Advances in Applied and Pharmaceutical Sciences Journal

Volume 1, Issue 2 (2017), 12-20
Available online at www.aapsj.in

Review Article

Radiopharmaceuticals and Applications: A Review

Vidya Navghire, S.R Shahi*, Pavankumar Ade, Pravin Bhalerao
*Goverment college of pharmacy opp. Goverment polytechnic osmanpura, Aurangabad-43100 (MH) India.

Article information
Received: 1 September 2017
Received in revised form: 22 October 2017
Accepted: 27 October 2017
Available online: 1 November 2017
Subject: Pharmaceutical Sciences
Branch: Pharmaceutics

*Corresponding author:
S.R.Shahi
Goverment college of pharmacy opp. Goverment polytechnic osmanpura, Aurangabad-43100 (MH) India.
Email: sadhanashahi@yahoo.com

DOI: 10.26768/AAPSJ.1.2.12-20
Quick Response Code

Abstract

Objective of writing this review article to emphasize on the Radiopharmaceuticals and highlight its application. Radiopharmaceuticals has therapeutic and diagnostic applications its radionuclides (radioisotopes) used for imaging, diagnostic purpose on the body organs depend on their radioactivity, purity & its half-life period. Their evaluation is carried out by observing their evaluation parameters particle size, pH & ionic strength particulate contamination & purity. Radioisotopes are production is done by some sources such as instruments Cyclotron, Nuclear Reactor and particle accelerator or radionuclide generator the radionuclide are identified by its half-life; nature & energy of radiation .they are applied according to their in vitro or in vivo studies in the treatment & diagnosis of diseases. this article also enlighted the techniques of estimation and future scope as well as advancement in the feild of Radiopharmaceuticals

Keywords: *Radiopharmaceuticals, Radioisotopes, imaging*

Cite this article
V Navghire, S.R Shahi, P. Ade, P. Bhalerao ,“ *Radiopharmaceuticals and Applications: A Review*“ *Advances in Applied and Pharmaceutical Sciences Journal 2017,1 (2);12-20*

Introduction

Radiopharmaceuticals, as the name suggests, are pharmaceutical formulations consisting of radioactive substances (radioisotopes and molecules labeled with radioisotopes), which are intended for use either in diagnosis or therapy or diagnosis.

Radiopharmaceuticals are unique medicinal formulations containing radioisotopes which are used in major clinical areas for diagnosis & therapy[2]

Radiopharmaceuticals are essential components of nuclear medicine practice Modality where radiopharmaceuticals are administered to patients for diagnosing, managing and treating number of diseases.

In imaging, the unique properties of γ-rays emitted from the radioactive isotopes allow the radiopharmaceutical to be traced or their distribution in target tissue imaged non-invasively, thus providing functional information of the target tissue or organ. In therapy, the β-ray energy from the radioisotope is delivered to the target tissue partially or completely to destroy the diseased tissue.

Radiopharmaceuticals are unlike conventional pharmaceuticals in many respects: the most striking feature is the property of the radionuclide, which disintegrates or decays with time, often resulting in a limited shelf life of the product. The physical half-life of the radionuclide used in radiopharmaceuticals is generally short, and hence the final preparation needs to be carried out before administration to the patient. Hence, the concept of "Hospital Radio pharmacy" unit to prepare radiopharmaceuticals has become a practice in Nuclear Medicine departments in hospitals. At the hospital radio pharmacy, a trained radio pharmacist prepares the various radiopharmaceutical formulations, tests each formulation for its quality (quality control). The formulations are then provides to nuclear medicine physician for administration into the patient for investigation or for therapy.

Radiopharmaceuticals are either ready to use, or prepared from 'cold kits' and radioisotopes from generators. Some of the hospitals synthesize the necessary ligands at the hospital radio pharmacy and formulate the radiopharmaceuticals. All are subjected to the required quality control tests, to ensure the radiological and pharmaceutical safety and efficacy in accordance with the specifications laid-down.

