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REVIEW ARTICLE

The use and importance of liposomes in Positron Emission Tomography

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Abstract:
Among different imaging modalities, Positron Emission Tomography (PET) gained importance in routine hospital practice depending on ability to diagnose diseases in early stages and tracing of therapy by obtaining metabolic information. The combination of PET with Computed Tomography (CT) forms hybrid imaging modality that gives chance to obtain better images having higher resolution by fusing both functional and anatomical images in the same imaging modality at the same time. Therefore, better contrast agents are essentially needed. The advance in research about developing drug delivery systems as specific nanosized targeted systems gained an additional importance for obtaining better diagnosis and therapy of different diseases. Liposomes appear to be more attractive drug delivery systems in delivering either drugs or imaging ligands to target tissue or organ of diseases with higher accumulation by producing in nano-scale, long circulating by stealth effect and specific targeting by modifying with specific ligands or markers. The combination of positron emitting radionuclides with liposomes are commonly in research level nowadays and there is no commercially available liposome formulation for PET imaging. However by conjugating positron emitter radionuclide with liposomes can form promising diagnostic agents for improved diagnosis and following up treatments by increasing image signal/contrast in the target tissue in lower concentrations by specific targeting as the most important advantage of liposomes. More accurate and earlier diagnosis of several diseases can be obtained even in molecular level with the use of stable and effectively radiolabeled molecular target specific nano sized liposomes with longer half-lived positron emitting radionuclides.

Keywords: Target imaging with liposomes, drug delivery systems, Positron Emission Tomography (PET), liposomes for PET, applications of PET radiopharmaceuticals

Introduction

PET is a considerably new nuclear medicine imaging technique supplying 3 dimensional images of the map of body functions and metabolism. PET is a desirable technique depending on the utilization of analogues of naturally existing elements as radionuclides. Generally short half-lived positron emitting radionuclides are used in PET imaging which is released from a radioisotope and then collides with an electron and composes two photons having 511 keV energy of each. When a positron is emitted, it travels some mm range and looses its energy by collisions with electrons, then annihilates and produces simultaneous emission of a pair of γ-rays at almost 180 degrees (Saha, 2004; Bailet et al. 2005).

A schematic representation of positron emission in PET has been shown in Figure 1 (Boellaard, 2007).

When two photons move to opposite directions, detectors can detect them in turn and obtain data. While many detectors can be used for PET, bismuth germanate (BGO) is the most commonly used one. PET uses multiple detectors distributed in two to eight circular rings around the patient. All counts are acquired simultaneously from different slices over 360° angles around the patient in a 64 × 64-pixel, 128 × 128-pixel, or higher pixel matrix in a computer. For reconstruction of images, these data are processed and activity distribution in each slice can be observed (Saha, 2004, Ahluwalia, 2000; Wagner, 1995; Zimmer et al. 2003).

The first commercial PET scanner was made in 1970s in medical field. Fluor-18-[2-Fluoro-2-DeoxyGlucose] (^{18}F-FDG) was the first PET radiopharmaceutical administered to the patients in 1976. In the middle of 1980s, it

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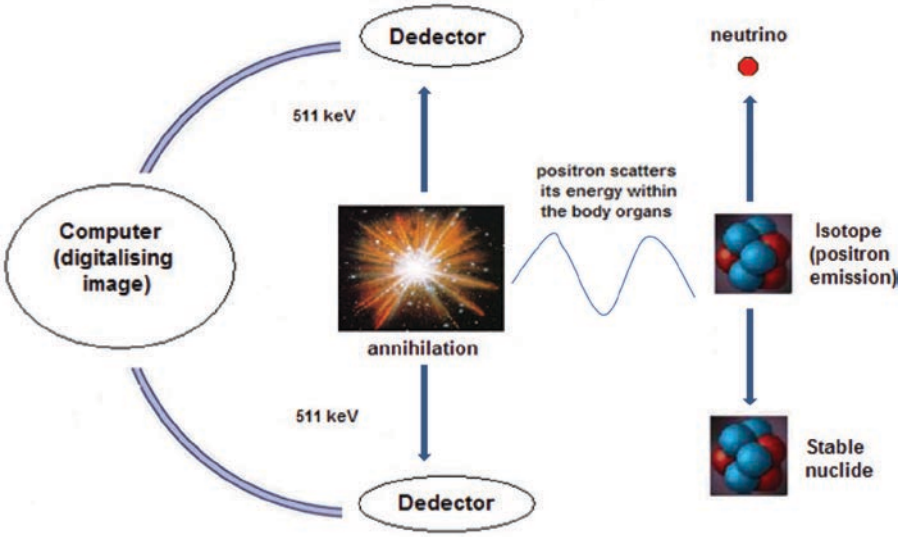

Figure 1. Positron emission in PET (Boellaard, 2007).

was mainly used for research. Commercial PET cameras having better resolution are served to market, nowadays. Due to short half-life of many positron emitter radionuclides, cyclotrons should be near the research centers or hospitals. Improving of smaller and self-shielded cyclotrons may supply PET imaging in many PET centers. Nowadays, microPET is constructed that is small enough for a rat or mice to wear on its head while walking around which is special for brain imaging. This allows animals to be scanned without exposing the effects of anesthesia for academic and pharmaceutical research (Bailey et al. 2005; Ahluwalia, 2000; Wagner, 1995).

In recent years, different from conventional imaging modalities such as γ-scintigraphy, CT, magnetic resonans imaging (MRI) and single photon emission computed tomography (SPECT), the combination of PET or SPECT with CT or MRI in a single unit supplies the combination of anatomical and functional images for better diagnosis and less background noise that is called hybrid imaging systems. Another advantage of these systems is the obtaining of these two images at the same time interval and in single imaging protocol and by this way more accurate results were acquired depending on lesser movement of the patient. First PET/CT scanning was performed in 2000. The combination of PET/MRI is not common nowadays, especailly in clinics. Presently, only head and brain can be imaged for research generally. The world's largest PET/MRI device was constructed in Julich Institute of Neurosciences and Biophysics in 2009. Although PET/MRI has quite high resolution, high magnetic field caused by MRI on PET detectors limits its usage (Saha, 2004; Wagner, 1995).

