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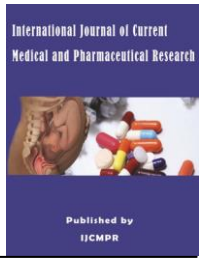

AN OVERVIEW OF PET RADIOPHARMACEUTICALS

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ABSTRACT

Introduction: In India since 2002,after the introduction of 18F-FDG for various clinical applications, different other PET radiopharmaceuticals have also been developed progressively. However, only a few of them make their place in routine clinical practices; partly because of stringent regulatory guidelines& facilities and also due to the physio-chemical properties of radionuclide itself. The most common radionuclides for PET radiopharmaceuticals include 18F, 68Ga,11C, 13N, 15O, 64Cu, and 82Rb. **AIMS and Objective**: This study aims to provide an overview of PET radiopharmaceuticals that are commonly synthesized either in-house (onsite) or in commercial distribution centers after fulfilling the regulatory and quality aspects. **Result and Discussion**: 18F radionuclide as PET radiopharmaceutical has made its place inevitable in oncology, Cardiology, and Neurology. Apart from this, various other PET radiopharmaceuticals like 68Ga, 11C, 64Cu, 13N, etc. play a vital role in the management of other malignancies like carcinoma prostate, neuroendocrine tumors, etc. PET radiopharmaceuticals are the basis for molecular imaging and their utilization for appropriate clinical indications in diseases. **Conclusion**: This review article will provide a basic understanding of various PET radiopharmaceuticals including their synthesis, properties, and clinical uses among physicians & technologists. Most of the PET radiopharmaceuticals are being used for diagnosing and treatment evaluations of various oncology and others diseases patients.

INTRODUCTION

After 1976, there was a gradually increased in PET radiopharmaceuticals, developed as the clinical introduction of 18F-FDG for various medical applications. The PET tracer plays a crucial role because it provides the basis both for image quality and clinical interpretation. It is composed of the radionuclide and the molecular vehicle which determines the (bio-)chemical properties (e.g. binding characteristics, metabolism, elimination rate).Though, few of them could be involved in routine clinical use in hospitals partly because of restrictions in regulations and facilities[(1)].

Positron emission tomography uses radioactive tracers and enables the functional imaging of several metabolic processes, blood flow measurements, regional chemical composition, and chemical absorption. The most common radionuclides for PET radiopharmaceuticals include 11C, 15O, 13N, 18F, 68Ga, and 82Rb (as mentioned in Table 1). The radiation issue and short half-life of these positron emitters result in unavoidable limitations on the manufacturing and clinical use of PET radiopharmaceuticals. Depending on the targeted processes within the living organism, different tracers are used for various medical conditions, such as cancer, particular brain pathologies, cardiac events, and bone lesions, where the most commonly used tracers are radio labeled with 18F is 18F-FDG. Oxygen-15 isotope is mostly involved in blood flow measurements, whereas a wide array of 11C-based compounds have also been developed for neuronal disorders according to the affected neuroreceptors, prostate cancer, and lung carcinomas.[(2)]

Over the last decade, the initial focus on medical imaging based on detection and diagnosis has reoriented towards prognosis, tissue characterization, and prediction of treatment efficacy. To do this, functional imaging, such as positron emission tomography (PET) has become essential in the clinical decision-making process in various fields of medicine [(3)]. Moreover, hybrid imaging, combining PET with computed tomography (CT) or magnetic resonance imaging (MRI), has increased the diagnostic accuracy of PET by the benefit of the morphological information obtained by the CT and MRI scans and the implementation of attenuation correction. PET represents a quantitative imaging tool that appears to surpass the other nuclear technique. However, the answer to the highly debated question of which modality will monopolize nuclear imaging technologies remains unsettled[(4)]. Traditionally, when compared with older modalities, PET technology provides better image resolution, less attenuation (due to higher photon energy) and scatter artifacts, and, consequently, superior diagnostic capabilities. Two of the most important advantages of PET are represented by PET's higher sensitivity and more robust and flexible tracers, making PET a versatile and powerful tool for clinical and research applications. These advantages, however, come with a high-cost burden that limits the availability of PET imaging. Most positron-emitting

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radioisotopes have short half-lives and require in-house cyclotron production [5].