The use of radioactive material necessitates careful and safe handling of these products by trained and authorized personnel, in approved/authorized laboratory facility as per the guide lines of Atomic Energy Regulatory Board (AERB) of India.[1]

Definitions and Terminology:

- **Radiopharmaceutical refers to** any medicinal or pharmaceutical product, which when ready for use contains one or more radionuclide's (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. The initial unstable nuclide is referred to as the 'parent radionuclide' and the nuclide after transformation as the 'daughter nuclide'. Such a transformation is also known as 'Radioactive transmutation' or 'radioactive disintegration' or 'radioactive decay'
- **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.
- **Units of Radioactivity:** in previous days unit of radioactivity is Ci [curie] named after Madame Marie curie, and Pierre curie and pioneers they studied phenomenon of radioactivity. Now a days the international SI unit used is Becquerel (Bq) i.e. one nuclear transmission per sec. One Ci is the number of disintegrations emanating from 1 g of Radium-226, and is equal to 3.7 x 1010 Bq The time of standardization should be expressed to the nearest hour. For radionuclides with a half-life period of less than one day
- **Half-Life Period:** The time in which a given quantity of a radionuclide decays to half its initial value is termed as half-life (T1/2). [1]
- **Radionuclide purity:** The ratio, expressed as a percentage, of the radioactivity of the radionuclide of interest to the total radioactivity of the radioactive preparation is referred to as the 'Radionuclide Purity'. In the context of radiopharmaceuticals, 'Radionuclide purity' is an important quality parameter and it is mandatory that the radionuclide impurities to be within the stipulated limits. Such radionuclide impurities, arise during the radionu-

clide production, are hence, dependent on the production method route. In the context of radiopharmaceuticals, the acceptable limits for the possible radionuclides are listed in the individual monographs.

- **Isotopic carrier** is a stable isotope of the element either present or added to the radioisotope of the same element. Often, the radionuclide contains isotopic carriers and their content depends on the route/method followed for the production of the radionuclide.
- **Radiochemical purity:** The ratio, expressed as a percentage, of the radioactivity of the radionuclide of interest in a stated chemical form, to the total radioactivity of that radionuclide present in the preparation, is referred to as 'Radiochemical Purity'. In the context of radiopharmaceuticals, radiochemical purity is an important quality parameter, which needs to be within the stipulated limits. The relevant radiochemical impurities are listed with their limits in the individual monographs for each Radiopharmaceutical.
- **Chemical purity** of a chemical substance is the percentage of the chemical of interest in the specified chemical form. In the monographs on radiopharmaceutical preparations, chemical purity of the active ingredient is indicated and controlled by specifying limits on chemical impurities.
- **Specific radioactivity:** The radioactivity of a radionuclide per unit mass of the element or of the chemical form of the radioactive preparation is referred to as the 'Specific Radioactivity'; sometimes also referred as 'specific activity'.
- **Radioactive concentration:** This refers to the radioactivity of a radionuclide per unit volume of the radioactive preparation.
- **Total radioactivity:** The radioactivity of the radionuclide per unit of the dispensed formulation (vial, capsule, ampoule, generator, etc.) is the total radioactivity, which is an important parameter in dispensing and administration of the radioactive material to the patient as well as from the regulatory requirement for safe handling of the radioactive materials in a facility.
- **Kit for radiopharmaceutical preparation: It is** a set of non-radioactive reagents to be reconstituted and/or combined with radionuclides following the protocol suggested by the manufacturer for preparing the final radiopharmaceutical formulations, prior to its administration.[1].

