# RADIOPHARMACEUTICALS

## Radioactivity

***Radioactivity*** is defined as the nuclear instability which results in the radiation or emission of particles from the nuclei. There are various types of radiations, amongst them the most common types of radiations are alpha, beta, and gamma.

***Radiopharmaceuticals*** are pharmaceutical formulations consisting of radioactive substances (radioisotopes and molecules labelled with radioisotopes), which are intended for use either in diagnosis or therapy.

A branch of pharmacy which deals with the manufacturing and dispensing of radioactive materials or radiopharmaceuticals is referred to as ***radiopharmacy***.

## Half-Life

Half-life ($t_{1/2}$) is the time period in which a substance is reduced by 50% of its initial amount. Radioactive decay or nuclear decay is first order reaction and does not depend on concentration of material.

$$\textbf{Half life, } t_{1/2} = \frac{0.693}{\lambda}$$

Where, $\lambda$ is disintegration constant in unit of $sec^{-1}$.

The half-life of a radionuclide substance determines its pharmaceutical importance. Successful experiments cannot be conveniently carried out due to very short half-life. On the other hand, if half-life is long the substance is not altered under any chemical or biological conditions; therefore, it is the most desirable property.

Examples of Half-life of Radioactive Isotopes

Iodine-131 - 8 days

Uranium-238 - 4.5x10 years

## Properties of Alpha, Beta and Gamma Radiations

### *Properties of Alpha Radiation*

The characteristic features of alpha particles are:

- These particles are equivalent to the nuclei of helium atoms (i.e.. $^{4}_{2}He$).
- Alpha particles are positively charged and heavy.
- They travel in air to a few centimetres and may penetrate up to 1mm of body tissues.
- They are highly energetic particles and have energy up to 4MeV; e.g
- Alpha-emitter isotopes are not useful in pharmaceutical formulations.
- As they are charged they are affected by both electric and magnetic fields.
- If the radiation sources are close to sensitive organs $\alpha$ -particle radiation is extremely dangerous.

- They are capable of ionising a large number of atoms over a very short range of penetration.

***Properties of Beta Radiation***

The characteristic features of beta particles are:

- Their mass is equal to an electron.
- They are mostly negatively charged (negatron or electron), but rarely may also be positively charged (positron).
- In air they may travel up to a few meters and may penetrate the body tissues about a centimetre.
- The maximum energy exhibited by beta particles is 1.5MeV and mean energy (E) is 0.6MeV.
- They are affected by electric and magnetic fields.
- Their ionising capacity is much less than that of $\alpha$ -radiation.

***Properties of Gamma Radiation***

The characteristic features of gamma particles are:

- Gamma particles are similar to X-radiation.
- These particles react with matter and behave like discrete packets(quanta) of energy, referred to as photons.
- It is an electromagnetic radiation therefore does not have any mass or charge and travels with the speed of light.
- Gamma particles are high energy particles, typically 2MeV.
- These particles have high penetration power and can pass through several feet of solid matter.
- The ionising capacity of $\gamma$ radiation is considerably smaller than that of beta-radiation.

**Applications of Radiations**

Radiations are widely used in various areas of research and development, some of them are given as:

- Radiations are used for diagnostic purposes, for example, X-rays are used to find out any injury of bone.
- Radiation has power to destroy tissues, thus they easily destroy bacteria and other microorganisms. This property is used for food preservation without the aid of chemicals and refrigeration.
- Various radioactive isotopes are used to supply power to satellites and provide electricity for space laboratories.
- They are utilised for estimating the degree of air pollution.
- The archaeologists use radiations to determine the age and authenticity of the ancient artifact.

**Measurement of Radioactivity**

The radioactivity of alpha, beta and gamma particles can be measured by the help of various techniques. These techniques involve detection and counting of either protons or individual particles.

The radiation detectors are divided into two distinct categories:

