A Review on Therapeutic Approach of Radiopharmaceutical in Health Care System

Reetesh Malvi*, Richa Bajpai², Sonam Jain³

¹Sagar Institute of Research, Technology & Science, Ayodhya Bypass, Bhopal-462041, India
²Sagar Institute of Pharmacy & Technology, Gandhinagar, Bhopal, 462036, India
³School of Pharmaceutical Science RGPV, Gandhi Nagar, Bhopal, 462033, India

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ABSTRACT
Radiopharmaceuticals play a critical role not only in modern medicine primarily for diagnostic purposes, but also for monitoring disease progression and response to treatment. As the use of image has been increased, so has the use of prescription medications. These trends increase the risk of interactions between medications and radiopharmaceuticals. The use of specific radiotracers for imaging organ function and disease states is a unique capability of nuclear medicine. Unlike other imaging modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Ultrasonography (US), nuclear medicine procedures are capable of mapping physiological function and metabolic activity and thereby giving more specific information about the organ function and dysfunction. The widespread utilization and growing demands for these techniques are directly attributable to the development and availability of a vast range of specific radiopharmaceuticals. Many of the radiopharmaceuticals used for the diagnostic purpose like C¹⁴ for pancreatic study and breath test, Cr⁵¹ used for red cell volume and GFR measurement, Co⁵⁷ used for gastrointestinal absorption, I¹²³ for thyroid uptake and renal imaging. We review the literature on radiopharmaceuticals so as to gather the more information on utilization of radiopharmaceuticals, its regulatory aspects and guideline for using the radioisotopes.

Key words: Radiopharmaceuticals, diagnostic imaging, isotopes, nuclear medicine.

INTRODUCTION
A radiopharmaceutical is a pharmaceutical that, when ready for use, incorporates one or more radionuclides (radioactive isotopes). Radiopharmaceuticals are used for diagnosis or therapeutic treatment of human diseases; hence nearly 95% of radiopharmaceuticals are used for diagnostic purposes, while the rest is used for therapy. Radiopharmaceuticals usually have no pharmacologic effects, as they are used in tracer quantities. There is no dose-response relationship in this case, which thus differs significantly from conventional drugs [1]. It has been used extensively in the field of nuclear medicine as non-invasive diagnostic imaging agents to provide both functional and structural information about organs and diseased tissues. They may be given to the patient in several ways, e.g. orally, parenterally, or placed into the eye or the bladder [2]. A radiopharmaceutical can be as simple as a radioactive element such as ¹³³Xe, a simple salt such as ¹³¹I-NaI, or a labeled compound such as ¹³¹I-iodinated proteins and ⁹⁹mTc-labeled compounds [1]. Although radiotracers were tried as a therapeutic medicine immediately after the discovery of radioactivity, the first significant applications came much later with the availability of cyclotrons for acceleration of particles to produce radioisotopes. Subsequently, nuclear reactors realized the ability to prepare larger quantities of radioisotopes. Radioiodine (iodine-131), for example, was first introduced in 1946 for the treatment of thyroid cancer, and remains the most efficacious method for the treatment of hyperthyroidism and thyroid cancer [3]. They are usually given only once, or sometimes on a few occasions, and contain only small amounts of the active substances with a radionuclide attached to them to allow scintigraphic imaging or measurement of biodistribution. Such radiopharmaceuticals do not often show any measurable pharmacodynamic effect. Radiation is a general property of all

*Corresponding Author: Reetesh Malvi, Email: reetesh12malviya@yahoo.com, Phone No: +9926401306
radiopharmaceuticals, which when administered gives the patient an inevitable radiation dose. In the case of therapeutic radiopharmaceuticals, the radiation effect is the wanted property. Evaluation of the safety and efficacy of radiopharmaceuticals should include radiopharmaceutical and radiation hygiene aspects and radiation dosimetry in addition to general parameters \[4\].

**RADIOPHARMACEUTICALS AND ITS CATEGORY**

Radiopharmaceuticals can be divided into four categories:

1. **Radiopharmaceutical preparation:** A radiopharmaceutical preparation is a medicinal product in a ready-to-use form suitable for human use that contains a radionuclide. The radionuclide is integral to the medicinal application of the preparation, making it appropriate for one or more diagnostic or therapeutic applications.

2. **Radionuclide generators:** A system in which a daughter radionuclide (short half-life) is separated by elution or by other means from a parent radionuclide (long half-life) and later used for production of a radiopharmaceutical preparation.

