10

Radioactive Compounds and Their Clinical Application

The preparation, handling and dispensing of radioactive materials that are being used for the diagnosis and/or treatment of diseases form a specialised area of pharmacy, the so-called nuclear pharmacy.

> ***Nuclear pharmacy*** *is defined as the area of pharmacy dealing with the compounding and dispensing of radioactive material to be used in nuclear medicine.*

In order to understand what a pharmacist's obligations are when handling nuclear material, it is important to understand what radioactivity is and how it is used in a clinical setting.

10.1 What is radioactivity?

10.1.1 The atomic structure

It is fundamental to look at the structure of an atom in order to understand what radioactivity is. As discussed in Chapter 1 and briefly summarised here, an atom consists of a positively charged nucleus formed from the so-called nucleons, which is surrounded by negatively charged electrons, which may occupy different energy levels. Protons and neutrons form the nucleus. Protons are nucleons with a positive charge and a mass of 1.6726×10^{-24} g. The atomic number (Z) expresses the number of protons. A neutron is a nucleon without a charge and a mass similar to that of protons (1.6749×10^{-24} g). The so-called neutron number (N) describes the total number of neutrons. Neutrons and protons are held together by nuclear binding forces and therefore form the nucleus. The letter A stands for the number of nucleons, which is the sum of number of protons (Z) and neutrons (N). Electrons have a mass of 9.1094×10^{-28} g and they move in energy levels around the nucleus. Lower orbitals, which are defined as the orbitals closer to the nucleus, possess a higher kinetic energy. If an electron moves to an orbital closer to the nucleus, energy is released, whilst the energy is required to move it

Essentials of Inorganic Chemistry: For Students of Pharmacy, Pharmaceutical Sciences and Medicinal Chemistry,
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E = element symbol

A = number of protons + number of neutrons = mass number

Z = number of protons = number of electrons = atomic number

Figure 10.1

away from the nucleus. The number of electrons should be equal to the number of protons in order to have an element without any charge. Typically, the number of neutrons equals the number of protons (Figure 10.1).

10.1.2 Radioactive processes

Radioactive decay, also known as *radioactivity*, describes the process by which an unstable nucleus spontaneously loses energy in order to form a stable nucleus. This energy loss is achieved by emitting particles of ionising radiation. An element or material that spontaneously emits energy in this form is considered as radioactive. Radiation can take place in the form of α, β^-, β^+, X-rays and γ-rays.

> ***Radioactivity*** *is defined as the process whereby an unstable nucleus spontaneously loses energy in order to form a more stable nucleus.*

The terms *nuclide* and *radionuclide* describe identifiable atomic species (nonradioactive or radioactive), which are characterised by their exact number of protons (*Z*) and neutrons (*N*). In contrast, an element is only defined by its number of protons (*Z*). The number of neutrons can vary, which leads to different isotopes of the same element as described in Chapter 1. An element can have a number of isotopes, some of which are stable and some are not stable and therefore are classified as radioactive.

10.1.3 Radioactive decay

It is important to understand the different forms of radioactive decay, as not all forms of radiation are useful for clinical applications. It is also crucial to understand the reason for the occurrence of radioactivity in order to provide the patient with the best and safest possible treatment option.

There are two reasons for the occurrence of radioactive decay: one is that the ratio of neutrons to protons is greater or less than 1. The second reason is that radioactive decay takes places as a result of an energy imbalance within the atom, which means that the atom needs to get rid of energy in order to reach a stable form. The different forms of radiation can be summarised as α, β, γ-decay and X-ray emission.

Alpha-(α-)*radiation* is defined as the emission of helium particles, precisely $^4_2He^{2+}$. α-Decay occurs in elements with a so-called heavy nucleus, principally in elements with a higher atomic mass (typically in elements with $Z > 82$). α-Particles are fairly heavy particles and follow a straight path when penetrating through a material. They only display a short-range activity and the radiation can be easily shielded off with a piece

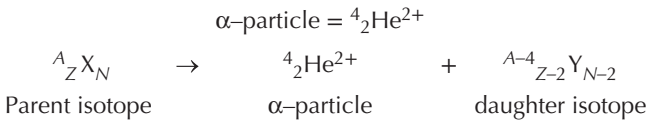

Figure 10.2 α-*Particle*

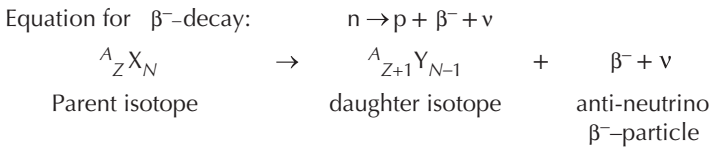

Figure 10.3 β⁻-*Radiation*

of paper. Their clinical application is very limited and includes only a few therapeutic examples. Current research includes the use of monoclonal antibodies as radiopharmaceuticals. The idea is to deliver radioisotopes directly to the tumour cells, minimising the exposure of healthy cells to radiation.

In general, interaction of α-radiation with neighbouring matter can occur in two ways – through ionisation or excitation. Excitation means that an α-particle can, upon collision, promote an electron to a higher energy level (higher outer shell). Once the electron falls back to its original energy level, energy is emitted. The more important interaction is the ionisation of an atom. This occurs when an α-particle collides with its target and 'strips' away an electron, leaving behind a positively charged molecule (Figure 10.2).

Beta-(β-)*decay* occurs when basically an electron is ejected from the nucleus. This occurs when the 'neutron to proton ratio' is >1. In order for this to happen, within the nucleus a neutron is converted into a proton and a negatively charged β-particle (negatron, β^{-}). Additionally a so-called antineutrino (ν) is 'produced', carrying away any excess binding energy from the nucleus. These processes result in an increase in the proton number (Z) to $Z+1$ and a decrease in the neutron number (N) to $N-1$. Negatively charged β-particles have the appearance of electrons, but they originate from the nucleus and carry energy. In contrast, electrons that are present in the orbit outside the nucleus have no energy and obviously their origin differs (Figure 10.3).

β-Particles differ significantly from α-particles as they are considered as extremely light and fast particles. As a consequence, they travel much further and their clinical applications include imaging methods as well as therapeutic ones, with the emphasis being on the latter.

Positron emission is the ejection of positively charged β-particles from a proton-rich nucleus. This occurs when the neutron to proton ratio is <1. For this to happen, a proton is converted into a neutron, a positron (β^{+}) and a neutrino (ν). A neutrino is the opposite of an antineutrino, a small particle carrying no mass or charge. These processes result in a decrease in the proton number (Z) to $Z-1$ and an increase in the neutron number (N) to $N+1$. The differences between a positron and a neutron manifest in a lower energy and range for positrons. Positrons and positron-emitting elements are used mainly for imaging purposes in the so-called positron emission tomography (PET, see Chapter 10) (Figure 10.4).