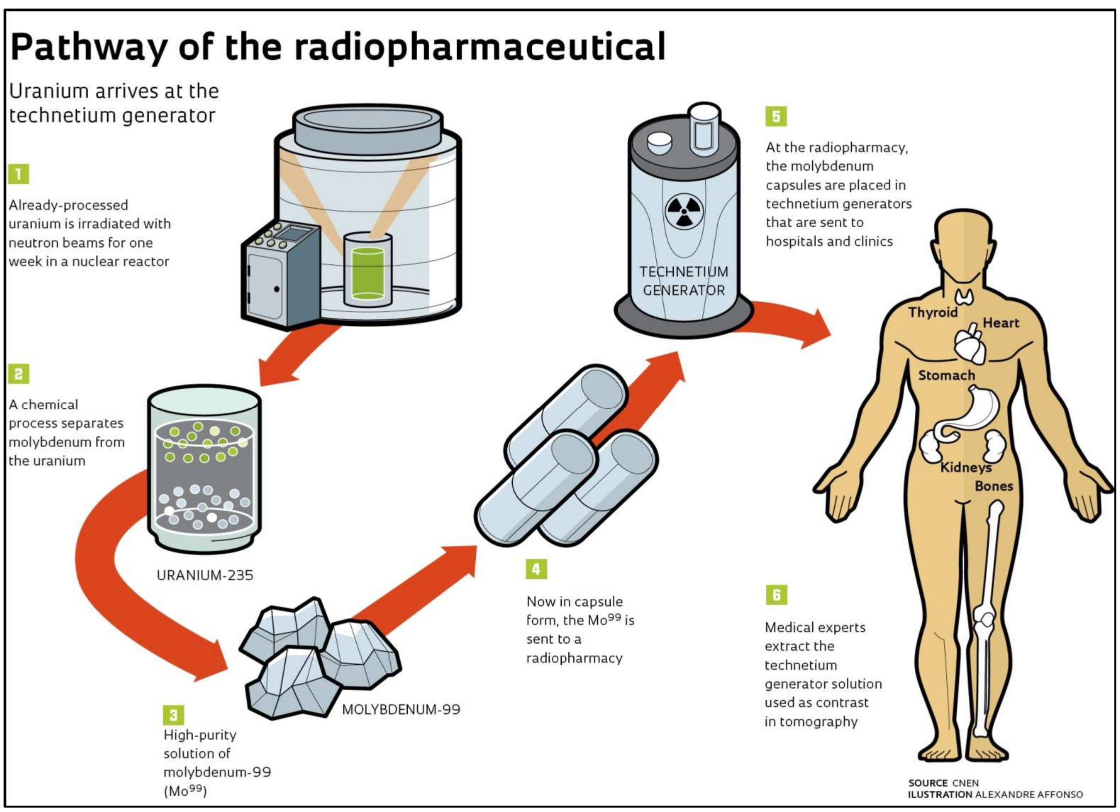

Fig.1 : Pathway for radiopharmaceuticals

Evaluation of radiopharmaceuticals products

The evaluation of the radiopharmaceutical products is important for its desired control test should be carried out for purity, potency, product identity, biological safety & efficacy. 2 type of Quality control tests are carried out for radiopharmaceutical product evaluation.

I] Physiochemical II] Biological test

I) Physiochemical test

1] Particle Size

Radiopharmaceutical consists of particulate suspension are of two type

A] The one used for the investigation of perfusion defects & include preparation such as macroaggregrated human serum albumin & microsphere.

B] The another one used for investigation of the reticuloendothelial system & includes preparation such as colloids & phytate formulation.

Number of particle & size are required for the safe & reproducible use of the product. 20 to 80 micrometer is the preferred range of the particle size. More than 100 micrometer is not suitable for the radiopharmaceutical products. Minimum 20 micrometer size is used for the radiopharmaceutical product. Not all p'ceutical colloids are true colloids. As per different formulation the mean particle of the colloidal varies widely of the same agent & different agent. Many techniques is used for the sizing over such large range. Filtration through nucleopore, electron microscopy of the sample evaporates on carbon grids, light scattering, &photon correlation. [4]

2] PH & ionic strength

Narrow range pH indicator paper are suitable if standard pH buffer are used in conjugation with the sample to give reference color to upper &lower pH limits. Universally pH meter is used for the determination of pH of radiopharmaceuticals. [5]

3] Particulate contamination

All product administered by injection should be free from gross particulate contamination. Visual examination is done through glass screen or between illuminated cross Polaroid screen provides adequate control on most small volume radiopharmaceutical. Those products which are not examined by the visual appearance (e.g. colloids, macroaggregrated, and microsphere) must be control through strict vigil which reference to cleaning of glassware & containers & purity of reagents. [6]

4] Radionuclide purity

The specified radionuclide impurity limits reflects the radiological hazards associated with the impurity, the clinical use of radiopharmaceutical & practicality of achieving better standard.

The radionuclide impurities have longer half-life than the principal radionuclide. & hence it degrades slowly that principle radionuclide & results in increased proportion of radio nuclide impurity.[7]

5] Radiochemical purity

Radiochemical purity is defined as per BP as the ratio expressed as % of the radioactivity of the radionuclide concerned that is present in the source in the chemical form compared to the total radioactivity of that radionuclide present in the source radiochemical purity is carried out with the use of the chromatographic technique such as plane chromatography, paper chromatography, thin layer chromatography, high pressure thin layer chromatography. [8]

Radionuclide Identification[8]

Radionuclide identification in it radioactive decay is at an exponential rate with a particular decay constant. Which is characteristic of each radionuclide?

