RADIOPHARMACEUTICAL SCIENCE

Abstract

In today's advancing world, we as humans have undergone a varied change in our lifestyles. Due to that, we are more prone to certain ailments. To cope up with that, we invented medications and new technologies. One remarkable invention is the use of radioparticles. Using radioactive elements for diagnosis and treatment purposes paved the way for better healthcare system. The study of such combinations of physics, chemistry and biology in pharmaceuticals refers to Radiopharmaceutical Science. They are helpful in treating cancer, Thyroid etc. For better imaging and clear Identification of diseases they are also useful. One leading advantage of using radioparticles Is targeted therapy. Therefore, usage of Radioisotopes in pharmaceuticals is Proving to be beneficial to humans.

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I. INTRODUCTION

Radiopharmaceutical science is defined as the science of incorporating a radionuclide with a biologically active molecule or pharmaceutical molecular entity. The radioactive compound present in a radiopharmaceutical emits radiation which is used for diagnosis and therapeutic treatment.

"Radiopharmaceuticals are radioactive compounds which comprise bound radionuclide in their structure, whose purpose is to direct radionuclide to the targeted location for obtaining images and for treatment".[1]

Radioactive materials include inorganic and organic compounds, peptides, proteins and monoclonal antibodies, labeled with radionuclides with half-lives from minutes to days. It gives relevant information about the anatomy and physiology of the organ.

Substances such as iodine radiotracers have been used in past decades for the detection and cure of thyroid disorders. However, use of radionuclides in treatment of cancer have been used from last two decades.[1][3]

Funkhouser et al. gave the term "Theranostics" which has been introduced as a combination of both diagnostic and therapeutic approaches. Dual- functioning radiopharmaceutical is also called as theranostics. Iobenguane can be an isotope with different emission potentials, such as iodine-131 or a mixture of isotopes with different emission potentials, such as Lutetium-177 and Gallium-68, used in combination for neuroendocrine diagnosis and therapy.

1. Benefits of Theranostic Systems:

- Targeted therapy
- Less tissue toxicity
- Better diagnosis and treatment
- Enhanced biological functions such as improved bio-distribution and cellular uptake. [6]
- Radiation therapy is a technique that delivers radiation dose to the affected tissue or lesion with tiny sealed radioactive source.
- Radiopharmaceuticals can be administered orally (in pill/ solid dosage form), injected intravenously or interstitially.[4]
- Once the drug is administered, then oncologist tracks the radioactivity throughout the body. Then gamma cameras detect these radiation and gives static and dynamic images of the concerned tissue.[4]

2. Radioactive Isotopes: These are defined as atoms with excess energy in their nucleus or unstable neutron- proton combinations. The natural decay of atoms produces a class of chemical elements known as radioactive isotopes or radioisotopes. They are used for diagnosis and treatment purposes.[5]

- Uranium is the naturally occurring radioisotope. Uranium- 235 is another form of uranium that has 3 fewer neutrons in its nucleus and s unstable or non- radiative. [7]

- Technetium-99m , a gamma emitter with minimal therapeutic efficacy and is mostly utilized in diagnostic imaging. It can be used to image several structures, including the thyroid, lacrimal, vascular and pulmonary perfusion.[7]
- A radioisotope with a wide range of uses is iodine-131. It undergoes beta decay, which causes alterations in the cells. It is used in the treatment of thyroid cancer as only thyroid is the organ that consumes iodine, making radioactive Iodine to cause thyroid ablations.[7]
- Ceasium-137 undergo beta decay and Gamma emission. It is chemically unstable and extremely reactive. Used for low dose transient intracavity brachytherapy.[7]
- Fluorine-18 mostly emits positrons. Used as a radiotracer for PET scans.[7]
- A radioactive isotope of xenon called xenon-133 undergo beta decay. It is an inhaled radionuclide that is used to measure cerebral blood flow and pulmonary function.[7]
- Rubidium-82 experiences both positron and gamma emission. It is mostly given intravenously to evaluate cardiac imaging.[7]

3. Synthesis of Radioisotopes[8]

- Bombardment with neutrons
- Bombardment with charge particles
- Decay of radioisotopes

II. RADIOPHARMACEUTICALS IN DISEASES

Radio pharmaceuticals can be used for both to detect (diagnose) medical conditions and to treat certain ailments.

