**Radiopharmaceuticals**

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**1.Introduction**

Radiopharmaceuticals are a class of pharmaceutical drugs that contain radioactive isotopes, and they are used in nuclear medicine for diagnostic and therapeutic purposes. These drugs are designed to target specific organs, tissues, or physiological processes in the body to provide valuable information or to treat certain medical conditions.

Here's a breakdown of the key aspects of radiopharmaceuticals:

* **Radioactive Isotopes:** Radiopharmaceuticals consist of a biologically active compound (e.g., a drug or ligand) coupled with a radioactive isotope. The radioactive isotope emits radiation in the form of gamma rays, positrons, or beta particles. Common isotopes used include technetium-99m, iodine-131, fluorine-18, and gallium-67.
* **Diagnostic Applications:** Radiopharmaceuticals are extensively used in nuclear medicine imaging to visualize and assess the functioning of organs and physiological processes. For instance, in Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) scans, radiopharmaceuticals are injected into the patient's bloodstream. As they accumulate in specific areas of interest, the emitted radiation is detected by specialized cameras to create detailed images, allowing physicians to diagnose various diseases and conditions.
* **Therapeutic Applications:** Some radiopharmaceuticals are designed for therapeutic purposes. In this case, the radioactive emissions are used to target and destroy specific diseased cells or tissues. For example, radioactive iodine-131 is used to treat certain types of thyroid cancer, and strontium-89 and samarium-153 are used for bone pain palliation in metastatic cancers.
* **Half-life:** The radioactive isotopes used in radiopharmaceuticals have different half-lives, which determine how long the radioactivity remains active. Shorter half-lives are ideal for diagnostic purposes, as they reduce patient radiation exposure, while longer half-lives are more suitable for therapeutic applications.
* **Safety:** Radiopharmaceuticals are carefully formulated to minimize the exposure of patients and medical staff to radiation. They are subject to stringent regulatory controls to ensure safety, proper handling, and appropriate disposal of radioactive materials.
* **Administration:** Radiopharmaceuticals can be administered in various ways, including intravenously (most common), orally, or by inhalation, depending on the specific application and the targeted organ or system.

It is essential to note that the use of radiopharmaceuticals requires trained medical professionals, and the selection of appropriate radiopharmaceuticals depends on the patient's condition and the specific medical purpose. These substances have significantly contributed to the field of nuclear medicine, enabling non-invasive imaging and personalized treatments for various diseases.

**1.1 Historical Timeline**

**Table No. 1 Historical Timeline**

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| **1896** | Henri Becquerel discovered mysterious "rays" from uranium. |
| **1897** | Marie Curie named the mysterious rays "radioactivity." |
| **1913** | Frederick Proescher published the first study on the intravenous injection of radium for therapy of various diseases. |
| **1932** | Ernest O. Lawrence and M. Stanley Livingston published the first article on "the production of high speed light ions without the use of high voltages." It was a milestone in the production of usable quantities of radionuclides. |
| **1937** | John Livingood, Fred Fairbrother and Glenn Seaborg discovered iron-59. |
| **1938** | Emilio Segre and Glenn Seaborg discovered technetium-99m. |
| **1941** | Saul Hertz gave a patient the first therapeutic dose of iodine-130. |
| **1948** | Abbott Laboratories began distribution of radioistopes. |
| **1951** | The U.S. Food and Drug Administration (FDA) approved sodium iodide 1-131 for use with thyroid patients. It was the first FDA-approved radiopharmaceutical. |
| **1955** | Rex Huff measured the cardiac output in man using iodine-131 human serum albumin. |
| **1957** | H. Knipping used xenon-133 to measure lung ventilation. |
| **1959** | Picker X-Ray Company delivered the first 3-inch rectilinear scanner. |
| **1960** | John McAfee and Henry Wagner imaged the kidneys with radiomercury labeled chlormerodrin. |
| **1961** | Allis-Chalmers installed the first U.S. "medical center" cyclotron at Washington University Medical School. The cyclotron was designed by M.M. Ter-Pogossian. |
| **1969** | C.L. Edwards reported the accumulation of gallium-67 in cancer. |
| **1993** | Medi-Physics/Amersham received FDA approval to market strontium-89 chloride for relief of bone pain. |
| **2002** | Formation of the National Institute for Biomedical Imaging and Bioengineering in the National Institutes of Health. |
| **2003** | FDA gives approval to IDEC Pharmaceuticals for clinical use of Zevalin™, a radioimmunotherapy agent. |
| **2008** | Molecular imaging sees increasingly widespread fusion of images with PET/CT scans, which permit a functional understanding of the underlying causes of disease in the body by joining functional and anatomical information in the same image. |

