PET Chemistry: Radiopharmaceuticals

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Contents

6.1 PET Radiopharmaceuticals in the Clinics – Precursors

Although many radiolabelled compounds for PET imaging have been developed so far, only a few have reached the status of a clinically established and routinely used PET radiopharmaceutical. At the early stage of development, a reasonable medical indication is obviously fundamental for a PET radiopharmaceutical to be further considered as clinically relevant. However, besides a favourable in vivo behaviour and appropriate imaging characteristics, certain criteria have to be fulfilled, such as a fast, straightforward and reliable radiosynthesis; an assured stability of the label as well as of the compound itself and a good availability of a suitable precursor. In particular, the ease and reliability of the radiochemistry is critical as the radiopharmaceutical needs to be available on demand in sufficient amounts. The precursors play the decisive role in the radiochemical approach as they specify the radiosynthetic route. Furthermore, the accessibility of the appropriate precursors is important for the applicability of radiosynthesis. Today, most precursors of the commonly used PET radiopharmaceuticals are commercially available and provided as approved medical products by suppliers such as ABX – advanced biochemical products GmbH Germany [1].

6.1.1 ^{18}F-Labelled PET Radiopharmaceuticals and Their Precursors

Fluorine-18 is clearly the most important radionuclide employed in clinical PET imaging. While it is available in large quantities, it also has further optimal physical and chemical properties for PET imaging. In its [^{18}F]FDG form it probably contributed most to the success of PET imaging in clinical diagnostics. Since the development of [^{18}F]FDG in the 1970s, it has become the most important and most commonly used PET radiopharmaceutical in nuclear medicine. However, during the past 30 years, several other useful ^{18}F-labelled PET radiopharmaceuticals have been

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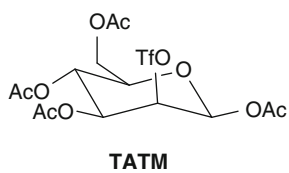
designed and some have been further developed to routine PET radiopharmaceuticals in nuclear medicine clinics. In the following paragraphs, some representative examples of clinically employed ^{18}F-labelled PET radiopharmaceuticals are outlined. Furthermore, their general production routes and most commonly used precursors are described.

6.1.1.1 [^{18}F]NaF

As mentioned earlier, ^{18}F-labelled sodium fluoride is the simplest form of a ^{18}F-labelled radiopharmaceutical and it was shown already in 1940 in in vitro tests that [^{18}F]NaF is uptaken by bone and dentine structures [2]. Since the 1960s, [^{18}F]NaF has been used in the nuclear medicine clinics for skeletal scintigraphy to identify malignant and benign mass in bones [3, 4]. N.c.a. [^{18}F]NaF can be produced directly by elution of the trapped [^{18}F]fluoride from the anionic exchange resin (solid phase extraction cartridge systems) using potassium carbonate solution. The obtained [^{18}F]fluoride solution can be used directly for administration.

6.1.1.2 2-[^{18}F]Fluorodeoxyglucose ([^{18}F]FDG)

^{18}FDG is the most important ^{18}F-labelled PET radiopharmaceutical, and its availability, broad applicability, and increasing use have made it a diagnostic method accepted worldwide. ^{18}FDG is most widely used as a diagnostic compound in oncology [5], but there are many more indications and applications for this versatile radiopharmaceutical [6–9]. The first approach towards 2-[^{18}F]FDG was based on an electrophilic ^{18}F-labelling with only low yields and in a mixture with the stereoisomer 2-[^{18}F]fluorodeoxymannose (see Chap. 5, Fig. 5.1) [10]. In the 1980s, a new precursor, mannose triflate (1,3,4,6-tetra-O-acetyl-2-O-trifluoro-methanesulfonyl-beta-D-mannopyranose, TATM) (see Fig. 6.1) [11], for an efficient nucleophilic n.c.a. ^{18}F-labelling of 2-[^{18}F]FDG became available and is still the precursor of choice for routine productions of n.c.a. [^{18}F]FDG with yields of up to 40–50 GBq per batch. Generally, TATM is n.c.a. ^{18}F-fluorinated in the Kryptofix2.2.2©/K_2CO_3 system in acetonitrile. The subsequent hydrolysis using hydrochloric acid provides [^{18}F]FDG in high radiochemical yields of ~50–70%. Recently, the deprotection procedure has been optimised by changing to an alkaline system [12–14]. The alkaline system sufficiently removes all acetyl protection groups already at 40°C in 0.3 N NaOH in less than 5 min. The reaction conditions must be strictly kept to reduce an alkaline epimerisation on the C-2 position towards 2-[^{18}F]fluorodeoxymannose to a minimum [13].



