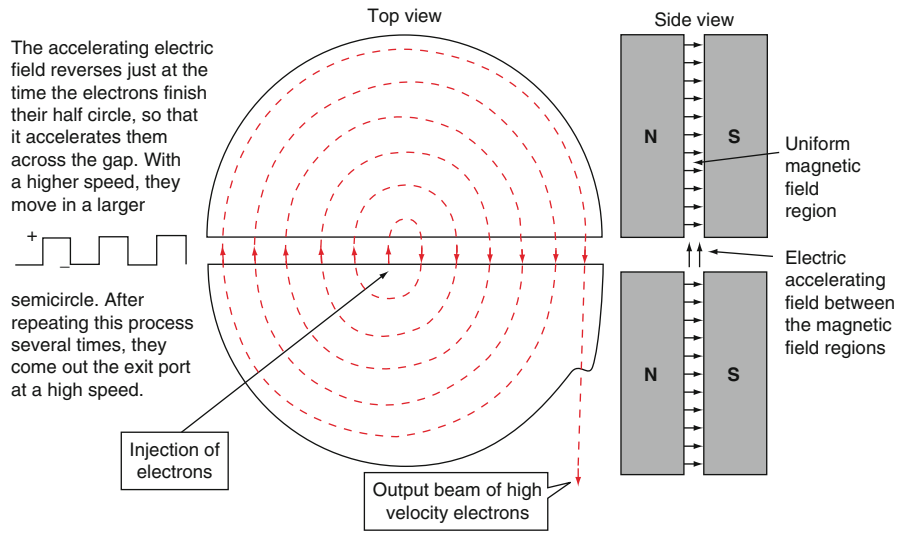

Fig. 2.1 Layout of cyclotron

cyclotrons accelerate negative ions (H^-). This design allows for a simple deflection system in which the beam is intercepted by a thin carbon foil that extracts the negative ions at the end of the trajectory, resulting in the formation of a positively charged H^+ beam. The beam then changes the direction without a deflector due to the magnetic field. The H^+ bombards the target in a manner similar to that in a positively charged ion cyclotron. It is also possible to extract the beam at two different points in the machine, allowing use of a negative-ion cyclotron for production of two different radioisotopes simultaneously [8]. Generally, when the target nuclei are irradiated by the accelerated particles, a nuclear reaction takes place. The incident particle, after interaction, may leave some of its energy in the nucleus or be completely absorbed by it, depending on its incident energy. In either case, the nucleus is excited, resulting in the emission of nucleons (protons and neutrons) followed by γ-ray emission.

Depending on the energy deposited by the incident particle, a number of nucleons may be emitted randomly from the irradiated nucleus, leading to the formation of different nuclides. As the energy of the irradiating particle is increased, more nucleons are emitted and therefore a greater variety of nuclides may be produced.

An example of a simple cyclotron-produced radionuclide is the production of ^{111}In by irradiation of ^{111}Cd with 12-MeV protons. The nuclear reaction can be expressed as follows:

$$^{111}Cd\ (p, n)^{111}In$$

In this case, a second nucleon may not be emitted because there is not enough energy left after the emission of the first neutron. The excitation energy insufficient to emit any more nucleons will be dissipated by γ-ray emission.

The target material must be pure and preferably monoisotopic or at least enriched in the desired isotope to avoid the production of extraneous radioisotopes. In addition, the energy and type of the irradiating particle must be chosen to avoid the presence of undesired radionuclides.

Table 2.1 represents the most common commercial cyclotrons presented by the International Atomic Energy Authority (IAEA) report for cyclotron distribution in member states in 2006 [9].

2.3.3 Generator-Produced Radionuclides

The first commercial radionuclide generator was produced in the United States in the early 1960s (Brookhaven National Laboratories); since then, a number of different types of generators have been developed for various purposes in nuclear medicine. Generators are "parent–daughter systems involving a long-lived parent radionuclide that decays to short half-life daughter" and is called a generator because of its ability to generate continuously a relatively short-lived daughter radionuclide. The parent and its daughter nuclides are not isotopes; therefore, chemical separation is possible. Table 2.2 represents the most

commonly used generators in nuclear medicine applications.