3. **Kit for radiopharmaceutical preparation:** In general a vial containing the non radionuclide components of a radiopharmaceutical preparation, usually in the form of a sterilized, validated product to which the appropriate radionuclide is added or in which the appropriate radionuclide is diluted before medical use. In most cases the kit is a multi-dose vial and production of the radiopharmaceutical preparation may require additional steps such as boiling, heating, filtration and buffering. Radiopharmaceutical preparations derived from kits are normally intended for use within 12 hours of preparation \[5\].

4. **Radiopharmaceutical precursor:** A radionuclide produced for the radiolabelling process with a resultant radiopharmaceutical preparation \[6\].

**METHODS OF PRODUCTION OF RADIOISOTOPES**

1. **Generator produced:** The first group includes Ga\(^{68}\), Kr\(^{81}\), Rb\(^{82}\), Tc\(^{99}\) and In\(^{113}\), all of which are generator produced radionuclides. Of particularly note is Tc\(^{99}\). Due to its ideal imaging energy and physical half life as well as the ability to bind to so many compounds, approximately 85% of all imaging procedures in US are preferred following administration of Tc\(^{99}\). An Ideal Generator Systems includes:

   1. If intended for clinical use, the output of the generator must be sterile and progeny-free.
   2. The chemical properties of the daughter must be different than those of the parent to permit separation of daughter from parent. Most often, separations are performed chromatographically.
   3. Generator should ideally be eluted with 0.9% saline solution and should involve no violent chemical reactions. Human intervention should be minimal to minimize radiation dose.
   4. Daughter isotope should be short-lived gamma-emitting nuclide (physical half-life = hrs days)
   5. Physical half-life of parent should be short enough so daughter re-growth after elution is rapid, but long enough for practicality.
   6. Daughter chemistry should be suitable for preparation of a wide variety of compounds, especially those in kit form.
   7. Very long-lived or stable granddaughter so no radiation dose is conferred to patient by decay of subsequent generations.
   8. Inexpensive, effective shielding of generator, minimizing radiation dose to users.
   9. Easily recharged (we do NOT recharge Mo/Tc generators, but store them in decay areas after their useful life is over).

2. **Thermal Neutron Reactor producer:** Radioisotopes used in Nuclear Medicine are almost all synthetic. For thermal neutron reactor-produced radioisotopes, reactor is source of thermal neutrons. An (n, gamma) reaction occurs and net effect: increase of a number by 1 and no change in Z number. Same element is therefore present. Example: Mo\(^{98}\) (n, gamma) Mo\(^{99}\) Reactor yield dependent up on following.

   1. Neutron flux in reactor (n/sec/cm\(^2\))
   2. Nuclear capture cross section
   3. Number of target atoms
   4. Decay of product after it is formed.
   5. Length of irradiation.
   6. Isotope enrichment of target

3. **Cyclotron produced:** It includes the positron emitting isotopes C\(^{11}\), N\(^{13}\), O\(^{15}\) and F\(^{18}\), all of which are cyclotron produced. The very short half-lives of the first three limit their use to a facility at or near the cyclotron site, while it is possible to transport F\(^{18}\) compounds but great dedication must be made to the transportation arrangements. The gamma emitters Co\(^{57}\), Ga\(^{67}\), In\(^{111}\) and I\(^{131}\) are also cyclotron
produced, they all have reasonably long half-lives and are easily transported across the country. The majority of photons collected by the camera for image formation are the low energy Hg$^{201}$ X-rays since the % abundance of the 135 and 167 keV gamma rays is so low. Co$^{57}$ is used for flood field, dose calibrator standards, spot markers, and other sealed sources. A cyclotron is a source of high-energy protons, deuterons, and other particles. Cyclotron yield is dependent upon:
1. Number of target atoms.
2. Energy of particles.
3. Decay of product after it is formed.
4. Length of irradiation.
5. Isotope enrichment of target

4. Fission reactor produced:
The final group of interest includes Xe$^{133}$, Mo$^{99}$, and I$^{131}$, all of which are byproducts of the fission of U$^{235}$. They are produced in great quantity in nuclear reactors; these isotopes are regarded by the nuclear power industry as waste products. However once they have been purified adequately, they are perfectly suitable for human use. The process involves the fission of U$^{235}$ when bombarded with neutrons. The result is formation of an unstable "compound nucleus" that fragments into two parts with molecular weights of approximately 100 and 135. As indicated by their atomic masses, Xe$^{133}$, Mo$^{99}$, and I$^{131}$ has molecular weights of 133, 99, and 131, respectively. Many other isotopes are produced which have commercial value. The reaction may be represented by the following equation. Note that 2.3 neutrons are released for each one participating in the reaction. The reaction becomes self-propagating and requires special care to prevent it from quickly running out of control.

