IJMPR 2019, 3(6), 54-60

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

POSITRON EMISSION TOMOGRAPHY (PET) DRUGS

R. Swetha Sri[1]*, Dr. K. Bhavya Sri[2] and P. Soundarya[3]

[1]Assistant Professor, [2]Associate Professor, [3]Research Scholar
Department of Pharmaceutical Analysis, RBVRR Women's College of pharmacy, Hyderabad, Telangana, India.

Received on: 10/09/2019
Revised on: 30/09/2019
Accepted on: 20//10/2019

***Corresponding Author**
R. Swetha Sri
Assistant Professor
Department of Pharmaceutical Analysis, RBVRR Women's College of pharmacy, Hyderabad, Telangana, India.

ABSTRACT

PET drugs are radioactive drugs injected into patients that create images that can be read with a special camera called a PET scanner. PET images show the chemical functioning of an organ or tissue. PET drugs contain a very small amount of radioactive material, similar to the material used in other diagnostic procedures. One of the distinctive properties of PET drugs is that, because of their short half-life, they must be administered to patients within minutes or hours of being produced. Current good manufacturing practice is a minimum manufacturing/production standard that ensures the drug meets the requirements of safety and has the identity strength, quality, and purity it is supposed to have. CGMP covers items such as control of ingredients used to make drugs, production procedures and controls, recordkeeping, quality system, and product testing. 21 CFR parts 210 and 211 contain the CGMP for non-PET drugs, while proposed 21 CFR part 212 will contain CGMP requirements for PET drugs.

KEYWORDS: PET drugs, Radiopharmaceuticals, CGMP for PET drugs.

INTRODUCTION

PET is a diagnostic imaging technique for measuring the metabolic activity of cells in the human body. It was developed in the mid 1970s and it was the first scanning method to give functional information about the brain. Existence first postulated in 1928 by Paul Dirac First observed in 1932 by Carl D. Anderson.[1] PET drugs may be produced in hospitals, academic institutions, and independent commercial facilities. Positron emission tomography (PET) drug producers better understand FDA's thinking concerning compliance with the current good manufacturing practice (CGMP) regulations.[2] In some cases, the guidance provides practical examples of methods or procedures that PET drug production facilities can use to comply with the CGMP requirements.

Section 121(c)(1)(A) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) directed FDA to establish CGMP requirements for PET drugs. Concurrently with the issuance of this guidance, FDA is establishing these requirements in 21 CFR parts 212.[3] The PET drug CGMP regulation found in part 212 currently provides that for investigational PET drugs for human use produced under an investigational new drug application (IND) in accordance with part 312 and PET drugs produced with the approval of a Radioactive Drug Research Committee (RDRC) in accordance with part 361, the requirement under the act to follow CGMP can be met by compliance with part 212 or by producing such drugs in accordance with radiopharmaceuticals. When we adopted the CGMP regulation, we indicated that it would not be appropriate to permit future changes to be incorporated into part 212 without conducting notice and comment rulemaking. Since that time, we have become aware that USP has revised radiopharmaceuticals of positron emission tomography, and we are considering whether to amend the regulations to address those changes.

Principle

The concept of PET is to radiolabel a bio-compound, inject it into the patient, and then measure its bio-distribution as a function of time to determine physiologic quantities associated with the biocompound. All PET compounds are radio labelled with positron-emitting radionuclides.[4] These radio nuclides have decay characteristics that enable localization in the body. A Positron is emitted from the nucleus, travels a shorter distance, and annihilates with its antiparticle (an electron), which results in two 511 -Kev photons traveling in opposite directions.[5] After both photons are detected, the activity is localized somewhere along the line defined by the detector.

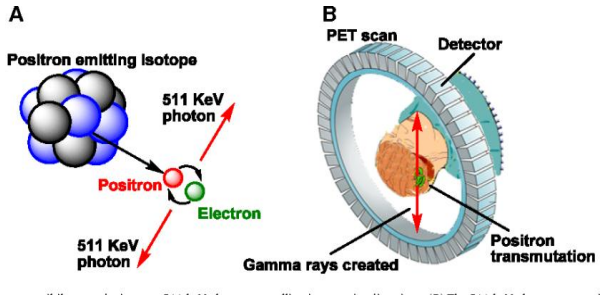

Fig. 1(A): A Positron and an electron annihilate producing two 511 keV photons travelling in detector array in the PET camera.