Gamma-(γ-)*emission* is the elimination of excess energy by the emission of photons. A γ-photon has no charge or mass and occurs as electromagnetic radiation. The radiation occurs at short wavelengths and is therefore of high energy. It has the longest range of all nuclear emissions discussed. The nucleus that emits the γ-photon does not undergo any change of the neutron number; mostly isomers are formed. Isomers are

Equation for β^+–decay: $p \rightarrow n + \beta^+ + \nu$

$$^{A}_{Z}X_{N} \rightarrow {}^{A}_{Z-1}Y_{N-1} + \beta^+ + \nu$$

Parent isotope — daughter isotope — neutrino, positron

Figure 10.4 *Positron emission*

^{99m}Tc

Figure 10.5 *Element symbol technetium*

$$^{0}_{0}\gamma$$

$$^{A(m)}_{Z}X \rightarrow {}^{A}_{Z}Y + \gamma$$

Figure 10.6 *γ-Emission*

defined as nuclides of the same atomic mass (A) and number (Z) with the only difference being that one isomer is in an excited (metastable (m)) state. This is marked with ^{Am}E as the atomic number (Figures 10.5 and 10.6).

γ-Emission normally occurs following another nuclear decay. It has a high penetrating power of several metres as the γ-photons are not charged. They typically interact with matter through direct collision with nuclei and electrons of the orbital. γ-Emission finds its clinical application mainly as part of radiopharmaceutical imaging processes.

Electron capture and X-ray emission constitutes another form of positron emission and occurs in unstable atoms where the 'neutron to proton' ratio is <1. In order to convert to a stable atom, a proton from the nucleus catches an electron from the orbital and transforms into a neutron and a neutrino, with the neutrino carrying any excess energy. Typically, a cascade reaction follows, in which electrons from the outer (higher energy) orbitals move closer to the nucleus and fill the vacated orbitals. Orbitals closer to the nucleus are of lower energy, and the energy difference is given off as X-rays, a form of electromagnetic radiation. In contrast to γ-decay, which originates predominantly from the nucleus, X-rays stem from outside the nucleus. Additionally, X-rays have a wavelength longer than γ-photons. The result of electron capture and X-rays are the so-called isobars, similar to β-decay.

Isobars *are nuclides with the same mass number (A) but different atomic number (Z) and different neutron number (N).*

Figure 10.7 shows the effect of charge on different forms of radiation. A radioactive sample is placed in a container, where radiation is released in only one direction. This directed radiation is then exposed to a negatively and a positively charged electrode. As a result, the α-particles (positive charged particles) are directed towards the negative charge, whereas the gamma rays are not affected by the charge at all. Consequently, the negatively charged β-particles are directed towards the positive charge.

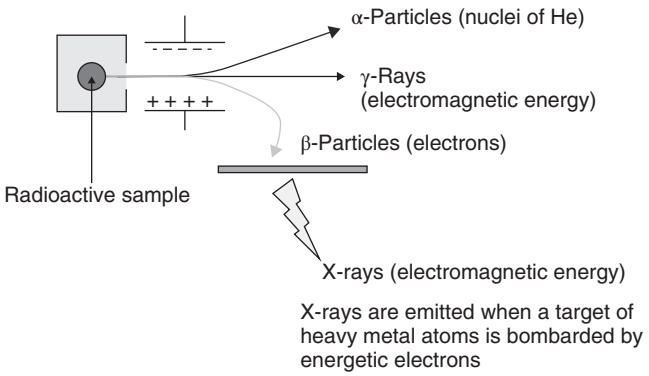

Figure 10.7 *Types of ionising radiation*

10.1.4 Penetration potential

It is important to understand the different penetration potentials of the various forms of radioactive decay in order to evaluate their clinical potential and the safety concerns of radiopharmaceutical compounds. α-Particles have the shortest range and can be stopped by paper. Skin is typically thick enough to provide sufficient protection. It is dangerous to ingest α-particles as it can cause serious damage to the affected areas. Unfortunately, it is difficult to monitor α-radiation. α-Particles have typically a long half-life and cause cell death, and therefore can sometimes be used in cancer treatment.

β-Particles cause ionisation and excitation (similar to α-particles) when they interact with matter. Ingestion is also a serious problem, as many β-radioisotopes are isotopes of carbon, hydrogen, sulfur, phosphorus and other essential elements and can easily be incorporated into biological material in the human body. This can lead to extensive damage of DNA and tissue. Additionally, many β-particles have relatively long half-lives. Fortunately, they can be shielded by a few millimetres of aluminium or plastic and are easy to monitor.

γ-Photons also cause ionisation and excitation, but not as successfully as α-particles or β-particles. The energy of γ-photons is usually larger than that of chemical bonds and can destroy biological structures in the human body. Their penetration potential is the highest amongst the types of radiation discussed here. γ-Photons can penetrate through skin and tissue easily. Shielding requires a few inches of lead or a few feet of concrete.

10.1.5 Quantification of radioactivity

Radioactivity can be quantified, and there are several units being used in order to describe the energy, exposure and the dose of radiation. It is crucial for a nuclear pharmacist to understand these units in order to dispense and handle radioactive material correctly.

10.1.5.1 Units of radioactivity

The activity of a radioactive source is defined as the number of transformations per unit time. The old traditional unit of radiation is curie (Ci). One curie is defined as 3.7×10^{10} disintegrations per second (dps). Nevertheless, the SI unit is becquerel (Bq), which is equal to 1 dps and is a metric unit (Figure 10.8, Tables 10.1 and 10.2).

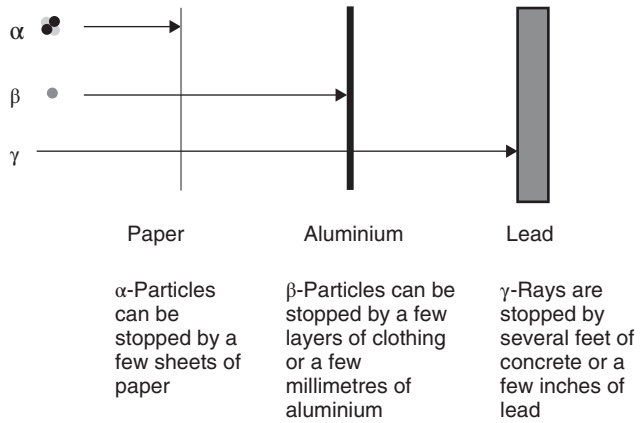

Figure 10.8 *Penetration potential of different forms of radioactivity*

Table 10.1 *Conversion between curie and SI units*

1 Bq (becquerel)	1 dps	2.7×10^{-11} Ci
1 kBq (kilobecquerel)	10^3 dps	2.7×10^{-6} Ci
1 MBq (megabecquerel)	10^6 dps	2.7×10^{-4} Ci
1 GBq (gigabecquerel)	10^9 dps	2.7×10^{-2} Ci
1 TBq (terabecquerel)	10^{12} dps	2.7 Ci

Table 10.2 *Conversion between curie and SI units*

1 Ci (curie)	3.7×10^{10} Bq	37 GBq
1 mCi (millicurie)	3.7×10^{7} Bq	37 MBq
1 mCi (microcurie)	3.7×10^{4} Bq	37 kBq
1 nCi (nanocurie)	3.7×10 Bq	37 Bq

For a pharmacist, it is crucial to know the specific activity of a radioactive preparation. This is the activity of a particular radionuclide per unit mass of this element, usually expressed in grams. The radioactive concentration of a solution is defined as the activity of a particular radionuclide per unit volume. The absorbed dose is the energy deposited per unit mass of the material. The unit 1 gray (Gy) is equal to 1 J of energy absorbed in 1 kg of material. As a comparison, ~25 Gy is need to kill bacteria when sterilising. The 'dose equivalent' takes also into account variations in the biological effectiveness of different radiation. The unit is sievert (1 Sv) (Figure 10.9).