1. **Radiopharmaceuticals in Diagnosis/ as Diagnostic Tools:** They produce diagnostic images of tissues and organs a process called scintigraphy. Radiopharmaceuticals are basically, radio isotopes bound to biological molecules that target specified organ tissue and cell inside the human body. Once they enter the body, they get incorporated into biological pathways, metabolized and excreted and further used for investigation for the flow of blood in the brain , heart, liver etc.[9]

Radiopharmaceutical comprises:

- Radioactive Element(Radionuclide) +Biologically active molecule (carrier/ligand)
- Radioactive element (radionuclide) permits external scan.
- Biologically active molecule, drug or cell (RBC & WBC labelled with radionuclide) conducts radionuclide to specific site. Also called as a carrier or ligand.

Targeted or specified radionuclide imaging gives convenience for disease detection. Radiopharmaceuticals labelled with PET and SPECT radionuclide are known to show high accuracy to detect tumors, neurological disorders, inflammation, bacterial infection. Most commonly used radionuclide is Technetium 99 m (detect bone metastasis). [11]

Some radiopharmaceuticals used for diagnosis are:-[10]

Disease	Radiopharmaceutical Used
Abscess and infection	Gallium Citrate Ga67, Indium In111 Oxyquinoline
Blood volume studies	Radioiodinated albumin, Sodium Chromate
Bone diseases	Sodium Fluoride F18, Technetium (^{99m}Tc) medronate, Technetium Oxidronate, Technetium phosphates
Brain diseases and tumors	Fludeoxyglucose F18, Iofetamine I123, Sodium Pertechnetate, Technetium Gluceptate
Cancer, tumor	ludeoxyglucose F18, Gallium citrate Ga67, Indium In111 Pentetreotide, Technetium Arcitumomab
Heart disease	Ammonia N13, Fludeoxyglucose F18, Rubidium Rb82, Technetium Sestamibi, Technetium Teboroxime, Thallous Chloride
Lung diseases	Krypton Kr81, Technetium Pentetate, Xenon (Xe 127, 133)
Red blood disease	Sodium Chromate
Spleen diseases	Sodium chromate, Technetium sulfur colloid
Stomach and intestinal problems	Sodium chromate, Technetium phosphates, Technetium sulfur colloid
Thyroid diseases	Fludeoxyglucose F18, Sodium iodide, Radioiodinated Iobenguane, Technetium Sestamibi
Urinary bladder diseases	Sodium Pertechnetate

2. **Radiopharmaceuticals in Treatment of Diseases [3][12][13]:** Radiopharmaceuticals in treating diseases or as therapeutic agents work by strongly binding with the tumor. They deliver targeted dosage of radiation directly to the tumors leaving normal healthy cells behind. The choice of molecule that carry the radiation depends upon it's affinity or binding power to the tumor target structure such as antigen.

   An ideal radiopharmaceutical for therapeutic purposes should:

   - Act only on the cells of malignant tumors;
   - Reach all the cells of malignant tumors wherever they are localized
   - Leave healthy tissues and organs unhurt while bringing maximum doses of radiation to the tumor
   - Eliminate malignant tumor cells with great effectiveness.

   Physical and biochemical characteristics of radiopharmaceuticals should be taken into consideration such as;

   - **Physical Characteristics**

     - Physical half life
     - Energy radiation
     - Type of emission daughter product
     - Production method
     - Radionuclide purity.

- **Biochemical Characteristics**

  - Tissue targeting
  - Radioactivity retention in the tumor
  - In- vivo stability
  - Toxicity
  - Effective half- life within patient's body.