TATM

Fig 6.1 Mannose triflate precursor for radiosynthesis of n.c.a. [^{18}F]FDG

6.1.1.3 6-[^{18}F]Fluoro-L-DOPA ([^{18}F]F-DOPA)

Similar to ^{18}FDG, the first ^{18}F-labelling approaches to [^{18}F]F-DOPA were based on direct electrophilic ^{18}F-labelling using [^{18}F]F_2 and L-DOPA as precursor (see Chap. 5, Fig. 5.2). This method led to a mixture of the three possible regioisomers 2-, 5- and 6-[^{18}F]F-DOPA and gave only 21% RCY of the desired 6-[^{18}F]F-DOPA. The introduction of the 6-trimethyltin precursor for electrophilic ^{18}F-fluorodemetallations offered enhanced ^{18}F-labelling with regioselective ^{18}F-introduction and higher RCY (see Chap. 5, Fig. 5.3) [15]. The electrophilic ^{18}F-fluorodemetallation reaction for 6-[^{18}F]F-DOPA was further developed and optimised, and is now applicable as a fully automated version [16–19]. Attempts for a nucleophilic approach of n.c.a. ^{18}F-labelling of 6-[^{18}F]F-DOPA have been made, but even the most promising ones are multi-step radiosyntheses using chiral auxiliaries and thus make automation difficult (Chap. 5, Fig. 5.17) [20, 21]. Consequently, the commonly used production route is still the electrophilic ^{18}F-fluorodemetallation using the trimethyltin precursor which is available in a few different versions with varying protection groups (see Fig. 6.2).

6-[^{18}F]fluoro-L-DOPA is the second ranked ^{18}F-labelled PET radiopharmaceutical after ^{18}FDG. It is the PET tracer of choice for studies of the dopaminergic system [22], particularly for studies of changes in the presynaptic dopaminergic nerve terminals in Parkinson's disease [23, 24]. Furthermore, 6-[^{18}F]F-DOPA has also shown applicability in oncology for detecting neuroendocrine tumours where a visualisation using [^{18}F]FDG PET imaging is not feasible [25].

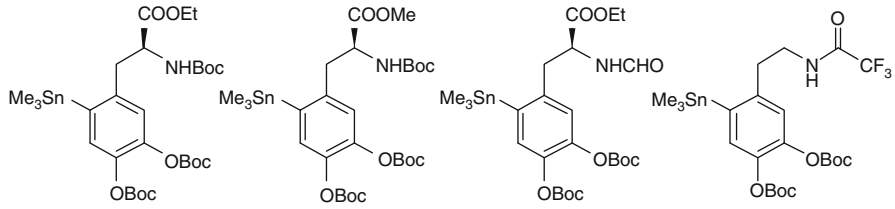


Fig. 6.2 Most important precursors for electrophilic radiofluorination of 6-[^{18}F]F-DOPA by regioselective ^{18}F-fluorodestannylation