Radionuclide generators are formed by a glass or plastic column fitted at the bottom with a filtered disk. The column is fitted with absorbent material such as alumina, on which the parent nuclide is absorbed. Daughter radionuclides are generated by the decay of the parent radionuclide until either a *transient* or *secular* equilibrium is reached; after that, the daughter appears to decay with the half-life of the parent. The daughter is eluted in a carrier-free state (because it is not an isotope of the parent radionuclide) with a sterile and pyrogen-free appropriate solvent; then, the activity of the daughter starts to increase again up to equilibrium, so the elution can be made multiple times. Figure 2.2 shows a typical generator system.

Table 2.1 Common commercial cyclotrons for cyclotron distribution

Company	Model	Description
CTI, Inc./ Siemens	RDS 111 RDS 112	11 MeV H−, 40,60 μA 11 MeV H−, 40 μA
GE	PETrace	16.5 MeV H−, 8.6 MeV D−, 80 μA
Ion Beam Applications (IBA)	Cyclone 18/9 Cyclone 30+	18 MeV H−, 9 MeV D−, 80 μA 30 MeV H−, 15 MeV D−, 60 μA
Sumitomo Heavy Industries	CYPRIS 370 AVF 930+	16 MeV H+, 10 MeV D+, 60 μA 90 MeV H+, 60 μA
Scanditronix Medical AB	MC40+	10–40 MeV H+, 5–20 MeV D+, 60 μA

Several methods can be adopted to obtain a sterilized eluted radionuclide:

- The entire column of the generator is autoclaved.
- Column preparation occurs under general aseptic conditions.
- Bacteriostatic agents are added to the generator column.
- A membrane filter unit is attached to the end of the column.
- Elution procedures are carried out under aseptic conditions.

2.3.3.1 Daughter Yield Equations

Assuming that there is initially no daughter activity in the generator, the daughter activity at any given time t is given by

$$A_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} A_1^0 (e^{-\lambda_1 t} - e^{-\lambda_2 t})$$

where

A_2 is the daughter activity at time t.
A_1^0 is the parent activity at time zero.
λ_1 and λ_2 are decay constants for the parent and daughter, respectively.

In case of transient equilibrium, as time t becomes sufficiently long, $e^{-\lambda_2 t}$ is negligible compared with $e^{-\lambda_1 t}$, and the equation becomes

$$A_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} A_1^0 (e^{-\lambda_1 t})$$

Table 2.2 Some generator systems used in nuclear medicine applications

Parent	Parent ($T_{1/2}$)	Nuclear reaction	Daughter	Daughter ($T_{1/2}$)	Mode of daughter decay	Principal keV (% abundance)	Column	Eluant
^{99}Mo	66 h	Fission	^{99m}Tc	6 h	IT	140(90)	$Al2O_3$	0.9% NaCl
^{87}Y	80 h	^{88}Sr(p,2n)	^{87}mSr	2.8 h	IT	388(82)	Dowex 1 × 8	0.15*M* $NaHCO_3$
^{68}Ge	271 days	^{69}Ga69 (p,2n)	^{68}Ga	68 min	B+	511(178)	Al_2O_3	0.005*M* EDTA
^{62}Zn	9.3 h	^{63}Cu(p,2n)	^{62}Cu	9.7 min	B+	511(194)	Dowex 1 × 8	2*N* HCL
^{82}Sr	25.5 days	^{85}Rb(p,4n)	^{82}Rb	75 s	B+	511(190)	SnO_2	0.9% NaCl

Adapted from [2].

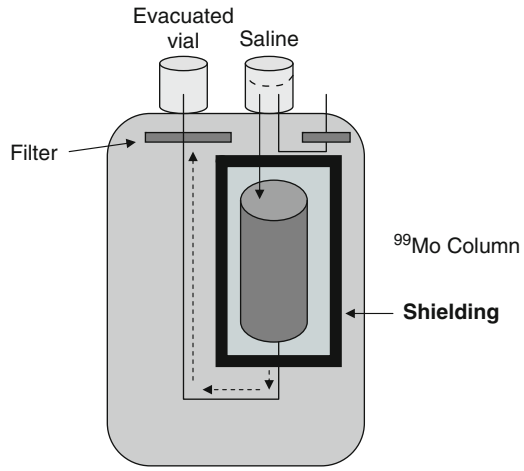

Fig. 2.2 Typical generator system

Since $A_1^0(e^{-\lambda_1 t})$ is the parent activity at time t, we can express it by A_1, and the equation can be rewritten as

$$A_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} A_1$$

In case of secular equilibrium, the parent activity does not decrease dramatically even after many daughter half-lives. As such, the decay constant of the parent λ_1 is much smaller than that of the daughter. So, we can make an approximation and assume that $\lambda_2 - \lambda_1 \approx \lambda_2$ and $A_1 = A_2$; thus, the daughter activity is equal to the parent activity.

