Chapter 8
Synthesis of PET Radiopharmaceuticals

Introduction

PET radiopharmaceuticals are uniquely different from SPECT radiopharmaceuticals in that the former have radionuclides that are positron emitters and the majority of them have short physical half-lives. The most common PET radionuclides are ^{11}C, ^{15}O, ^{13}N, ^{18}F, and ^{82}Rb, which are short-lived (see Table 7.2) and put limitations on the synthesis time for PET radiopharmaceuticals and their clinical use. The attractive advantage of PET radiopharmaceuticals, however, is that the ligands used in radiopharmaceuticals are common analogs of biological molecules and, therefore, often depict a true representation of biological processes after in vivo administration. For example, ^{18}F-fluorodeoxyglucose (FDG) is an analog of glucose used for cellular metabolism and $H_2^{15}O$ for cerebral perfusion.

Automated Synthesis Device

Conventional manual methods of synthesis of radiopharmaceuticals using a high level of radioactivity are likely to subject the personnel involved in the synthesis to high radiation exposure. This is particularly true with short-lived positron emitters such as ^{11}C, ^{13}N, ^{15}O, and ^{18}F, because the quantity of these radionuclides handled in the synthesis is very high. To minimize the level of exposure, automated modules have been devised for the synthesis of PET radiopharmaceuticals.

The automated synthesis device, often called the *black box*, is a unit controlled by microprocessors and software programs to carry out the sequential physical and chemical steps to accomplish the entire synthesis of a radiolabeled product. The unit consists of templates or vials prefilled with required chemicals attached to the apparatus via tubings that are connected to solenoid valves to switch on and off as needed. Most black boxes are small enough to be placed in a space of

$20 \times 20 \times 20$ in. and are capable of self-cleaning. In some units, disposable cassettes (cartridges) are employed so that new cassettes can be used for each new synthesis, thus minimizing contamination and radiation exposure. Various parameters for synthesis such as time, pressure, volume, and other requisites are all controlled by a remote computer using appropriate software. The unit has a graphic display showing the status of the ongoing process. After the synthesis, a report with the date and start and end time of the radiosynthesis and the calculated yield is printed out. Technologists can operate these units very easily. Automated synthesis modules for ^{18}F-FDG, ^{13}N-NH$_3$, ^{11}C-CH$_3$I, ^{11}C-HCN, ^{11}C-acetate, and a few other PET tracers are commercially available. Versatile automated modules are commercially available to use for the synthesis of a variety of PET tracers in the single module. This is accomplished by simple exchange or modification of various segments inside the unit to suit the specific product synthesis. To minimize radiation exposure, often the synthesis box is placed inside a minicell (see Chap. 7). After each synthesis, the product is passed through a high-performance liquid chromatography (HPLC) described later to achieve a high-purity finished product. A schematic diagram of a black box for ^{18}F-FDG synthesis is shown in Fig. 8.1. Often the synthesis box is placed inside a minicell to minimize radiation exposure. An automated multi-synthesis module (FASTlab2) for the synthesis of different PET radiopharmaceuticals marketed by GE Healthcare is shown in Fig. 8.2. Other vendors include Siemens Medical Solutions, Inc. (Explora), IBA (Synthera), and Eckert & Ziegler (FDG-Plus).