6.1.1.4 O-(2-[^{18}F]Fluoroethyl)-L-Tyrosine ([^{18}F]FET)

[^{18}F]FET is a ^{18}F-labelled amino acid derivative and is routinely used for PET imaging of brain tumours as it has only minor uptake in normal brain and provides excellent tumour-to-background contrast [26]. Furthermore, it is not uptaken by inflammatory tissue like ^{18}FDG and allows a more exact detection of tumour mass and size in general tumour imaging [27]. In combination with magnetic resonance imaging (MRI), PET imaging of cerebral gliomas using [^{18}F]FET significantly enhanced the diagnostic assessment [28]. The first radiosynthesis was based on a two-step ^{18}F-labelling using the primary precursor ethyleneglycol-1,2-ditosylate [29]. After ^{18}F-labelling and a semi-preparative HPLC purification, the 2-[^{18}F]fluoroethyltosylate was coupled to the unprotected (S)-tyrosine to give [^{18}F]FET. The two-step method could be circumvented by the advancement of a new precursor, (2 S)-O-(2′-tosyloxyethyl)-N-trityl-tyrosine-tert-butyl ester (TET) for a direct ^{18}F-labelling (see Fig. 6.3) [30]. Although the precursor for direct ^{18}F-labelling offers a shorter, more convenient and more efficient preparation of [^{18}F]FET, both methods are routinely used. A very recently developed precursor is based on a chiral Ni(II) complex of a (S)-tyrosine Schiff base and led to an enantiomerically pure (S)-2-[^{18}F]FET and furthermore, this approach could avoid toxic TFA in the hydrolysis step [31].

6.1.1.5 3-Deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT)

This ^{18}F-labelled thymidine derivative is a substrate of the thymidine kinase-1 (TK1) and thus phosphorylated and trapped in the cell [32]. The TK1 is correlated with cell proliferation as its designated substrate thymidine is essential for DNA and RNA synthesis. Hence, [^{18}F]FLT can be used for PET imaging of cell proliferation and of tumours with increased TK1 levels [33]. [^{18}F]FLT has proven clinical importance, even in comparison with [^{18}F]FDG in several tumour imaging studies [34–40]. The first radiosynthesis of 3-Deoxy-3′-[^{18}F]fluorothymidine gave only low RCY of 7% [41]. Several improvements of the radiosynthesis, precursors and the HPLC systems for purifications have increased the availability of [^{18}F]FLT [42–47], but still, the radiosynthesis remains tedious and causes difficulties in routine productions [47]. The most commonly used precursors for ^{18}F-labeling of [^{18}F]FLT are depicted in Fig. 6.4.

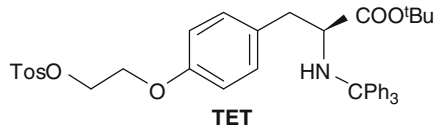


Fig 6.3 Precursor TET for the direct ^{18}F-labelling of [^{18}F]FET

6.1.1.6 16α-[^{18}F]Fluoro-17β-Estradiol ([^{18}F]FES)

^{18}F-labelled estrogens have been developed as PET radiopharmaceuticals for imaging the estrogen hormone receptor [48]. The estrogen receptor expression is a crucial factor in breast cancer development and critical for the response of endocrine therapies [49, 50]. The first ^{18}F-labelled derivatives of estrogen were the 4-[^{18}F]fluoroestranone and the 4-[^{18}F]Fluoroestradiol which were achieved only in low radiochemical yields of ~3% [51, 52]. Several other ^{18}F-labelled estrogen derivatives have been developed and evaluated preclinically [53–57]. However, the most promising candidate and, today, routinely used ^{18}F-labelled estrogen derivative is the 16α-[^{18}F]Fluoro-17β-estradiol ([^{18}F]FES) [54, 55]. The synthesis and preparation methods for [^{18}F]FES have been improved and automated and [^{18}F]FES can be achieved in radiochemical yields of 70% within 60 min synthesis time [58–60]. As precursor, the cyclic sulphate