2.3.3.2 ^{99}Mo-^{99m}Tc Generator

The ^{99}Mo-^{99m}Tc generator has been the most commonly used radionuclide generator in nuclear medicine practice worldwide since its first commercial introduction in 1965. It has several characteristics and attractive properties, which are summarized as follows [10]:

- Cost effective and simple to use
- Sterile and pyrogen free
- High radionuclide and radiochemical purity
- Used to produce many ^{99m}Tc-labeled radiopharmaceuticals frequently used in nuclear medicine departments
- Ideal half-life of the daughter nuclide (6 h) and optimum energy (140 keV, ~90% abundance)
- ^{99}Mo produced by the (n, f) fission reaction instead of the (n, γ) reaction (to have a carrier-free ^{99}Mo radionuclide) has a half-life of 66 h and decays by β-emission (87%) to metastable state technetium (^{99m}Tc) and in 13% to ground state (^{99}Tc), while ^{99m}Tc has a half-life of 6 h and decays to ^{99}Tc by an isomeric transition with the emission of 140-keV gamma photons [11].

2.3.3.3 Liquid Column (Solvent Extraction) Generator

The basic principle of the liquid column (solvent extraction) generator involves placing a 20% NaOH solution of ^{99}Mo in a glass column and then letting methyl ethyl ketone (MEK) flow through that column to extract $^{99m}TcO_4$, leaving ^{99}Mo in an aqueous solution. The advantage of this generator is that it is extremely cost effective, but it needs many manipulations in the overall method and causes more radiation exposure to staff involved. Its use in nuclear medicine is diminishing.

2.3.3.4 Solid Column Generator

A solid column ^{99}Mo-^{99m}Tc generator is made initially with alumina (Al_2O_3) loaded in a plastic or glass column where the^{99}Mo radionuclide is adsorbed on alumina in the chemical form $^{99}MoO_4$ (molybdate). The column is washed with isotonic saline to remove any undesirable activity. The amount of alumina used is about 5–10 g, depending on the total ^{99}Mo activity used. ^{99m}Tc radionuclide is eluted as a product of ^{99}Mo decay in the form of sodium pertechnetate ($Na^{99m}TcO_4$) with a 0.9% NaCl solution. After elution, the ^{99m}Tc activity starts to grow again up to equilibrium [12]. Elution may be carried out even before equilibrium if needed, and the amount of activity obtained depends on the time elapsed between the previous and the present elution.

For radiation protection purposes, the generator columns are shielded with lead or depleted uranium in generators with high ^{99}Mo activity because ^{238}U has a higher Z number and therefore attenuates γ-rays more efficiently.

There are two types of solid column ^{99}Mo-^{99m}Tc generators: wet and dry column. Dry column

generators are preferable due to the repeated withdrawal of saline from the column after routine generator usage by an evacuated tube, which prevents the formation of hydrogen peroxide (H_2O_2) and perhydroxyl free radical (HO_2), which if present in the ^{99m}Tc eluate can interfere with the ^{99m}Tc labeling procedures because they can act as oxidants. In addition, in wet column generators, saline in the tubing may possibly freeze in extremely cold weather, thus preventing elution until thawed.

2.3.3.5 ^{99m}Tc Yield in the ^{99}Mo-^{99m}Tc Generator

Since ^{99}Mo and ^{99m}Tc radionuclides decay to ^{99}Tc, the generator eluate contains both ^{99m}Tc and ^{99}Tc in various concentrations. The fraction of ^{99m}Tc decreases due to the rapid decay of ^{99m}Tc, especially when the time between elutions increases. ^{99m}Tc and ^{99}Tc have the same chemical structure, so ^{99}Tc can interfere with the preparation of ^{99m}Tc radiopharmaceuticals, especially with kits containing small amounts of stannous ions. This situation becomes critical when the generators are left without elution for several days [13].

The ^{99m}Tc content in the generator eluate can be expressed by the following equation:

$$F = N_A/(N_A + N_B)$$

where F is the ^{99m}Tc mole fraction. N_A and N_B are the number of ^{99m}Tc and ^{99}Tc, respectively.

