ISSN 0976 – 3333

Available Online at www.ijpba.info.

**International Journal of Pharmaceutical & Biological Archives 2011; 2(4):1062-1067**

***REVIEW ARTICLE***

# A Review on Radiopharmaceuticals and Radiochemical Method in Analysis

**Patei Riddhi D*[1], Dr. P.M.Patel[1], Dr. N.M.Patel[2]**

[1]*HOD of Quality Assurance, Shri B.M.Shah College of Pharmaceutical Education and Research, Modasa, Dist: Sabarkantha, Gujarat, India*

[2]*Principal, Shri B.M.Shah College of Pharmaceutical Education and Research, Modasa, Dist: Sabarkantha, Gujarat, India*

Received 22 May 2011; Revised 10 Aug 2011; Accepted 14 Aug 2011

**ABSTRACT**

Quality assurance is the sum of all parameters concerning the preparation and control of a finished product. It is a wide term commonly used for the confirmation and validity of various ways and measurements adopted to obtain a high quality procedure for intended use with guaranteed performance. Biological quality control of pharmaceutical products becomes essential as they are ultimately to be consumed by living organisms, in particular the humans. In thisreview, we have discussed the importance and significance of biological qualitycontrol in nuclear medicine. The current and new procedures for sterility, apyrogenecity and the biodistribution quality control have been discussed and evaluated in view of the future needs and modern trends in this important area of research. There are ionization chamber, scintillation and semi conductor detectors, liquid scintillation counter, Beta emitting radionuclide, Gamma emitting radionuclide methods used in radiopharmaceuticals.

**Keywords:** Radiopharmaceutical definition, introduction, radiopharmaceutical methods.

## INTRODUCTION

**Defination :** Radiopharmaceuticals can be divided into four categories:

**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.

**Radionuclide generator:** 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.

**Radiopharmaceutical precursor:** A radionuclide produced for the radiolabelling process with a resultant radiopharmaceutical preparation.

**Kit for radiopharmaceutical preparation:** Any preparation to be reconstituted and/or combined with radionuclides in the final radiopharmaceutical preparation, usually prior to its administration.

**General consideration of radioactivity:**

- It's a property of radionuclide
- The radionuclide is a substance which continuously emits the radiation
- Generally this radiation consist of
  - alpha-rays
  - beta-rays
  - gama-rays
- Radioactive isotops
  - Radioactive subs having same proton number but different neutron number.

## Identification:

- Radioactive decay
  - The decay of radionuclide follows first order rate law
    - $A = A_o e^{-t\lambda}$
    - Half life of radionuclide
    - $T_{1/2} = 0.693/\lambda$

The Quality control tests falls into two categories:

1) Physicochemical test
2) Biological test

**1] Physicochemical tests**

The physicochemical tests indicate the level of radionuclidic, radiochemical impurities and determine the pH, ionic strength,osmolality.

**2] Biological tests**

***Corresponding Author:** Patei Riddhi D, **Email:** Pharm.riddhi@gmail.com

The biological tests indicate the sterility, apyrogenicity, toxicity.

## 1] Physicochemical tests:

**a) Radionuclidic purity**: It is defined as the fraction of the total radioactivity in the from the desired radionuclide present in a radiopharmaceuticals.

**b) Radiochemical purity:** It is defined as the fraction of the total radioactivity in the desired chemical form in the radiopharmaceuticals.

**c) pH and Ionic strength:** All radio pharmaceuticals should have an appropriate hydrogen ion concentration or pH for their stability and integrity.

**d) Chemical purity**: In monograph radiopharmaceutical preparation chemical purity is controlled by specifying limit on chemical impurities.

## 2] Biological tests:

**a) Sterility:** It indicates the absence of any viable bacteria or microorganism in a radiopharmaceutical preparation.

- All preparations for human administration must be sterilized by suitable a method that depends on the nature of the product, the solvent, various additives.
- When the size of the batch of a radiopharmaceutical is limited to one or few samples (e.g. therapeutic or very short-lived radiopharmaceutical preparations), sampling the batch may not be possible.

**b) Bacterial endotoxin**: For certain radiopharmaceutical preparations a test for bacterial endotoxins is prescribed. The test is carried out as described in the general method, *taking the necessary* precautions to limit irradiation of the personnel carrying out the test. The limit for bacterial endotoxins is indicated in the individual monograph.

-When the nature of the radiopharmaceutical preparation results in interference by inhibition or activation and it is not possible to eliminate the interfering factor(s), the test for It is sometimes difficult to carry out these tests before releasing the batch for use when the half-life of the radionuclide in the preparation is short. The test then constitutes a control of the quality of production.

