A REVIEW ON RADIOPHARMACEUTICALS AND RADIOCHEMICAL METHOD IN ANALYSIS

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ABSTRACT

A radiopharmaceutical is only as good the care taken in each preparation step throughout compounding process. Since radiopharmaceuticals are intended for human use, it is imperative that they undergo strict quality control measure. Quality control is a set of operation, which involve observation, testing and analysis performed in order to certify that product matches set of standards and hence is suitable for intended use. Quality control testing assures purity, integrity, potency, product identity, biological safety and efficacy of radiopharmaceuticals. The success of diagnostic radiopharmaceutical is reflected in the quality of images of diseased site. Therapeutic radiopharmaceuticals must pass quality control test otherwise results could be life-threatening to the patient.

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INTRODUCTION
Nuclear medicine imaging using radiopharmaceuticals is unique, because it is safe, painless, simple, cost effective technique; at the same time it provides useful information to doctors about both structure and function of organ to treat disease.  

Radiopharmaceuticals:

Radiopharmaceuticals are compounds where the molecules have radioisotope attached to it and are used as drugs routinely in nuclear medicine for diagnosis and therapy of various diseases. The choice of radioisotope determines whether the application is diagnostic or therapeutic. These are used at very low concentrations in the range of 10^-6 to 10^-9 M and are not intended to have any pharmacological effect.

The chemical composition of a radiopharmaceutical could be considered to consist of a target/ carrier molecule, which is generally an organic moiety with a biological role, to which a radioactive isotope of an element is chemically attached either by covalent or coordinate bond.

Radionuclide is the radiation source. The choice of radionuclide for diagnostic or therapeutic applications depends largely upon its nuclear properties such as half-life, type of radiation, energy, and presence or lack of other particulate radiation emissions. The radioisotopes used for labelling are non-metals, transition metals and lanthanides. Particulate emitting isotopes such as ^{111}\text{In}, ^{32}\text{P}, ^{153}\text{Sm}, ^{90}\text{Y}, ^{177}\text{Lu}, etc. are used for therapeutic purposes whereas gamma emitting radioisotopes most commonly used for diagnostic purposes are ^{18}\text{F}, ^{99m}\text{Tc}, ^{123}\text{I}, etc.

Radionuclide generator:
A generator is a system where the daughter radionuclide (short half-life) co-existing with its longer lived parent radionuclide (long half-life) can be preferentially separated by chemical process or by elution. From a generator system a daughter product is repeatedly obtained.

Cold Kit for radiopharmaceutical preparation:
The kits are sterile, pyrogen free formulation containing non-radioactive chemicals which are dried by lyophilization and stored under nitrogen in glass vials. A kit contains active ingredients, a reducing agent, and may contained authorized excipients and additives such as antimicrobial agents, antioxidants, buffer, stabilizer, filler, etc. Kits are generally required to produce a specific radiopharmaceutical after reaction with radionuclide.

Radiopharmaceuticals are broadly classified into two categories viz. diagnostic and therapeutic, based on their medical application.

Diagnostic radiopharmaceuticals
Diagnostic radiopharmaceuticals are molecules chemically attached with gamma emitting isotope or positron emitting isotopes. Some of the radioisotopes most commonly used for diagnostic purposes are ^{18}\text{F}, ^{99m}\text{Tc} etc. These are designed to obtain the detailed description of the morphologic structure of organ or tissues and physiological function of specific organ. Some of the radiopharmaceuticals used for diagnostic applications are:

- Brain Perfusion imaging agent - ^{18}\text{F}-FDG, ^{99m}\text{Tc-d}-d-L-HMPAO, ^{99m}\text{Tc-ECD}
- Lungs Perfusion ^{99m}\text{Tc-HSA microspheres}
- Heart Perfusion imaging agent ^{99m}\text{Tc-Sestamibi}, ^{99m}\text{Tc-RBC}
- Renal static imaging agent- ^{99m}\text{Tc-DMSA}, ^{99m}\text{Tc-GHA}

Two different types of computed tomography systems namely, SPECT and PET are presently being used for imaging in nuclear medicine.