RESULTS AND DISCUSSION

PET is a powerful imaging modality, which gives us quantitative information on the bio-distribution of positron-emitting labeled radiopharmaceuticals in the body. Positrons (β+) are positively charged beta particles. They are emitted when the atom is proton enriched. A positron has only a transient existence. The PET is based on the coincidence detection of the two photons. Coincidence detection is a powerful method enhancing the sensitivity and dynamic-imaging capabilities of PET. PET camera systems contain a ring of detectors that encircles the patient [6].

Four positron-emitting radioisotopes are considered the biologic tracers, carbon11, nitrogen-13, oxygen-15, and fluorine-18. 11C, 15O, and 13N are referred to as the fundamentals of life. They can be easily substituted directly into bio-molecules without changing the properties of the molecule. As 18F is not a normal constituent of biological molecules but it can often be substituted for a hydroxyl group as in the case of deoxyglucose or can be substituted for a hydrogen atom in a molecule or placed in a position where its presence does not significantly alter the biological behavior of the molecule. Currently, there are four PET radiopharmaceuticals officially recognized by the FDA: sodium fluoride (Na18F) for bone imaging, rubidium chloride (82RbCl) for assessment of regional myocardial perfusion in the diagnosis and localization of myocardial infarction, 18F-FDG for identifying the regions of abnormal glucose metabolism and primary and metastatic malignant diseases and 13N-NH3 for assessment of myocardial blood flow. 18FDG is currently the most widely used PET radiopharmaceutical in clinical oncology in addition to its clinical applications in cardiology and neurology. The application of PET in clinical oncology is increasing since many molecular targets relevant to cancer can be labeled with positron emitter radionuclides [7].

Table 2 List of FDA-approved PET radiopharmaceuticals

S.N.	Radionuclide	Radiopharmaceuticals
1	18F	18F-FDG, 18F-FCholine, 18F-FDOPA, 18F-FET, 18F-FLT, 18F-NaF, 18F-FMISO
2	68Ga	68Ga-Citrate, 68Ga-DOTA-TOC
3	11C	11C-CO,11C-Methionine, 11C-Flumazenil, 11C-Spiroperidol 11C-Raclopride, 11C-Sodium Acetate
4	13N	13N-NH3
5	15O	15O-CO, 15O-H2O
6	82Rb	82Rb-Rubidium chloride

QC procedure of PET radiopharmaceutical is usually very critical and very important since it is synthesized every day or is small-scale "prepared "in the radiopharmacy laboratory of a hospital[8]. A typical QC program of a PET radiopharmaceutical is involved from radionuclide production to final product release and a series of QC tests for PET radiopharmaceuticals include:

1. Appearance, by visual assessment,
2. pH determination,
3. Radionuclidic identification, by gamma-ray spectrometry or half-life measurement,
4. Radionuclidic purity, by gamma-ray spectrometry,
5. Chemical purity, by high-pressure liquid chromatography (HPLC) or by thin-layer chromatography (TLC),
6. Radiochemical purity, by HPLC with a radioactivity detector or by TLC with a radioactivity scanner;

Table1 Main Characteristics of common positron-emitting radioisotopes.

S.N.	Name of radionuclide	Half-Life	ß + (%)	Max Eß (MeV)	Max ß+ range (mm	Methods of Production
1	18F	110 min	97	0.635	2.4	Cyclotron
2	68Ga	68 min	88	1.9	8.2	Cyclotron/Generator
3	11C	20 min	99	0.96	4.1	Cyclotron
4	15O	123 sec	100	1.19	5.1	Cyclotron
5	13N	10 min	100	1.72	7.3	Cyclotron
6	82Rb	78 sec	85	3.35	14.1	Cyclotron

PET Radiopharmaceuticals

18F-Labeled Compounds

Subsequently, 18F is more stable as a radioisotope, its labeling has been the most widely used option in the manufacture of PET radiopharmaceuticals. Nevertheless, due to the higher electronegativity of the F atom (4.0) compared with the H atom (2.1), 18F labeling exhibits a great impact on the vehicle molecule's physicochemical properties. Moreover, the C-F bonds are more stable (in vivo) and stronger than the C–H bonds. Therefore, the inclusion of F in the biological molecule structures implies an extension of their half-lives within the organism, affecting the molecules' metabolization, biodistribution, and protein-binding kinetics. The gold standard PET radiopharmaceutical, the 18F-FDG compound, is being taken up by the cancerous cells trusting on the enhanced metabolic and glycolytic rates inside the intracellular matrix.