**c) Apyrogenicity:** All radiopharmaceuticals for human administration are required to be pyrogen free.

- Pyrogens are either polysaccharides or proteins produced by the metabolism of microorganism. No specific method for making a sample apyrogenic, pyrogens arise mainly from the metabolism of bacteria.
- The most prevent pyrogenic contamination is to use sterile glassware, solution, equipment under aseptic condition in any preparation procedure.
- There are a number of formulation containing radioisotopes, which are used internally for therapeutic and diagnostic purpose. The majority of radiopharmaceuticals are used for diagnostic purpose, but increasingly, highly specific radiotherapeutic agents are being developed which have the potential for delivery of effective treatment, particularly in cancer therapy.

Radio isotopes are extensively used in medicine for diagnosis, either in vivo or in vitro, for therapeutic and also for investigation purpose.

**Diagnostic radiopharmaceuticals** are used to derive detailed description of the morphology and dynamic functioning of various internal organs of the body. The radiopharmaceutical accumulated in an organ of interest emit gamma radiation which are used for imaging of the organs with the help of an external imaging, device called gamma camera. A typical example is the imaging of a neuro endocrine tumour using $^{131}I$ – meta- iodobenzyl guanidine.

The following are examples of radiopharmaceuticals which are in practice worldwide for various diagnostic purposes.

- Absence and infection Gallium citrate Ga 67, Indium In 111 oxyquinoline.
- Appendicitis – Technetium (99m Tc) Fanolesomab.
- Billiary tract blockage – Technetium Tc 99m Disofenin, Technetium Tc 99m Mebrofenin.
- Blood volume studies – Radioiodinated Albumin.
- Blood vessel diseases – Sodium pertechnetate Tc 99m.
- Blood vessel diseases of the brain – Ammonia N13, Iofatamine I 123, Technetium Tc 99m, Bicisate, Technetium Tc 99m Exametazime, Xenon Xe 133.
- Bone diseases – Sodium Fluoride F18, Technetium Tc 99m Medronate, Technetium Tc 99m Oxidronate, Technetium Tc 99m pyrophosphate, Technetium Tc 99m phosphate.

- Bone marrow diseases_– Sodium chromate Cr 51, Technetium Tc 99m Albumin colloid Technetium Tc 99m sulfar colloid.
-Brain diseases and tumours – Fludeoxyglucose F18, Indium In 111 pentetreotide, Iofetamine I 123, Sodium pertechnetate, Tc 99m, Technetium Tc 99m, Exametazime, Technetium Tc 99m, Gluceptate, Technetium Tc 99m pentetete.
- Cancer tumours – Fludeoxyglucose F 18, Gallium citrate Ga 67, Indium In 111 pentetrotide Methionine C 11, Ratiodinated zobenguane, sodium Fluoride F 18, Technetium Tc 99m Arcitumomab Merpentane.
- Colorectal diseases – Technetium Tc 99m Arcitumomab.
- Disorder of iron metabolism and absorption – Ferrous citrate Fe 59.
-Heart dieses___– Ammonia, N13, Fludeoxyglucose F18, Rubidium Rb 82, Sodium pertechnetate Tc 99m.
- Impaired flow of cerebrospinal fluid in brain – Indium In 111 pentetate.
-Lung diseases – Krypton Kr 81 m Technetium Tc 99m Albumin Aggregated, Technetium Tc 99m pentetate, Xenon Xe 127, Xenon Xe 133.
-Parathyroid disease; parathyroid cancer – Technetium Tc 99m sestamibi, Thallium chloride Tl 201.
- Pernicious anemia; improper absorption of vitamin B12 from intestine – cvanocobalamine Co 57.
- Red blood cell diseas
- Salivary gland disease – Sodium chromate Cr 51.
– Sodium pertechnetate Tc 99m.
- Spleen disease - Sodium chromate Cr 51, Technetium Tc 99m Albumin colloid, Technetium Tc 99m sulfar colloid.
- Stomach problems – Technetium Tc 99m sulfar colloid.
- Tear duct blockage – Sodium pertechnetate Tc 99m.
-Urinary bladder disease – Sodium pertechnetate Tc 99m.

**Therapeutic Radiopharmaceuticals** are radio labeled molecules designed to deliver therapeutic doses of ionizing radiation to specific diseased sites. Therapeutic application of radiopharmaceuticals have emerged from the concept that certain radionuclide possessing particulate emission such as alpha and beta radiation or low energy low range electrons posses the ability to destroy diseased tissues.