10.1.5.2 Half-life ($t_{½}$)

For nuclear pharmacists, it is also important to understand the term *half-life* ($t_{½}$), as this gives information on how fast the radioactive decay takes place. The shorter the half-life, the faster the radioisotope decays. The

The **activity** of a radioactive source is the number of nuclear transformations per unit time

- 1 becquerel (Bq) is one nuclear transformation per second

1 megabecquerel (1MBq) =	10^6 Bq
1 kilobecquerel (1kBq) =	10^3 Bq

- 1 curie (Ci) –3.700 × 10^{10} nuclear transformations per second or disintegrations per second (dps)

1 millicurie (1 mCi) =	10^{-3} curie
1 microcurie (1 μCi) =	10^{-6} curie
1 nanocurie (1 nCi) =	10^{-9} curie

Figure 10.9 *Radiation units and definitions*

Dose equivalent = Absorbed dose × Quality factor

The quality factor for β- and γ-radiation is 1 and therefore 1 Sv = 1 Gy

Figure 10.10 *Dose equivalent*

half-life of radioactive elements can vary from several years to less than a second. Typical examples include ^{14}C (5730 years), ^{24}Na (15 h) and ^{18}Kr (13 s). Radiopharmaceuticals are typically divided into products with long (>12 h) and short (<12 h) half-lives.

Half-life ($t_{1/2}$) *is defined as the time it takes for the activity (or the amount of radioactivity) to reduce by 50%. The shorter the half-life, the faster the isotope decays and the more unstable it is. The half-life is unique for any given radioisotope.*

Radioactive decay follows an exponential curve and it is therefore possible to determine the half-life by plotting a graph of activity versus time (see Figure 10.10). The first half-life is the point on the time axis at which only 50% of the initial activity remains. Subsequently, the second half-life is the time point at which the activity has halved again, that is, 25% of the original activity is left (Figure 10.11).

The so-called decay constant λ is related to half-life $t_{1/2}$ and can be calculated by using the following formula:

$$\lambda = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{t_{1/2}}$$

Example

The decay constant for ^{99m}Tc is 0.1153 h^{-1}. Calculate the half-life ($t_{1/2}$) of this radioisotope (Table 10.3).

$$\lambda = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{t_{1/2}}$$

$$t_{1/2} = \frac{0.693}{\lambda} = \frac{0.693}{0.1153\,h^{-1}} = 6.01 \text{ hours}$$

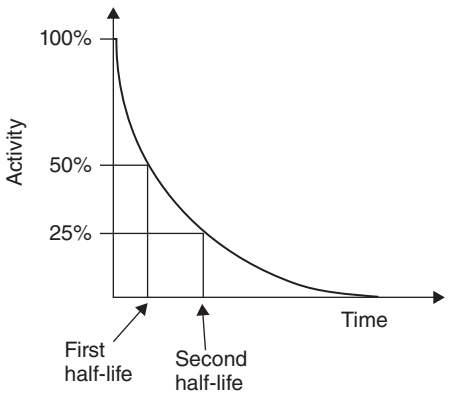

Figure 10.11 *Exponential graph depicting half-life*

Table 10.3 *Half-life of commonly used radioisotopes [1]*

Radioisotope	Half-life
Tritium (^{3}H)	12.33 yr
^{11}C	20.385 min
^{15}O	122.24 s
^{32}P	14.26 d
^{33}P	25.34 d
^{66}Ga	9.49 h
^{67}Ga	3.26 d
^{68}Ga	67.63 min
^{89}Sr	50.53 d
^{90}Sr	28.74 yr
^{99}Mo	65.94 h
^{99m}Tc	6.01 h
^{123}I	13.27 h
^{125}I	59.402 h
^{126}I	13.11 d
^{131}I	8.02 d

10.1.5.3 Calculation of radioactive decay

It is important for the healthcare professional to predict the activity of the radioactive material at any point in time before or after the assay being undertaken, as it is crucial to know the exact activity at administration to the patient. The radioactive decay can be described as the average number of radioactive isotopes (N) disintegrating per unit time (=disintegration rate). The disintegration rate is defined as $-\mathrm{d}N/\mathrm{d}t$. The disintegration rate is proportional to the number of undisposed radioisotopes, and can be also expressed as the activity (A).

$$-\frac{\mathrm{d}N}{\mathrm{d}t} = \lambda \times N = A$$

$$A = A_0 \cdot e^{-\lambda \cdot t}$$

A – specific activity at time t
A_0 – initial activity
$\lambda = \ln 2/t_{1/2} = 0.693/t_{1/2}$ – decay constant
t – elapsed time

Figure 10.12 *Radionuclide decay equation*

Upon integration, the radioactive decay of any radioactive sample can be calculated by applying the so-called radionuclide decay equation (see Figure 10.12). In order to calculate the radioactivity at a specific time point t, it is important to know the initial activity A_0, the elapsed time t and the decay constant λ. Half-life is the time that passes by until the activity has halved.

Example

A radioactive sample has a half-life of 8.05 days and contains 150 mCi radioactivity. Calculate the radioactivity left after 20 days.

$$A_0 = 150\,\text{mCi} \quad t_{1/2} = 8.05\,\text{days} \quad t = 20\,\text{days}$$

$$\lambda = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{t_{1/2}} = \frac{0.693}{8.05\,\text{days}} = 0.0861\,\text{days}^{-1}$$

$$A_t = A_0 \times e^{-\lambda t} = 150\,\text{mCi} \times e^{-0.0861 \times 20} = 26.8\,\text{mCi}$$

10.1.5.4 Dispensing of radioisotopes: percentage activity and activity concentration

For the dispensing pharmacist, it is crucial to know the activity of a radioactive sample at any given time. The factor $e^{-\lambda t}$ from the decay equation $A = A_0 e^{-\lambda t}$ is called the *decay factor* and can be used to calculate the percentage activity remaining after given time t. The percentage activity can be calculated using the following equation:

$$\text{Percentage activity} = 100 \times e^{-\lambda t}$$

Example

^{131}I has a half-life of 8.05 days. Calculate the percentage of ^{131}I remaining after 4.5 days.

$$\lambda = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{t_{1/2}} = \frac{0.693}{8.05\,\text{days}} = 0.0861\,\text{days}^{-1}$$

$$\text{Percentage activity after } 4.5\,\text{days} = 100 \times e^{-\lambda t} = 100 \times e^{-0.0861 \times 4.5} = 67.88\%$$

Radioactive decay charts, that is, charts showing the percentage activity at certain time points, are often used in hospitals for quick reference. A representative table illustrating the percentage activity for the radioisotope ^{99m}Tc is shown in Table 10.4.