Although PET imaging is a simple, painless and rapid non-invasive process, some patients especially having heart diseases or claustrophobia may have stress when they lie inside PET device. Patients should not be fed for a few hours before administration of the radiopharmaceutical in order not to affect the glucose uptake by organs (Delbeke et al. 2006). Images can be acquired 30-90 min after the administration of the radiopharmaceutical (Ahluwalia, 2000; Miller et al. 2004).

Most commonly used radionuclides in PET imaging are ^{11}C ($t_{1/2}$ = 20 min), ^{13}N ($t_{1/2}$ = 10 min), ^{15}O ($t_{1/2}$ = 2 min) and ^{18}F ($t_{1/2}$ = 110 min). Apart from these commonly known radionuclides ^{94m}Tc, ^{68}Ga, ^{64}Cu, ^{86}Y, ^{76}Br, ^{89}Zr, ^{124}I and ^{89}Zr are other PET radionuclides that can be especially used for radiolabeling of mAb for imaging antibodies depending on their relatively longer half-lives. ^{94m}Tc and ^{64}Cu may have radionuclidic impurities after generation. ^{94m}Tc, ^{68}Ga, ^{64}Cu, ^{86}Y and ^{124}I require enrichment of target material causing an increase in costs. ^{18}F, ^{68}Ga, ^{64}Cu, ^{86}Y and ^{89}Zr need indirect labeling methods while ^{94m}Tc, ^{124}I and ^{76}Br can be directly coupled to mAb. Different from other positron emitters, ^{68}Ga can be easily produced from a generator which is a cheaper process and it can also be used for research purposes frequently. (Wagner, 1995; Miller et al. 2004; Verel et al. 2005). These commonly used radionuclides are administered after binding some normal body components like glucose, water or ammonia. ^{18}F-FDG, ^{18}F-Sodium Floride, ^{18}F-Fluorodopa, ^{18}F-Fluorotimidin (FLT), ^{15}O-H_2O, n-^{15}O-Butanol, ^{13}N-Amonnium, ^{11}C-Sodium Acetate, ^{11}C-Flumazenil, ^{11}C-Methylspiperon (MSP), ^{11}C-L-Methionine, ^{11}C-choline, ^{11}C-acetate, ^{11}C-Raclopride, ^{82}Rb-Rubidium Chloride are some of PET radiopharmaceuticals that are used for different objectives (Wagner, 1995; Miller et al. 2004; Verel et al. 2005).

Advantages of PET

As a functional imaging modality, PET has some advantages when compared with conventional nuclear medicine imaging techniques. These advantages can be listed as (Saha, 2004; Ahluwalia, 2000; Wagner, 1995; Zimmer et al. 2003);

The acquisition of quantitative information about the diseases.

The availability of radiolabeling of many molecules with ^{18}F or ^{11}C. ^{18}F is a bioisosteric substitute for hydrogen or hydroxyl groups.

The radiolabeled molecules do not change its biochemical or pharmacological characteristics after β^+ labeling depending on the isotopes being a part of the biological structure.

It has higher sensitivity with sub-picomolar detection. High specific radioactivity can be obtained with tracer doses. PET can detect small lesions and by this way it can improve tumor detection and localization by 25% by differentiating metastases in very early stages.

PET detectors do not need any collimator.

Molecular and functional data can be obtained.

Due to the better images acquired by PET, the results of preclinical studies mainly correspond to the results of clinical studies.

The use of PET radiopharmaceuticals in different medical fields

PET imaging gives an opportunity to nuclear medicine specialists to measure the abnormal molecular cell activity in several diseases like cancer, brain and heart disorders by the use of positron emitting radiopharmaceuticals (Wagner, 1995; Miller et al. 2004; Silindir et al. 2008).

Oncology

Nowadays oncologic PET screening involves 90% of all PET screenings. It is possible to define cancers, metastases and treatment evaluation by PET. PET can characterize benign or malign character of tumor correctly and diagnose metastases early (Kumar et al. 2003). ^{18}F-FDG can be used in the diagnosis and evaluation of outcome prediction and disease extension in several tumors such as small cell lung cancer (Arslan et al. 2011), head and neck canncers (Kondo et al. 2011), extranodal lymphoma (Ilica et al. 2011), cervical carcinoma (Cetina et al. 2011), colorectal tumors (Peng et al. 2011) and so on. Therefore, depening on its sensitivity the physician can decide therapy plan such as applying chemotherapy or surgery. ^{18}F-FDG dose regimen in oncologic scanning is 200-400 MBq in adults generally. Although PET/CT imaging with ^{18}F-FDG is highly specific and sensitive for several kinds of cancers and has many applications in the last 15 years, many alternative PET tracers have been developed for preclinical and clinical studies that are more specific to some kind of tumors.While ^{18}F-Fluorothymidine (^{18}F-FLT) which is a thymidine analoge and is used for the diagnosis of breast cancer, ^{18}F-Fluoromisonidazole (MISO) is used for hypoxia as a marker of oxygen deficit in diagnosis of solid tumors like head and neck (Vallabhajosula, 2007; Kumar et al. 2008). ^{11}C-Choline is more specific for the imaging of prostate cancer. ^{18}F-FDG has relatively low sensitivity in staging of primary prostate cancer and poor detection of abdominopelvic nodes because it eliminates rapidly (Apolo et al. 2008; Kumar et al. 2008; Tuncel et al. 2008).^{18}F-labeledfluoride,fluorodihydroxyphenylalanine (FDOPA), fluorothymidine (FLT), fluoromisonidazole (FMISO), fluoroestradiol (FES) and fluoromethylated choline (FCH) are some of them (Bailey et al. 2005; Wagner, 1995; Miller et al. 2004; Vallabhajosula, 2007; Ishiwata et al. 1990; Sun et al. 2007).