\[ \text{U}^{235} + n \rightarrow \text{**U}^{236} \rightarrow 2.3 \text{ n + I}^{131}, \text{Mo}^{99}, \text{Xe}^{133} \text{and Others} \]

Role of Radiopharmaceutical Isotopes in Healthcare [8]

<table>
<thead>
<tr>
<th>Element</th>
<th>Mol. Wt.</th>
<th>Half life</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molybdenum</td>
<td>99</td>
<td>66 h</td>
<td>Used to generate the Tc-99m</td>
</tr>
<tr>
<td>Technetium</td>
<td>99</td>
<td>6 h</td>
<td>Imaging of Skeleton, Heart muscles, Brain, Liver etc</td>
</tr>
<tr>
<td>Bismuth</td>
<td>213</td>
<td>46 min</td>
<td>Used for TAT</td>
</tr>
<tr>
<td>Chromium</td>
<td>51</td>
<td>28 days</td>
<td>Labeled RBC, quantify gastrointestinal Protein loss.</td>
</tr>
<tr>
<td>Copper</td>
<td>64</td>
<td>13 h</td>
<td>Studying of Wilson’s and Menke’s Diseases.</td>
</tr>
<tr>
<td>Erbium</td>
<td>169</td>
<td>9.4 d</td>
<td>Arthritis pain.</td>
</tr>
<tr>
<td>Holonium</td>
<td>166</td>
<td>26 d</td>
<td>Liver tumors.</td>
</tr>
<tr>
<td>Iodine</td>
<td>125</td>
<td>60 d</td>
<td>Cancer Brachytherapy, filtration rate of Kidneys, diagnose deep vein thrombosis.</td>
</tr>
<tr>
<td>Iodine</td>
<td>131</td>
<td>8 d</td>
<td>Thyroid cancer.</td>
</tr>
<tr>
<td>Iridium</td>
<td>192</td>
<td>74 d</td>
<td>cancer treatment.</td>
</tr>
<tr>
<td>Iron</td>
<td>59</td>
<td>46 d</td>
<td>Studies of iron metabolism in the spleen.</td>
</tr>
<tr>
<td>Palladium</td>
<td>103</td>
<td>17 d</td>
<td>Brachytherapy.</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>32</td>
<td>14 d</td>
<td>Polycythemia vera.</td>
</tr>
<tr>
<td>Potassium</td>
<td>42</td>
<td>12 h</td>
<td>For determination of exchangeable potassium in coronary blood flow.</td>
</tr>
<tr>
<td>Selenium</td>
<td>75</td>
<td>120 d</td>
<td>Seleno-methionine to study the production of digestive enzymes.</td>
</tr>
<tr>
<td>Sodium</td>
<td>24</td>
<td>50 d</td>
<td>Study of electrolytes within the body.</td>
</tr>
<tr>
<td>Strontium</td>
<td>89</td>
<td>50 d</td>
<td>Pain relief of prostate and bone.</td>
</tr>
<tr>
<td>Xenon</td>
<td>133</td>
<td>5 d</td>
<td>Pulmonary (lung) ventilation studies.</td>
</tr>
<tr>
<td>Ytterbium</td>
<td>169</td>
<td>32 d</td>
<td>Cerebrospinal fluid studies in the brain.</td>
</tr>
<tr>
<td>Ytterbium</td>
<td>177</td>
<td>1.9 h</td>
<td>Progenitor of Lu-177.</td>
</tr>
<tr>
<td>Yttrium</td>
<td>90</td>
<td>64 h</td>
<td>Cancer brachytherapy</td>
</tr>
<tr>
<td>Cobalt</td>
<td>57</td>
<td>272 d</td>
<td>Organ size determination, in-vitro diagnostic kits.</td>
</tr>
<tr>
<td>Gallium</td>
<td>67</td>
<td>78 h</td>
<td>Tumor imaging</td>
</tr>
<tr>
<td>Indium</td>
<td>111</td>
<td>2.8 d</td>
<td>Brain studies, infection and colon transit studies.</td>
</tr>
<tr>
<td>Rubidium</td>
<td>82</td>
<td>65 h</td>
<td>Convenient PET agent in myocardial perfusion imaging.</td>
</tr>
</tbody>
</table>