The mole fraction of ^{99m}Tc (F) at any time t can be calculated as

$$F = 0.87\lambda_1(e^{-\lambda_1 t} - e^{-\lambda_2 t})/(\lambda_2 - \lambda_1)(1 - e^{-\lambda_1 t})$$

where λ_1 and λ_2 are decay constants for the ^{99}Mo and ^{99m}Tc, respectively. The factor 0.87 indicates that 87% of ^{99}Mo decays to ^{99m}Tc.

2.3.3.6 Other Generator Systems

^{113}Sn-^{113}In Generator

Indium-113 can be used to prepare a number of radiopharmaceuticals used for imaging of lungs, liver, brain, and kidneys. ^{113}Sn has a half-life of 117 days, while the daughter ^{113}In has a half-life of 100 min and energy of 393 keV [14]. The generator is made up of hydrous zirconium oxide contained in a plastic or glass column. Sn-113 produced in a reactor by neutron irradiation and in the stannic form is adsorbed on the column, and the daughter ^{113}In is eluted with 0.05*N* HCl [15].

Due to the relatively long half-life of ^{113}Sn (117 days), the ^{113}Sn-^{113}In generator can be used for 6–12 months, making it one of the most economical generators. The disadvantage of this generator is the improper energy of 393-keV photons from ^{113}In with routinely used gamma camera detectors. ^{113}Sn-^{113}In generators generally have been replaced by moly generators; however, they are still useful in some developing countries and isolated regions of the world [3].

^{81}Rb-^{81}Kr Generator

^{81}Kr is a gamma-ray-emitting radionuclide with a photon energy of 190 keV (192% abundance). It is commonly used as a lung and myocardial perfusion imaging agent [16]. The generator is formed of a column containing a cation exchange resin (Bio-Rad AGMP-50), where the cyclotron-produced ^{81}Rb ($t_{1/2} = 47$ h) is loaded. The noble gas ^{81}Kr ($t_{1/2} = 13$ s) is eluted by passing humidified oxygen over the generator column [17]. The ^{81}Kr and O_2 are delivered to the patient through a nonbreathing face mask. The major disadvantages of the ^{81}Rb-^{81}Kr generator are the high cost and the 12-h expiration time of the nuclide of the generator [3].

^{82}Sr-^{82}Rb Generator

Rubidium-82 is a positron-emitting radionuclide and is used primarily as a myocardial perfusion agent for PET imaging. It serves as an alternative to the accepted oxygen-15 and nitrogen-13 with an increasing trend for use in research and clinical practice [18]. Its importance also lies in the fact that the production process does not require a cyclotron system and its associated complexities.

^{82}Sr ($t_{1/2} = 25$ days) decays by electron capture to ^{82}Rb ($t_{1/2} = 75$ s), which decays by β^+ emission. To make the generator, the cyclotron-produced ^{82}Sr is loaded on a SnO_2 column, and ^{82}Rb is eluted with

0.9% NaCl solution to obtain it in the form of rubidium chloride. Because of its short half-life, ^{82}Rb elution can be repeated every 10–15 min with maximum yield [19]. The disadvantage of this generator is the short half-life of the ^{82}Rb daughter radionuclide. In an effort to overcome the short half-life, a calibrated continuous infusion system has been developed, allowing elution of the generator directly into an intravenous catheter [20].

The activity of ^{82}Rb produced from a ^{82}Sr-^{82}Rb generator is dependent on elution conditions (volume and eluent flow rate) and sampling conditions (time and position of collection). There is a characteristic curve for the elution of Rb-82 from the generator that depends on the flow rate and the Sr-82 activity within the generator. This results in a variation of the infusion profile, thus altering the amount of tracer injected [21].

^{68}Ge-^{68} Ga Generator

^{68} Ga is primarily used for brain tumor imaging, but with the availability of positron systems and its emission of 2.92-MeV positrons in 89% abundance, its use has increased in PET applications [22]. This generator is made up of alumina loaded in a plastic or glass column. Carrier-free ^{68}Ge ($t_{1/2}$ = 271 days) in concentrated HCl is neutralized in EDTA (ethylenediaminetetraacetic acid) solution and adsorbed on the column. Then, ^{68} Ga ($t_{1/2}$ = 68 min) is eluted with 0.005*M* EDTA solution. Alternatively, ^{68}Ge is adsorbed on a stannous dioxide column, and ^{68} Ga is eluted with 1.0*N* HCl. This generator can be eluted frequently with a maximum yield in a few hours [23].