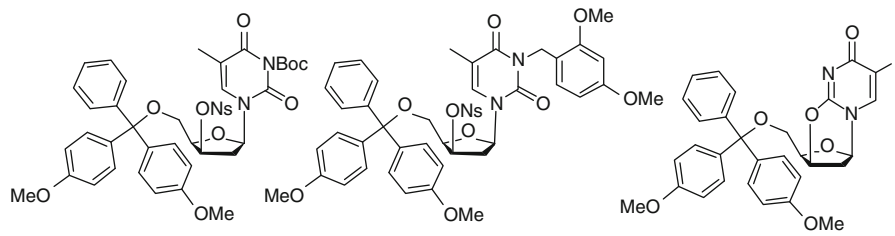


Fig 6.4 Various precursors for the ^{18}F-labelling of [^{18}F]FLT

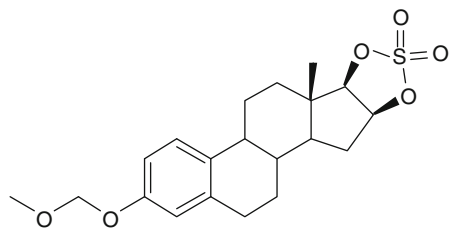


Fig. 6.5 Cyclic sulphate precursor for the ^{18}F-labelling of [^{18}F]FES

3-O-methoxymethyl-16β,17β-O-sulfuryl-estra-1,3,5(10)-triene-3,16β,17β-triol (see Fig. 6.5) has prevailed and is commonly employed. After radio-fluorination, a hydrolysis step using 1 N HCl yields the 16α-[^{18}F]Fluoro-17β-estradiol. The product is then purified by semi-preparative HPLC and formulated.

6.1.1.7 [^{18}F]Fluorocholine ([^{18}F]FCH)

The ^{11}C-labelled derivative of choline, [^{11}C]choline, was found to be a suitable radiopharmaceutical for tumour imaging, especially for prostate cancer [61, 62]. As a consequence, also the ^{18}F-labelled derivative [^{18}F]fluorocholine was developed and showed similarly good imaging characteristics in PET tumour imaging [61, 63, 64]. Furthermore, [^{18}F]FCH was also found to clearly visualise brain tumours [65] and in comparison with [^{18}F]FDG, it gave better PET images for brain tumours, prostate cancer, lung cancer, head and neck cancer [64]. Generally, [^{18}F]fluorocholine can be obtained in RCY of 20–40% from a coupling reaction of N,N-dimethyl-ethanolamine with the ^{18}F-labelling synthon [^{18}F]fluorobromomethane ([^{18}F]FBM) (see Fig. 6.6) [63]. The ^{18}F-labelling of [^{18}F]FBM is based on the precursor dibromomethane, and [^{18}F]FBM is isolated by a subsequent gas chromatography purification [66, 67].

6.1.1.8 [^{18}F]Fluoromisonidazole ([^{18}F]F-MISO)

[^{18}F]F-MISO (1H-1-(3-[^{18}F]Fluoro-2-hydroxypropyl)-2-nitroimidazole) is used as an indicator for the oxygenation status of cells as is accumulated in hypoxic tissue. Particularly in oncologic radiotherapy and chemotherapy, hypoxia is of major interest for the therapy prognosis [68–70]. Although [^{18}F]F-MISO shows some unfavourable pharmacological characteristics such as slow clearance from norm-oxygenated cells (background) and a relatively moderate uptake in hypoxic cells in general, it is the most widely used PET radiopharmaceutical for imaging hypoxic tumours. Recently, other hypoxia PET tracers have been developed and showed very promising results, but they have not reached the clinics yet [71–73]. Generally, two variants of the radiosynthesis towards [^{18}F]F-MISO are available [74–79]. The first successful attempts of an efficient radiolabelling of [^{18}F]F-MISO were based on a two-pot reaction. The primary precursor (2R)-(-)glycidyl tosylate (GOTS) was labelled with [^{18}F]fluoride to yield [^{18}F]epifluorohydrin ([^{18}F]EPI-F) which subsequently reacted with 2-nitroimidazole (2-NIM) in a nucleophilic ring opening to give [^{18}F]F-MISO in RCY of 20–40% (see Fig. 6.7) [75, 76]. The development of a direct ^{18}F-labelling of [^{18}F]F-MISO in one-pot has made radiosynthesis of this PET radiopharmaceutical more convenient and reliable [77, 78]. Starting from the precursor 1-(2′-nitro-1′-imidazolyl)-2-O-tetrahydropyranyl-3-O-toluenesulphonyl-propanediol (NITTP) (see Fig. 6.7), [^{18}F]F-MISO can be obtained in an one-pot procedure within 70–90 min [77–79]. Both approaches are capable for [^{18}F]F-MISO preparation, while the one-pot method usually gives RCY of 35–40% and it is much more suitable for automated routine productions [74]. Furthermore, the radiosynthesis based on the NITTP precursor is normally more reliable and more robust.