I. Single Photon Emission Computed Tomography (SPECT)
- SPECT is used when the diagnosis is performed using the radiotracers containing gamma emitting radionuclides such as ^{99m}\text{Tc}, ^{111}\text{In} and ^{123}\text{I}.

II. Positron Emission Tomography (PET)
- PET images have superior sensitivity and better resolution. This imaging modality can be used when radiotracer contains a positron emitting radionuclide such as ^{18}\text{F}, ^{11}\text{C}, ^{13}\text{N}, ^{15}\text{O} and ^{68}\text{Ga}.

Therapeutic radiopharmaceuticals
Therapeutic radiopharmaceuticals are the molecules designed to deliver therapeutic doses of ionizing radiation at specific diseased tissue sites, ^{111}\text{In}, ^{153}\text{Sm}, ^{177}\text{Lu}, etc. are some of the radioisotopes used for therapeutic purposes.

Therapeutic doses of radiation can be delivered in three different ways: external beam irradiation, implantable ‘seeds’ or systemic administration. To maximize therapeutic efficacy of radiopharmaceuticals, a radionuclide must be particulate emitter (α,β and auger electrons). To reduce radiation damage to normal tissue, a radionuclide must have a suitable half life with specific in vivo-localisation in particular target organ.

Radiopharmaceuticals should pass the quality control test (QC) prior to administration to patient to ensure product safety, efficacy and avoid unnecessary radiation exposure to the patient.
The quality control tests fall into two categories:

I. Physico-chemical test
II. Biological tests

Physico-chemical test:
Various in-vitro physicochemical tests are essential for the determination of the purity and integrity of any pharmaceutical preparation. Some of these tests are unique for radiopharmaceuticals because they contain radionuclides and are not applicable to conventional drugs.

Physical characteristics
The physical appearance of radiopharmaceuticals is important during the entire shelf life of the product. Clarity and color must be inspected before administration to a patient. If radiopharmaceuticals are true solution, it should be free from particulate matter, foreign particulates like black particles. The colloidal preparations must have a proper size range to localize in the target organ of interest. In colloidal preparations, the particle size generally used for radiopharmaceutical applications is within a narrow range of 10-100 μm.

pH and ionic strength
To maintain stability and integrity of radiopharmaceuticals, it should have an appropriate pH. The ideal pH of a radiopharmaceutical should be 7.4 but due to high buffer capacity of the blood, it may vary between 3 to 9. They must have proper ionic strength, isotonicity, and osmolarity.

Radioactivity content
Total radioactivity should be measured and radioactive concentration determined. It can be measured using a precalibrated dose calibrator or ionization chamber.

Radionuclide identification
The identification of radionuclide can be done by recording γ spectrum (Eγ) using the gamma camera.

Radionuclidic purity
The radionuclidic purity is defined in terms of percentage. It is the ratio of stated radionuclidic activity to total radioactivity. The radionuclidic impurities can interfere in quality of image and at the same time increase the radiation exposure to the patient. The accurate determination of the level of radionuclidic impurity is mostly done by γ-ray spectrometry using an HPGe detector. The radionuclidic impurities due to pure β emitters are checked by using β-spectrometer or by liquid scintillation counter. For example, the presence of radioactive 99Mo impurity in 99mTcO4- eluate obtained from 99Mo-99mTc generator.

Radiochemical purity
It is the fraction of total radioactivity in the desired chemical form. Radiochemical impurity may interfere in specific in-vivo localization of radiopharmaceuticals. Sometime they may decrease target/non-target ratio by localizing in an unintended organ.

For example, radioiodine may exist as molecular iodine, iodide, iodate, periodate and as iodo-organic compound. However, the desired active chemical form of the radiopharmaceutical is sodium iodide (NaI). A number of analytical techniques are used to determine the radiochemical impurities. These include paper chromatography (PC), thin layer chromatography (TLC), high performance liquid chromatography (HPLC) etc.