It describes that the positron emitter is used to mark a tracer, which is injected into a living organism. By e+e- annihilation inside the organism two 511 keV photons are produced

A PET study consists of following

- Producing radiotracers.
- Synthesizing radiopharmaceuticals from the tracers.
- Administering the radiopharmaceutical to a patient.
- Measuring the resulting radioactivity distribution in an organ of interest.
- Interpreting activity distribution as a function of physiologic parameters.

Positrons: A Positron is an anti-matter of electron it is identical in mass but has an opposite charge of +1. Positron can come from different number of sources, but for PET they are produced by nuclear decay. Nuclear decay is basically when unstable nuclei are produced in a cyclotron by bombarding the target material with protons, and as a result a neutron is released.[6] In PET the target material is chosen so that the product of the bombardment decays to a more stable state isotope by emitting a positron

Annihilation of a positron and electron The positron will encounter an electron and completely annihilate each other resulting in converting all their masses into energy. This is the result of two photons, or gamma rays. 511keV is the ideal rest state annihilation value.[7]

Tracers the radiotracer, injected into a vein, emits gamma radiations as it decays. A gamma camera scans the radiation area and creates an image.

Fluorodeoxyglucose is glucose analog.[8] Its full chemical name is 2-fluoro 2-deoxy- D-glucose commonly abbreviated to FDG.

Pet Drugs

PET drugs are radioactive drugs. PET images show the chemical functioning of an organ or tissue.[9] This imaging is useful for patients with certain conditions affecting the brain and the heart as well as in patients with certain types of cancers. PET drugs because of their short half-life, they must be administered to patients within minutes or hours of being produced. These drugs are intended for diagnostic use and are not intended to provide a therapeutic effect.

Pet Radiopharmaceuticals

Table 1: Properties of PET Radiopharmaceuticals.

Nuclide	Halflife	Tracer	Application
O-15	2min	water	Cerebral blood flow
C-11	20 min	methionine	Tumor protein synthesis
N-13	10min	Ammonia	Myocardial blood flow
F-18	110min	FDG	Glucose metabolism
Ga-68	68 min	DOTNAC	Neuro endocrine imaging
Rb-82	72 sec	Rb-82	Myocardial perfusion

Scanner Design

Detectors are 18-40 rings of crystals forming a cylindrical field of view about 15cm long that can acquire many slices of coincidence data. PET scanners used crystals with higher density& higher Z numbers due to sensitivity. Group of crystals is put together into a block.[10] Four PMT's to each block of crystal[6]. Use "electronic collimation" to detect location of annihilation event.

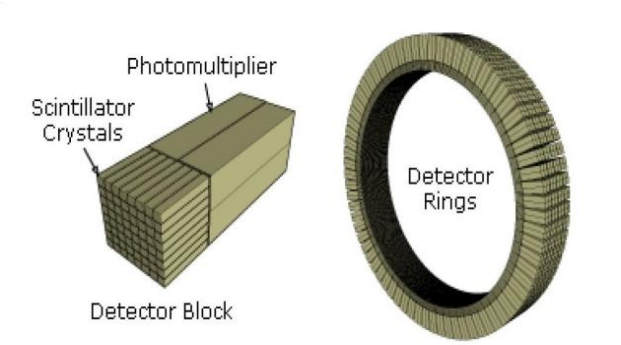

Fig. 2: Schematic view of a detector block and ring of a PET scanner.

It describes that photons are detected when they reach scintillation in the scanning device, creating a burst of light which is detected by photo multiplier tubes.

Working

Injection of short lived most commonly used is fdg (fluro-2-deoxyglucose) radioactive isotope in body. Wait till tracer gets accumulated in tissues of interest. Subject is placed in the imaging scanner. Tissue concentration is recorded with time. As isotope decays in body it releases a positron in body. on interaction with an electron it produces a pair of photons.[11] Different colors or degrees of brightness on a PET image represent different levels of tissue or organ function.