Inflammatory diseases

Sarcoidosis, atherosclerosis, vasculitis, inflammatory bowel disease, rheumatoid arthritis and degenerative joint disease are some examples of the use of ^{18}F-FDG (Basu et al. 2009). PET has especially used for the evaluation of chronic inflammatory bowel disease (IBD) having indefinite radiological findings (Halpenny et al. 2009). Another group (Bonaventure et al. 2009) observed that PET/CT overestimated the degree of tumor extension due to false-positive increased uptake in areas of chronic inflammation from IBD which is hard to differantiate. Another study was performed for PET/CT evaluation of five patients having five bowel segments each before and after successful medical therapy in patients with IBD (Spier et al. 2010). It was seen that the uptake of ^{18}F-FDG was decreased after a successful treatment of inflammation in active IBD by PET.

Neurology

Normally brain is a rapid glucose user but in brain pathologies, glucose and oxygen usage decreases greatly which provides a gold standart in brain imaging by PET. A study was conducted for evaluating effects of different dose of corticotropin-releasing factor receptor type 1 (CRF1) receptor antagonist R317573 that is a theraputic agent for mood and anxiety disorder therapy on regional brain activity (Schmidt et al. 2010). For defining glucose metabolism, ^{18}F-FDG was applied to 12 healthy volunteers receiving single 30 and 200 mg doses of R317573. Dose-related changes were obtained in regional cerebral metabolism by PET. Alzheimer's Disease is a progressive disease related with the reduction of the activity of cholinergic neurons and can efficiently be determined by PET. ^{11}C-Pittsburgh Compound-B (PIB) and ^{18}F-FDDNP (2-(1-(6-[(2-[18F]fluoroethyl)(methyl)amino]-2- naphthyl)ethylidene) malononitrile are most effective radiopharmaceuticals for imaging of amyloid plaques in Alzheimer's Disease (Shoghi-Jadid et al. 2002; Klunk et al. 2004; Rosa-Neto et al. 2009). PET provides early diagnosis supplying early therapy and increasing chance of curing the disease (Wagner, 1995; Antoch et al. 2002; Mistur et al. 2009; Mosconi et al. 2010; Guilloteau et al. 2007). Parkinson's Disease is also a neurodegenerative disease that is related with the death of dopamine-generating cells in the substantia nigra and a region of the midbrain. PET can be used in the determination of Parkinson's Disease by monitoring brain depending on the dopaminergic system with some radiotracers like ^{18}F-DOPA, ^{11}C-Dihydrotetrabenazine (DTBZ) and ^{11}C-Raclopride (RAC) (Nandhagopal et al. 2008; Olanow et al. 2001; Piccini et al. 2006; Guilloteau et al. 2007; Wagner, 1995; Baker, 2009). Epilepsy is another neurologic disorder that can

be detected by PET. PET can effectively monitor the area that is responsible from epilepsy comas (Wagner, 1995). A research group (Yakushev et al. 2010) tried to image the brain of rat having epilepsy by PET. [^{18}F]-fallypride was used as a PET tracer which is highly specific to dopamine D2/3 receptor ligand on six rats treated with pilocarpine exhibiting spontaneous recurrent seizures and nine control. Dopamine D2/3 receptor availability of pilocarpine-treated rats was found 27% lower in bilateral anterior caudate-putamen comparing to controls, but binding was unaffected in other striatal or extrastriatal regions (Lassonde et al. 2006).

Cardiology

PET can be efficiently used for imaging coronary arterial disease and myocardial infarction (MI) for identifying blood flow to cardiac muscle. Aortic, iliac and carotid plaques can also be diagnosed functionally by PET. Assessment of myocardial blood flow both at rest and during vasomotor stress is important for early diagnosis of subclinical abnormalities in coronary arterial vascular functions (Ahluwalia, 2000; Wagner, 1995; Sheikine et al. 2010; Schindler et al. 2010; Tajouri et al. 2010; Beller, 2010). Apart from ^{18}F-FDG, ^{11}C-Acetate can be used for assessing cardiac efficiency, oxygen consumption and metabolism (Lindner et al. 2006).

Psychiatry

For the determination of psychiatric disorders, radioligands can be used that bind to dopamine receptors (D1, D2), serotonin receptors (5HT1A, 5HT2A), opioid receptors and the alterations in glucose metabolism can also be detected successfully. For defining the state of these receptors, studies have been done in patients compared to healthy controls in patients having schizophrenia, substance abuse, mood disorders and other psychiatric conditions. Determination of the effects and development of novel antipsychotics on patients can be identified by PET depending on the change in glucose metabolisms (Wagner, 1995; Antoch et al. 2002; Takano, 2010). ^{18}F-fluorine-18-labeled 4-(2;-methoxyphenyl)-1-[2;-(N-2"-pirydynyl)-p-fluorobenzamido]ethylpiperazine (MPPF) is able to pass BBB and is used in 5HT1A receptor studies, sexual disfunctions, psychiatric diseases like anxiety and depression (Vallabhajosula, 2007; Kumar et al. 2008). Another group (Hu et al. 2010) assessed changes in behavior and glucose metabolism of brain in rat having chronic mild stress of depression with ^{18}F-FDG. Behavioral changes such as decreased central activity and increased grooming and also altered ^{18}F-FDG were observed.