Radioisotopes are often dispensed according to their specific activity and activity concentration. The specific concentration is defined as the amount of radioactivity, usually expressed in curie, per unit mass. For example, a sample of containing 50 mg of ^{99m}Tc-albumin has an activity of 100 mCi. Therefore, the specific activity can be determined as 100 mCi/50 mg = 2 mCi/mg.

Table 10.4 *Radioactive decay chart for* ^{99m}Tc

Time (h)	% Activity remaining
2	79.4
4	63.1
6	50.1
8	39.8
10	31.6
12	25.1
14	19.9

The decay constant (λ) is calculated as ($0.693/6.01\ h^{-1}$). The decay factor is $e^{-\lambda t}$. The percentage activity remaining (in percentage) is calculated as $100 \times e^{-\lambda t}$.

Most radioactive products are dispensed as solutions, and therefore the term *activity concentration* is important to understand. The activity concentration is defined as the radioactivity expressed in curie, per unit volume. A 5 ml solution of ^{99m}Tc-albumin has a radioactivity of 100 mCi. Therefore, the activity concentration is 100 mCi/5 ml = 20 mCi/ml. Once the activity concentration is known, the right dose (volume) containing the correct radioactivity can be dispensed.

$$\text{Quantity(ml)} = \frac{\text{Activity required}}{\text{Activity concentration}}$$

Example

The current activity concentration of a radiopharmaceutical is 20 mCi/ml. A solution with a dose of 15 mCi has been ordered. What quantity needs to be dispensed in order to provide a sample with the correct radioactivity?

activity concentration : 20 mCi/ml activity requested : 15 mCi

Quantity needed = 15 mCi/20 mCi/ml = 0.75 ml = amount to be dispensed

10.2 Radiopharmacy: dispensing and protection

Radiopharmacy deals with the manufacture and dispensing of radioactive materials that are used as radioactive medicines (or better known as *radiopharmaceuticals*). Radiopharmaceuticals can be used as diagnostic or therapeutic tools. Radionuclides that are used for a diagnosis should have as little an impact as possible on the health of the patient. Therefore, radioactive elements with a short-half-life and ones that only emit γ-radiation are seen as ideal. The radionuclide ^{99m}Tc in combination with a gamma camera is often used for imaging purposes, as the former has a half-life of 6 h and only emits γ-rays. Radionuclides that emit β-particles are more suitable for a therapeutic use. ^{131}I with its β-radiation is used for the treatment of hyperthyroidism (overactive thyroid) and metastatic diseases of the thyroid gland. ^{131}I also emits gamma radiation, which can be used to diagnose renal function and determine exactly the glomerular filtration rate (see Section 10.3.1).

Radiation can cause harmful effects in humans, which include nausea, skin burns, cancer, sterility, hair loss and even death. Nevertheless, all of these side effects depend on the type of radiation and its energy, the penetration power and the time scale of exposure. If radiation is used correctly, it can offer a range of

useful applications. These include the treatment of cancer, sterilisation of medical instruments and, away from clinical applications, the generation of energy and dating of archaeological remains.

The correct protection from radiation is crucial for the safe handling of radioactive material. Radiation protection can be achieved by shielding; plastic and aluminium can shield from β rays, whereas lead or tungsten is needed to effectively shield from gamma rays. Furthermore, distance and time scale of exposure are important factors for the effective protection from radiation. The radiation dose is inversely proportional to the square of the distance from the radiation source. Also, minimising the time of exposure helps to reduce the risk of side effects from radiation.

The role of a specialised pharmacist, amongst other things, focusses on the correct dispensing of the radiopharmaceutical, which is more complicated than the dispensing of a nonradioactive item. The pharmacist is responsible to ensure that the proper prescribed dose is prepared and dispensed. This is not as simple as it sounds, as radioactive material undergoes continuous decay. Therefore, it is important to state when the activity was measured and what the half-life of this radionuclide is. Radiopharmaceuticals are typically dispensed in doses of units of activity (mainly kilobecquerel or megabecquerel).

10.3 Therapeutic use of radiopharmaceuticals

Radiopharmaceuticals that are used therapeutically are molecules with radiolabelling. This means that certain atoms in this molecule have been exchanged by their radioactive isotopes. These radiolabelled molecules are designed to deliver therapeutic doses of ionising radiation (mostly β-radiation) to specific disease sites around the body. The more specific the targeting is, the fewer the side effects expected. For any design of a treatment regime including radiopharmaceuticals, it is important to consider what the decay properties of the radionuclide are and what the clearance route and rate from nontarget radiosensitive tissue is.

10.3.1 ^{131}Iodine: therapy for hyperthyroidism

Iodine has the chemical symbol I and atomic number 53. It is a member of the halogens (group 17 of the periodic table of elements) (Figure 10.13).

Elemental iodine is characterised by the purple colour of its vapour. Free iodine typically exists (like the other halogens) as the diatomic molecule I_2. Iodide (I^-) is the highly water-soluble anion, which is mainly found in the oceans. Iodine and its compounds are mainly used in nutrition. It has relatively low toxicity and is easy to include into organic compounds, which has led to its application as part of many X-ray contrast agents. Iodine is required by humans to synthesise the thyroid hormones, and therefore iodine will accumulate in the thyroid gland. Iodine has only one stable isotope ($^{127}_{53}$I), but it has several radioactive isotopes. Some of these are used for medicinal purposes including diagnostic tests and treatment. Radioisotopes of iodine will accumulate in the thyroid gland and therefore can be used clinically. The radioactive isotope ^{129}I has a half-life of 15.7 million years, ^{125}I has 59 days and ^{123}I has 13 h. The last one is used in nuclear medicine as an imaging agent because of its gamma radiation and its short half-life. Using a gamma camera, images of the human body can be made showing areas of accumulation of the radioisotope.

^{131}I is the product of nuclear fission (as experienced during the Chernobyl disaster) and is a β-emitting radioisotope which will be transported to the thyroid gland if inhaled. Fortunately, it can be replaced by treatment with potassium iodide (nonradioactive), which will replace the radioisotope. Nevertheless, ^{131}I can be used as a therapeutic agent against thyroid cancer when applied in high doses. Paradoxically, the β-emitting radioisotope causes cancer when it is applied in low doses, but it will destroy its surrounding tissue if the dose is high enough. Therefore, preparations containing $^{131}I^-$ are often used to treat hyperthyroidism. These preparations are normally administered orally either as capsules or solution.