^{62}Zn-^{62}Cu Generator

Copper-62 is also a positron-emitting radionuclide (98% abundance) and is used widely for PET imaging. ^{62}Zn ($t_{1/2}$ = 9.3 h) decays to ^{62}Cu ($t_{1/2}$ = 9.7 min) by electron capture (92%) and β^+ emission (8%). ^{62}Cu decays by β^+ emission (97%) and electron capture (3%). ^{62}Zn in 2*N* HCl is adsorbed on a Dowe 1 × 8 column, and ^{62}Cu is converted to ^{62}Cu-PTSM, copper-62 (II) pyruvaldehyde bis-(N-4-methyl)thiosemicarbazone which is used for myocardial and brain perfusion imaging [24]. The biggest disadvantage of this generator is the short half-life of the daughter radionuclide, limiting its use only to the day of delivery [25].

Most nuclear medicine procedures that use single-photon emitters are based on Tc-99m or Tc-99m-labeled compounds, and the recent shortage of this radionuclide (2010 international moly crisis) demonstrated the wide and extensive importance of its clinical utility. However, there are other radiopharmaceuticals that are of particular interest in many diagnostic applications.

2.4 Common Radiopharmaceuticals

2.4.1 *Thallium-201*

Thallium-201 is a frequently used radiopharmaceutical in cardiac imaging in addition to its role in scanning of tumors and parathyroid adenomas [26].

^{201}Tl, which is commercially available as thallium chloride, is produced by exposing pure natural ^{203}Tl to a high-energy proton beam, resulting in production of Pb-201:

$$^{203}\mathrm{T1}[\mathrm{p}, 3\mathrm{n}]\ \mathrm{Pb}\text{-}201$$

Pb-201 is then chemically separated from the target Tl-203 and allowed to decay to Tl-201.

Tl-201 decays to mercury (Hg-201) by Electron Capture with a half-life of 73 h and gives off a mercury-characteristic x-ray (69–80 keV) with 95% abundance and two gamma rays of 135 and 167 keV with a combined abundance of 12%. The commercially produced thalous chloride should contain 95% of its content in the form of Tl-201 [1]. The maximum concentration of thallium in the heart is obtained approximately 10–30 min after injection in the resting state and 5 min after stress induced either physically or pharmacologically. Uptake of Tl-201 into the myocardium is dependent on tissue oxygenation, which governs the blood flow as oxygen is essential in supporting Tl-201 uptake through the Na-K-ATPase (adenosine triphosphatase) concentration mechanism (Tl-201 and K^+ are similarly involved in the Na-K-ATPase pump) [27]. Tl-201 has been extensively used as a myocardial perfusion imaging agent in evaluating patients with coronary artery disease and in viability assessment. In addition, its role in tumor imaging has been recognized.

2.4.2 Gallium-67

Gallium-67 is a cyclotron-produced radiopharmaceutical; it can be produced by one of the following nuclear reactions:

$$\text{Zn-67}[\text{p, n}]\text{Ga-67}$$

$$\text{Zn-68}[\text{p, 2n}]\text{Ga-67}$$

Ga-67 decays by EC with a half-life of 78 h with the following gamma-ray energy and abundances: 93 keV (40%), 184 keV (24%), 296 keV (22%), and 388 keV (7%).

Ga-67 is delivered from the manufacturer as gallium citrate with radiochemical purity greater than 85%. Gallium is presented as Ga^{+3} in aqueous solutions, making radiopharmaceutical production easier than that with ^{99m}Tc because reduction does not have to be performed.

It is considered the master radiopharmaceutical for tumor imaging and detection of inflammatory sites. Its role is highly affected after the introduction of FDG-PET, fluorodeoxyglucose applications. On injection of gallium citrate, more than 90% of gallium becomes bound to plasma proteins, mainly *transferrin*, resulting in slow clearance from plasma. The Ga-transferrin binding procedure can be affected when transferrin is saturated with stable gallium or iron before gallium injection. Under these conditions, gallium distribution is shifted from soft tissue to bones with no change in the tumor uptake, while increasing Ga-transferrin binding causes an increase in soft tissue activity and decreased tumor activity [28].

2.4.3 Iodine Radiopharmaceuticals

Radioisotopes of iodine are widely used in nuclear medicine for diagnostic and therapeutic purposes. Radioiodine can substitute into many iodine radiopharmaceuticals (e.g., ^{131}I-MIBG, ^{123}I-MIBG, meta-iodobenzylguanidine and orthoiodohippurate [OIH]), and when oxidized for iodination (by chloramine T or chloroglycoluril), it can attach itself to aromatic rings to make different radiopharmaceuticals. The most common iodine isotopes are I-131, I-125, I-123, and ^{123}I-ioflupane.