Radioisotopes used internally or externally. If the radio isotopes used externally or implants in sealed capsules in a tissues, the dose could be terminated by removal of sources. If they give internally as unsealed sources they do not stopped removal by the sources.

**RADIOCHEMICAL METHOD IN ANALYSIS:**

They are as below:

- IONIZATION CHAMBERS
- SCINTILLATION AND SEMICONDUCTOR DETECTORS
- LIQUID-SCINTILLATION COUNTERS
- BETA-EMITTING RADIONUCLIDES
- GAMMA-EMITTING RADIONUCLIDE

**IONIZATION CHAMBERS:**

An ionization chamber is an instrument in which an electric field is applied across a volume of gas for the purpose of collecting ions produced by a radiation field. The positive ions and negative electrons drift along the lines of force of the electric field, and are collected on electrodes, producing ionization current. In a properly designed well-type ionization chamber, the ionization Current should not be too dependent on the position of the radioactive specimen, and the value of the current per unit activity, known as the calibration factor, is characteristic of each gamma-ray emitting radionuclide.

The ionization current produced in an ionization chamber is related to the mean energy of the emitted radiation and is proportional to the intensity of the radiation. If standard sources of known disintegration rates are used for efficiency calibration, the ionization chamber may then be used for activity determinations between several microcuries and several hundred millicuries or more.

The upper limit of activity that may be measured in an ionization chamber usually is not sharply defined and may be limited by saturation considerations, range of the amplifier, and design of the chamber itself. The data supplied with or obtained from a particular instrument should be reviewed to ascertain the useful ranges of energies and intensities of the device.

Reproducibility within approximately 5% or less can be readily obtained in about 10 seconds, with a deep re-entrant well-type chamber. The most commonly used form of ionization chamber for measurement of the activities of radiopharmaceuticals is known as a dose calibrator.

Although the calibration factor for a radionuclide may be interpolated from an ionization chamber energy-response curve, there are a number of sources of error possible in such a procedure. It is therefore recommended that all ionization chamber calibrations be performed with the use of authentic reference sources of the individual radionuclides, as described hereinafter.

The calibration of a dose calibrator should be maintained by relating the measured response of a standard to that of a long-lived performance standard, such as radium 226 in equilibrium with its daughters. The instrument must be checked daily with the $_{226}$Ra or other source to ascertain the stability over a long period of time. This check should include performance standard readings at all radionuclide settings employed. To obtain the activity ($A_x$) of the radionuclide being measured, use the relationship:

$$A_x = \frac{R_x R}{R_n},$$

in which $R_n$ is the new reading for the radium or other source, $R_c$ is the reading for the same source obtained during the initial calibration procedure, and $R$ is the observed reading for the radionuclide specimen.

## SCINTILLATION AND SEMICONDUCTOR DETECTORS:

When all or part of the energy of beta or gamma radiation is dissipated within scintillators, photons of intensity proportional to the amount of dissipated energy are produced. These pulses are detected by an electron multiplier phototube and converted to electrical pulses, which are subsequently analyzed with a pulse-height analyzer to yield a pulse-height spectrum related to the energy spectrum of the radiation emitted by the source. In general, a beta-particle scintillation pulse-height spectrum approximates the true beta-energy spectrum, provided that the beta-particle source is prepared in such a manner that self-absorption is minimized. Beta-ray spectra may be obtained by using calcium fluoride or anthracene as the scintillator, whereas gamma-ray spectra are usually obtained with a thallium-activated sodium iodide crystal or a large-volume lithiumdrifted germanium semiconductor detector.

The spectra of charged particles also may be obtained using silicon semiconductor detectors and/or gas proportional counters. Semiconductor detectors are in essence solid-state ionization chambers, but the energy required to create an electron-hole pair or to promote an electron from the valence band to the conduction band in the semiconductor is about one-tenth the energy required for creation of an ion-pair in a gas-filled ionization chamber or proportional counter and is far less than the energy needed to produce a photon in a NaI(Tl) scintillation crystal. In gamma-ray spectrometry, a Ge(Li) detector can yield an energy resolution of 0.33% for 1.33 MeV gamma-rays from $_{60}$Co, while a 3- × 3-inch NaI(Tl) crystal can give a value of 5.9% for the same gamma-ray energy.

The energy resolution is a measure of the ability to distinguish the presence of two gamma rays closely spaced in energy and is defined by convention as the full width of the photopeak at its half maximum (FWHM), expressed in percentage of the photopeak energy.