18F-FDG

Since its synthesis in 1976, 18F-FDG has been the most widely used radiotracer for PET studies in neuroscience, cardiology, and oncology as mentioned in Table 3(82-83). After FDA approval in 1997, the 18F-FDG PET-CT scanner became an established imaging tool in the clinical assessment of many neoplasms, as well as non-malignant diseases including dementia, myocardial ischemia, inflammation, and infection (9-10).

18F-FDG PET has become an established modality in the management of many cancers. It can be used for initial treatment strategy planning, like baseline staging- in lymphomas, and lung cancers, or for subsequent treatment strategy, as a follow-up of treatment in Head and neck tumors, pancreatic tumors, oesophageal cancers, etc. It is one-stop-shop imaging to look for any distant metastasis and can upstage or downstage the tumors with high sensitivity and negative predictive value. Radiotherapy planning is also

Table 3 Summary of the clinical utility of 18F-FDG

Sl No.	Discipline	Diseases	Application
1	Oncology	Tumour Evaluation	Differentiate recurrent/residual tumor from necrosis
		Tumour Staging	Malignant vs. benign. Lung nodules, primary breast and colon cancers.
		Tumour Monitoring	Response to therapy
		Tumour Localization	Metastases, abnormal sites
2	Neurology	Epilepsy	Pre-surgical evaluation for epileptogenic foci (85–90% accuracy).
		Alzheimer's Disease	
3	Cardiology	Myocardial Viability	Assessment of myocardial viability before cardiac surgery
		Identify high-risk patients	Select patients who will benefit from bypass
4	Infection and Inflammation	Orthopedic infections	
5	Psychiatry	Schizophrenia, Depression	

assisted by FDG-PET-CT which ensures targeted therapy and protects the normal tissues from its harmful effects. Where appropriate to support qualitative findings, specific measures including standardized uptake values (SUV), metabolic tumor volume and lesion dimensions should be included.

18F-FEDORA

Dihydroxyphenylalanine (DOPA) has been known as an intermediate in the catecholamine synthesis pathway. One of the 18F-radiolabeled analogs, 3,4-dihydroxy-6-18F-fluoro-phenylalanine (18F-DOPA), was first reported as a PET tracer for imaging pre-synaptic dopaminergic functions in 1983. The utility of 18F-FDOPA for the visualization of various peripheral tumor entities via PET can be attributed to the up-regulation of amino acid transporters in malignant tissues due to an often increased proliferation. 18F-FDOPA has shown diagnostic advantages in the imaging of neuroendocrine cell-related malignancies like neuroendocrine tumors (NETs), pheochromocytoma, pancreatic adenocarcinoma, and neuroblastoma (NB) regarding diagnostic efficiency and sensitivity (11-21).

18F-FET

Na+ -independent system L amino acid transporters (LATs) preferentially transport amino acids with large neutral side chains, including L-leucine, L-phenylalanine, and L-tyrosine. O-(2-18F-fluoroethyl)-L-tyrosine (18F-FETbelongs to the class of large neutral amino acids, which are transported via specific amino acid transporters, especially LATs. Though data today still do not reveal which transporter(s) are responsible for 18F-FET accumulation in cells, 18F-FET has been well known for its high uptake in brain tumors and its potential for grading tumors, particularly gliomas. Summarily, 18F-FET has been well-investigated in differential diagnosis, grading, prognostication, treatment response assessment, and differentiating pseudo-progression from non-specific post-therapeutic changes (22-29).

18F-FLT

Cellular proliferation plays an important role in cancer and has been an important imaging target of PET radiopharmaceuticals, especially with the aim targeting of DNA synthesis. 18F-fluorothymidine 18F-FLT, also known as 18F Alovudine) has been designed with intracellular trapping of its phosphorylated metabolite within cells. Up to now, 18F-FLT has been widely investigated in oncologic settings comprising tumor detection, staging, restaging, and response assessment to treatment and 18F-FLT imaging has several clinical advantages including non-invasive procedure, three-dimensional tumor images, and simultaneous detection of multiple tumor sites. Also, 18F-FLT is capable to evaluate tumor heterogeneity in day-to-day practice (30-35).