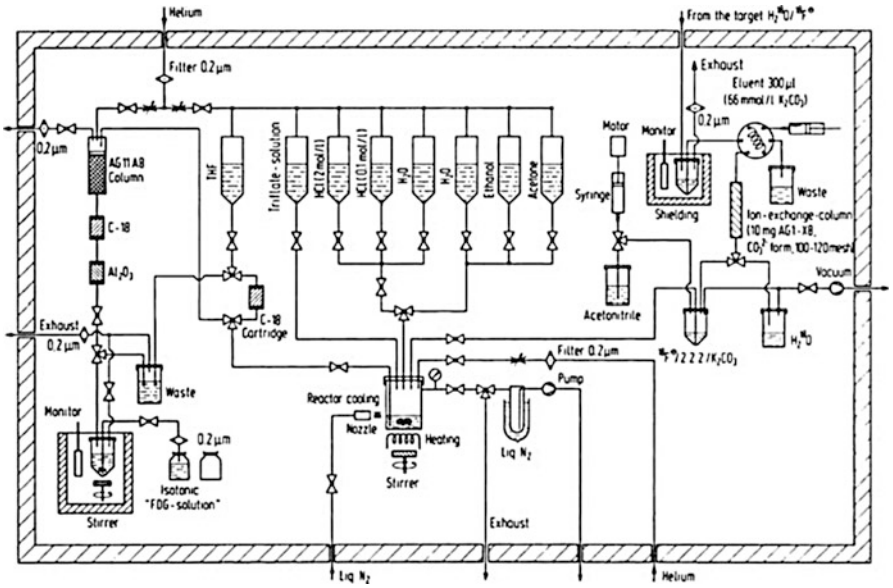

Fig. 8.1 A schematic block diagram showing different components in the ^{18}F-FDG synthesis box (Reproduced with kind permission of Kluwer Academic Publishers from Crouzel C et al. (1993) Radiochemistry automation PET. In: Stöcklin G, Pike VW (eds) Radiopharmaceuticals for positron emission tomography, Kluwer Academic, Dordrecht, the Netherlands, p 64. Fig. 9)

Fig. 8.2 Automated synthesis box, FASTlab2, from GE Healthcare (Courtesy of GE Healthcare)

PET Radiopharmaceuticals

Many radiopharmaceuticals have been used for PET imaging; however, only a few are routinely utilized for clinical purposes. Almost all of them are labeled with one of the four common positron emitters: ^{11}C, ^{13}N, ^{15}O, and ^{18}F. Of the four, ^{18}F is preferred most, since it has a relatively longer half-life ($t_{1/2} = 110$ min) that allows its supply to relatively remote places. In all cases, a suitable synthesis method is adopted to provide a stable product with good labeling yield, high specific activity, high purity, and, most importantly, high in vivo tissue selectivity. The following is a description of the syntheses of the common clinically used PET radiopharmaceuticals and a few with potential for future use.

^{18}F-Sodium Fluoride

Fluorine-18 ($t_{1/2} = 110$ min) is produced by irradiation of ^{18}O-water with 10–18 MeV protons in a cyclotron and recovered as ^{18}F-sodium fluoride by passing the irradiated water target mixture through a carbonate-type anion-exchange resin column. The water is forced out of the column with neon gas, whereas $^{18}F^-$ is retained on the column, which is recovered by elution with potassium carbonate solution. Its pH should be between 4.5 and 8.0. While ^{18}F-sodium fluoride is most commonly used for the synthesis of FDG, it is also used for other ^{18}F-labeled PET radiopharmaceuticals.

The US FDA has approved it for bone scintigraphy, since it localizes in bone by exchanging with PO_4^- ion in the hydroxyapatite crystal.

^{18}F-Fluorodeoxyglucose

^{18}F-2-fluoro-2-deoxyglucose (2-FDG) is normally produced in places where a cyclotron is locally available. Its molecular formula is $C_8H_{11}{}^{18}FO_5$ with molecular weight of 181.3 Da. ^{18}F-2-FDG can be produced by electrophilic substitution with ^{18}F-fluorine gas or nucleophilic displacement with ^{18}F-fluoride ions. The radiochemical yield is low with the electrophilic substitution, so the nucleophilic displacement reaction has become the method of choice for ^{18}F-FDG synthesis. Deoxyglucose is labeled with $^{18}F^-$ by nucleophilic displacement reaction of an acetylated sugar derivative followed by hydrolysis (Hamacher et al. 1986). In nucleophilic substitution, a fluoride ion reacts to fluorinate the sugar derivative. A solution of 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethane-sulfonyl-*β*-D-mannopyranose in anhydrous acetonitrile is added to a dry residue of ^{18}F-fluoride containing aminopolyether (Kryptofix 2.2.2) and potassium carbonate (Fig. 8.3). Kryptofix 2.2.2 is used as a catalyst to enhance the reactivity of the fluoride ions. The mixture is heated under reflux for about 5 min. The solution is then passed through a C-18 Sep-Pak column, and acetylated carbohydrates are eluted with tetrahydrofuran (THF), which are then hydrolyzed by refluxing in hydrochloric acid at 130 °C for 15 min. ^{18}F-2-fluoro-2-deoxyglucose (2-FDG) is obtained by passing the hydrolysate through a C-18 Sep-Pak column. The yield can be as high as 60%, and the preparation time is approximately 50 min. The final solution is filtered through a 0.22-μm filter and diluted with saline, as needed. According to USP specifications, it should have pH of 4.5–7.5 and a specific activity of more than 1 Ci (37 GBq)/μmol. The chemical purity is limited to 50 μg/mL of Kryptofix 2.2.2 and 1 mg of 2-chloro-2-deoxy-D-glucose per total volume. Radiochemical purity should be >90%, as determined by the TLC method