Apart from its clinical use, PET can be used for monitoring the biodistribution and metabolism of novel drugs and PET radiopharmaceuticals. The efficiency of target specific drug delivery systems can be observed by PET by radiolabeling with a positron emitter radionuclide. Not only drugs and drug delivery systems but also peptides and mAb can also be radiolabeled with a radionuclide and they can be monitored by this way.

Pharmacology

The accumulation, biodistribution, metabolism and elimination of novel drugs can be monitored effectively by PET that is an important issue in drug development. Additionally identifying mechanism, assessing pharmacodynamic-pharmacokinetic relationship, screening and selecting clinical candidates and their clinical doses and monitoring response to drug treatment may be performed by PET. Microdoses are sufficient for imaging the biodistribution of novel drugs. Quantitative PET studies help to determine the amount of drug that binds to its target (Saha, 2004; Bailey et al. 2005; Ahluwalia, 2000; Wagner, 1995; Lee et al. 2006). PET can detect penetration of drugs or some markers. One group (Kreisl et al. 2010) quantitatively determined P-glycoprotein function at BBB in humans by ^{11}C-desmethyl-ioperamide after administration of tariquidar administration which is a P-gp inhibitor. Greater brain uptake due to greater brain entry depends on increased radioactivity uptake that was observed by PET. Another group (Koehler et al. 2010) evaluated the radiosynthesis and radiopharmacology of cyclin-dependent kinase 4 (Cdk4) inhibitors. The synthesis, design and the radiopharmacological evaluation of two ^{124}I-labeled Cdk4 inhibitors ([^{124}I]CKIA and [^{124}I] CKIB) were studied by PET imaging of the biodistribution and metabolism of tracers.

Target specific applications

For the observation of the binding effectiveness of mAb or mAb fragment with its target can be monitored by PET after radiolabeling with a positron emitting radionuclide. Its half-life must be compatible with the time needed for a mAb or mAb fragment for achieving maximum tumor uptake that is typically 2-4 day and 2-6 hours, respectively. These radiolabeled antibodies are used in tumor detection, treatment planning and radioimmunotherapy (Verel et al. 2005; Cai et al. 2008). The biodistribution and clearence of humanized anti-VEGF mAb (HuMV833) from tissues was investigated (Jayson et al. 2002). ^{124}I labelled HuMV833 was administered to the patients having progressive solid tumors and the biodistribution and clearence of this antibody from tissues were evaluated. Fairly heterogeneous results between and within the patients and also for the individual tumors were obtained. Another group (Collingridge et al. 2002) was developed a novel radiotracer for PET imaging of VEGF. ^{124}I labeled VG76e, which is specific to human VEGF was administered to mice for PET imaging of solid tumors and found very specific (Cai et al. 2008; Scheer et al. 2008; Yagi et al. 2010; Nagengast et al. 2007).

One of the most promising issues in target specific applications is the use of drug delivery systems, especially liposomes in target imaging by modifying surface properties to be conjugated with both a specific ligand to target and a positron emitter radionuclide for target imaging by PET.

The use of drug delivery sytems especially liposomes for PET Imaging

The rise of drug delivery systems takes its roots from improving the undesired properties of drug molecules like bad taste and odor, low bioavailability, adverse reactions, insufficient targeting and localisation in desired tissue/organ (Langer, 1990). However, development of drug delivery systems is generally more expensive and time consuming than conventional drugs depending on longer process time and the need of special instruments for their production. Apart from these drawbacks, they are effective in increasing safety, efficacy ratio and decreasing dose and by this way they are capable in decreasing adverse reactions and toxicity of drugs (Robinon et al. 1991; Hnatyszyn et al. 1994). Another essential advantage is delivering the drug to the desired target tissue at controlled rate which can be achieved by altering the pharmacokinetic profile of drugs. Both passive and active targeting can be performed by modifying the surface properties of drug delivery systems (Torchilin, 2010). A variety of drug delivery systems such as liposomes (Ostro et al. 1989), niosomes (El-Ridy et al. 2011), micelles (Yokoyama, 2010; Torchilin, 2007), nanoparticles (Lembo et al. 2010), nanocapsules (Mayer, 2005), microparticles (Ravi-Kumar, 2000), dendrimers (Klajnert et al. 2001), carbon nanotubes (Liu et al. 2010), cyclodextrins (Uekama et al. 1987) and so on can be used for delivering not only drug molecules for therapy but also radionuclides and contrast agents for the diagnosis of the diseases.

Some examples of different drug delivery systems that are labeled with different positron emitter radionuclides for observing different applications by PET are given in Table 1 (Seo et al. 2011; Oku et al. 2011; Sun et al. 2011; Yang et al. 2011; Duconge et al. 2008; Wunderlich et al. 2010; Ruggiero et al. 2010; Kulkarni et al. 2010; Avila-Rodriguez et al. 2007; Fukukawa et al. 2008; Kondo et al. 2004). Although they have been used for different imaging modalities over almost 15 years, their combination with some targeted ligands like mAb, antibody fragments, small peptides, vectors or avidin-biotin complexes (Zavaleta et al. 2007) have gained more importance recently. The convenience in modifying the surface properties of these systems makes them more attractive. For instance incorporation of some amphiphilic polymers such as Poly-L-Lysin based polychelating amphiphilic polymers (PAP) on the surface of liposomes enhance the signal intensity (Torchilin, 2000; Weissig et al. 1998; Erdogan et al. 2008; Erdogan et al. 2006). Additionally, as a relatively novel approach, conjugating some ligands such as TAT peptide on the surface of liposomes help them to provide effcient intracellular delivery by penetrating cell membrane can also increase the targeting efficacy (Torchilin et al. 2001). In the light of continuous multidisiplinary studies, nanoparticular/nanovesicular based drug delivery systems will provide much better molecular diagnosis and/or therapy for targeting and imaging a variety of diseases in the future (Cai et al. 2008; Singh, 2010; Sofou, 2008; Vasant, 2004; Kshirsagar, 2000).