How It is performed: by a nurse or technologist will take you into a special injection room, where the radioactive substance is administered as an intravenous injection. It will then take approximately (30-90) minutes for the substance to travel through your body and accumulate in the tissue under study. After that time, scanning begins [12]. This may take 30 to 45 minutes. Some patients, specifically those with heart disease, may undergo a stress test in which PET scans are obtained while they are at rest and again after undergoing the administration of a pharmaceutical to alter the blood flow to the heart.

CGMPs for PET drugs

CGMP 21 CFR 212: According to Current good manufacturing practices the PET drug products are the minimum requirements for the methods to be used in, and the facilities and controls used for production, quality control, holding, or distribution of a safe and effective PET drug product intended for human use.[13] PET CGMP Regulations: provisions of USP chapter 823 apply when pet drugs are produced under, following:

- Investigational new drug application (IND)
- Radioactive drug research committee (RDRC)

Objectives in developing CGMP for PET drugs

- Safeguards to assure safety, identity, strength, quality and purity of PET drugs
- Quality built into production process
- Sufficiently flexible to accommodate all PET production without unreasonable regulatory burden
- Mechanism to proactively identify potential problems, eliminate them, and promote continuous improvement

Major Elements in PET drug CGMPs are

- Personnel and resources
- Quality Assurance
- Facilities and equipment
- Control of components, containers, and closures
- Production and process controls
- Laboratory controls
- Drug product controls and acceptance criteria
- Packaging and labeling controls
- Distribution controls
- Complaint handling
- Record keeping

Personnel and Resources

- Sufficient number of qualified and trained personnel to perform their assigned tasks. Facilities where few individuals are employed, one individual can be assigned to perform both production and quality assurance tasks.
- Sufficient resources including equipment, facilities and personnel to produce a quality PET drugs.

Quality Assurance

- Person or organizational element responsible for the duties relating to quality control.
- Overseas production operations to ensure that a quality PET drug is produced
- Examines and approves or rejects components, containers, closures and the finished PET drug.
- Approves or rejects procedures and/or specifications. Reviews production records for accuracy & completeness.
- Ensures that investigations have been conducted and corrective action taken.
- Approves change control.
- Oversees complaints, adverse reactions.
- It's possible for a certain part of the QA function to be at a centralized off-site location however, batch release must be signed off on-site by a responsible QA individual.

Facility and Equipment System

Equipment: clean, suitable for its intended purposes, properly installed and maintained.

Facilities: adequate to assure the orderly handling of materials and equipment, prevent mix-ups and contamination of equipment and the pet drugs.[14]

Materials System

Control of Components, Containers, and Closures

- Procedures for the handling of components.
- Establish appropriate specifications, and examine each lot upon receipt with established specifications.
- Each lot must meet all established specifications to be used in production.
- Instead of full testing, a certificate of analysis (COA) may be accepted provided the PET center establishes the reliability of test results.

Recycling of[18] O water

Establish procedure for the recycling and specification of the recycled ^{18}O water.

Production System

Production & Process Controls

- Ensure consistent and quality production
- Establish written procedures, master and batch production and control records.

- Include inspection of the production area and all equipment for suitability and cleanliness before use.
- Process verification results must be documented when the production batch is not fully verified through finished product testing. Prepare batch production and control record for each batch of PET drug produced.
- Batch record should include the critical production steps and test results
- Deviations from established procedures must be investigated and documented
- The process must be validated.

Packaging & Labeling Controls

- Packaging and shipping containers should protect against damage during storage, handling, distribution, and use.
- In part, the label should also contain the product name, strength, batch number, date/time prepared, expiration date/time.
- Operations should be controlled to prevent mix-ups.
- Labels must be legible.

Laboratory Control System

Laboratory Controls

Follow written procedures and document each laboratory test results.

- Analytical methods should be suitable, sensitive, specific, accurate, and reproducible.
- Control the identity, purity and quality of reagents, solutions and supplies used in testing procedures.
- All testing equipment must be suitable for its intended purpose and capable of producing valid results.

Program to assess the stability of a PET drug, including suitable storage conditions, use of reliable and specific test methods, and expiration dates/ times.