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 10.13 *Periodic table of elements showing the element iodine (highlighted)*

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 10.14 *Periodic table of elements showing the element strontium*

10.3.2 ^{89}Strontium

Strontium is an alkaline-earth element with the atomic number 38, is a member of group 2 in the periodic table of elements and has the chemical symbol Sr (Figure 10.14).

Strontium is a soft grey metal and is more reactive with water than calcium. On contact with water, it produces strontium hydroxide and hydrogen gas. In order to protect the element, strontium metal is usually kept under mineral oil to prevent oxidation. Natural strontium is formed of a mixture of four stable isotopes – ^{84}Sr, ^{86}Sr, ^{87}Sr and ^{88}Sr, with the last one being the predominant one.

^{89}Sr is an artificial radioisotope and is a β-emitter with a half-life of 50.5 days. It is a product of the neutron activation of ^{88}Sr and decays to the stable ^{89}yttrium. Metastron is a product containing ^{89}Sr and is licensed by the FDA. It comes in a ready-to-use vial and expires within 28 days. It is supplied with a calibration vial, so that the pharmacist will be able to ensure that the patients get the accurate dose prescribed [2].

Because of the similarity of strontium and calcium (neighbouring elements in the periodic table of elements), strontium is believed to be metabolised in the human body in a similar way and accumulates, for example, in the bones. This has led to its application as a treatment option for pain caused by bone metastasis. It is known that >50% of patients with prostate, breast or lung cancer will develop painful bone metastasis. The exact mechanism of relief from bone pain is not known. $^{89}SrCl_2$ is administered intravenously and, as its distribution in the human body is similar to that of calcium, it is quickly cleared from the blood and deposited in the bone mineral. Strontium can be found in the hydroxyapatite cells of the bones rather in bone marrow cells. The radioisotope ^{89}Sr delivers localised β-radiation, inducing a pain relieving effect. A majority of the administered $SrCl_2$ is actively distributed to the metastases. Any free $SrCl_2$ is excreted renally or along with the faeces [2].

Low platelet count is the most likely side effect occurring in patients being treated with $^{89}SrCl_2$. Platelet counts should return to preadministration levels after 6 months once treatment is finished. Treatment with $^{89}SrCl_2$ is not recommended in patients with an already low platelet or white blood cell count, and for patients receiving this treatment the blood parameters have to be regularly checked even after the treatment is completed.

10.3.3 Boron neutron capture therapy (BNCT)

Boron has two stable isotopes, ^{10}B and ^{11}B, and 14 radioisotopes with very short half-lives. ^{11}B is the most abundant isotope and represents 80% of natural boron, whilst ^{10}B (∼20%) finds a significant clinical application in the so-called boron neutron capture therapy (BNCT).

BNCT is a noninvasive treatment option for malignant tumours, especially brain tumours and head and neck cancers, and is currently under clinical trials. The patient is injected with a nonradioactive ^{10}B-containing compound that acts as a neutron-capturing agent and shows high selectivity to cancer tissues. Once the compound has reached the tumour, the patient is exposed to a beam of low-energy neutrons, the so-called epithermal neutrons. These neutrons lose their energy once they penetrate the skin, but they can still interact with the neutron-capturing agent and initiate a nuclear reaction. This reaction of ^{10}B with a neutron results in the conversion to the nonradioactive isotope ^{7}Li and low-energy gamma radiation together with the emission of α-radiation ($^{4}{}_{2}He^{2+}$ particles). α-Radiation is a radiation with a short range and bombards the local tumour tissue from within the tumour cells. The linear energy transfer (LET) of these α-particles ranges approximately one cell diameter, which means there is minimum exposure to healthy tissue (Figure 10.15).

$$^{10}B + n_{th} \rightarrow [^{11}B] \rightarrow {}^{4}He + {}^{7}Li + 2.31\,MeV$$

A variety of carrier molecules for ^{10}B have been investigated, including carbohydrates, antibodies, liposomes and amino acids. There are currently only two boron compounds as BNCT delivery agents used in clinical trials. Sodium mercaptoundecahydro-*closo*-dodecaborate ($Na_2B_{12}H_{11}SH$), known as *borocaptate* (BSH), was mainly used in clinical trials in Japan, whereas the boron-based amino acid (L)-4-dihydroxy-borylphenylalanine (BPA, boronophenylalanine) is used in clinical trials in Europe and the United states (Figure 10.16) [3, 4].

10.4 Radiopharmaceuticals for imaging

Radiopharmaceuticals are typically administered intravenously and then distributed to a particular organ. The molecule itself, and not the radiolabelling, will determine to which organ the radioactive molecule is transported. γ-Radiation is detected externally by using a special scintillation detector, also known as a *gamma*

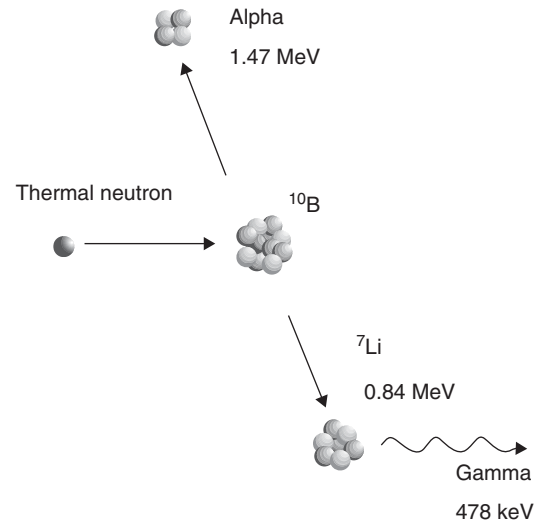

Figure 10.15 *The mechanism of BNCT [3] (Reproduced with permission from [3]. Copyright © 2005, John Wiley & Sons, Ltd.)*

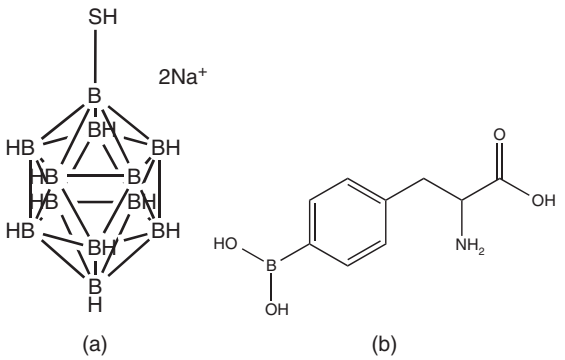

Figure 10.16 *Chemical structure of sodium mercaptoundecahydro-*closo*-dodecaborate (BSA) (a) and (L)-4-dihydroxy-borylphenylalanine (BPA) (b)*

camera. The camera captures the emitted radiation and forms a two-dimensional image. This diagnostic test is also called *scintigraphy*.