- Iodine-131
  Iodine-131 is produced as a by-product of uranium fission. I-131 decays by β emission with a half-life of 8.05 days to X-133. As a result of that decay, four γ-rays are emitted with the following energies and abundances: 364 keV (82%), 637 keV (7%), 284 keV (6%), and 723 keV (2%). The 364-keV energy photons are mainly used diagnostically. The accepted radiochemical purity from the manufacturer for I-131 as NaI is 95%, as MIBG or Norcholesterol is 95%, and as OIH is 97%. I-131 is used as NaI in thyroid therapy and diagnosis in addition to imaging of the adrenal gland (as iodomethyl-norcholestrol or MIBG) and renal tubular system (as ^{131}I-OIH). Due to the high thyroid radiation uptake (1 rad/μCi), it has been replaced by I-123 for thyroid imaging and ^{99m}Tc-MAG_3, Mercaptoacetyltriglycine for renal tubular scan. Recently, I-131 was applied for radioimmunotherapy of non-Hodgkin lymphoma (NHL) when labeled with anti-CD20 monoclonal antibody (^{131}I-tositumobab) in a therapeutic regimen called BEXXAR [29].
- Iodine-125
  Iodine-125 is produced from Xe-124 through the following reaction:

$$\text{Xe-124}[\text{n}, \gamma]\ \text{Xe-125}$$

  Then, Xe-125 decays by EC to I-125. I-125 decays by EC with a half-life of 60 days and 35-keV gamma rays. I-125, when labeled with albumin-producing radioiodinated serum albumin (RISA), is frequently used for plasma volume and GFR, Glomerular filtration rate determination. I-125-labeled antibodies are used widely for radioimmunoassay.
- Iodine-123
  Iodine-123 is a cyclotron-produced radiopharmaceutical. Different methods have been used for I-123 production, although the current method of production uses the following reactions with 31-MeV protons from the cyclotrons:

  1. Xe-124[p, 2n]Cs-123. Cs-123 then decays by EC and β^+ emission to Xe-123, which decays to the target radiopharmaceutical (I-123), also by EC and β^+ emission.

$$\text{Xe-124}[\text{p, pn}]\ \text{Xe-123}$$

  2. Then, Xe-123 decays to I-123 by electron capture. I-125 is present as the only contaminant

with the previous methods at a concentration of less than 0.1%. I-123 decays by EC with a 13-h half-life and emits 159-keV photons with 83% abundance (ideal for imaging). Radiochemical purity of I-123 preparations from the manufacturer must exceed 95%.

I-123 is the preferred thyroid imaging agent, imparting 1% of the thyroid dose per microcurie when compared with I-131. ^{123}I-labeled compounds are commonly used as ^{123}I-MIBG for an adrenal scan, ^{123}I-OIH for a tubular renal scan, and ^{123}I-iodoamphetamine (^{123}I-IMP) for a cerebral perfusion scan [2].

- ^{123}I-Ioflupane (DaTSCAN)

  DaTSCAN is a widely used ^{123}I derivative for detection of the loss of nerve cells that release dopamine in an area of the brain called the striatum; dopamine is a chemical messenger, and therefore it will be useful in diagnosis of the following:

  1. *Movement disorders*: DaTSCAN is used to help distinguish between Parkinson disease and essential tremor (tremors of unknown cause) with a sensitivity of 96.5% [30].
  2. *Dementia*: DaTSCAN is also used to help distinguish between "dementia with Lewy bodies" and Alzheimer disease with 75.0–80.25% sensitivity [31].

  Dopamine transporter (DAT) imaging with tropane derivatives such as FP-CIT Fluoropropyl-Carbomethoxy-Iodophenyl-Tropane (^{123}I-Ioflupane) and β-CIT, Beta Carbomethoxy-Iodophenyl-Tropane has been developed to directly measure degeneration of dopamine presynaptic terminal and may be used to quantify changes in DAT density. Ioflupane binds specifically to certain structures of the nerve cells ending in the brain striatum that are responsible for the transport of dopamine. This binding can be detected using tomographic imaging [32].

2.4.4 Indium-111 Radiopharmaceuticals

In-111 is produced in a cyclotron through the following reaction:

$$\text{Cd-111 } [p, n] \text{ In-111}$$

Indium-111 decays with a 67-h half-life by EC as a pure gamma emitter with 173-keV (89%) abundance and 247-keV (94% abundance) photons. The gamma energies of In-111 are in the optimum range of detectability for the commercially available gamma cameras. Like Ga-67, In-111 in aqueous solutions exists only as In^{3+} and behaves chemically like iron, forming strong complexes with the plasma protein transferrin.