Advancements in nuclear medicine is been stimulated by introducing new radionuclides and radiopharmaceuticals. The biological action of radiopharmaceutical is determined by the form of ionizing radiation emitted by the radionuclide. Alpha and beta (emit radiation) are used as radionuclides due to short penetrating power and also they release their energy within the target.

- **Beta Particles:** Beta particles are produced by the process of beta decay, which promotes the conversion of neutrons to protons, giving rise to energetic electrons (beta particles). These are negatively charged materials with a low electron transfer (LET) of about 0.2 KeV/µm. High-energy beta particles such as 90Y and 188Re can cause chemical burns to nearby cells.

  For small tumors, low-energy beta radiation such as lutetium 177 (177Lu) is better. The most common and widely used beta particle is iodine 131 (131I), which is used in the treatment of hyperthyroidism and thyroid cancer. Samarium 153 (153Sm) is a beta-emitting radionuclide used to treat breast and prostate cancer with bone metastases.

- **Auger Electrons:** These are very short emissions around 1-1000 nm. Auger electrons are in the middle of the LET (4-26 keV/µM). If inside the radiopharmaceutical core, the emissions are usually very cytotoxic. Bromine 77, Indium 111, Iodine 123 and Iodine 125 are the most commonly used Auger electron emitters. Many in vitro experiments have shown that when tumor cells are populated with targeted vectors, subcellular radiation can be close to cellular DNA, resulting in efficient and specific tumor cell death.

- **Alpha Particles:** Alpha particles have the same structure as 4 He nuclei (sometimes called He2+) without electrons. They are produced in alpha decay. Alpha particles – more cytotoxic than beta particles. It is known that alpha particles ionization products travel shorter distances than beta particles, thus reducing the damage to healthy cells. This effect is independent of dose and oxygen during the cell cycle.

  Targeted alpha therapy (TAT) is a good option for the treatment of various micrometastases. Alpha particles can bind to biomolecules such as monoclonal antibodies with the aid of bispecific binding reagents or carriers. Thus, the RPT selectively delivers high doses of radiation directly to the target and provides limited toxicity to the surrounding tissue.

Some alpha particles are- bismuth 212,bismuth 213,actinium 225, radium 223 and thorium 227. $RaCl_2$ is the first alpha emitting radiopharmaceutical for prostate and breast cancer patients. Bismuth and astatine labeled monoclonal antibodies treats leukaemia and brain tumors.

- **Concept of Therapy:** For effective treatment various alpha and beta radiation emitting isotopes are labeled with peptides or antibodies to target specific tumor used as vehicles to deliver ionizing radiations to the tumor tissue. For targeting molecular receptors different radioligands are being developed. For more therapeutic effect to target cells radionuclides are coupled with ligands to recognize and bind with tumor associated molecules. Unlike radiotherapy, radiopharmaceuticals are administered intravenously to a target tumor. Radiopharmaceuticals treat systemic malignancy in areas such as bone or brain, which cannot be treated using external radiotherapy. The targeted cell absorbs radiation dose which exponentially decreases with time.

3. **Radiopharmaceuticals in Treatment of Cancer [3][12][14]:** Radiopharmaceutical therapy is used in the treatment of cancer. Radiopharmaceutical therapy can be targeted at tumors including matastasis sites. As compared to others, radiopharmaceutical therapy is more suitable as it does not require many cycles of therapy, like as in chemotherapy, side effects are also less severe in this. Alpha or beta particles and auger electrons are used for therapy purposes. Radiopharmaceuticals are administered intravenously which attacks the target tumor. Some studies suggest that targeting radiation therapy at basic or cellular level has the potential to eliminate the risk of both long and short term side effects of treatment while enabling any deposits of cancer cells to be killed from the body. Once a radiopharmaceutical has been inserted with the cancer cell the radioactive compound naturally breaks down leading to release of energy that damages DNA of nearby cells. When the cell's DNA is damaged the cell dies, cancer cells are particularly sensitive to radiation induced DNA damage.