Gamma-ray spectra exhibit one or more sharp, characteristic photopeaks, or full-energy peaks, as a result of total absorption in the detector of the full energy of gamma radiations from the source; these photopeaks are useful for identification purposes. Other secondary peaks are observed as a consequence of backscatter, annihilation radiation, coincidence summing, fluorescent X-rays, etc., accompanied by a broad band known as the Compton continuum arising from scattering of the photons in the detector and from surrounding materials. Since the photopeak response varies with gamma-ray energy, calibration of a gamma-ray spectrometer should be achieved with radionuclide standards having well-known gamma-ray energies and emission rates. The shape of the gammaray spectrum is dependent upon the shape and size of the detector and the types of shielding materials used.

When confirming the identity of a radionuclide by gamma-ray spectrometry, it is necessary to make a comparison of the specimen spectrum with that of a specimen of known purity of the same radionuclide obtained under *identical instrument parameters and specimen geometry.* Where the radionuclides emit coincident X- or gamma-radiations, the character of the pulse-height distribution often changes quite dramatically because of the summing effect of these coincident radiations in the detector as the efficiency of detection is increased (e.g., by bringing the source closer to the detector). Such an effect is particularly evident in the case of iodine 125. Among the more useful applications of gamma-ray spectrometry are those for the identification of radionuclides and the determination of radionuclidic impurities.

Where confirmation of the identity of a given radionuclide by means of a direct comparison with the spectrum of a specimen of the same radionuclide of known purity is not possible, the identity of the radionuclide in question must then be established by the following method. Two or more of the following nuclear decay scheme parameters of the

radionuclide specimen to be identified shall be measured, and agreement shall be within ±10%: (1) half-life, (2) energy of each gamma- or X-ray emitted, (3) the abundance of each emission, and (4) $E_{max}$ for those radionuclides that decay with beta-particle emissions. Such measurements are to be performed as directed in the *Identification* and *Assay* sections of this chapter.

Agreement of two or more of the measured parameters with the corresponding published nuclear decay scheme data constitutes confirmation of the identity of the radionuclide.

## LIQUID-SCINTILLATION COUNTERS:

Alpha- and beta-emitting radionuclides may be assayed with the use of a liquid-scintillation detector system. In the liquid scintillator, the radiation energy is ultimately converted into light quanta that are usually detected by two multiplier phototubes so arranged as to count only coincidence radiation.

The liquid scintillator is a solution consisting of a solvent, primary and secondary solutes, and additives. The charged particle dissipates its energy in the solvent, and a fraction of this energy is converted into fluorescence in the primary solute. The function of the secondary solute is to shift the fluorescence radiation to longer wavelengths that are more efficiently detected by the multiplier phototubes. Frequently used solvents are toluene and *p*xylene; primary solutes are 2,5-diphenyloxazole (PPO) and 2-(4′-*tert*-butylphenyl)-5-(4-biphenylyl)- 1,3,4-oxadiazole (butyl-PBD); and secondary solutes are 2,2′-*p*-phenylenebis[4-methyl-5- phenyloxazole] (dimethyl-POPOP) and *p*-bis(*o*-methylstrylyl)benzene (bis-MSB).

As a means of attaining compatibility and miscibility with aqueous specimens to be assayed, many additives, such as surfactants and solubilizing agents, are also incorporated into the scintillator. For an accurate determination of radioactivity of the specimen, care must be exercised to prepare a specimen that is truly homogeneous. The presence of impurities or color in solution causes a decrease in photon output of the scintillator; such a decrease is known as quenching. Accurate radioactivity measurement requires correcting for count-rate loss due to quenching.

The disintegration rate of a beta-particle source may be determined by a procedure in which the integral count rate of the specimen is measured as a function of the pulse-height discriminator bias, and the emission rate is then obtained by extrapolation to zero bias. Energetic alpha-particle emitters may be similarly measured by this method. Identification A radionuclide can be identified by its mode of decay, its half-life, and the energies of its nuclear emissions. The radioactive half-life is readily determined by successive counting of a given source of the radionuclide over a period of time that is long compared to its half-life.

The response of the counting assembly when employed for the decay measurement of long-lived radionuclides should be monitored with an even longer-lived reference source to assess and compensate for errors arising from electronic drift. In the case of short-lived radionuclides, when the counting period constitutes a significant fraction of the half-life of the radionuclide, the recorded count rate must be corrected to the time when the count is initiated, as follows:

$$R_t = \frac{r\lambda t}{1 - e^{-\lambda t}},$$

in which $R_t$ is the count rate at the beginning of a counting period, $r$ is the count rate observed over the entire counting period, $t$ is the duration of the counting period, is the decay constant of the radionuclide, and $e$ is the base of the natural logarithm. When $t$ is small compared to the half-life of the radionuclide under study so that $_t < 0.05$, then $(1 - e^{-}{}_t)$ approaches $t$, and no such correction is necessary.