Because of the great stability of In-111 with transferrin, only strong chelates can be used in vivo to direct the localization of the radiopharmaceuticals to other sites. Strong chelators like DTPA, Diethlenetriaminepentaacetate or EDTA can be easily used with indium using citrates or acetates as a transfer ligand. ^{111}In-DTPA has been used for renal and brain imaging and is currently used for cisternography. ^{111}In-colloids can be used as liver/spleen imaging agents, and larger colloidal particles are commonly used for lung imaging.

The most common applications of In-111 are in labeling blood cells (white blood cells and platelets) for imaging inflammatory processes, thrombi, and proteins [33]. In protein labeling, by which proteins are primarily labeled to DTPA, choosing proper the In-111-specific concentration is of greater importance. In blood cell labeling, the plasma transferrin competes for the In-111 and reduces the labeling efficiency because In-111 binds with higher efficiency to transferrin than blood cells; therefore, isolation of the desired blood component from plasma permits easy labeling of either platelets or white blood cells.

^{111}In has been conjugated to octreotide as an agent for the scintigraphic localization of primary and metastatic somatostatin receptor-positive neuroendocrine tumors. A labeled form of octreotide is commercially available as the DTPA chelated compound ^{111}In-DTPA-octriotide (^{111}In-pentetreotide, Octreoscan) [34].

^{111}In contributes also in labeling of monoclonal antibodies (MAbs) using bifunctional chelates. The chelating agent (mainly DTPA) is first conjugated to the antibody, and then ^{111}In binds to the conjugated MAb via the chelating agent [35]. The commercially available kit is called Oncoscint. Indium In-111 satumomab pendetide (Oncoscint) is indicated for use in immunoscintigraphy in patients with known colorectal or ovarian cancer. It helps determine the extent and location of extrahepatic foci of disease and can be helpful in the preoperative determination of the resectability of malignant lesions in these patients [36].

A murine monoclonal antibody produced against prostate carcinoma and prostate hypertrophy is chelated to GYK-DTPA, glycyl-tyrosyl-(N,epsilon-diethylenetriaminepentaacetic acid) and lypophilized to give capromab pendetide. After ^{111}In labeling, a ^{111}In-capromab pendetide (ProstaScint) kit is produced for detecting primary and metastatic prostate cancer [37].

2.4.5 Xenon-133

Xenon-133 is an inert gas used mainly for lung ventilation scans and for the assessment of cerebral blood flow. It is a by-product of uranium fission with a 5.3-day half-life and 35% abundance for 81-keV photons. This photon energy requires starting lung scans with ventilation followed by the ^{99m}Tc-MAA (macroaggregated albumin) perfusion scan [1].

2.4.6 Chromium-51

Chromium-51 has a half-life of 27.7 days and has long been used for labeling red blood cells as a method for determination of red cell mass and red cell survival [38].

2.4.7 Phosphorus-32

Phosphorus-32, which is delivered commercially as ^{32}P-sodium phosphate, is produced by irradiating sulfur with neutrons in a reactor. P-32 decays by β^- emission with a half-life of 14.3 days. ^{32}P-sodium phosphate is indicated for therapeutic treatment of polycythemia vera, chronic myelocytic leukemia, and chronic lymphocytic leukemia and for palliation of metastatic bone pain. Chromic ^{32}P-phosphate is used for treatment of peritoneal or pleural effusions caused by metastatic disease [39, 40].

2.4.8 Strontium-89

Strontium-89 (pure β^- emitter) is produced in the reactor and decays with a half-life of 50.6 days [41]. ^{89}Sr-chloride (Metastron) is used for relief of bone pain since the compound behaves biologically as calcium does and localizes at the sites of active osteogenesis [42].

2.4.9 Rhenium-186

Rhenium-186 is a reactor-produced radiopharmaceutical that decays by β^- emission and has a half-life of 3.8 days. Re-186 is complexed with hydroxyethylene diphosphonate (HEDP) after reduction with stannous ions like Tc-99m. ^{186}Re-HEDP with radiochemical purity over 97% is useful for bone pain palliative therapy [43]. A whole-body scan can also be obtained using its 137-keV energy photons [44].