Drug Product Controls and Acceptance Criteria

- Sterility testing must be performed but need not be completed prior to drug product release.
  – Must begin < 30 hrs after completion of PET production.
- Establish procedures for release: – complete laboratory testing and review data
  – release authorized by designated person.
- Each batch must meet its established acceptance criteria prior to release.
  – If product does not meet acceptance criteria: reject product; conduct investigation and take action to correct any identified problems.

Conditional Release

Conditional release is permitted, if one finished product test cannot be completed due to an analytical equipment malfunction, when the following conditions are met:

– Prior history demonstrates that the final release of the product will meet the established specifications.
– The malfunctioning analytical equipment is immediately fixed or replaced.
– Product identity, purity, and specific activity are verified.
– No additional batches of product are released until the problem is corrected and the omitted finished product test is reinstated.

All other finished product acceptance criteria must be met. Document all actions that justify the conditional release of product.

Distribution Controls

Drug products should be shipped in accordance with labeling conditions.

- Establish and follow procedures if the drug is distributed or shipped.
- Keep adequate distribution records – The chain of distribution of each batch of drug product must be readily determined to permit its recall if necessary.

Complaint Handling

- Establish procedures to handle complaints pertaining to the quality and labeling, or possible adverse reactions.
  – A written record of each complaint, the investigational findings, and follow-up must be maintained.
  – A drug returned due to a complaint must be destroyed.
  – Corrective action should be taken immediately if there is reason to believe that an adulterated drug was implicated in the complaint.
- Written complaint records must include:
  – Drug name, strength
  – Batch number
  – Date and nature of complaint
  – Response to complaint
  – Findings of investigation, follow-up

Record Keeping

- Maintain records at location that is reasonably accessible.
- Keep records for 1 year from the date of drug product release.
- Records to include:
  – Composition and quality.
  – Production operations, batch records, and out-of-specification results
  – Distribution and complaints.
- Records: legible and readily available for review and copying by FDA.

PET Drug Inspection

- Pre-approval inspections-For new NDA and ANDAs
- CGMP inspection of facilities-Every 2 years, as resources & priorities allow
- District officers will have a trained investigator.

Benefits of PET

- Image information unique-high sensitivity
- Yields most useful information compared to the other imaging techniques from a pathological view.
- High spatial resolution.
- More precise, cheaper, and more esthetical than exploratory surgery.
- Can detect a disease at an earlier stage than ex CT scans or MRI.
- Result in low radiation exposure.(observed not more than any other type of imaging method)

Risks with PET

- Allergic reactions to radiopharmaceuticals may occur but are rare.
- Injection of the radiotracer may cause slight pain and redness which should rapidly dissolve.
- Expensive- due to cyclotrons needed to produce short lived radio nuclides.
- Low accessibility
- Takes time

Applications of pet

Neuroimaging

- The greatest benefit of PET is that it can show blood and oxygen flow and glucose metabolism to different tissues of working brain these measurements help in understanding amount of brain activity and allow us to know more about how brain works.
- PET is superior to all other imaging techniques because of its resolution and speed of completion.
- PET scans of the brain are used to evaluate patients who have memory disorders of an undetermined cause, suspected or proven brain tumors or seizure disorders that are not responsive to medical therapy and are therefore candidates for surgery.

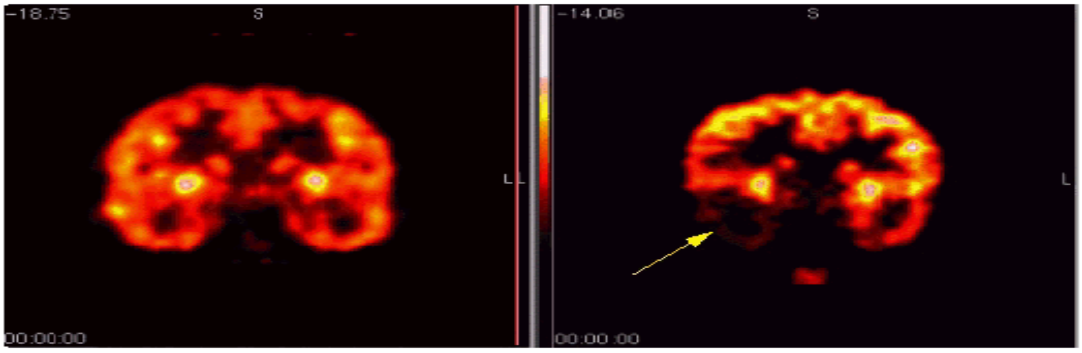

Fig. 3: PET Imaging identifies the area of the brain responsible for seizures.