In contrast, PET produces a three-dimensional image of the functional processes in the human body. The method is based on the use of positron-emitting radionuclides and their indirectly emitted gamma rays. Radionuclides, the so-called tracers, are introduced to the body as parts of biologically active molecules. PET also uses gamma cameras to detect the internally applied radiation, but in modern scanners, three-dimensional images are often achieved with the aid of a CT X-ray scan performed at the same time as part of the same machine.

Diagnostic X-ray uses external radiation, which is sent through the body to produce a two-dimensional image, whereas scintography is based on the internal accumulation of radionuclides.

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 10.17 *Periodic table of elements showing the element technetium (highlighted)*

10.4.1 ^{99m}Technetium

Technetium has the chemical symbol Tc and atomic number 43. It is the lightest element that has no stable isotope. It is a silvery-grey transition metal (Figure 10.17).

^{99m}Tc (also referred to as *technetium-99m*) is the metastable isomer of ^{99}Tc, which is a gamma-emitting nuclide routinely used in diagnostic medicine. It has a short half-life of around 6 h, which is ideal for diagnostic applications (but not for therapeutic applications) as it helps to keep the radiation exposure to the patient low. The use of a gamma camera allows detection of the radioactive tracer in the body and creates images of the area in question (Figure 10.18).

One challenge of using a radioactive material is to safely manufacture the products and deliver them to the clinical setting. Radionuclides with long half-lives are usually prepared commercially using a nuclear reactor and supplied as the finished product. Products containing radionuclides with a short half-life cannot be delivered as the finished product because of their rapid decay. Therefore, they are delivered to the clinical setting as radionuclides with a long half-life and the desired radionuclide is then generated and formulated at the moment of use. ^{99m}Tc and its compounds are generated *in situ* for use as an imaging agent using a so-called ^{99m}Tc generator. The generator is loaded with molybdenum-99 (^{99}Mo), which is often referred to as the commercially available transportable source of ^{99m}Tc. The general idea is that the generator contains a long-lasting 'parent' compound, which decays and produces the 'daughter' radionuclide. In the case of the ^{99m}Tc generator, it contains $^{99m}MoO_4^{2-}$ absorbed on an alumina column. $^{99m}MoO_4^{2-}$ decays to $^{99m}TcO_4^-$, which can be removed as $Na^{99m}TcO_4$ when the column is washed with a NaCl solution. Hospitals tend to buy these generators on a regular basis to provide a continuous supply of $^{99m}TcO_4^-$ (Figure 10.19).

Compounds containing ^{99m}Tc can be used for imaging a variety of functions and structures in the human body. The use of different molecules containing ^{99m}Tc determines to which part of the body the radionuclide is transported and which structure can be imaged. There are a variety of different molecules, but, for example, ^{99m}Tc-aerosol can be used for the imaging of lung ventilation, whereas ^{99m}Tc-albumin is generally used for judging cardiac function. ^{99m}Tc-albumin is an injectable solution prepared by combining sodium pertechnetate ($NaTcO_4$) and human albumin in the presence of a reducing agent such as a tin salt [1].

^{99m}Tc-medronate is used for skeletal imaging, and the succimer analogue is used for preparing images of the kidney. ^{99m}Te succimer injection is prepared by reacting sodium pertechnetate ($NaTcO_4$) with *meso*-2,3-dimercaptosuccinic acid in the presence of a reducing agent such as a stannous salt (Figure 10.20) [1].

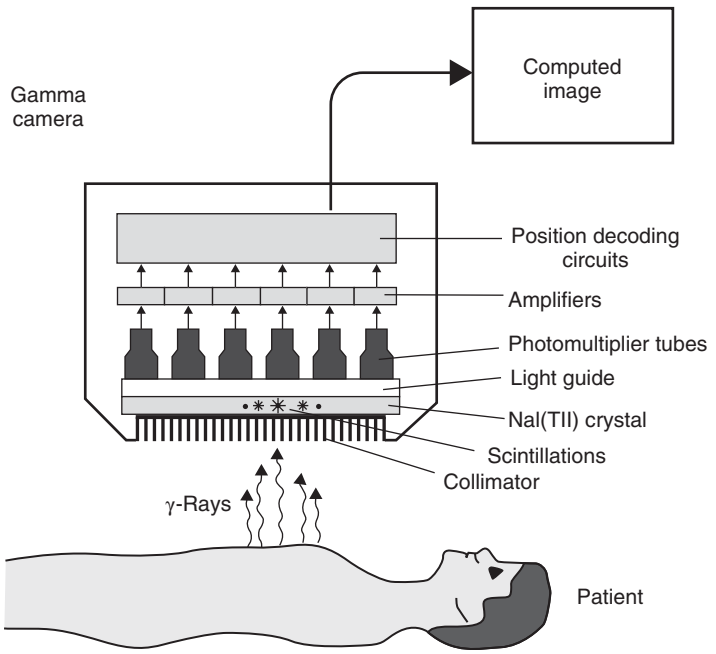

Figure 10.18 *Scheme showing the use of a gamma camera on a patient treated with a ^{99m}Tc imaging agent [5] (Reprinted with permission from the Federation of American Scientists. http://www.fas.org/irp/imint /docs/rst/Intro/img003.gif.)*

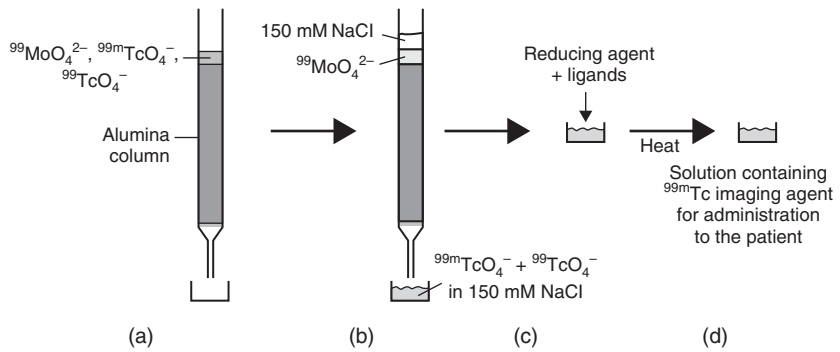

Figure 10.19 *(a–d) Illustration of a ^{99m}Tc generator [5] (Reproduced with permission from [5]. Copyright © 2009, John Wiley & Sons, Ltd.)*

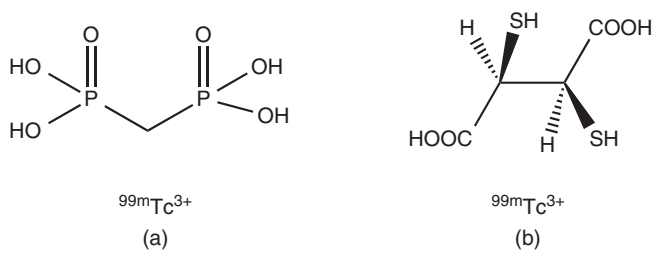

Figure 10.20 *Chemical structures of ^{99m}Tc-medronate (a) and ^{99m}Tc-succinate (b)*

Cardiolite is an organometallic compound based on ^{99m}Tc, which has become one of the most used nuclear imaging agents to visualise the heart muscle and abnormalities of the parathyroid. Cardiolite is the trade name of ^{99m}Tc-sestamibi, which is a coordination complex of ^{99m}Tc with six so-called MIBI ligands. MIBI stands for methoxyisobutylisonitrile. The full chemical name is (OC-6-11)-hexakis[1-(isocyano-κC)-2-methoxy-2-methylpropane][^{99m}Tc]technetium(I) chloride. A typical solution for injection is prepared by heating a solution tetrakis[(2-methoxy-2-methylpropyl-1-isocyanide)copper(I)] tetrafluoroborate, which is a weak chelating agent, and sodium pertechnetate ($NaTcO_4$) in the presence of a stannous salt (Figure 10.21) [1].