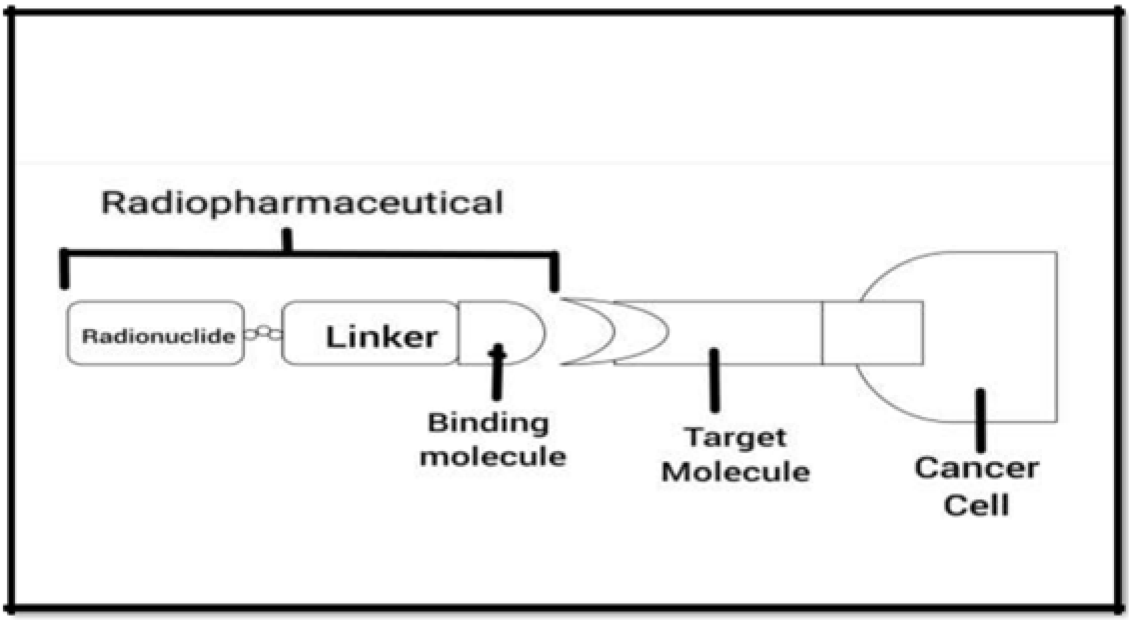

Figure 1: Radioactive Compound Attacking Cancer Cell.

Radionuclides with alpha and beta emitting particles treat bulky solid tumors while radionuclides containing auger elements usually treats tiny cluster of Cancer cells.

These particles allow ionization radiation to be emitted by radionuclides linked to the carrier kill cancer cells by damaging their DNA, causing the tumors to shrink.

Radiopharmaceuticals approved by the U.S. Food and Drug Administration for treating cancer are:

- Radium-223 dichloride for metastatic prostate cancer in bones
- Sodium iodide for thyroid cancer
- Lutetium 177 for neuroendocrine tumors of digestive tract
- Yttrium 90 for non- Hodgkin lymphoma

III. PRODUCTION OF RADIONUCLIDES

Radionuclides are artificially produced by radioactive decay of other radioactive atoms. The preparation of radiopharmaceuticals involves three basic steps:

- Production of the Radionuclides,
- Synthesis of the non-radioactive compound, and
- Reaction of the radionuclide with the non-radioactive compound.