18F-FMISO

Hypoxia means insufficient oxygen availability of a cell occurring. Hypoxia is an important prognostic indicator of response to either chemotherapy or radiation therapy in cancer management. Hypoxia is also an independent factor for predicting the metastases tendency of a tumor cell, because of its enhancement in DNA mutations of atypical cells and further appearance of more aggressive cells. Consequently, 1-(2-hydroxy-3-[18F] fluoropropyl)-2-nitroimidazole (18F-MISO) is the most established agent for assessing hypoxia and has been used for cancer imaging over the past 30 y for glioblastoma, non-small-cell lung cancer, and head and neck tumors. In addition, the high accuracy of 18F-MISO PET imaging for determining the duration of survival without relapses and for predicting the radiotherapy efficiency in patients with malignant tumors of various localizations has been reported. Furthermore, the prognostic potential of 18F-FMISO for the therapeutic tumor oxygenation status has been confirmed for glioblastoma, head and neck cancer, lung cancer, breast cancer, pancreatic cancer, gynecologic cancers, cervical cancer, and sarcoma (36-44).

18F-NaF

The bone is the most common place of tumor metastases next to the lung and liver. Therefore, an early and accurate diagnosis of metastatic bone diseases thus plays an important role in the establishment of an adequate therapeutic strategy. 18F-Sodium fluoride was introduced in 1962 and approved by FDA in 1972. 18F-NaF is a highly sensitive bone-seeking PET radiopharmaceutical. The clinical use of 18F-NaF keeps increasing worldwide. Additionally, uptake of 18F-NaF reflects blood flow and bone remodeling, and 18F-NaF has been proposed for use in the detection of benign and malignant osseous abnormalities that also allows the regional characterization of lesions in metabolic bone diseases (45-51).

68 Ga-citrate

In addition to war and famine, the bacterial infection has still been one of the major worldwide causes of human morbidity and mortality for centuries. Because of the trapping of gallium in the extra vascular compartment for inflammatory or infectious sites with the increased capillary permeability, and

the iron-like binding characteristics in bacterial siderophores and activated lactoferrin in neutrophils, gallium is thought to be indirectly uptaken by macrophages or directly uptaken by bacteria. Thus, 68Ga-Citrate) has been used for clinical imaging of infection and inflammation since 1984. The utilities of 68Ga-Citrate include the monitoring of osteomyelitis, diskitis, intraabdominal infection, tuberculosis, and interstitial nephritis, as well as the localization of infection in patients with cellulitis and abscesses (52-55).

68 Ga-DOTA-TOC

NETs arose from neuroendocrine cells and are slow-growing tumors with year-by-year increased incidence rate and 75% of overall 5-years survival, which is strongly dependent on the stage and grade of the tumor. Because NETs have been known for their unique overexpression of somatostatin receptors (SSTrs) on tumor cells, SSTr-targeting PET radiopharmaceuticals provide a promising and useful approach for both diagnostic imaging and further peptide receptor radionuclide therapy (PRRT), such as 68Ga-labeled DOTA-(Tyr3)- octreotide acetate 68Ga-DOTA-TOC). Because octreotide is a subset of the amino acid in somatostatin and has been demonstrated to avidly bind to SSTr. 68Ga-DOTA-TOC has been recognized for its affinity toward both the type 2 somatostatin receptor (SSTr2) and the type 5 somatostatin receptor (SSTr5). Also, 68Ga-DOTA-TOC was the first PET radiopharmaceutical to clinically localize to NETs in 2001 and has been widely used in Europe and several other countries to assist the therapy planning and accurate diagnosis of NETs patients. In addition, 68Ga-DOTA-TOC is valuable for neuroectodermal tumors, Hurthle cell thyroid carcinoma, prostate cancer patients with bone metastases, and autoimmune thyroid diseases like Graves' disease and Hashimoto's disease (56-65).