**GENERAL PRINCIPLES OF RADIATION PROTECTION** [1]

1. **Justification:** All procedures involving radioactive material must be justified.
2. **Optimization:** The radiation exposure to any individual should be as low as reasonably achievable. This principle is the widely known ALARA concept (as low as reasonable achievable).
3. **Limitation:** The radiation dose received by the personnel handling radioactive material will never exceed the legally established dose limits. When planning facilities and procedures for handling of radioactive materials according to the ALARA principle, it is important to keep in mind the basic principles for reduction of radiation doses.
4. **Time:** The shorter the time of exposure to radiation, the lower the dose to the operator.
5. **Distance:** The radiation dose decreases with a factor equal to the square root of the distance from the radiation source. The operator’s distance from the source can be increased by using forceps, tongs, or manipulators in handling the radioactive material.

6. **Shielding:** The radiation dose can be reduced by placing shielding material between the source and the operator. For protection against gamma radiation, walls made of heavy concrete or lead bricks are used. For transport containers, material such as tungsten may be used for higher energy gamma irradiation radionuclides, giving a higher shielding per weight unit when compared to lead.

**RADIOPHARMACEUTICALS AND QUALITY ASSURANCE (Q.A.)** [6]

Quality Assurance is a wide ranging concept that covers all matters which individually or collectively influence quality of a product. It is the sum total of organized arrangements made with the objective of ensuring that products are of the quality required for their intended use. The system of Quality Assurance appropriate for the manufacture of radiopharmaceutical products should ensure that:

1. Products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice and Good Laboratory Practice.
2. Manufacturing and control operations are clearly specified and Good Manufacturing Practice applied.
3. All staff responsibilities are clearly specified.
4. Arrangements are made for the manufacture, supply and use of the correct raw and packaging materials.
5. All necessary controls on intermediate products, and any other in-process controls and validations are carried out.
6. The product is correctly processed and checked, according to the defined procedures.
7. Products are not sold or supplied before an authorized person has certified that each production batch has been produced and controlled in accordance with the requirements of the Saudi Food & Drug Authority (SFDA) and any other regulations relevant to the production, control and release of products.
8. Satisfactory arrangements exist to ensure that the products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life.
9. There is a procedure for self-inspection and/or quality audit which regularly appraises the effectiveness and applicability of the quality assurance system.

**DIAGNOSTIC IMAGING TECHNIQUES**

**CT (Computer tomography):**
The principal of CT is the measuring of the spatial distribution of physical material to be examined from different directions and to compute superposition free images from this data. It is basically a technique of X-ray photography by which a single plane of a patient is scanned from various angles in order to provide a cross-sectional image of the internal structure of that plane. A CT scan has many diagnostic clinical applications. It improves the diagnosis accuracy by delineating details of the organs including soft tissues and bones. CT scan can provide information about the spread of an infection or tumors to different body parts and can assist surgical interventions, biopsies, and radiotherapies [9].

**MRI (Magnetic resonance imaging):**
An MRI is similar to a computerized topography (CT) scanner in that it produces cross-sectional images of the body. Looking at images of the body in cross section can be compared to looking at the inside of a loaf of bread by slicing it. Unlike a CT Scan, MRI does not use X-rays. Instead, it uses a strong magnetic field and radio waves to produce very clear and detailed computerized images of the inside of the body. MRI is commonly used to examine the brain, spine, joints, abdomen, and pelvis. A special kind of MRI exam, called Magnetic Resonance Angiography (MRA), examines the blood vessels [10].

**Echography/Ultrasound:**
Ultrasound uses high-frequency sound waves to look at organs and structures inside the body. Health care professionals use them to view the heart, blood vessels, kidneys, liver and other organs. During pregnancy, doctors use ultrasound tests to examine the fetus. Unlike x-rays, ultrasound does not involve exposure to radiation. During an ultrasound test, a special technician or doctor moves a device called a transducer over part of your body. The transducer sends out sound waves, which bounce off the tissues inside your body. The transducer also captures the waves that
bounce back. Images are created from these sound waves\textsuperscript{[11]}.  

**Optical imaging:**  
Optical imaging is a technique based on interference and the bending of light that is fired onto a body or tissue from a laser or infrared light source. The body is injected with proteins marked by, for example, a fluorescent marker. Optical imaging may be subdivided into diffusion and ballistic imaging systems. Since the penetrability of the body in relation to light is relatively small, optical imaging is unsuitable in certain contexts, for example organ examinations.