The radionuclide is generally identified by its half-life or by the nature and energy of radiation or radiations emitted as prescribed in the monograph. [1]

Table 1 :-Radioisotopes and identification[8]

Radioisotopes	Identification
Indium(In_{111}) Chloride solution	It's gamma-ray spectrum is identical to that of a specimen of "In that exhibit major photo peaks having energy of 0.171& 0.245 MeV
Indium (In_{111}) Oxyquinolone solution	It's gamma-ray spectrum is identical to that of specimen of "In that exhibit major photo peak having energies of 0.171&0.245 MeV
Gallium Citrate (Ga_{67}) Injection	It's gamma –ray spectrum is identical to that of specimen of "^{67}Ga of known purity that exhibits major photo peaks having energies of 93.3,187.6 and 300.2 keV
Sodium Iodide (I_{123}) Solution	It's gamma ray spectrum is identical to that of a specimen of(^{123}I) of known purity that exhibits major photoelectric peaks having energies of 0.159 MeV

Table 2: Radioisotopes wise chromatographic techniques [8]

•	Radioisotope	Chromatographic technique	Mobile Phase	Detector
1.	Sodium fluoride injection	Liquid chromatography	Degassed solution of 0.003N sulfuric acid in H_2O	Gamma ray detector or conductivity detector
2.	Flurodopa F_{18}	Liquid chromatography	Degassed mixture of 0.1% acetic acid & menthol (97.3)	UV Detector (range - 260 to 290nm)
3.	Sodium iodide I_{123} Solution	Paper chromatography	Menthol	Collimated radiation Detector
4.	Gallium Citrate Ga_{67}	Paper chromatography	Mixture of sodium acetate ,glacial acetic acid & H_2O	Collimated radiation detector
5.	Indium In_{111} Chloride solution	Instant thin layer chromatography	Mixture of ammonium acetate & menthol (1:1)	-----
6.	Indium In_{111} capromab pendetide	TLC	0.9% NaCl solution	Scanning with suitable collimated radio chromatography strip scanner.

Radionuclide Production[9]

Radionuclide production is done by some sources such as instruments Cyclotron, Nuclear Reactor and particle accelerator or radionuclide generator these are used for source of radioisotope. there are 730 radionuclide with half-life longer than 60 minutes .with the longest half-live are 32 primordial radionuclide that have survived from creation of solar system.

Fig: 2 modern cyclotrons for production of radionuclides

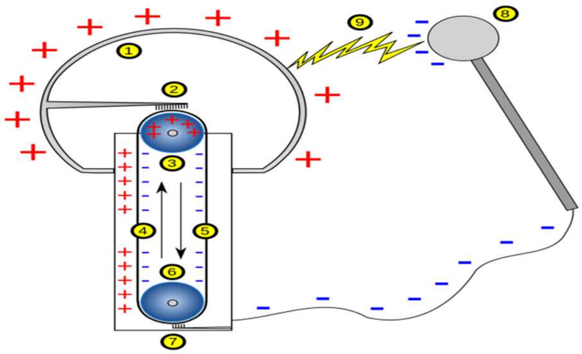

Fig.: 3 Particale accelerator / radionuclide generator

Applications of radiopharmaceuticals

Diagnostic applications of radiopharmaceuticals

For diagnosis the radiation dose is delivered to patient is maintained as low dose

For diagnosis isotopes are used as radioactive tracer

In vitro studies[7]

Radioactive materials are not administered into body of the individual but they are used as a reagent used to carry out measurement of substances in biological fluid which removed from body.

In vivo studies[8]

They are administered to body & then radioactive material measured by detection of radioactivity in body fluids or tissues.

Radioactive material are used in performing assays on biological material

In this the radioactive material are used as reagents. In carrying out measurements of substances in biological fluids removed from the body.

Imaging studies

Now a days scanning technique is develop rapidly as it give the special information about the disease condition i.e. scanning tissues and organ can be visualized and such visualization facilitates the detection of abnormalities in their function radioactive material are administered to the individual and distribution of the radioactive material in the body is measured by using imaging technique.