The chemical and isotopic composition of Target molecules is also taken into consideration while producing radionuclides.[16]

This production can be done either by:-[15]

1. **By Radionuclide Generator:** A radionuclide generator is a glass or plastic column (ion exchange column) which contains resin or alumina and the bottom of the column is filled with adsorbent material on which parent nuclide is absorbed. In radionuclide generators, sometimes known as ―cows, (long –lived) radionuclide, or ―parent nuclide is present. This parent nuclide will eventually decay into a short-lived radionuclide of interest, or ―daughter nuclide. Production of ^{68}Ga , ^{82}Rb, ^{99m}Tc and ^{113m}I radionuclide is involved. It is a device that helps in the production of short lived radionuclide known as 'daughter' from the radioactive transformation of a non-medical long lived radionuclide called as 'parent'.

2. **Nuclear Fission:** It is a process that causes the nucleus of an atom to split into two lighter nuclei. Nuclides with large atomic numbers are known to show such process. This process is typically seen in nuclides with high atomic numbers, such as when Uranium-235 is fissioned in a nuclear reactor using neutrons. Either spontaneous nuclear fission or nuclear excitation can cause nuclear fission to occur.

   During the fission process, a significant quantity of energy is released, resulting in the creation of radioactive materials and the emission of many neutrons. These neutrons have the potential to start a chain reaction by further inducing nuclear fission in neighbouring fissionable nuclei. The tremendous amounts of energy that are then released as a result of this chain reaction have the potential to create an atomic bomb if left unchecked. Nuclear fission can produce radioisotopes in a laboratory setting that can be employed for diagnostic and/or therapeutic procedures. All individuals involved in such a regulated procedure must have had the necessary training, and it must be carried out inside of machinery intended to handle radioactive materials.

3. **Charged Particle Bombardment:** The target materials are bombarded with charged particles within particle accelerators like cyclotron to create radionuclides.

4. **Neutron Bombardment:** In nuclear reactors, radionuclides are often created by blasting the target material with neutrons, which is similar to the procedure described above. In essence, the target material‘s purity, isotopic composition, and incoming particle energy all play a key part in causing the desired nuclear reaction.

IV. TESTING OF RADIOPHARMACEUTICALS [17][18]

- **Activity Check:** The extent of radioactivity that is to be administered have some limit to it. The limit is set by a committee or government bodies of different countries. The radioactive preparations or dosage forms are examined for their activity before administered to an individual.

  In radio pharmacy radionuclide calibrators are used and more specifically the ionization chambers are employed. They work by taking the ionizing ability of the isotope and have scaling element for different radionuclides. The reading Is given in kBq or MBq or mCi but here is to note that these calibrators are not appropriate for all radionuclides.

  In case of low energy releasing radiations , the radiations are weakened before reaching the gas chamber and may cause lack of precised readings. In the case of high energy beta radiations , the readings or measurement are based on Bremsstrahlung radiations produced. The calibrators have precision rate of approximately 2-5%. These calibrators must undergo strict QA inspection to ensure accuracy when compared to a durable reference, such as cobalt. Radionuclides that emit X-rays and gamma rays can be measured using a scintillation counter. This contains a scintillant crystal that, when a photon strikes it, emits a flash of light. Crystals of sodium iodide triggered by thallium are the greatest detectors of gamma radiation. Beta ray emitters such as are monitored for activity using liquid scintillation.

- **Radionuclide Identifying:** It can be identified by two methods

  - **By measuring the Half Life of Radionuclide:** A detector is used to measure half life. Multiple readings are taken at least for 3-4 times so that dead time losses are minimized. The readings are to be taken at similar geometrical conditions.

    Half-life is computed using a graph that is drawn with the instrument's logarithm against time. The graphs of various measurements shouldn't deviate from the half-life described in the pharmacopoeia by more than 5%.

- **By governing the Energies of Radiations:** Different procedures are employed on the basis of the type of radiations that are emitted and their spectrum. For instance; Gamma spectroscopy is used in the determination of X-rays. The spectrum in which the radiations lie help in governing the type of nuclides present and in how much quantity.