82Rb-Rubidium Chloride

Just like previously described 13N-NH3 and 15O-H2O, 82Rb-Rubidium chloride (82Rb-RbCl) has been reported for a directly proportional relationship between its uptake and MBF since 1954. In addition, several studies have demonstrated the good diagnostic accuracy of 82Rb-RbCl in the monitoring of cardiac flow. Subsequently, the 82Sr-82Rb generator (CardioGen-82®) of Bracco Diagnostics has been approved by FDA for clinical cardiac imaging since 1989. Therefore, the production and administration of 82Rb-RbCl can be well coordinated with the 82Sr-82Rb generator in the clinic, although a short half-life (78 sec) of 82Rb. In brief, the clinical advantages of 82Rb-RbCl cardiac imaging include its capacity to accurately quantify MBF and low delivered radiation exposure for a rest/stress test resulting from its very short half-life (66-69)

11 C-Labeled Compounds

The 11C radionuclide emits maximum energy of 960 keV and has a half-life of only 20.4 min. The substitution of the carbon with a positron-emitting isotope in biological structures makes possible the development of specific labeled compounds, enforcing identical biochemical and pharmacological/ pharmacokinetic properties to those of the natural molecules (70-71). The short radioactive half-life of 11C involves that the radiopharmaceuticals labeled with this radionuclide do not require substantial radiation exposure, and allows the conduct of multiple studies for a short time interval and in the same individual. In addition, even though carbon-11 has a short half-life, it is also long enough for synthesis and purification. However, due to its radioactive decay, the radiosynthesis time should be kept as short as possible (72). The manufacture of 11C-labeled compounds requires the availability of a cyclotron facility near the hospital where the study is to be performed since it must be developed on-site at the time of use (73). Carbon-11 decays to stable boron-11 mostly by positron emission (99.79%) and, to a lower extent, by electron capture (0.21%). Carbon-11 can be produced with a high molar activity in the range of 40–750 GBq/µmol at the end of synthesis (74). Since acetate is an essential substrate in cell energy and is quickly metabolized into acetyl-CoA in human cells, another salt vector-based compound is 11C-acetate [60] widely used for general cancers (75). The tracer was employed in urological malignancies, renal cell carcinoma, and bladder cancer. Moreover, several studies reported that 11C-acetate PET has also been considered and used in other types of malignancies (76), such as lung carcinomas and brain tumors, and that this tracer can detect rare tumors (e.g., multicentric angiomyolipoma of the kidney, thymoma, and cerebellopontine angle schwannoma). In the context of prostate cancer, 11C-acetate cannot accurately distinguish between benign prostatic hyperplasia and prostate cancer, presenting comparable uptake in both conditions. In contrast, other studies reported higher uptake affinities of 11C-acetate in tumor cells than in normal prostate tissue. However, potential false-positive uptakes might also account for the inflammatory effects within the cancer cells. In 2012, Schöder *et al*. supported these findings due to the large number of false-positive lymph nodes observed in their study, generated by chronic granulomatous disease (CGD). For the assessment of pelvic lymph nodes' involvement, several studies reported both acceptable sensitivity (68%) and specificity (78%) of 11C-acetate uptake or lower patient-based sensitivity of only 38% for lymph node detection. Intriguingly, the other two studies reported 11C-acetate as a suitable predictor of lymph nodes' involvement [68] and a pelvic lymph nodes detection with higher sensitivity (90%) and specificity (67%). As a predictive biomarker, 11C-acetate uptake was associated with higher prostate-specific antigen velocities. Last but not least, a study conducted by Spick *et al*. showed comparable conventional bone scans and11C-acetate PET on patient-based analysis, suggesting that PET imaging using this tracer can accurately assess distant (bone) metastatic involvements. Another small-molecule-based radiotracer, known as 11C-erlotinib, is heavily used nowadays in PET scans for lung carcinomas and colorectal cancer. In 2016, Bahce *et al*. studied the effects of erlotinib (the medication used to treat non-small-cell lung and pancreatic cancers) treatment on 11C-erlotinib uptake in lung cancer patients. Five years later, Petrulli and coworkers showed that, among subjects with non-small-cell lung cancer (NSCLC) and various epidermal growth factor receptor mutations, the kinetic properties of the tracer varied substantially. In addition, they also implemented a novel scanning protocol that highlighted the pronounced heterogeneity of (non-small) CLC and its impact on 11C-erlotinib (77-83).

CONCLUSION

With the progressive development of imaging modality, more and more pharmaceutical industries and hospitals worldwide have paid attention to the clinical potential of emerging PET radiopharmaceuticals. Though, of the special characteristics of PET radiopharmaceuticals, current pharmaceutical regulations are probably inapplicable and would be a hurdle for clinical

use of PET radiopharmaceuticals in most countries. Thus, allpharmacopeia must work together for the betterment of PET radiopharmaceuticals in the future.

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