Cardiovascular imaging [7]

In cardiovascular imaging it provide the information of regional myocardial blood perfusion. They are administered to provide information at peak cardiac output in this the patient is stressing with output in this the patient is with even on trade mill or giving an injection of thallium chloride or Tc 99 mc is then given &then imaging is carried out technetium sodium pyrophosphate is also used for cardiac imaging in the diagnosis of acute myocardial cardiac infraction.

Lungs imaging

Lung imaging involves in the diagnosis of pulmonary emboli and evaluation pulmonary perfusion and pulmonary ventricle and to assess pulmonary function prior to pneumonectomy.The agent used is ^{99mc}Tc macro aggregates albumin. It's in vivo distribution was studied by causing it accumulation in the target organ. The radioactivity of lungs was compared with that of lungs was compared with that of the liver, kidney, stomach & heart the percentage of the accumulation was higher in the lungs than in other organ albumin.

Renal imaging

Radio isotope is used to determine renal function, renal vascular flow & morphology.

These are also used for evaluation of renal transplant patient for complication such as obstruction infraction, leakage, tubular necrosis & rejection 99mcTc- diethylenetriamio penta acetic acid & ^{131}I – Ibdunippurate are commonly used radiopharmaceuticals.

Bone imaging

Bone imaging is required in the diagnosis of benign and malignant primary & metastatic bone tumor. Also used in the fracture , arthritis ,metabolic bone disease ,vascular necrosis ,bone infracts & bone healing. Bone imaging radiopharmaceutical consists of diagnostic (primarily single photon emitters)and therapeutic agent

The therapeutic radiopharmaceutical are utilized on the basis of their particulate emission (primarily beta) & thus are treated differently than single photon bone imaging agent. For in vivo studies ^{99mc} Tc labeled polyclonal human immune gamma globulin (^{99mc}Tc-HIG) was used. It demonstrates arithmetic lesions by gamma scintigraphy.

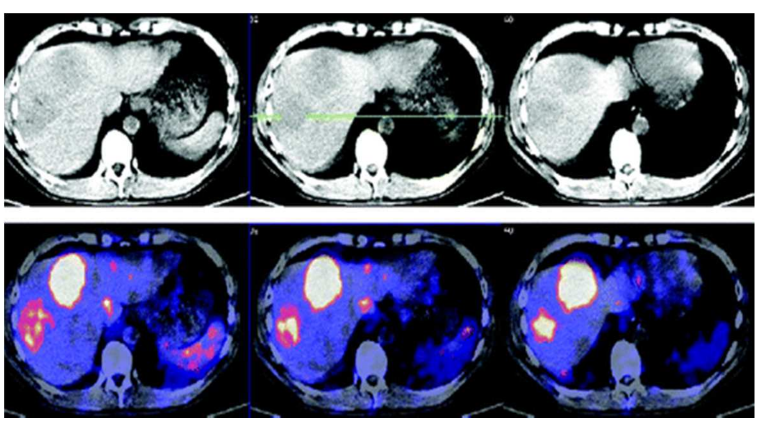

Fig.: 4 – Pediatric bone imaging

Spleen imaging

Spleen imaging is performed using ^{99mc}Tc denaturated erythrocyte Ercan & Bernay presented a new method of labeling human RBC with 99mc Tc by the use of sn-alpha D-glucose -1-phosphate for spleen imaging

Gastrointestinal imaging

Latex particle coated with either amino or carboxyl group can be efficiently labeled with 99mcTC & Used in studies.

Brain imaging

Brain imaging can be performed using radiopharmaceutical by single photon emission computed tomography (SPECT) & positron emission tomography (PET). PET & SPET are classified according to blood brain barrier (BBB) permeability .Cerebral perfusion and metabolisms receptor- binding and antigen antibody binding. The BBB SPECT agent such as Ga67 citrate are excluded by normal brain cells but enter into tumor cells because of altered BBB in comparison accumulation of radiopharmaceutical into normal tissue is relatively low. Imaging of brain tumor requires a disrupted BBB however , It is intact in the early stages of brain tumor growth when diagnosis is most critical.

Therapeutic Application Of Radio-Pharmaceuticals

Treatment of hyperthyroidism[9]

I^{131} Iodine is used extensively for the treatment of hyperthyroidism. Upon oral administration of the radionuclide approximately 60% of the radioactivity is taken up by the overactive gland the main disadvantage of the radio iodine therapy is high incidence early &late hypothyroidism making it necessary to monitor patient adequately after treatment. Although there is possibility of radiation induce cancer or genetic defects.