1) Detectors Based on Ion Collection

i) Gas filled detectors

- Electroscopes
- Ion chambers
- Proportional counters
- Geiger counters

ii) Solid state detectors

- Barrier-state detectors
- Lithium-drifted detectors

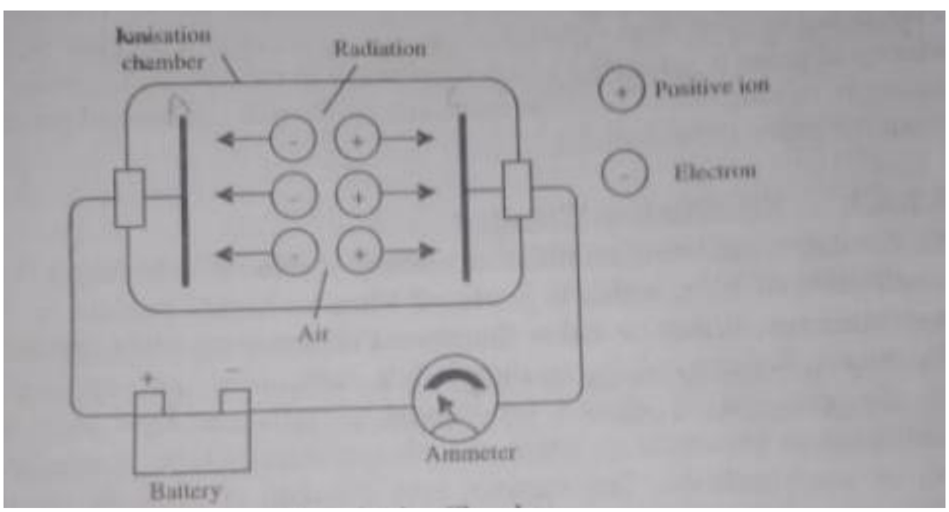
2) Detectors Based on Photon Collection
i) Sodium iodide scintillation counters
ii) Liquid scintillation counters

The detection and measurement of radioactive radiation can be done by many methods which are stated above, but in modern practice following equipment are used:
1) lonisation chamber
2) Geiger-Muller counter
3) Scintillation counter

***1) Ionisation Chamber***

Ionisation chamber simply measures the radiation strength. It is filled with two metallic plates, separated by air. On passing the radiation through the chamber, the atoms of air molecules are knocked off and the positive ions are formed. The electrons move towards the anode while positive ions towards the cathode. This results to the passage of mild current between the plates, which is measured with the help of an ammeter.

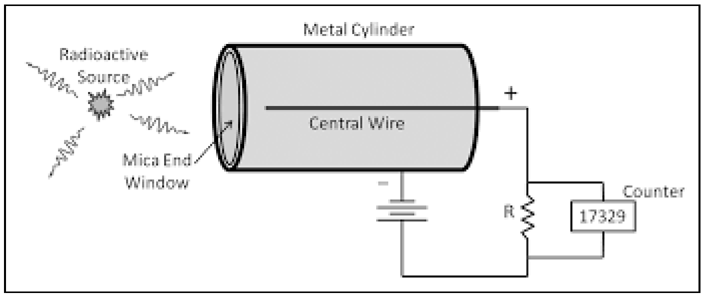
The strength of current helps in the determination of radiation passing through the ionisation chamber. The total amount of charge passing between the plates in a given time is measured by dosimeter, which is present in the ionisation chamber. This is proportional to the total amount of radiation that has gone through the chamber.




***2) Geiger-Muller counter***

The rate of emission of a- or B-particles can be detected and measured by the Geiger-Muller Counter as shown in figure 8.3. It comprises of a cylindrical metal tube which acts as a cathode, and for anode a wire is placed centrally. The metal tube has very low pressure of around 0.1atm and is filled with argon gas.

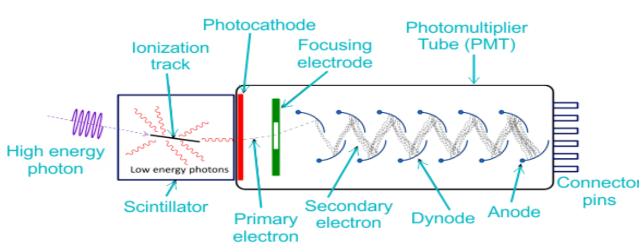
A potential difference of 1000 volts is maintained across the electrodes. The alpha or ß-particle enters the tube through the mica window and the argon atoms present in tube gets ionised along the path of alpha or ß-particles.




The positively charged argon ions (Ar) move towards the cathode while the negatively charged electrons move towards the anode. The circuit is completed in very short duration of time (in-microseconds), after which electrical poise is generated which is recorded in the automatic counter. The intensity of radioactivity can be measured by the pulse generated per minute from the radioactive material.

***3) Scintillation Counter***

As the name indicates; scintillation counter works on detecting a flash or scintillation of light, which is produced when a charged particle, or X-ray, or gamma ray, strikes on either fluorescent screen or on some specific type of crystals. Sodium iodide, caesium iodide, anthracene, and certain plastics are the material of choice for typical scintillators. One side of the scintillator is cemented to which the photomultiplier tube is attached and acts as photocathode. The vacuum tube consists of multiple electrodes, called dynodes. These dynodes are kept at high voltage in increasing manner.