Table 1. Some examples of different drug delivery systems that are radiolabeled with different positron emitter radionuclides for different applications imaged by PET (Seo et al. 2011; Oku et al. 2011; Sun et al. 2011; Yang et al. 2011; Duconge et al. 2008; Wunderlich et al. 2010; Ruggiero et al. 2010; Kulkarni et al. 2010; Avila-Rodriguez et al. 2007; Fukukawa et al. 2008; Kondo et al. 2004).

Drug Delivery System	Positron Emitter Radionuclide	Purpose of Application	Reference No
Liposomes	^{64}Cu	To characterize the in vivo clearance and stability of radiolabed liposomes.	Seo et al. 2011
Liposomes	[^{18}F]FDG	Imaging of brain cancer.	Oku et al. 2011
Rare-earth nanoparticles	^{18}F	Imaging of sentinel lymph node	Sun et al. 2011
Super paramagnetic iron oxide nanoparticles	^{64}Cu	Targeted anticancer drug delivery.	Yang et al. 2011
Phospholipid quantum dot micelles	^{18}F	Imaging of dynamic quantitative whole body biodistribution and pharmacokinetics of micelles.	Duconge et al. 2008
Human serum albumin microspheres (DOTA-HSAM)	^{68}Ga	Determining the stability of therapeutic (^{90}Y, ^{177}Lu) or diagnostic (^{68}Ga) microspheres.	Wunderlich et al. 2010
Carbon nanotubes	^{89}Zr	Imaging (with ^{89}Zr) and treating (with ^{225}Ac) tumor vasculature.	Ruggiero et al. 2010
Quinoline-n-butylcyanoacrylate-based nanoparticles	^{124}I	Diagnosis of Alzheimer's Disease.	Kulkarni et al. 2010
Resin microspheres	^{86}Y, ^{89}Zr	As surrogates of ^{90}Y SIR-Spheres for the treatment of hepatic metastases along with treatment using intrahepatic floxuridine.	Avila-Rodriguez et al. 2007
Core-shell star copolymers	^{64}Cu	Carrier system for invivo imaging.	Fukukawa et al. 2008
Peptide modified liposomes	[2-^{18}F]FDG	Active targeting of tumor angiogenic vessels for therapy with 2′-C-cyano-2′- deoxy-1-beta-D-arabino-pentofuranosylcytosine (DPP-CNDAC).	Kondo et al. 2004

Among several drug delivery systems, liposomes are one of the most attracting systems in the delivery of drugs and/or radionuclides to the desired target organ, tissue of the disease depending on their convenient properties such as biocompatibility, biodegredability and being nontoxic. Liposomes can deliver different drugs having various physicochemical properties (Mitra et al. 2006; Huynh et al. 2010; Goins et al. 1994). The use of liposomes as drug delivery systems that are mimicking the behaviour of natural membranes due to its safe phospholipid vesicles was fist performed in 1965. After that time, there has been a huge improvement in the development of liposomal delivery systems (Bangham et al. 1965; Betageri, 1993). Apart from conventional drugs, liposomes tend to accumulate in the inflammation, infection and tumor. Generally, four reasons are known to be responsible from this accumulation that are the existance of cholesterol, particle size, lipid dose and lipid charge (Ostro et al. 1989). Although, liposomes are still under in research intensively, there are several examples of liposomes that are in the market or are in different stages of phase trials for therapy commonly or imaging rarely. Some examples of diagnostic or therapeutic liposomes that are commercially available or in different parts of clinical trials are given in Table 2 (Weissig et al. 2010; Goyal et al. 2005; Mirafzali, 2011; Turner et al. 1988; Kubo et al. 1993).

The use of radiolabeled liposomes in tumor imaging was first done in 1970s (Neerunjun et al. 1977; Richardson et al. 1977; Hamoudeh et al. 2008). Since then with the developing technology in the engineering and computer science, lots of imaging modalities were developed in recent years. Radiolabeling of liposomes with radionuclides generally requires the use of anchor molecules in the aqueous core or conjugation on the lipid bilayer. While deferoxime or nitrilotriacetic acid (Hamoudeh et al. 2008; Ogihara-Umeda et al. 1992; Gabizon et al. 1990) can be used for the encapsulation in the aqueous core, diethylene triamine penta acetic acid (DTPA) (Hamoudeh et al. 2008; Hnatowich et al. 1981; Goto et al. 1989; Harrington et al. 2000; Silindir et al. 2009) and polyamphiphilic polymer (PAP) (Torchilin, 2000; Silindir et al. 2010; Trubetskoy et al. 1994; Torchilin, 2006) can be used for anchoring on the lipid bilayer for radiolabeling of the liposomes. A significant increase in the signal intensity of the image can be obtained with the modification of the lipid surface of nanovesicles with PAP that provides binding of increase number of radionuclides or contrast agnets on the surface (Torchilin, 2006).