Treatment of thyroid carcinoma [10]

Radioiodine has been used several decades in the treatment of differentiated thyroids carcinoma, a tumor which metastases to bone, lungs & other soft tissues. Repeating radionuclide imaging with radioiodine can access response to therapy.

Treatment of neuroendocrine tumor [11]

With the development of new radiopharmaceuticals there is tendency to apply nuclear medicine therapy for malignancies of higher incidence than the one that have been treated for many year (Thyroid cancer , neuroendocrine tumor). The radio immunotherapy is showing important advance in the treatment of the medullary thyroid carcinoma, malignant lymphomas & brain tumor with potential extension to neuroblastoma therapy

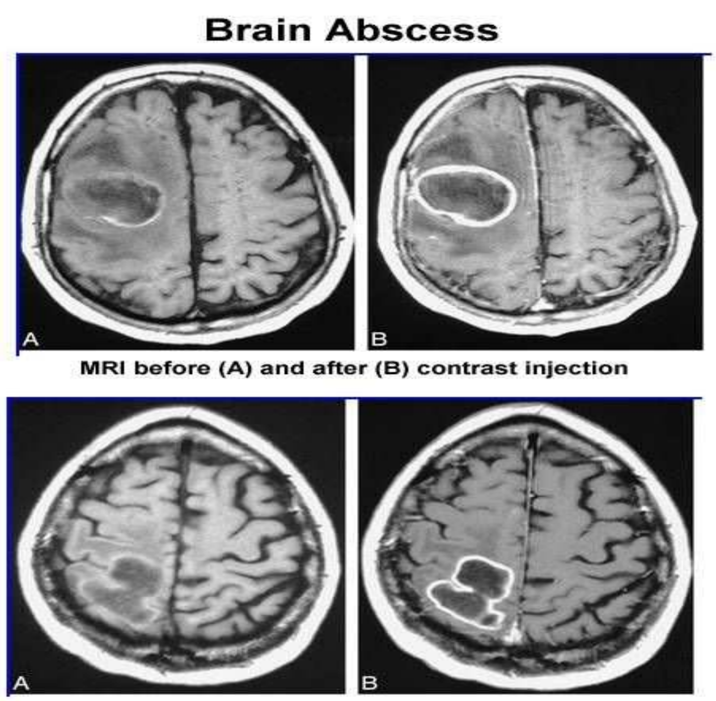

Fig 5.- Brain Imaging

Treatment of bone tumor [12]

Bone metastases are a common finding in a patient suffering from cancer of the prostate, breast, & lungs & these patient control bone pain is significant clinical problem. External beam therapy , in combination with analgesic drug remains the mainstay of treatment but the proportion of the body that can be treated is limited several of beta emitting radionuclide's in variety of chemical forms, can be used for the treatment of bone metastases. 186 Rhenium &153 Samarium are the newer agent used in the treatment other agent such as 117m strontium diethyleneamine pent acetic acid which are at an earlier stage of development will have improved therapeutic effects with the minimum myelosuppresion.[13]

Categories of radiopharmaceuticals

1. Radiopharmaceuticals have following category
2. Ready to use radiopharmaceuticals
3. Ready instant kits for preparation of Tc99 m products
4. Products requiring heating Example Distinction between radiopharmaceutical and radio chemical1[4]

Properties of ideal therapeutic Radiopharmaceutical

1. Pure beta minus emitter.
2. High target non target ratio.
3. Effective half-life equal to moderately long e.g. days .
4. Patient safety
5. Medium/ high energy.
6. Minimum radiation dose to patient and nuclear medicine personal.
7. Simple preparation.
8. Simple quality control if manufactured in house .
9. It is Inexpensive.
10. Readily available radiopharmaceutical .[14]

Examples of radioisotopes

1. Technetium -99
2. Gallium -67
3. Iodine -123
4. Rubidium -82
5. Yttrium-90 &
6. Lutetium -177 etc. [15]

Marketed formulation

1. Florodopa f-18 injection USP
2. Sodium Iodine I^{123} solution USP
3. Iodinated I^{125} Albumin injection USP
4. Indium In^{111} oxyquinoline solution USP
5. Indium In^{111} chloride solution USP
6. Technetium Tc^{99m} albumin injection USP
7. Gallium citrate Ga^{67} Injection USP
8. Technetium Tc^{99m} albumin aggregated injection USP
9. Technetium Tc^{99m} albumin colloid injection USP
10. Technetium Tc^{99m} apcitide injection USP
11. Sodium Fluoride f-18 injection USP [16]