- **Radionuclidic Purity:** In this the measured activity of the radiopharmaceutical is compared with the radioactivity of the nuclide. The amount of radionuclide impurities that are allowed is mentioned in pharmacopoeiae‘s monograph. It is measured in percentage. The impurities can lead to alteration in the biological responses produced by the radiopharmaceutical preparation. The impurities can be caused due to improper manufacturing process. For example; impurities can be produced by energy of reaction or due to the pre presence of contaminants in the cyclotron. Yttrium used in PET [Positron Emission Tomography] is result of reaction on a target of strontium protons of 16 Mev. Energy exceeding to 30 MeV then it may target bones causing serious damage.

  Impurities can also form when a parent nuclide is present in a claimed nuclide that was acquired using a separation method like generator elution. Molybdenum in technetium solution, for instance. Due to the radionuclide's beta emission and its lengthy [66 hours] half life, this could be fatal. Radionuclide impurity identification uses gamma spectroscopy or half-life analysis. Due to the contrast in half lifetimes of various radionuclides found in medicinal preparations, the radionuclidic purity fluctuates with time.

- **Radiochemical Purity [RCP]:** RCP is the total radioactivity present in the radioactive pharmaceutical. RCP must be quick, accurate and economical. In recently introduced methods , thin layer and paper chromatography are on the move.

  - **Paper and Thin Layer Chromatography:** In this strips of chromatography paper are introduced to microliter sample of radiopharmaceutical. It is then put into a container having small amount of solvent [e.g. 0.9% saline, methyl ethyl ketone etc.]. The solvent migrates up the strip. The constituents of radiopharmaceuticals gets separated based on their solubility in the solvent and extent of adsorption to the support media.

  - **Detection of Radioactivity in the Chromatographic Strip:** The most easiest and quick method is by cutting the strip and counting the segments in the radionuclide counter.

    For e.g. - strip is cut into two sections i.e. A and B
    Then percentage if radioactivity is (A = A x 100/A+B)

    But this method has higher chances of lack of accuracy and limited to low activity radiopharmaceuticals.

    - A gamma camera can be used to image the strip. Count percentage in regions of strips can be determined. Relics of strips can be seen by imaging the chromatography. But this method is not economical for most users because of the camera used.

- Radiochromatograph scanner can be used in the analysis of the chromatography strips. It consist of sodium iodide detector to detect the radioactive rays. On a note it is unable in counting of certain isotopes like chromium due to low activity statistics.
- Phosphorous imaging is also employed in strip analysis. A latent image is accumulated in a phosphorous screen. The image shows the distribution of radioactivity in the strip. The screen is later scanned with a laser and the strength of radioactivity is detected. This can be further stored for future reference.

- **Solid Phase Extraction:** Disposable cartridges with different bonded silica sorbents are accessible. The sorbent present in the cartridges has the ability to retain certain chemical compounds from the sample that is to be analyzed. Elution of different solvents can be performed by employing different solvents based on their activity. Then the eluates having satisfactory activity can be counted in the radionuclide calibrator. It takes so less time that the RCP can also be determined just before dose administration to an individual or patient.

- **High-Performance Liquid Chromatography [HPLC] :** HPLC separation works on the hydrophilic/lipophilic properties of the constituents. It has higher responsiveness and responsiveness than simple TLC. Gamma radiation emitters can be detected with the help of scintillation counter that is further attached with rate meter. They can be connected in series which helps in the identification of different compounds for other detectors. Licensed cold kits are important for performing HPLC in radiopharmaceuticals. It reduces the chances of any abnormal patient scan. HPLC do not find colloidal contaminants, instead TLC method is used.

- **Electrophoresis:** In electrophoresis, the components are separated on the basis of charge and size of radioactive molecules. The most persistent method in radio-pharmacy is in the RCP determination of radio-labeled albumin in which a barbitone buffer is used into which the sample is run with the aid of a filter.

1. Methods for Assessing Pharmaceutical Parameters:

- **pH:** pH of the radiopharmaceuticals should be between a range of 5.5-8 . It is essential in determining the pH of PET radiopharmaceuticals because during the preparation of the formulation may reach extreme pH which may require neutralization. pH can be determined by using pH paper and then comparing it to the calorimetric pH scale. In recent times micro pH papers are available which reads a drop of liquid [10 ul] that is further placed on the electrode.