With the use of firstly developed liposomes, RES organs such as liver and spleen are the most common parts of the body for their accumulation (Richardson et al. 1977). For this reason, the first attempts with the use of firstly developed liposomes were the diagnosis or therapy of RES organs. With an improvement, it was found that liposomes can be modified with the help of amphiphilic polymers. By the enhancement in the technology and the surface modification, stealth liposomes were developed by coating the surface of liposomes with a hydrophilic, inert and biodegradable polymer such as PEG, monosialoganglioside GM1 and glucuronide derivatives (Oku, 1994) that decrease the number of blood proteins that were bound on the surface of these liposomes and they were less recognised by macrophages and RES organs (Immordino et al. 2006). This facilitates liposomes stay longer in the blood circulation (long circulating liposomes) (Medina et al. 2004). By the use of extra techniques such as extrusion or ultrasonication, the particle size of liposomes can be reduced to nanosizes such as 100-200 nm (Oku, 1994) which gives the chance of imaging of small lesions and tumors depending on enhanced permeability and retention (EPR) effect (Maeda et al. 2000; Muggia, 1999; Matsumara et al. 1986). Angiogenesis (Pandya et al. 2006), enhanced leaky arrangement of endothelial cells and decreased lymphatic drenage are generally responsible from EPR effect that is a gold standart for the delivery and high amount of accumulation of drugs or diagnostics in tumor and metastasis (Maeda et al. 2000; Muggia, 1999; Matsumara et al. 1986). By the production of finally developed liposomes, active targeting can be performed with the help of target specific ligands such as mAb (Blakey, 1992), avidin-biotin complexes (Zavaleta et al. 2007) or receptor specific peptides. Researchers, also, study on novel liposomal carrier systems called theragnostic liposomes that can be formulated by encapsulating therapeutic drugs in the aqueous core and anchoring the radionuclide, contrast agent or paramagnetic contrast agent on the lipid bilayer that provides both diagnosis and therapy at the same time with the same carrier system (Bae et al. 2011; Janib et al. 2010). Additionally by the modification of some cell penetrating peptides and protein transduction domains such as trans-activating transcriptional activator peptide (TATp) (Torchilin et al. 2001; Torchilin et al. 2003), polyarginines, PEP-1, penetratin (Sawant et al. 2010), some molecular probes or triphenylphosphonium cations for subcellular targeting to mitochondria (Boddapati et al. 2010; Boddapati et al. 2005)molecular imaging and/or therapy can be performed by delivering drugs (Weissig et al. 2006), antisense oligonucleotides and small interfering RNA (Fattal et al. 2009), DNA (Weissig et al. 2006), gene (Kulkarni et al. 2010) or proteins (Pisal et al. 2010) inside the cell.

With the increasing use of PET and PET/CT in the Nuclear Medicine departments in routine hospital practice, the research about the use of drug delivery systems especially liposomes rise in a great deal for the purpose of obtaining better images of the diseases or tracing the biodistribution of drugs within the body (Cai et al. 2008; Massoud et al. 2003).

Commonly used PET radionuclides have relatively short half-life and this problem limits their usage in combination with a drug delivery systems. However, by stable labeling of positron emitters having relatively longer half-life, drug delivery systems can be used more effectively for obtaining better images. Longer half-lived PET radionuclides like ^{64}Cu (12.7 h) and ^{124}I (4.2 days) may be

Table 2. Some examples of diagnostic or therapeutic liposomes that are commercially available or in different parts of clinical trials (Weissig et al. 2010; Goyal et al. 2005; Mirafzali, 2011; Turner et al. 1988; Kubo et al. 1993).

Drug or Diagnostic Marker	Application	Company	Position
^{111}In radiolabel	Imaging of tumors such as melanoma, sarcoma and lymphoma	Vestar Inc.	Vescan® Clinical trial phase II/III
Daunorubicin	Treatment of AIDS, ovarian, breast cancer and Kaposi's sarcoma	Sequus	Doxil® (USA)
		Sequus	Caelyx® (Europe)
		NeXstar	Phase III
		Liposome Co.	Clinical trial phase II
Doxorubicin	Cancer treatment	Sun Pharmaceutical Industries Ltd.	LipoDox®
Daunorubicin,	Treatment of AIDS, cancer	NeXstar	DaunoXome®
Daunorubicin citrate		NeXstar	Clinical trial
Doxorubicin	Cancer treatment	Celsion Corporation	Thermodox®
			Clinical trial phase III
Doxorubicin	Treatment of recurrent breast cancer	The Liposome Company, Inc.	Myocet®
Paclitaxel	Treatment of ovarian, breast and lung cancer	NeoPharm	LEP-ETU® Completing of clinical trial phase II
Vincristine	Treatment of metastatic malignant uveal melanoma	Talon Therapeutics	Marqibo®
Cisplatin	Cancer treatment	Regulon, Inc.	Lipoplatin®
Cisplatin	Treatment of head and neck cancer	-	SPI-077™ Clinical trial phase I-II
Amphotericin B	Treatment of fungal infection	NeXstar	AmBisome®
Amphotericin B	Treatment of fungal infection	Liposome Co.	Abelcet®
Amphotericin B	Treatment of fungal infection	Sequus	Amphocil®
Amikacin	Bacterial infection	NeXstar	Mikasome®
Trans-retinoic acid	Cancer treatment	Aronex Pharma.	Antagen®
Anamycin	Cancer treatment	Aronex Pharma.	Phase I/ II
Nystatin	Treatment of fungal infection	Aronex Pharma.	Nyotran®
Vincristine	Cancer treatment	Sequus	Clinical trial
Cisplatin	Cancer treatment	Sequus	Phase I
Muramyl tripeptide	Tumor macrophage activation	Ciba- Geigy	Clinical trial
Prostaglandin E1	Respiration hardness,	Liposome Co.	Phase III
	Myocardial infarction	Liposome Co.	
Verteporfin	Treatment of age-related macular degeneration, pathologic myopia and ocular histoplasmosis	Novartis Pharmaceutical Corporation	Visudyne®
Morphine sulfate	Treatment of postoperative pain following major surgery	EKR Therapeutics	DepoDur®
Cytarabine	Treatment of neoplastic meningitis and lymphomatous meningitis	Skye Pharma.	DepoCyt®
Amikacin	Treatment of lung infections	Transave Inc.	Arikace™
			Phase III
Hepatitis B	Vaccine	Swiss Serum and Vaccine Institute	Hexapel®
Hepatitis A	Vaccine	Crucell company Berna Biotech Ltd.	Epaxal®
Influenza	Vaccine	Crucell company Berna Biotech Ltd.	Inflexal V®