^{99m}Tc-exametazime is a ^{99m}Tc preparation that can be used to visualise damage to the brain, for example, in the evaluation and localisation of stroke damage, head trauma, dementia and cerebral function impairment (Figure 10.22 and Table 10.5) [2].

Each of these ^{99m}Tc-containing compounds is freshly prepared by the radiopharmacist strictly following a standard protocol issued by the supplier. Usually, all ingredients are supplied in closed vials, mostly

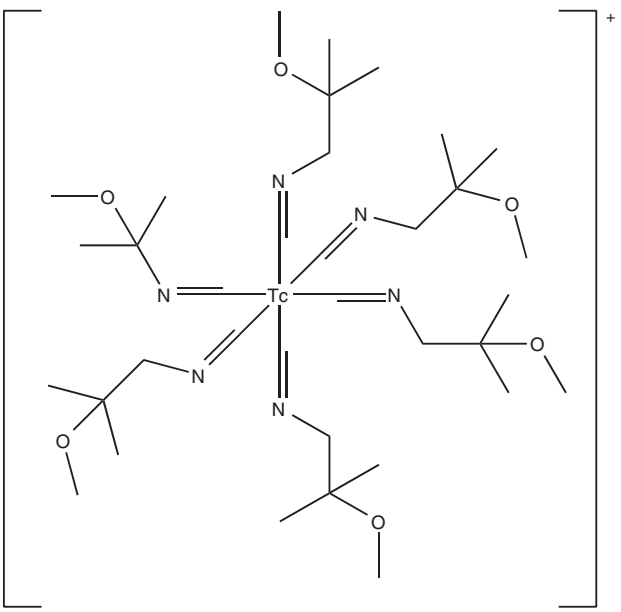

Figure 10.21 *Chemical structure of Cardiolite™*

Table 10.5 *Some examples of common ^{99m}Tc radiopharmaceuticals for imaging procedures*

Radiopharmaceutical	For imaging of
^{99m}Tc-aerosol	Lung ventilation
^{99m}Tc-sestamibi	Heart
^{99m}Tc-albumin	Cardiac function
^{99m}Tc-exametazime	Brain
^{99m}Tc-medronate	Bones
^{99m}Tc-succimer	Kidney

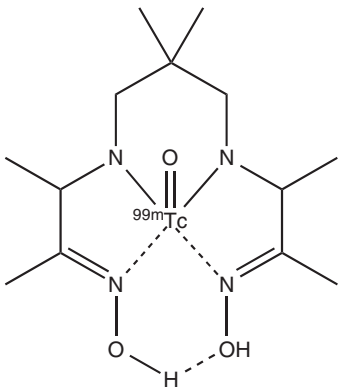

Figure 10.22 *Chemical structure of ^{99m}Tc-exametazime*

characterised as reagent vials, buffer vials and, if applicable, a vial containing stabiliser. For illustration purposes, only the preparation of ^{99m}Tc-exametazime for injection (as supplied by GE Healthcare) is explained in the following. The nonstabilised formulation is prepared by adding 54 mCi of $^{99m}TcO_4^-$ to a 5 ml reagent vial. The reagent vial contains the racemic mixtures of the ligand exametazime [(3*RS*,9*RS*)-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime] and stannous chloride dehydrate as reducing agent together with sodium chloride [1]. The preparation should have a pH of 9.0–9.8 and should be used within 30 min [2].

10.4.2 ^{18}Fluoride: PET scan

Fluorine has the chemical symbol F and atomic number 9 and is the most electronegative element. It belongs to group 17 of the periodic table, the so-called halogens. Fluorine typically exists as a diatomic molecule at room temperature.

There are 18 isotopes known of fluorine, but only 1 (^{19}F) is stable. Most of the radioactive isotopes have a very short half-life, mostly <1 min. Only the radioisotope ^{18}F has a longer half-life of around 110 min and is clinically used (Figure 10.23).

^{18}F is a positron-emitting radioisotope and is used in radiopharmaceutical imaging such as PET scanning. Two compounds, namely fluorodeoxyglucose (^{18}F-FDG) and derivatives of ^{18}F choline, are under intense clinical investigation and/or use.

^{18}F-FDG is a glucose derivative that contains a radiolabel (^{18}F) at the 2′ position replacing the hydroxyl group. ^{18}F-FDG is administered intravenously and is used as an assessment of problems with glucose metabolism, especially in the brain, often associated with epilepsy and in cancer. Areas where an increased absorption of ^{18}F-FDG are visible correlate to areas where an increased glucose metabolism is present. ^{18}F-FDG is distributed around the body similar to glucose and is cleared renally. There are no known contraindications known to ^{18}F-FDG (Figure 10.24).

^{18}F-FDG is the main radioimaging agent used in PET scanning. Examples include studies of heart, where it is used to differentiate between dead and live tissue in order to assess the myocardium. In neurology, it can be used to diagnose dementia, seizure disorders or tumours of the brain. ^{18}F-FDG is generally used to assess the extent of the tumour in a cancer patient. Cancerous tissue is characterised by increased cell proliferation, which requires energy, and therefore an increased amount of glucose. This leads to an accumulation of ^{18}F-FDG in

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 10.23 *Periodic table of elements showing the element fluorine (highlighted)*

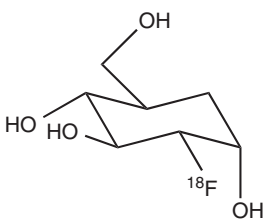

Figure 10.24 *Chemical structure of ^{18}F-FDG*

malignant tumours and allows judging the degree of metastasis formed. This information is important for any surgical procedure and also for the initial assessment of the cancer stage.

Unfortunately, there are limitations to the use of ^{18}F-FDG, as its uptake is not very specific. As a result, other conditions can also cause an accumulation of ^{18}F-FDG and can lead to misdiagnosis. These conditions include inflammation and healing of wounds, which also show increased glucose metabolism.