The photocathode produces electrons (photoelectrons) which accelerated towards the first dynode. The photoelectron strikes on first dynode with large amount of kinetic energy, resulting in emission of more electrons. This process is continued towards the second and third dynode and so on and the multiplication of electrons continued.

When a scintillator is struck by gamma rays or by charged particles, the molecules of scintillator gets excited and emits energy as light for returning to their ground state. This emitted light is incident on the photocathode of the photomultiplier and emits photoelectron. Since the potential difference increment in electrons as they finally reach the ultimate dynode. Due to this multiplication, a weak pulse is also amplified up to $10^6$-$10^8$ times, before reaching to the counting equipment. The output electrical pulse is proportional to the energy of the incident particle or photons.

Small amount of impurities (activators) are also added to the crystal for reducing self-absorption of light and for enhancing the photon emission probability. Thallium is the most commonly used activator.

Thallium-activated sodium iodide is very efficient in detecting gamma rays. Anthracene crystal which is not very sensitive to gamma rays is used for the detection of B-rays.

**Radioisotopes**

A radioisotope is an atom with an unstable nucleus. This nucleus carries large amount of energy which is utilised either by a newly-formed radiation particle within the nucleus, or by an atomic electron. Radioisotopes are atoms with an unstable combination of neutrons and protons.

Radioisotopes also have medicinal importance, for example, the cancer cells growth may be inhibited by radiations of cobalt-60. Some radioisotopes are used as markers for diagnosing diseases, and are also used in research on metabolic processes. For example, hyperthyroidism is effectively treated using iodine-131; Heliobacter pylori (the bacteria causing ulcers) can be detected in a breath test using carbon-14.

Before using a radioisotope for diagnostic and therapeutic purpose, it is added in small quantity to large quantities of the stable element. Such radioisotopes chemically behave like an ordinary isotope. Though, any detector device like Geiger counter may trace presence of even small amount of radioactive isotopes in such compounds.

The following two categories of radioisotopes are available:

*1) Stable Radioisotopes:* These isotopes (e.g., C, C1, H' (protium), H (deuterium), etc.) are stable and do not emit radiations.

*2) Radioactive Radioisotopes:* These are either naturally occurring (eg uranium, radium, etc.) or artificially produced unstable isotopes. They emit radiation to lose energy. This phenomenon of emission of radiation is known as radioactivity and such compounds are radioactive compounds or radioactive isotopes.

**Study of Radioisotopes**

Examples of some frequently used radioisotopes are:

<u>1) Carbon Element:</u>

*Carbon has three isotopes:*

i) Carbon-12: It has six protons and six neutrons. It is a stable isotope with atomic number 6 and atomic mass or mass number 12.
ii) Carbon-13: It has six protons and seven neutrons in its nucleus. It is also a stable isotope with atomic number 6 and atomic mass 13.
iii) Carbon-14: It has six protons and eight neutrons in its nucleus. It is an unstable isotope with atomic number 6 and atomic mass 14. It has radioactive property and hence is a radioisotope. The above mentioned all three isotopes of carbon has same atomic number, i.e., 6, while their atomic mass is different. They have same chemical properties.

2) Iron Element:

These are of two types:

- Stable – $^{54}_{26}Fe$, $^{56}_{26}Fe$, $^{57}_{26}Fe$, $^{58}_{26}Fe$
- Unstable Radioactive - $^{55}_{26}Fe$, $^{59}_{26}Fe$

All isotopes of iron have same atomic number, i.e., 26, but they differ in atomic mass (54, 56, 57, 58, and 59). They have same chemical properties.

3) Phosphorus Element:

It has two isotopes:
i) Phosphorus-31($^{31}_{15}P$): It has 15 protons and 16 neutrons. It is a stable isotope with atomic number 15 and atomic mass 31.
ii) Phosphorus-32 ($^{32}_{15}P$): It has 15 protons and 17 neutrons. It is an unstable radioisotope with atomic number 15 and atomic mass 32.

4) Iodine Element:

lodine has two isotopes:
i) Iodine-127: It has 53 protons and 74 neutrons in its nucleus. It is a stable isotope with atomic number 53 and atomic mass 127.
ii) Iodine-131: It has 53 protons and 78 neutrons in its nucleus. It is an unstable, radioactive isotope with atomic number 53 and atomic mass 131.