used as an option for tracking the biodistribution of novel drugs or drug delivery systems. By this way, the diagnostic or therapeutic effect of novel carriers can be monitored within different parts of the body like brain and heart (Philips et al. 2009). One of the most important point in PET imaging is the labeling process of drug delivery systems. It should perform in a proper way for performing in vitro and in vivo stability of the radiolabel. A research group (Seo et al. 2008) developed a novel labeling method of preformed liposomes with ^{64}Cu for molecular imaging and drug delivery monitoring by PET. A simple chelation procedure was performed at low temperature and under mild conditions. For radiolabeling of liposomes, ^{64}Cu specific chelator (6-[*p*-(bromoacetamido) benzyl]-1,4,8,11-tetraazacyclotetradecane-*N,N′,N″,N‴*-tetraacetic acid) was conjugated with an artificial lipid. After the preparation procedure,liposomes were administered to mice and successful results were

obtained by monitoring its biodistribution. The same group (Seo et al. 2010) also developed two bifunctional ^{64}Cu chelators such as (6-(6-(3-(2-pyridyldithio)propionamido)hexanamido)benzyl)-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid (TETA-PDP) and 4-(2-(2-pyridyldithioethyl)ethanamido)-11-carboxymethyl-1,4,8,11-tetraazabicyclo(6.6.2)hexadecane (CB-TE2A-PDEA) for conjugating to liposomes to create ^{64}Cu-TETA, ^{64}Cu-TETA-PEG2k and ^{64}Cu-CB-TE2A-PEG2k liposomes. The stability of radiolabel on the liposome was found more than 86% after 48 h incubation with mouse serum that indicated their sufficient stability. Another study was performed (Peterson et al. 2011) about developing a remote loading method for ^{64}Cu labeling of liposomes for PET imaging. An ionophore (2-hydroxyquinoline) was used for crossing ^{64}Cu across the membrane of the preformed liposomes and delivered to an encapsulated copper-chelator. Better PET images were performed with high resolution and direct quantification of blood clarence and tissue distribution by the application of ^{64}Cu labeled liposomes to the healthy and tumor bearing mice. In a study about ^{18}F labeling method, ^{18}F was incorporated into the dipalmitoylglycerol by nucleophilic substitution of *p*-toluenesulfonyl moiety before radiolabeling of liposomes (Philips et al. 2009). By this method, PET images can have higher resolution depending on the higher localisation in desired tissue. The only drawback of the use of ^{18}F is its short half-life (110 min). However, ^{18}F can sufficiently be used for tracking the distribution and localisation mechanisms of carriers having short biological half-life (less than 8 h). Another group (Urakami et al. 2007) developed both novel ^{18}F-labeled compounds and methodology for one-step labeling of liposomes after preparation. Solid-phase transition method was utilized and high labeling efficiency and visualization of liposomal trafficking in mice by real-time analysis were obtained by PET. Radiolabeling of PEGylated liposomes with [^{18}F]fluorodipalmitin ([^{18}F]FDP) was performed by a group in 2007 (Marik et al. 2007). Radiolabeled diglyceride was synthesized by the incorporation of ^{18}F into the lipid molecule by nucleophilic substitution of *p*-toluenesolfonyl moiety.While free [^{18}F]FDP was fastly taken by the liver, spleen and lungs, liposome incorporated [^{18}F] FDP was observed to circulate in blood vessels for nearly 90 min. An easy, rapid and efficient labeling method was also performed by another group (Urakami et al. 2009). The biodistribution of ^{18}F-labeled liposome-encapsulated hemoglobin (LEH) was investigated in the rat brain under ischemia by microPET. The oxygen transfer even in an ischemic brain can be monitored by dynamic PET.

Tiwari *et al* (Tiwari et al. 2010) investigated cerebral metabolic rate of oxygen in rats with $^{15}O_2$-labeled hemoglobin-containing liposome vesicles (HbV). In this method for enhancing the labeling efficiency, bubbling was combined with vortexing. The mean radioactivity of $^{15}O_2$-HbV was foud as 214.4 ± 7.8 MBq.mL^{-1} and this preparation method was found as the most effective for $^{15}O_2$-HbV in animal models to measure oxygen metabolism in brain. Another study with hemoglobin containing liposomes was performed by Kawaguchi *et al* (Kawaguchi et al. 2010) as oxygen carriers in the therapy of ischemic stroke. PET was used for quantifying the metabolism of ^{15}O-gas that was inhalated. It was observed that in non-human primate models, the administration of hemoglobin containing liposomes may help to decrease the damage formed after ischemic stroke in early phases. According to the images, while the administration of small dose such as 24 mg.kg^{-1} of hemoglobin containing liposomes was found effective for the preservation of cerebral metabolic rate of O_2, the administration of higher doses such as 120 mg.kg^{-1} and 600 mg.kg^{-1} were found protective for the infarction of ischemia. Paoli *et al* (Paoli et al. 2010) evaluated the biodistribution of thermally-sensitive liposomes in mice having Met-1 tumor model after i.v. aministration via tail vein. MicroPET and optical imaging were obtained afterwards and the accumulation of a hydrophilic drug was found to increase up to 177 times by encapsulating in liposomes when compared with free drug at 24 h.

Recently, developed ultrasound contrast agents like lipid-shelled microbubbles are used for the delivery of air to the desired tissue for imaging however, their biodistribution can not be clearly characterized. Tartis *et al* (Tartis et al. 2008) incorporated [^{18}F]FDP in microbubbles and measured the biodistribution in rats quantitatively by microPET. According to the images, ^{18}F label is eliminated through the urine and [^{18}F]FDP was metabolized within the liver. Different from free lipids, microbubbles and liposomes were reported to remain longer in circulation depending on the pharmacokinetic profiles. The activity in treated kidneys was obtained significantly higher at 0 and 60th min when compared with untreated kidneys depending on the delivery of lipids from microbubbles by ultrasound.