**1.2 Definitions and terminology:**

* **Radiopharmaceutical refers to**any medicinal or pharmaceutical product, which when ready for use contains one or more radionuclides (radioactive isotopes) intended for human use either for diagnosis or therapy.
* **Nuclide**is an elemental species characterized by its mass number ‘A’, (the sum of the number of protons and neutrons in its nucleus), its atomic number ‘Z’ (number of protons which is also same as number of electrons in a neutral atom) and also by its nuclear energy state.
* **Isotopes**of an element are nuclides with the same atomic number ‘Z’ but different mass numbers ‘A’. They occupy the same place in the periodic table and have similar chemical properties.
* **Radionuclide**Nuclides containing an unstable arrangement of protons and neutrons that transform spontaneously to either a stable or another unstable combination of protons and neutrons with a constant statistical probability by emission of radiation. These are said to be radioactive and are called radionuclides.
* **Radioactivity**The phenomenon of emission of radiation owing to the spontaneous transformation or disintegration of the radionuclide is known as ‘Radioactivity’. However, the term radioactivity is also used to express the physical quantity (activity or strength) of this phenomenon. The radioactivity of a preparation is the number of nuclear disintegrations or transformations per unit time.

They put out radiation, mostly in the form of alpha and beta particles that target the affected areas. They’re most often used in small amounts for imaging tests, but larger doses can be used to deliver radiation [2,3,5].

**1.3 Units of radioactivity:**

Radioactivity, the measure of the amount of radiation emitted by a radioactive substance, is expressed in several units. The three most common units of radioactivity are:

* **Becquerel (Bq):** The Becquerel is the International System of Units (SI) unit of radioactivity. It is defined as one radioactive decay per second. In other words, one Becquerel corresponds to one disintegration of a radioactive nucleus per second. This unit is commonly used to measure the activity of a radioactive source.
* **Curie (Ci):** The Curie is a non-SI unit of radioactivity, but it is still used in certain contexts, especially in the United States. One Curie is equal to the activity of 1 gram of radium-226, which corresponds to approximately 3.7 x 10^10 disintegrations per second or 37 gigabecquerels (GBq). While the Curie is not part of the SI system, it is still used in some legacy applications.
* **Gray (Gy):** The Gray is the SI unit of absorbed dose of ionizing radiation. It is defined as the absorption of one joule of radiation energy per kilogram of matter. This unit is used to quantify the amount of radiation energy deposited in a material.

It's important to distinguish between the units of radioactivity (Becquerel and Curie) and the units of absorbed dose (Gray). Radioactivity measures how many radioactive decays occur per unit of time, while absorbed dose measures the amount of radiation energy deposited in a material. For practical purposes and adherence to the SI system, the Becquerel is the primary unit used to express radioactivity. The Curie is less commonly used but may still be encountered in specific situations, particularly in older literature or when dealing with legacy equipment or regulations.