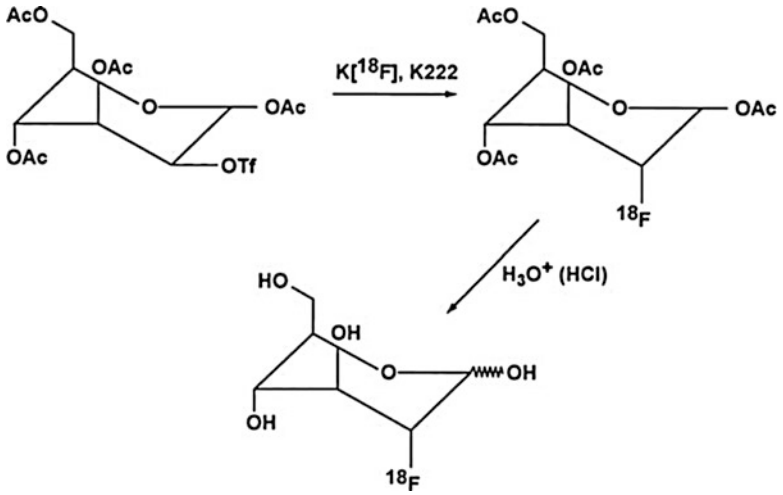

Fig. 8.3 Schematic synthesis of ^{18}F-2-fluoro-2-deoxyglucose (FDG) (Reprinted with the permission of the Cleveland Clinic Center for Medical Art and Photography ©2009. All rights reserved)

using activated silica gel as the solid phase and a mixture of acetonitrile and water (95:5) as the liquid phase.

Since Kryptofix 2.2.2 is toxic causing apnea and convulsions, modifications have been made to substitute it with tetrabutylammonium hydroxide or bicarbonate, which have been adopted by many commercial vendors. Also, in some other methods, the C-18 Sep-Pak column separation has been eliminated so as to carry out the acidic hydrolysis in the same vessel. In methods where Kryptofix 2.2.2 is still used, several Sep-Pak columns are used to separate Kryptofix 2.2.2 and reduce it to practically a negligible quantity.

The FDA has approved ^{18}F-2-FDG for many clinical uses such as the metabolism in the brain and heart and the detection of epilepsy and various tumors. In metabolism, ^{18}F-2-FDG is phosphorylated by hexokinase to 2-FDG-6-phosphate which is not metabolized further. It should be noted that 3-fluorodeoxyglucose (3-FDG) is not phosphorylated and hence is not trapped and essentially eliminated rapidly from the cell. This is why 3-FDG is not used for metabolic studies. Detailed protocols of ^{18}F-FDG usage in humans are given in Chap. 13.

Because of the relatively longer half-life of ^{18}F among the PET radionuclides, commercial and institutional facilities having cyclotrons produce ^{18}F-FDG in bulk quantities and supply to nearby clinics and hospitals as needed. Supply can be made as far as 200 miles away with a loss of activity, which can be compensated by adding more activity. The details of ^{18}F-FDG distribution is given in Chap. 10.

6-^{18}F-L-Fluorodopa

Like ^{18}F-2-FDG, 6-^{18}F-L-fluorodopa is also produced in places where a cyclotron is available locally. There are several methods of synthesizing 6-^{18}F-fluoro-3,4-dihydroxyphenylalanine (6-^{18}F-L-fluorodopa), of which the method of fluorodemetallation using electrophilic fluorinating agents is most widely used. Electrophilic reactions involve the reaction of fluorine in the form of F^+ with other molecules. Only the L-isomer of dopa is important, because the enzymes that convert dopa to dopamine, which is targeted by the radiopharmaceutical, are selective for this isomer. Initially, a suitably protected organomercury precursor (*N*-[trifluoroacetyl]-3,4-dimethoxy-6-trifluoroacetoxymercuriophenylalanine ethyl ester) of dopa is prepared. [^{18}F]-labeled acetylhypofluorite prepared in the gas phase is then allowed to react with the mercury precursor in chloroform or acetonitrile at room temperature. Other precursors using metals such as tin, silicon, selenium, and germanium have been reported. Acid hydrolysis with 47% HBr provides a relatively high yield (10–12%) of 6-^{18}F-L-fluorodopa (Luxen et al. 1992) compared with other available methods. Substitution at position 6 is most desirable, because this does not alter the behavior of dopa, whereas substitutions at 2 and 5 do. It is sterilized by filtering through a 0.22-μm membrane filter and is supplied at pH between 6 and 7. Normally EDTA and ascorbic acid are added to the final preparation for stability. Its specific activity should be more than 100 mCi (3.7 GBq)/mmol and radiochemical purity >95% as

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