The images describes that left side image is normal brain while right side image is the brain of a 9 year old female with a history of seizures poorly controlled by medication. PET imaging identifies the area (indicated by the arrow) of the brain responsible for the seizures. Through surgical removal of this area of the brain, the patient is rendered "seizure-free.

Oncology

Most widely used Application of PET. Tracer used is FDG-18. Highly accurate as tumor cells consume lot of glucose and tracer is glucose analog [15]. Also, tracer is bound in tumour cell once it got there until it decays. Thereby, giving more accurate results.

Musculo-Skeletal Imaging

One of the main advantages using PET is that it can also provide muscle activation data about deeper lying muscles as compared to other muscle studying techniques.

But there is a disadvantage also as provides no timing information, about muscle activation because it has to be measured after the exercise [16] is complete.

Heart Conditions

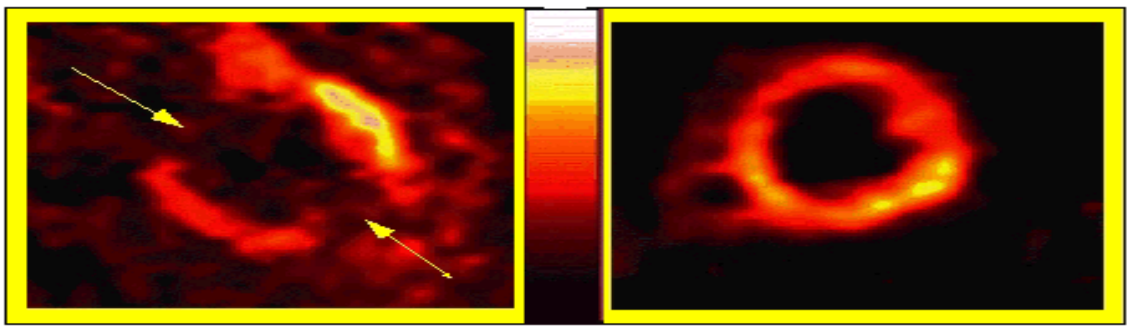

Fig. 4: PET images of heart conditions identify that arrow points to areas that have been damaged by the attack, indicating "dead" myocardial tissue.

Cancer patients

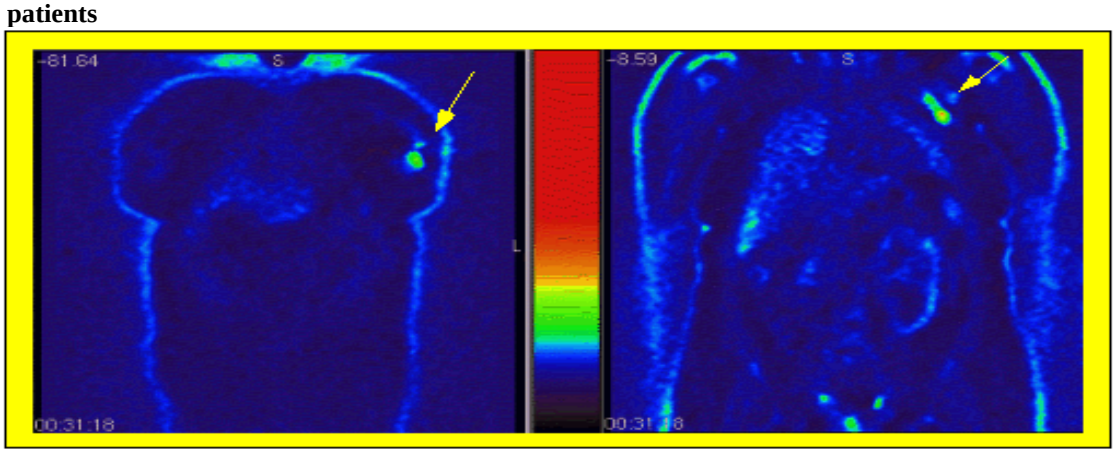

Fig. 5: PET images of cancer patients describe imaging scans reveals that a mass in the left breast that was malignant.