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**2. Properties of α, β, γ Radio active radiations**

All substances are made of atoms. These have **electrons** (**e**) around the outside, and a nucleus in the middle. The nucleus consists of **protons** (**p**) and **neutrons** (**n**), and is extremely small. (Atoms are almost entirely made of empty space.). In some types of atom, the nucleus is unstable, and will decay into a more stable atom. This radioactive decay is completely spontaneous. When an unstable nucleus decays, there are three ways that it can do so. It may give out:-

* an alpha particle (**α**)
* an beta particle (**β**)
* an gamma ray (**γ**)

**2.1 Alpha particles**

* Alpha particle radiation consists of two neutrons and two protons, as they are charged they are affected by both electric and magnetic fields.
* The speed of the **α** -particle depends very much on the source, but typically are about 10% of the speed of light.
* The capacity of the **α** -particle to penetrate materials is not very great, it usually penetrates no more than a few centimetres in air and is absorbed by a relatively small thickness of paper or human skin. However, because of their speed and size, they are capable of ionising a large number of atoms over a very short range of penetration.
* This makes them relatively harmless for most sources that are about a metre or more away, as the radiation is easily absorbed by the air.
* But if the radiation sources are close to sensitive organs **α** -particle radiation is extremely dangerous.

**2.2 Beta particles**

Beta particles are a type of ionizing radiation that can be emitted by certain unstable atomic nuclei during radioactive decay. There are two types of beta particles: beta-minus (β-) particles and beta-plus (β+) particles, which have different properties.

**I. Beta-minus (β-) particles:**

* These are high-energy electrons (e-) that are emitted from the nucleus of an atom during beta decay.
* Beta-minus decay occurs when a neutron in the nucleus is converted into a proton, and an electron and an antineutrino are produced in the process.
* The electron is then emitted from the nucleus, carrying away the excess energy.
* The atomic number of the nucleus increases by one during this decay, as a neutron is transformed into a proton.

**II. Beta-plus (β+) particles:**

* Beta-plus decay, also known as positron emission, happens in some radioactive nuclei. In this process, a proton in the nucleus is converted into a neutron, and a positron and a neutrino are generated.
* The positron is an antiparticle of the electron, and when it encounters a regular electron, both particles annihilate each other, releasing gamma radiation in the process.

Both types of beta decay serve to make an unstable nucleus more stable by adjusting the ratio of protons to neutrons. Beta decay plays a crucial role in the natural radioactive decay of certain isotopes and is also utilized in various applications, such as medical imaging (positron emission tomography or PET scans) and in the field of nuclear physics and engineering. It is essential to handle beta-emitting radioactive materials safely due to their ionizing nature, which can cause damage to living tissues if exposed to high levels of beta radiation.

**2.3 Gamma radiation**

* Gamma rays are high-energy electromagnetic radiation emitted during radioactive decay.
* They have no charge and are highly penetrating, capable of passing through tissues.
* Gamma radiation is commonly emitted by radionuclides such as technetium-99m (Tc-99m), iodine-131 (I-131), gallium-67 (Ga-67), and indium-111 (In-111).
* They can penetrate our bodies and hit sensitive organs. They are particularly dangerous if ingested or inhaled.

**3. Measurement of Radioactivity**

The measurement of radioactivity is essential for various purposes, including monitoring radiation exposure, assessing radioactive contamination, and understanding the behavior of radioactive substances. The unit used to measure radioactivity is the becquerel (Bq), which represents one decay event per second. Another commonly used unit is the curie (Ci), where 1 Ci equals 3.7 x 10^10 becquerels.

There are several methods to measure radioactivity, and the choice of method depends on the specific application and the type of radiation being emitted. Here are some common techniques:

**3.1 Geiger-Muller Counters:**

Geiger-Muller (GM) counters are portable and widely used devices for detecting and measuring radioactivity. They work by ionizing gas in a tube when a radioactive particle or photon passes through it. The ionization triggers a discharge that can be detected, and the device provides a count rate of radiation events. GM counters are often used for quick assessments of radiation levels in various environments.

**3.2 Scintillation Counters:**

Scintillation counters are instruments that use certain materials (scintillators) that emit light when they interact with ionizing radiation. Photomultiplier tubes then amplify the emitted light, and the number of photons generated is proportional to the energy of the incident radiation. Scintillation counters are used in research, medical imaging, and environmental monitoring.

**3.3 Ionization Chambers:**

Ionization chambers are devices that measure the amount of charge produced when ionizing radiation interacts with a gas (usually air). By measuring the ionization current, the radiation dose can be determined. Ionization chambers are widely used in radiation dosimetry for medical and industrial applications.