- **Visual Examination:** Visual examination is an essential part of the testing of radiopharmaceutical preparations. This examination takes into consideration the radiation protection issues for the operator. The preparation is examined behind a suitable shielding. These vials are examined for cracks, closures, etc. Syringes are also checked for particulate contamination.

- **Apyrogenicity:** This test is done to check the presence of pyrogens in the preparations. Pyrogens are bacterial endotoxins having polysaccharide cell membranes. Pyrogens are known for inducing fever and can cause leukopenia in immune suppressed patients. Therefore it is important that the radiopharmaceuticals must be pyrogen-free. The most commonly employed method is Limulus amoebocyte lysate test.

2. Radiopharmaceutical Benefits in Healthcare System [15] :

- It can be used for diagnosis and treatment of patients.
- Rapid pain relief
- Cures cancer
- Cure many ailments
- Direct treatment of tumors, such as bone metastasis.
- In some patients, single dose is therapeutic.
- Children can undergo Nuclear medicine tests with no side effects
- Nuclear tests are safe with no side effects on patients.

3. Radiopharmaceutical Drawbacks in Healthcare System [15]:

- When several fractions are administered, patients may have long-lasting discomfort and inconvenience
- Head and neck radiation at higher levels has been linked to heart problems, thyroid issues, and pituitary axis issues.
- Pregnant women should not undergo nuclear medicine examinations since developing children and adults are more sensitive to radiation than unborn babies.
- The patient's teeth, braces, and permanent bridges may deform the area around the patient's mouth.
- May cause some allergic responses.
- There is a risk of radiation.
- Myelosuppression is a possibility, particularly after chemotherapy.

V. APPLICATIONS OF RADIOPHARMACEUTICALS[15]

1. **For Identification Purposes:** Radiations for identification purposes should be strong enough to pass through tissues from inside the body to the detecting device. Some radioisotopes that are used for diagnosis are-

   Iodine - 131
   Phosphorus - 32 ($_{15}P^{32}$)
   Chromium-51 ($_{24}Cr^{51}$)
   Cobalt – 57 ($_{27}Co^{57}$) & Cobalt - 58 ($_{27}Co^{58}$)
   Technetium-99m

   For Scanning and Imaging Purposes: Optical imaging, brain imaging, gastrointestinal imaging, imaging of inflammatory lesions, cardiovascular imaging, bone imaging, lung imaging, spleen imaging, and renal imaging.

2. **Radiotherapy:** It helps in the treatment of thyroidcarcinoma, cancer, bone tumors, neuroendocrine tumors, lymphomas,

- Radiopharmaceuticals for Radiation Synovectomy: Radiosynoviorthesis or radiation synovectomy is a method in which radiopharmaceuticals are delivered to the affected synovial joints in patients with joint pain such as RA(Rheumatoid Arthritis).Phosphorus 32, yttrium 90, samarium 153, holmium 166, erbium 169, lutetium 177, rhenium 186, etc, are used in the treatment of arthritis.
- Radiopharmaceuticals containing radionuclides such as strontium 89, samarium 153, and rhenium-186/188 are effective in reducing pain of bone metastases. Continuing research for Lutetium 177 radiopharmaceutical for treatment of osteoporosis is undergoing.

3. **Sterilization Techniques:** Radioisotopes are used for radiation sterilization of heat sensitive drugs (such as hormones, vitamins, antibiotic and disposable syringes).

   Cobalt-60 ($_{27}Co^{60}$): Sterilization of disposable syringes, catheters and surgical dressings by y-irradiation.

4. **Research Applications:** In biochemical research, radioactive isotopes are used to determine reaction mechanisms. lodine - 131: Sodium iodohippuric – determines renal plasma flow.

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