**Sodium Iodide $I^{131}$**

It is a radiopharmaceutical substance used in the treatment of malignant thyroid. The ionising radiations of iodide $I^{131}$ are absorbed by the thyroid tissue. Tissue damage results due to direct exposure because the molecules dissociate due to the ionisation and excitation. The sodium iodide $I^{131}$ emits about 90% of beta radiation and the remaining 10% is the gamma radiation.

**Mechanism of Action** The iodide enters in the thyroid through the sodium/iodide symporter and accumulates there. Here it oxidises into iodine and emits radiations. These -radiations emitted by sodium iodide $I^{131}$ destroy the thyroid tissue.

**Properties**

- Sodium iodide is a colourless solution having a pH between 7-10.
- Half-life of sodium iodide $I^{131}$ is 8.4 days.
- It emits beta and gamma radiations.
- About 99% of its energy released in the form of radiations is expanded within 56 days.

**Assay**

Using an appropriate counting instrument, sodium iodide I is assayed by comparing its activity with a standard 1131 solution. It is also tested for the purity of radionuclide and radiochemical.

**Uses**

- Hyperthyroidism and some cases of thyroid malignancy are treated using sodium iodide $I^{131}$.
- Sodium iodide mainly acts on thyroid gland. In cases of hyperthyroidism (thyroid gland becomes hyperactive), the radioactive iodine emits radiation which destroys some cells of thyroid gland and normalises its activity.
- After the surgical removal of cancerous thyroid gland, radioiodide is given in large doses to destroy the remaining diseased thyroid tissue and the diseased neighbouring tissues.
- In small doses radioiodide is used for diagnosis. It is used to detect normal functioning of thyroid gland and detecting tumour.

**Toxicity**

Sialadenitis, chest pain, tachycardia, iododerma, itching, skin rashes, hives, hypothyroidism, hyperthyroidism, thyrotoxic crisis, hypoparathyroidism and local swelling are some adverse effects of sodium iodide $I^{131}$ occuring during the treatment of Benign disease.

Radiation sickness, bone marrow depression, anaemia, leucopoenia, thrombocytopenia, blood dyscrasia, leukaemia, solid cancers, lacrimal gland dysfunction, salivary gland dysfunction, congenital hypothyroidism, chromosomal abnormalities, cerebral oedema, radiation pneumonitis, and pulmonary fibrosis are some severe dose related adverse effects which sodium iodide $I^{131}$ produces while treating malignancy.

**Precautions in Handling of Radiopharmaceuticals**

Great care has to be taken in handling and storage of radioactive material for protecting people and personnel handling it. The precautions that should be taken are:

- The radioactive material should not contaminate the working area.
- In case the radioactive material is liquid, the material should be carried in trays having absorbent tissue paper for absorbing any accidental spillage.
- While handling liquid radioactive materials, rubber gloves should be used.
- Mouth operated pipettes should not be used. Moreover, it should be ensured that the glass apparatus should be inactivated, before their usage. Before disposition of radioactive material, they should have very low activity; otherwise they are stored till the activity reduces to safer levels.
- Activities such as smoking, eating, and drinking are strictly prohibited in the area of radioactive work.
- Forceps should be used while handling the radioactive emitter.
- Shielding devices should be used sufficiently.
- The radioactive material should be stored in well-labelled containers using bricks (for shielding). It is preferred to store radioactive material in a remote corner.
- The area in which the radioactive material is stored should be monitored constantly.
- The disposal of radioactive material is done with utmost care.

**Storage Conditions**

The radiopharmaceuticals are stored in airtight containers in a shielded place. This place should be organised as per the national and international regulations set forth for the storage of radioactive substances. Personnel should not be exposed to any primary or secondary emissions.

The containers of radiopharmaceuticals may become dark due to irradiation, although this does not indicate that the substance has degraded. Radioactive substances are suggested to be used within a short time period and the expiry period should also be clearly mentioned. The parenteral radiopharmaceuticals should not lose their purity during storage, thus, optimum storage conditions should be maintained.

**Pharmaceutical Applications of Radioactive Substances**

For medical purpose, radiopharmaceuticals can be used by the following two ways

***1) Therapeutic Applications:***

The therapeutic effect radiopharmaceuticals utilises the destructive features of the radiations. These radiations destroy abnormally multiplied cells and further inhibit the formation of new cells and tissues. Hence, it is frequently used in the treatment of disorders like cancers which involves extensive cellular malfunction.

Isotopes can be selected on the basis of the following factors:

- ✓ Characteristics of the radiation required for treatment
- ✓ Types of radiation,
- ✓ Energy and intensity of radiation, and
- ✓ Type of tissues.