The formulation, surface architecture and design of drug loading are essential issues for the development of novel drug delivery systems. Their pharmacokinetic behaviour within the body may be monitored by PET with the modification of proper positron emitter radionuclides. Another group (Ferrara et al. 2009) labeled the shell and drug core of lipid-shelled particles with ^{18}F and monitored by PET and optical imaging. Radiolabel was conjugated on a lipid molecule before inserting within a nanoparticle and remained stable until lipid was metabolized. According to the images, with the use of radiolabeled long-circulating nanoparticles, the vascular structure of tumor was monitored with a high resolution. For the diagnosis of Alzheimer's disease, Kulkarni *et al* (Kulkarni et al. 2010) studied the activity of n-butyl-2-cyanoacrylate (PBCA) nanoparticles for brain targeting. ^{125}I-clioquinol (CQ, 5-chloro-7-iodo-8-hydroxyquinoline) was encapsulated in PBCA nanoparticles.^{125}I-CQ-PBCA nanoparticles were observed to penetrate in BBB and particles were accumulated in amyloid plaques efficiently in mice having Alzheimer's disease. Another research was performed about investigating the stability of long

circulating liposomes containing ^{64}Cu labeled dipalmitoyl phosphatidyl ethanolamine (DPPE) and distearoyl phosphatidyl ethanolamine (DSPE) lipids having different acyl chain lengths having two C16 achyl chain and two C18 acyl chain respectively in 1% mol lipid (Seo et al. 2011). For radiolabeling of liposomes, ^{64}Cu-incorporated bifunctional chelators (TETA-PDP) were used and these liposome formulations were injected to FBV inbread mice. The radioactivity depending on the clearance from liver and kidney was found higher with the injection of ^{64}Cu-DPPE-labeled liposomes than ^{64}Cu-DSPE-labeled liposomes at 6, 18 and 28th h by PET. Medina *et al* (Medina et al. 2011) developed a novel method for targeting liposomes containing radioiodinated anilinoquinazoline core-based epidermal growth factor receptor (EGFR) inhibitor SKI 212243 (SKI 243) to EGFR in tumor for PET imaging. The pharmacokinetic profiles, blood circulation and tumor targeting were found higher with the liposomal SKI 243 than SKI 243 itself. The additional effect of CT to PET was evaluated with the use of iodine containing liposomal contrast agents labeled with ^{18}F-FDG for detecting the localisation of the inflammation and tumor (Zheng et al. 2010). Liposomes were administered to rabbits and while almost similar amount of tumor detection was obtained in both of the administered systems, with iodine containing liposomes almost 4 times more images were obtained by CT. By the use of iodine containing liposomes, the difference between tumor and inflammatory lessions can be significantly discriminated. Qin *et al* (Qin et al. 2009) developed a drug delivery system labeled with both optical and positron emitter probes on the lipid vesicles for determining its pharmacokinetic profile in vivo. The rate of transport to RES was found higher for long circulating liposomes than temperature sensitive ones and the release rate of temperature sensitive liposomes was observed faster than the long circulating ones. The additional effect of ultrasound on the drug release from lipid shell of drug delivery systems such as liposomes and lipid shelled gas microbubbles was also performed by another group (Ferrara et al. 2009). The additional effect of ultrasound was evaluated by PET in defining the biodistribution and pharmacokinetics with the help of positron emitting radionuclides such as ^{18}F and ^{64}Cu having relatively longer half-life for anchoring on the lipid shell of vesicles. It was observed that the drug release and drug transport through the blood vessels to the tissue were facilitated by the mild heating effect of ultrasound which gave a facilitating effect (Ferrara et al. 2009**).**

Conclusions

Depending on the rapid development in the technology, science and medicine, novel imaging modalities such as hybrid imaging techniques that use PET for obtaining functional images are developed for performing better and earlier diagnose of the diseases. For this reason, there is an essential need for the novel contrast agents that specifically delivering to the target, giving sufficient signal/contrast intensity and less target/background contrast ratio for obtaining better images within shorter time. Drug delivery systems are the reason of choice for delivering contrast agents like radionuclides to the target tissue specifically. Liposomes are one of the most popular drug delivery systems that are used for diagnosis and/or therapy of a variety of diseases by conjugating radiolabel on the lipid bilayer or encapsulating inside the aqueous core. The combination of radionuclides with liposomes supply the advantage of specific target tissue/organ imaging with lesser radionuclide concentrations by PET. By the use of liposomes labeled with positron emitting radionuclides and/or encapsulated with contrast agents that are specific for CT, more sensitive images can be acquired in identifying body functions and metabolism for the diagnosis of a variety of diseases and therapy tracing by PET/CT in many different clinical fields such as oncology, cardiology, brain mapping, neurophysiology and drug development in pharmacology. Especially in oncology field, tumor diagnosis may be performed in very early stages such as in cellular or molecular level by using target specific mAb-modified and radiolabeled immunoliposomes by molecular imaging. In conclusion, apart from the high costs of constructing a cyclotron for the production of short-half lived radionuclides, very promising drug delivery systems may be developed in the future for the diagnosis of different kinds of diseases with the combination of proper positron emitting radionuclides having a sufficiently longer half-life and with the efficient and stable labeling. Thereby, a close relationship between preclinical and clinical studies may be achieved by the production of better and novel contrast agents for microPET imaging systems. These developments may lead to prepare personalized medicine for imaging or even for both imaging and therapy of diseases at early stages in the future.

Declaration of interest

The authors of this review article explicitly state that there are none declaration of interest.

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