Therefore, a variety of other ^{18}F-labelled compounds are under intense scrutiny as alternative PET scanning agents, mainly compounds with a more specific biological pathway. This includes ^{18}F-choline. Choline is a compound incorporated into the cell membrane and therefore cells dividing at a fast rate have an increased need for this substance. Studies for a range of tumours were undertaken, but most studies focussed on prostate cancer. In comparison to ^{18}F-FDG, ^{18}F-choline showed less activity in the bladder and a prolonged elimination via the kidneys. Additionally, biological processes other than cancer also include rapid division of cells and can lead to misdiagnosis (Figure 10.25).

10.4.3 ^{67}Gallium: PET

As previously mentioned (see Chapter 4), gallium consist of two stable isotopes (^{69}Ga and ^{71}Ga) and there are two radioisotopes (^{67}Ga and ^{68}Ga) that are commercially available. ^{67}Ga has a half-life of 3.3 days, whereas ^{68}Ga has an even shorter half-life of 68 min (Figure 10.26).

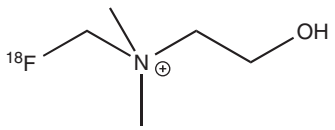

Figure 10.25 *Chemical structure of ^{18}F-choline*

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 10.26 *Periodic table of elements showing the element gallium (highlighted)*

^{67}Ga decays via electron capture and subsequently emits γ-rays, which can be detected with a gamma camera. ^{68}Ga is a positron-emitting isotope and is used for PET. Because of its short half-life, fresh ^{68}Ga for clinical applications is obtained through generators. The generator is equipped with the parent compound ^{68}Ge, which has a half-life of 271 days and decays via electron capture to form the 'daughter' ^{68}Ga.

It has been reported that radioactive gallium-67 citrate accumulates in malignant cells when injected into animals that are infected with tumours. This has led to the development of ^{67}Ga scans, which have been used over the past two decades mostly for the detection of residual cancer cells in patients with Hodgkin's and non-Hodgkin's lymphomas after chemo or radiotherapy. The level of ^{67}Ga present in lymphoma cells correlates with their metabolic activity and directly with their proliferation rate. Therefore, a positive ^{67}Ga scan (mostly undertaken after chemotherapy) indicates the survival of malignant cells and the need for further treatment (Figure 10.27).

As previously mentioned (see Chapter 4), Ga^{3+} is mainly transported by transferrin. *In vitro* studies have shown that the uptake of the radioactive gallium into the cancer cells was significantly increased when transferrin was added to the medium [6].

10.4.4 ^{201}Thallium

The element thallium belongs to the boron group, and has the chemical symbol Tl and atomic number 81. Thallium is a soft grey metal, which cannot be found as the free metal in nature (Figure 10.28).

The common oxidation states for thallium are +3, which resembles the oxidation states of other group members, and +1, which is actually the far more dominant oxidation state for thallium ions. Thallium ions

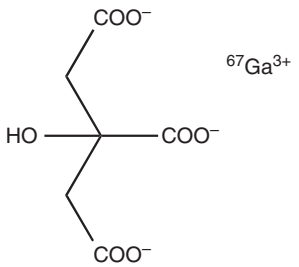

Figure 10.27 *Chemical structure of gallium citrate*

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 10.28 *Periodic table of elements showing the element thallium*

with the oxidation state +1 follow alkali metals in their chemical behaviour and are handled in biological systems similar to potassium (K^+) ions.

Thallium and many of its compounds are toxic. In particular, the Tl^+ cation displays good aqueous solubility and it can enter the body via the potassium-based uptake processes as its behaviour is similar to that of K^+. Unfortunately, there are differences in the chemistry of both ions that affect, for example, their binding to sulfur-containing molecules and lead to the toxicity of thallium ions. Thallium-based compounds were used as rat poison, but their use is nowadays discontinued as their toxic properties are not very specific. Signs of thallium poisoning include hair loss, nerve damage and, ultimately, at high enough doses, sudden death.

The radioactive thallium isotope ^{201}Tl was the main substance used for nuclear imaging in cardiology. It was used for the so-called thallium nuclear cardiac stress test, where a radiotracer such as $^{201}TlCl$ (thallous chloride-201) is injected into a patient during exercise. After a short waiting period (in order to ensure good distribution of the radioactive substance), images of the heart are taken with a gamma camera and the blood flow within the heart muscle is evaluated. Nowadays, the radio isotope has been mostly replaced by ^{99m}Tc imaging. The radio isotope ^{201}Tl has a half-life of 73 h and can be generated using a transportable thallium-201 generator. This generator uses ^{201}Pb (lead-201) as the 'parent', which decays via electron capture to the 'daughter' ^{201}Tl. ^{201}Tl decays by electron capture and has good imaging characteristics [7].

10.5 Exercises

10.5.1 Write the elemental formula for the following radioisotopes:

(a) Technetium containing 48 neutrons
(b) Radon containing 136
(c) Francium containing 136 neutrons
(d) Radium containing 138 neutrons

10.5.2 Write the equation for the radioactive decay of the following elements:

(a) ^{210}Po (α-emitter)
(b) ^{226}Ra (α-emitter)
(c) ^{91}Tc (β-emitter – positron)
(d) ^{227}Ac (β-emitter – negatron)

10.5.3 A ^{201}Tl chloride injection has a labelled activity of 450 μCi. Express this answer in megabecquerel.

10.5.4 A radioactive material has an activity of 12.25 mCi. How many disintegrations per second are represented by this?

10.5.5 A radioactive material has been labelled with an activity of 112 MBq. Convert this activity into curie.

10.5.6 If a radioactive element has a half-life of 2 h, what percentage of material is left after

(a) 2 h
(b) 6 h
(c) 8 h

10.5.7 The disintegration constant of ^{24}Na is 0.0462 year^{-1}. Determine the half-life of this radioisotope.

10.6 Case studies

10.6.1 A sample containing ^{99m}Tc was found to have a radioactivity of 15 mCi at 8 a.m. when the sample was tested.

(a) Research the half-life of ^{99m}Tc.
(b) Calculate its activity at 5 a.m. on the same day, when it was prepared.
(c) Calculate its activity at 3 p.m. on the same day, when it was administered to the patient.

State your answer in curies and SI units.

10.6.2 A typical intravenous dose of ^{99m}Tc-albumin used for lung imaging contains a radioactivity of 4 mCi

(a) Convert the dose to SI unit.
(b) What radioactive dose is left after 12 h, when the technetium is cleared from the body?
(c) The pharmacist prepared the sample actually 2 h before the administration. What activity did this sample have at that point of preparation?
(d) The pharmacist prepared a 2 ml solution for injection. What is the activity concentration at the point of administration?

10.6.3 Develop a quick-reference radioactive decay chart for ^{131}I

Research the half-life of ^{131}I and calculate the percentage activity remaining for 20 days using 1-day intervals. Create your own quick-reference radioactive decay chart.

Day	Percentage activity remaining (%)
1	
2	
3	
4	
5	
6	
⋮	

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