Both external and internal radiation sources are utilised in the therapy:

***i) External Sources***

a) Teletherapy Sources: $^{60}$Co, $^{137}$Cs are neutral chargedparticles.

b) Surface Sources: $^{90}$Sr, $^{32}$P (beta emitters).

c) Extracorporeal Irradiation: $^{60}$Co, $^{90}$Sr, $^{90}$Y

***ii) Internal Sources:***

a)Infusion: $^{196}$Au, $^{32}$P

b) Interstitial Implant: $^{192}$Ir, $^{125}$I

c) Selectively Absorbed or Concentrated: $^{32}$P, $^{131}$I, $^{90}$Y

The therapeutic preparations containing radioisotopes are collectively referred to as radiopharmaceuticals, for example:

i) Teletherapy: This technique mostly utilises highly active gamma- emitting isotopes (as high as 2000°C) like $^{60}$Co or $^{137}$Cs. These isotopes are used to treat lesions by applying them directly on the affected area.

ii) Implantation Therapy: In this technique sealed radioactive sources are introduced directly into the tumour tissues. Isotopes like $^{60}$Co, $^{192}$Ir, $^{198}$Au and $^{182}$Ta are typically used in this way.

iii) Surface or Contact Therapy: Pure beta emitters like $^{32}$P and $^{90}$Sr are used for treating dermatological and ophthalmological tumour, whereas bladder tumours are treated by introducing $^{32}$P isotope in the affected area.

iv) Extracorporeal Irradiation: $^{60}$Co sources are used to determine the depletion of lymphocytes in blood. This depletion may alter the immunological response. Other examples of different radioisotopes used in the treatment:

a) Iridium ($^{192}$Ir): It emits beta and gamma radiations and produces local destructive effects on cells.

b) Sodium Phosphate ($^{32}$P): It is used in the treatment of polycythaemia and decreases the rate of erythrocyte formation.

c) Yttrium ($^{90}$Y): It has a half life of 64 hours. It emits only a single beta particle (2.27 Mev) with no gamma radiation. It can chelate with N-hydroxy ethylenediamine tetraacetic acid and thus can be localised in the bone. This chelate has been used to treat leukaemia and multiple myeloma.

d) Iodine ($^{125}$I): It has a half life of 60 days and is used for permanent implant and treatment of deep-seated tumours like tumour of chest which cannot be removed by surgery.

***2) Diagnostic Applications:***

| Diagnostic Purpose | Radiopharmaceuticals |
|---|---|
| **1) Brain Imaging**<br>i)Evaluate cerebral function<br>ii) Evaluate cerebral perfusion | To-99m labelled lipophilic agents Ceretec, Neurolite |
| **2) Thyroid Imaging**<br>i) Determine function (as % uptake of iodine)<br>ii) Evaluate shape, size and location of thyroid gland | I-131 sodium |
| **3) Heart Imaging**<br>i) Assess myocardial perfusion<br>ii) Determine myocardial function<br>a) Wall motion<br>b) Ejection fraction | TI-201 chloride |
| **4) Gastric Imaging**<br>i) Gastric Emptying/ Reflux/ Aspiration<br>ii) GI Bleeding<br>iii) Hepatobiliary Imaging<br>iv) Liver/Spleen | Tc-99m SC<br><br>Tc-99m SC, Tc-99m RBC<br>Tc-99m IDA compounds<br>Tc-99m SC |
| **5) Bone Imaging**<br>i) Assess trauma, bone pain, primary bone tumour, infection & prosthetics<br>ii) Detect and stage metastatic disease | Tc-99m phosphate compounds |
| **6) Pulmonary Imaging**<br>i) Evaluation of pulmonary ventilation<br>ii) Evaluation of pulmonary perfusion | Tc-99m DTPA, Xe-133 gas<br><br>Tc-99m labelled MAA |
| **7) Renal Imaging**<br>i)Assessment of flow and function<br>ii) Evaluation of renal morphology | Tc-99m labelled agents for filtration and secretion<br>Tc-99m labelled morphology agents |
| **8) Infection Imaging**<br>Localise internal sources of infection | Tc-99m or In-111 labelled white bloodcells<br>Ga-67 |
| **9) Tumour Imaging**<br>i) Evaluating location and spreading of tumour<br>ii) Evaluating metabolic activity of tumour cells | Ga-67<br>F-18 FDG |
| **10) Bone Pain Palliation**<br>Palliative treatment for pain associated with metastatic disease to the bone | Sr-89, Sm-153 |