Brain PET scans of different addicts

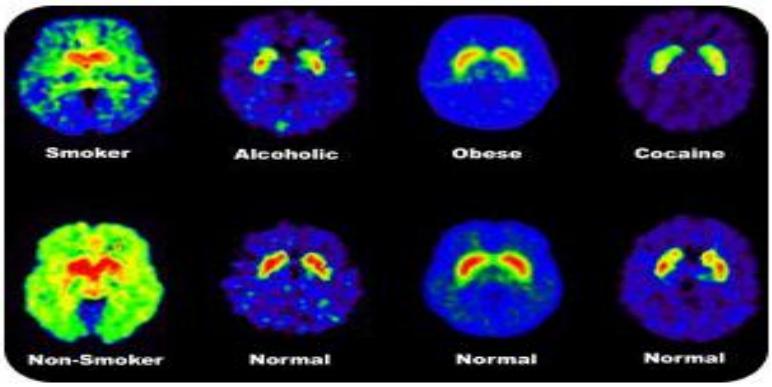

Fig. 6: PET scan of dopamine binding in brains of normal and addicted individuals.

It shows the binding of chemicals that attach to dopamine receptors. The non-addicted individuals have large numbers of receptors for dopamine.[17] The addicted persons show less binding to these receptors, indicating that fewer receptors are present. Since dopamine is somehow linked with the sense of pleasure, these data may help to bring a better understanding to the biochemical processes in drug addiction.[18]

ACKNOWLEDGEMENTS

The author would like to express her gratitude to Mrs.R.Swetha sri, Dr K.Bhavya Sri and Dr.M. Sumakanth for their guidance and reviews, grateful to RBVRR Women's College of pharmacy for help and support.

REFERENCES

1. Bailey DL, Townsend DW, Valk PE, Maisey MN, eds. Positron Emission Tomography – Basic Sciences. Springer-Verlag London Limited, 2005.
2. https://www.fda.gov/drugs/pharmaceutical-quality-resources/positron-emission-tomography -pet-drugs-proposed-cgmp-rule-and-draft-guidance-questions-and-answers.
3. PET Drugs—Current Good Manufacturing practice (CGMP); Small Entity Compliance Guide.
4. U.S. Pharmacopeia. Radiopharmaceuticals for Positron Emission Tomography — Compounding. USP 32, NF 27, 2009.
5. Mohr, P. J, Taylor, B. N, Newell Reviews of modern physics, 2008; 633–730.
6. http://en.wikipedia.org > wiki > Positron_emission_ tomography
7. L. Sodickson, W. Bowman, J. Stephenson; R. Weinstein. "Single-Quantum Annihilation of Positrons", 1970; 124(6): 1851–1861.
8. Michael E. Phelps. PET: physics, instrumentation, and scanners. Springer, 2006; 8–10.
9. Dirac, P. A. M-. "Theory of electrons and protons."*(PDF)*. *Proceedings of the Royal Society*, 1930; (801): 360–365.
10. PET/CT Scanner at Penn a First in the World".University of Pennsylvania. June 15, 2006. Retrieved February 22, 2010.
11. Kelloff GJ; Hoffman JM; Johnson B; Scher HI; et al. "Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development", April 2005; 61-85.
12. https://www.radiologyinfo.org/en/info.cfm?pg=pet.
13. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-registration-and-listing-system-drls-and-edrls.

14. https://www.snmmi.org/files/docs/PET%20Drugs%20Webinar.pdf.
15. ARSAC - Notes for Guidance on the Clinical Administration of Radiopharmaceuticals and use of Sealed Sources, March 2018; 35//
16. Oi N, Iwaya T; Itoh M; Yamaguchi K; et al. FDG-PET imaging of lower extremity muscular activity during level walking, 2003; (1): 55–61.
17. Catafau AM, Searle GE, Bullich S, Gunn RN; et al. "Imaging cortical dopamine D1 receptors using 11C NNC112 and ketanserin blockade of the 5-HT 2A receptors", 2010*;* 85–93.
18. Brownell GL, Sweet WH. Localization of brain tumors with positron emitters. Nucleonics, 1953; 11: 40.