2.4.10 Samarium-153

Samarium-153 is a reactor-produced radionuclide that decays by β^- emission and has a half-life of 46.3 h. Sm-153 is complexed with a bone-seeking agent, ethylenediaminetetramethylene phosphonic acid (EDTMP), which localizes in bone metastases by chemisorption. ^{153}Sm-EDTMP is approved by FDA for relief of metastatic bone pain. Its duration of response is 1–12 months. In addition, its 103-keV photons allow scintigraphic imaging of the whole body [45]46.

2.4.11 ^{111}In- and ^{90}Y-Ibritumomab Tiuxetan (Zevalin)

Zevalin (^{111}In- and ^{90}Y-ibritumomab tiuxetan) consists of a murine monoclonal anti-CD20 antibody covalently conjugated to the metal chelator DTPA, which forms a stable complex with ^{111}In for imaging and with ^{90}Y for therapy. ^{90}Y-ibritumomab tiuxetan is used for the treatment of some forms of B-cell NHL, a myeloproliferative disorder of the lymphatic system, while its ^{111}In derivative is used to scan the predicted distribution of a therapeutic dosage of ^{90}Y-ibritumomab in the body [47].

The antibody binds to the CD20 antigen found on the surface of normal and malignant B cells (but not B-cell precursors), allowing radiation from the attached isotope (yttrium-90) to kill it and some nearby cells. In addition, the antibody itself may trigger cell death via antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis. Together, these actions eliminate B cells from the body, allowing a new population of healthy B cells to develop from lymphoid stem cells [48].

An earlier version of anti-CD20 antibody, Rituximab, has also been approved under the brand name Rituxan for the treatment of NHL. Ibritumomab tiuxetan was the first radioimmunotherapy drug approved by the FDA in 2002 to treat cancer. It was approved for the treatment of patients with relapsed or refractory, low-grade or follicular B-cell NHL, including patients with rituximab-refractory follicular NHL. In September 2009, ibritumomab received approval from the FDA for an expanded label for the treatment of patients with previously untreated follicular NHL, who achieve a partial or complete response to first-line chemotherapy.

2.4.12 ^{90}Y-Labeled Microspheres

Treatment of hepatic carcinomas and metastasis have experienced many trials [49] of the use of ceramic or resin microspheres with certain types of beta-emitting radiation to enhance their response rate. However, many side effects observed can contraindicate their usage for this purpose (e.g., secondary medullary toxicity with the release of ^{90}Y from the microspheres). Accordingly, modification of these methods was applied to develop new microspheres containing yttrium-90 in a stable form, preventing the release of the radioactive material in the surrounding matrix. Two products have been presented: SIR-Spheres with a 35-μm diameter (Medical Sirtec Ltd., Australia) and TheraSphere with a 20- to 30-μm diameter (MDS Nordion, Ottawa, Canada) [50]. This therapeutic module should be initiated with a diagnostic estimation of the possibility of locating and quantifying a possible pulmonary shunt. This is achievable by injection of ^{99m}Tc-MAA into the hepatic artery [51]. When yttrium-90 is incorporated into the tiny glass beds, it can be injected through the blood vessels supplying the liver through a long and flexible plastic tube (catheter) with guided fluoroscopy. This procedure allows a large local dose of radiation to be delivered to the tumor with less risk of toxicity to other parts of the body or the healthy liver tissues. The radiation from the induced ^{90}Y activity is contained within the body and becomes minimally active within 7 days after treatment due to physical decay [52].

2.4.13 Lutetium-177 Compounds

Lutium-177 ($T_{1/2} = 6.71$ days) is a radionuclide of exciting potential. It is used in a manner similar to yttrium-90; however, it has slightly different advantages:

1. It has both beta particle emissions ($E_{max} = 497$, 384 and 176 keV) for therapeutic effect and gamma emissions (113 and 208 keV) for imaging purposes.
2. It has a shorter radius of penetration than Y-90, which makes it an ideal candidate for radioimmunotherapy for smaller and soft tumors.

Many Lu-177 derivatives have been developed for many therapeutic purposes, such as

1. Lu-177 labeled EDTMP and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaminomethylenephosphonate (DOTMP) for bone pain palliation [53]
2. Lu-177 labeled radioimmunoconjugates (Lu-177 monoclonal antibody, 7E11) constructs for radioimmunotherapy of prostate cancer [54]
3. Lu-177-DOTA, tetra-azacyclododecanetetra-acetic acid octreotate for targeted radiotherapy of endocrine tumors [55].

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