**3.4 Solid-State Detectors:**

Solid-state detectors, such as semiconductor-based detectors, are increasingly used for radiation measurement. They are more compact and efficient than older technologies and are commonly used in handheld dosimeters and personal radiation monitors.

**3.5 Liquid Scintillation Counting:**

Liquid scintillation counting is a technique used to measure low-energy beta and alpha particles. Radioactive samples are mixed with a liquid scintillator, which emits light when interacting with radiation. The emitted light is then detected and measured to determine the radioactivity.

**3.6 Gamma Spectrometry:**

Gamma spectrometry involves using high-resolution detectors to identify and quantify the energies of gamma-ray photons emitted by radioactive sources. This technique allows researchers to identify specific radioactive isotopes in a sample.

Regardless of the method used, it's crucial to calibrate the instruments regularly and follow proper safety protocols when working with radioactive materials. Radioactivity measurements are subject to stringent regulations and guidelines to ensure the safety of both workers and the public.

**4. Measurement of Radioactivity of Specific ionizing radiation**

The measurement of radioactivity is based on the detection and quantification of ionizing radiation emitted by radioactive materials. The most common types of ionizing radiation are alpha particles, beta particles, and gamma rays. Each type of radiation requires different methods of measurement. Here's a more detailed overview of the techniques used to measure radioactivity:

**4.1 Alpha Particle Detection**:

* Alpha particles are large, positively charged particles, which means they have limited penetration through materials. Therefore, alpha particle detection is typically conducted using specialized instruments such as alpha particle spectrometers or alpha scintillation detectors.
* Alpha spectrometry involves the use of semiconductor detectors or gas-filled proportional counters to measure the energies of alpha particles emitted by radioactive sources. This allows researchers to identify specific alpha-emitting isotopes in a sample.
* Scintillation detectors with special screens or mica windows can also be used to detect alpha particles. When an alpha particle interacts with the scintillator material, it produces light flashes that can be detected and measured.

**4.2 Beta Particle Detection:**

* Beta particles are high-energy electrons (β-) or positrons (β+) emitted during beta decay. As they have greater penetration compared to alpha particles, beta particle detection can use a broader range of instruments.
* Geiger-Muller (GM) counters and scintillation detectors can detect beta particles, providing a count rate of radiation events.
* Solid-state detectors, such as silicon diodes or silicon carbide detectors, are also used to measure beta radiation.

Liquid scintillation counting is commonly used to measure low-energy beta particles emitted by certain isotopes. The radioactive sample is mixed with a liquid scintillator, and the emitted light is measured to determine the radioactivity.

**4.3 Gamma Ray Detection:**

* Gamma rays are high-energy photons that can penetrate through materials, making gamma ray detection more challenging.
* Scintillation detectors, such as sodium iodide (NaI) or bismuth germanate (BGO) crystals coupled with photomultiplier tubes, are widely used for gamma ray spectroscopy. They can identify and quantify the energies of gamma rays, allowing researchers to determine the specific radioactive isotopes present in a sample.
* High-purity germanium (HPGe) detectors are also used for precise gamma ray spectroscopy due to their superior energy resolution.

The choice of the appropriate method depends on factors such as the type and energy of the radiation, the specific isotopes being measured, the required sensitivity, and the nature of the sample. Proper calibration, quality assurance, and adherence to safety regulations are essential when conducting radioactivity measurements to ensure accurate results and protect personnel and the environment from potential radiation hazards.