It is important that the determination of RCP be quick, accurate, and economical while maintaining radiation exposures at Low As Reasonably Achievable (ALARA).

RADIATION DETECTION INSTRUMENTATION
Determination of RCP can be done by various radiation detection instruments: scintillation well counters, dose calibrators, and radiochromatogram scanners. The instrument used for determination of radiochemical purity depends upon the amount of radioactivity.

Well Scintillation Counters
A sodium iodide [NaI(Tl)] crystal well detector is an best used for determination of radioactive counts from paper and Instant Thin Layer Chromatography strips (ITLC). The amount range 10^2 to 10^4 Bq of activity can be well counted with NaI (Tl) counters. Increase amount of radioactivity exceeds the detection time which may give dead-time and decrease in count rate. There are various methods are available to avoid exceeding the maximum counting capabilities.

- By considering inverse square law, increase the distance between the radioactive sample and detector.
- By using attenuator over the opening of the sodium iodide [NaI(Tl)] crystal well counter.
- By using a smaller sample size when concentration of radiopharmaceutical activity is high.
- By using well counters with dead time correction device. Prior to relying on this device, it should be tested to verify its accuracy. Whichever method is utilized, background counts should be subtracted from the counts on the chromatography strips.
**Dose Calibrators**

A dose calibrator is used for measuring chromatographic samples, which should not be less than 0.1 mCi.\(^{10}\)

It must be accurate in micro-curie range to avoid percent error.

**Radiochromatogram Scanners**

A radiochromatogram scanner is used when sample contains multiple impurities such as \(^{18}\)F and other fluorinated PET radiopharmaceuticals. It determines the radiochemical purity of radiopharmaceuticals when better resolution is required.

The drawback of radiochromatogram scanner is that it is expensive and procedure takes more time as compared to a well scintillation counter.

**Chemical Purity**

The chemical impurities may arise in a radiopharmaceutical preparation due to decomposition of active chemical ligand before and after labeling or may come from the active radionuclide solution. For example, alumina is an impurity in the \(^{99m}\)Tc-eluate obtained from alumina column \(^{99}\)Mo-\(^{99m}\)Tc generator. The presence of chemical impurities in a radiopharmaceutical preparation is tested using tools such as precipitation technique, colorimetry, molecular and atomic absorption spectroscopy (UV-visible spectroscopy), quantitative potentiometric assay and HPLC analysis.

**Biological tests :**

Some radiopharmaceutical compounds are used for diagnosis purpose in human. It must be given by intravenous route. Before administration of radiopharmaceuticals, biological test are performed to examine the sterility, apyrogenicity and toxicity\(^{1}\).

**Sterility**

Radiopharmaceutical preparations are required to be free from any viable micro-organism. The radiopharmaceutical preparation is rendered sterile by either autoclaving or membrane filtration through 0.22 \(\mu\)m membrane filter. The method of sterilization is basically depends on the nature of products.

**Apyrogenicity**

Radiopharmaceuticals must be free from pyrogen. Pyrogens are produced by the metabolism of microorganisms. Pyrogens are water soluble, heat stable and not removable by membrane filtration. The administration of pyrogens can cause a variety of symptoms such as fever, chills, leucopenia, pain in joints and headache. Thus, apyrogenicity of radiopharmaceuticals must be ensured before human administration. Presently, limulas ameobocyte lysate (LAL) test is done for the detection of pyrogen in radiopharmaceuticals preparation. The best recourse to prevent pyrogenic contamination is to use sterile glasswares, solutions and equipments.

**CONCLUSION**

Among the various molecular imaging techniques, nuclear medicine that employs radiopharmaceuticals is the most convincing, as it detects molecular and cellular changes of diseases with high precision. These techniques have the potential to detect diseases at the level when molecular and cellular changes occur. Such functional imaging helps to gather medical information that would otherwise be unavailable, require surgery, or necessitate more expensive diagnostic tests. Hence it has a great relevance in improving patient care and treatment.
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