## BETA-EMITTING RADIONUCLIDES:

Mass Absorption Coefficient Procedure— Deposit and dry an aliquot of the radioactive phosphorus 32 solution on a thin plastic film to minimize backscattering, and place it under a suitable counter.

Determine the counting rates successively, using not less than six different “thicknesses” of aluminum each between 20 and 50 mg/cm$_2$ and a single absorber thicker than 800 mg/cm$_2$, which is used to measure the background. (The absorbers are inserted between the test specimen and the counter but are placed nearer the counter window to minimize scattering.) Net beta-particle count rates are obtained after subtraction of the count rate found with the absorber having a thickness of 800 mg/cm$_2$ or greater.

Plot the logarithm of the net beta-particle count rate as a function of the total absorber “thickness.” The total absorber “thickness” is the “thickness” of the aluminum absorbers plus the “thickness” of the counter window (as stated by the manufacturer) plus the air-equivalent “thickness” (the distance in centimeters of the specimen from the counter window multiplied by 1.205 mg/cm$_3$ at 20 and 76 cm of mercury), all expressed in mg/cm$_2$. An approximately straight line results. Choose two total absorber “thicknesses” that differ by 20 mg/cm$_2$ or more and that fall on the linear plot, and calculate the mass absorption coefficient, μ, by the equation:

$$\mu = \frac{1}{t_2 - t_1} \cdot \ln \left( \frac{N_{t_1}}{N_{t_2}} \right) = \frac{2.303}{t_2 - t_1} (\log N_{t_1} - \log N_{t_2})$$

in which $t_1$ and $t_2$ represent the total absorber "thicknesses," in mg/cm$_2$, $t_2$ being the thicker absorber, and $Nt_1$ and $Nt_2$ being the net beta-particle rates with the $t_1$ and $t_2$ absorbers, respectively. For characterization of the radionuclide, the mass absorption coefficient should be within ±5% of the value found for a pure specimen of the same radionuclide when determined under identical counting conditions and geometry.

Other Methods of Identification— Other methods for determining the identity of a beta emitter also rely upon the determination of $E_{max}$. This may be accomplished in several ways. For example, (1) utilization of the range energy relationships of beta particles in an absorber, or (2) determination of $E_{max}$ from a beta-particle spectrum obtained on an energy-calibrated beta-spectrometer using a thin source of the radionuclide (see *Scintillation and Semiconductor Detectors* in this chapter).

**GAMMA-EMITTING RADIONUCLIDES:**

The gamma-ray spectrum of a radionuclide is a valuable tool for the qualitative identification of gamma-ray emitting radionuclides. The full-energy peak, or the photopeak, is identified with the gamma-ray transition energy that is given in the decay scheme of the radionuclide. In determining radionuclidic identity and purity, the gamma-ray spectrum of a radioactive substance is obtained with either a NaI(Tl) crystal or a semiconductor Ge(Li) detector.

The latter has an energy resolution more than an order of magnitude better than the former and is highly preferred for analytical purposes. The spectrum obtained shall be identical in shape to that of a specimen of the pure radionuclide, measured with the same detection system and in the same geometry.

The gamma-ray spectrum of the radiopharmaceutical shall contain only photopeaks identifiable with the gamma-ray transition energies found in the decay scheme of the same radionuclide. For low geometrical efficiencies, the areas under the photopeaks, after correction for the measured detector efficiency, shall be proportional to the abundances or emission rates of the respective gamma-rays in the radionuclide.

**REFERENCE:**


1. **S. JAVAID KHURSHID AND M. ZUBAIR SADIQ**
   Biological Quality Control Section
   Nuclear Chemistry Division
   PINSTECH, P.O. Nilore, Islamabad
2. *The International Pharmacopoeia* **(November 2008)** WORLD HEALTH ORGANISATION
3. United state pharmacopoeia national formulary – 2007
4. Fundamental of nuclear pharmacy
   Gopal B. Saha.
5. Chatwal GR: pharmaceutical chemistry inorganic
6. Block JH, Roche EB, Soine TO, Wilson CO: Inorganic Medicinal and pharmaceutical
   Chemistry.