**5. Radiopharmaceuticals uses**

Radiopharmaceuticals are a class of drugs that contain a radioactive component and are used in nuclear medicine for diagnostic or therapeutic purposes. These drugs are designed to target specific organs, tissues, or biological processes, allowing healthcare professionals to visualize or treat various medical conditions. Radiopharmaceuticals can be categorized into two main groups based on their primary use:

**5.1 Diagnostic Radiopharmaceuticals:**

Diagnostic radiopharmaceuticals are used for medical imaging to visualize and assess the physiological or biochemical functions of organs and tissues. They emit gamma rays or other forms of radiation that can be detected externally using imaging devices like gamma cameras or PET scanners. Some common types of diagnostic radiopharmaceuticals include:

a. **Technetium-99m** (Tc-99m) Radiopharmaceuticals: Tc-99m is the most widely used radioisotope for diagnostic imaging. It has a short half-life and can be easily attached to various compounds to target specific organs or functions. Examples include Tc-99m MDP for bone scans and Tc-99m sestamibi for cardiac imaging.

b. **Fluorine-18 (F-18)** Radiopharmaceuticals: F-18 is used in positron emission tomography (PET) imaging. Common F-18 radiopharmaceuticals include FDG (fluorodeoxyglucose) used to assess glucose metabolism and various other tracers targeting specific molecules or receptors in the body.

c. **Iodine-131 (I-131)** Radiopharmaceuticals: I-131 is used in thyroid scans and therapy for certain thyroid disorders, as it is taken up by the thyroid gland.

d. **Gallium-67 (Ga-67)** and **Indium-111 (In-111)** Radiopharmaceuticals: These are used for infection or inflammation imaging.

e. **Technetium-99 (Tc-99)** Radiopharmaceuticals: Tc-99 imaging agents, although less common than Tc-99m, are also used in certain diagnostic procedures.

**5.2 Therapeutic Radiopharmaceuticals**:

Therapeutic radiopharmaceuticals are used for targeted radiation therapy to treat specific diseases, particularly cancer. These drugs deliver radiation directly to the diseased cells, minimizing damage to surrounding healthy tissues. Some examples of therapeutic radiopharmaceuticals include:

a. **Iodine-131 (I-131)** Radiopharmaceuticals: I-131 is used in targeted radiation therapy for thyroid cancer.

b. **Yttrium-90 (Y-90)** Radiopharmaceuticals: Y-90 is used for radioembolization, a treatment for liver cancer.

c**. Lutetium-177** (Lu-177) Radiopharmaceuticals: Lu-177 is used in peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors.

d. **Radium-223 (Ra-223)** Radiopharmaceutical: Ra-223 is used for the treatment of bone metastases in prostate cancer.

These categories represent some of the most commonly used radiopharmaceuticals. The field of nuclear medicine continues to advance, and researchers are continuously exploring new radiopharmaceuticals and applications for both diagnostic and therapeutic purposes.

**Bibliography**

1. Reetesh Malvi, Richa Bajpai, Sonam Jain. A Review on Therapeutic Approach of Radiopharmaceutical in Health Care System, Int. J Pharma and Bio Archi., 2012; 3(3):487-492.
2. Radiopharmaceuticals- European Medicines Agency.  Available at URL:  http://www.ema.europa.eu/docs/en\_GB/document\_library/Scientific\_guideline/2009/09/WC500003653.pdf.
3. Wynn A Volkert, Timothy J. Hoffman. Therapeutic Radiopharmaceuticals,  Chem. Rev. 1999, 99:2269−2292.
4. Graham MM. Clinical molecular imaging with radiotracers: current status. Med Princ Pract. 2012, 21(3):197-208.
5. Radiopharmaceuticals-American Cancer Society. Available at URL: http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/radiation/radiationtherapyprinciples/radiation-therapy-principles-how-is-radiation-given-radiopharmaceuticals.
6. Nan-Jing Peng. New Trends in the development of radiopharmaceuticals, Annals of Nuclear Medicine and Molecular Imaging. 2013, 26:1-4.
7. Radiopharmaceuticals: Production and availability. Available at URL: https://www.iaea. org/ About/Policy/GC/GC51/GC51InfDocuments/English/gc51inf-3-att2\_en.pdf
8. Therapeutic applications of radiopharmaceuticals. International atomic energy agency. Available at URL: http://www-pub.iaea.org/MTCD/publications/PDF/te\_1228\_prn.pdf.
9. KOJIMA, M. (1984) ‘Future trend of radiopharmaceuticals’, RADIOISOTOPES, 33(7), pp. 510–512. doi:10.3769/radioisotopes.33.7\_510.