**Nuclear medicine:**  
Nuclear medicine is a mainly medical diagnostic discipline for imaging metabolism and other functional processes in the human body. Prior to the imaging process a radioactively labeled tracer is administered to the patient. The strength of the technique lies in the fact that substances move to organ systems in very selective ways. Labeling these substances to radioactive tracers (particularly technetium) enables imaging of the distribution of such substances in the human body with the aid of gamma cameras or PET scanners. Three different modalities are available for this process: planar scintigraphy, SPECT (single-photon emission computed tomography) and PET (positron emission tomography).

**Planar scintigraphy:** is the simplest available technique, yielding a two dimensional projection image of tracer activity distribution in the human body. The technique is based on gamma radiation that is created in the decay process of a radionuclide.

**SPECT (single-photon emission computed tomography):**  
It was developed on the basis of planar imaging, which involves gamma cameras taking series of planar shots during rotations around the patient. It generates three dimensional images of nuclear activity distribution, enabling the physician to view activity distributions in cross-sections of the human body.

**PET (positron emission tomography):**  
It has entered clinical practice in the last few decades. PET is an imaging technique whereby a radioactive isotope (a PET radionuclide) is administered into the patient’s body. During decay, the isotope produces positrons (particles with the mass of electrons but with a positive charge). Electron and positron interaction causes the annihilation of both particles, releasing energy in the form of two gamma photons. The resulting gamma rays are detected by a ring of hundreds of detectors\textsuperscript{[12]}.

**Market Analysis and Future Prospectus:**  
U.S. sales of therapeutic radiopharmaceuticals were still on the threshold in 2005, with total sales of $71 million. Rapid growth is anticipated over the next 5-6 years. By 2012, therapeutic product sales should reach $1.9 billion, with high continuing growth beyond that time. This will be based on the introduction of new therapeutic radiopharmaceuticals for treating lymphoma, colon cancer, lung cancer, prostate cancer, bone cancer and other persistent cancers. These agents will be used in conjunction with traditional therapies, enhancing their effectiveness, with better specificity and reduced side effects. As interest in new therapeutic radiopharmaceuticals increases, it will prompt investigators to utilize different isotopes with more focused capabilities for treating various tumors, reducing the bystander effect on neighboring healthy cells. Use of these new agents will reduce treatment time and accelerate recovery for many patients. It will also offer an attractive investment opportunity for many of the companies and venture groups supporting these programs\textsuperscript{[13]}.

**DATABASE SOFTWARE FOR RADIOPHARMACY OR DATABASE LABORATORY FOR SOFTWARE IN RADIOPHARMACY**

1. **Venus Pro Evolution:**  
   It is a client/server Web application; several users can be connected to the software, connected to the dose calibrator. Venus Pro Evolution is a hot lab management system which records all patient injection traceability from the order to waste\textsuperscript{[14]}.

2. **Radiolab:**  
   Radiolab is software designed for hospitals and institute that prepare radiopharmaceuticals within their own facilities only for in-house use. It consist in a database application, storing and managing practically all the information generated by the activity of hospital radio pharmacies, thus providing an immediate and complete traceability of all preparations, controls, radiopharmaceutical dispensing, as well as a great help in the management of reports, order, stock and radioactive waste\textsuperscript{[15]}.

3. **Datinrad (database information radiopharmaceuticals):**  
   It is a software application for easily managing a database with information on radiopharmaceuticals, such as adverse effects or interaction with drugs or other agents. All data entered into the database of this application come
from the scientific literature and are accompanied by bibliographic references. Users of Datinrad can input and retrieve information of radiopharmaceuticals interaction and adverse effects through intuitive interfaces [16].  

4. **Dosisrad:**
Dosisrad is a software program for automatic calculation of the radiation dosimetry of radiopharmaceuticals administered to patients, according to the patient’s age the type of radiopharmaceuticals and the administered activity in mCi or MBa. The resulting dosimetry is shown in a report that specifies the absorbed doses for each organ (in mGy), sorted from highest to lowest, and the effective dose (in mSv) [17].

5. **Nucleolab:**
Nucleolab is a software application for performing calculations of nuclear medicine and radiopharmacy, with the aim of facilitating these calculations, reducing error and improving the efficiency and accuracy. The program’s associated database also provides a means of generating reports and storing the results of calculations [18].

**CONCLUSION**

Nowadays there are different types of radiopharmaceuticals available and having an important role in diagnosis of disease. They are mainly used in cancer therapy by giving the radiation on the tumors cells. This review enlightened the different type of methods and techniques regarding the radiopharmaceuticals and their uses.

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