Future scope

Numerous advances in radiopharmaceutical synthesis, quality assurance and regulatory control have occurred in recent years and are continuing to develop. Advances have been clearly observed for those radiopharmaceuticals based on positron emitters & radio halogens radioisotopes. These include radio pharmaceutics for the heart, brain & adrenal glands.
Other branching fields such as use of liquid chromatography automation and computer applications have gained a tremendous momemtum and exhibited a big leap to enter the 90's with an increasing number of applications.

When we look at a vast majority of research and development in the field of radio pharmaceutics, we can pinpoint major trends such as:

1. Development, testing, and evaluation of new tracers emphasizing receptor targeting.
2. Quality assurance as an integral feature of radiopharmaceutical production
3. Establishing protocols &regulatory measures to ensure safe and efficient production and delivery of radio pharmaceutics.
4. Setting software and hardware for production &quality control & compartmental modeling
5. Investigations and evaluation of the economic aspects of production and application of radio pharmaceutics.[21]

Conclusion

1 Radiopharmaceuticals are radioactive drugs that when used for the purpose of diagnosis or therapy, they do not elicit any physiological response.
2 They are designed to imaging and diagnosis purpose of targeted organ.
3 Radionuclides are used in nuclear medicine are mostly artificial
4 For easy & fast treatment of diseases
5 Radiopharmaceuticals are intended for human administration.
6 The specific measures & tests are used to measure their purity, identity, safety & efficacy.

7 Varieties of radionuclides have been used for their therapeutic & diagnostic purpose.
8 In the radio therapy treatment of some diseases they does not guarantee the safety of normal tissues.
9 Their administration can offers wide opportunity to treat wide spread diseases.
10 Safeguarding the patients is important.
11 Safety of the patients from the hazardous effect of radiation.

Reference

1. Introduction Indian pharmacopoeia Commission. articlewww.ipc.gov.in.
2. World Health Organization , radiopharmaceuticals final text for addition to the 4th edition 2008 international pharmacopoeia www.who.int>medicines>Radagenmono
3. USP -NP- 2008 Edition Asian Edition the official compendia of Standards. volume -1
4. Frier ,M. and wood H, Nucl Med Commun 1980,34
5. Rhodes ,B.A. ,Quality Control in Nuclear Medicines , Mosby, St Lois , 1978
6. British institute of radiology Guidelines for the Preparation of Radiopharmaceuticals in Hospitals, BIR, London, 1979.
7. Schomaker, k., Gerad, H., Gabrukostak, B. And Malija, S.,Nuklearmedezin, 1994, 33,33
8. USP-NP- 2008 Asian Edition the official compendia of Standards. volume -2
9. www.lumen.luc.edu
10. Chase,G.D,In , Gennaro .A.R. Eds, HMSO publication, London 2010 Saha G.b, In; Fundamental of Nuclar pharmacy 3rd edition, Springer Verlag New York 1992,121
11. Tubis M and water w. In; Radiopharmacy John. wiely and sons London 1975
12. https://en.m.wikipedia.org/wiki/Radionuclide
13. https://en.m.wikipedia.org/wiki/Cyclotron
14. https://en.m.wikipedia.org/wiki/Nucler generator
15. Saha G.b,In; Fundamental of Nuclar pharmacy 3rd edition, Springer Verlag New York 1992,121
16. Tubis M and water w. In; Radiopharmacy John. wiely and sons London 1975
17. Tuncay M., Calis; S kas, H.S. Eran, M.T & piskin.EJ. Microencasul , 1993 , 10, 67
18. Beirwalles, W.H.J. Hucl. Med, 1991, 18, 984
19. Valdes, olmos, P.A. Huefngel, & C.A., Bais, E, Boot, H, Toal B. & P.A., Rev. Med. Nucl , 2001,20, 547.
20. Campa, J.A. & Payne,R; Sem. Nucl , Med 1992 XXTI ,1,3
21. Atkins. H.L. ,Radiology , 1993 , 186 , 279
22. New trends in radiopharmaceutical synthesis Quality assurance & Regulatory control Edited by A.M. Emran, plenum, New York 1991.