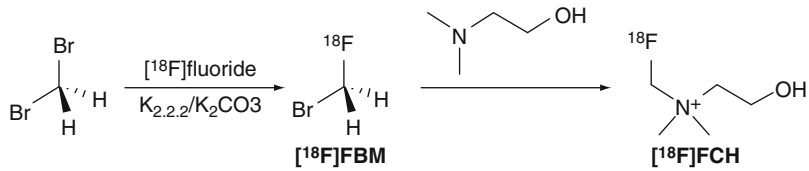


Fig. 6.6 Preparation of [^{18}F]choline via the ^{18}F-labelling synthon [^{18}F]FBM

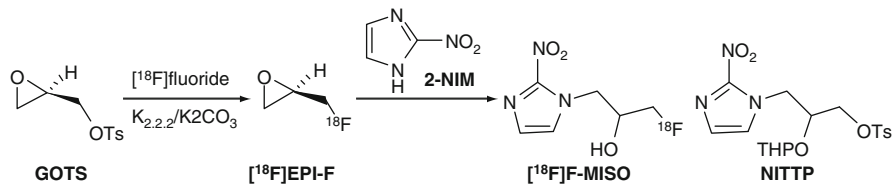


Fig. 6.7 Preparation of [^{18}F]F-MISO using a two-pot radiosynthesis (left hand side) and the precursor NITTP for the one-step ^{18}F-labelling procedure (right hand side)

6.1.1.9 [^{18}F]Altanserin

This ^{18}F-labelled PET radiopharmaceutical is the most widely used PET tracer for studies of the 5-HT$_{2A}$ receptor system as it is, so far, the most suitable ^{18}F-labelled 5-HT$_{2A}$ receptor ligand. Among other ^{18}F-labelled ligands for this receptor system, [^{18}F] altanserin shows the highest affinity to 5-HT$_{2A}$ receptors and a good selectivity over the other receptor systems, dopamine D$_2$, histamine H$_1$, adrenergic α_1 and α_2 and opiate receptor sites (μ-opiate) [80, 81]. [^{18}F]Altanserin can be obtained from direct ^{18}F-labelling of the appropriate nitro precursor (nitro-altanserin) (see Fig. 6.8) with good RCY in a one-step procedure. As no functional groups are present which need to be protected, the radiopharmaceutical is readily available after HPLC purification [82, 83].

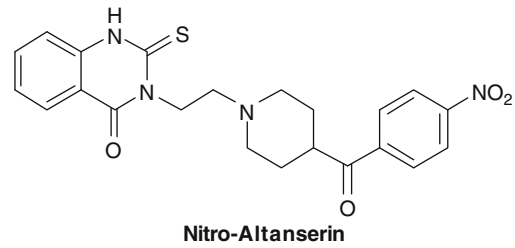


Fig. 6.8 Nitro-precursor for the direct ^{18}F-labelling of [^{18}F]altanserin

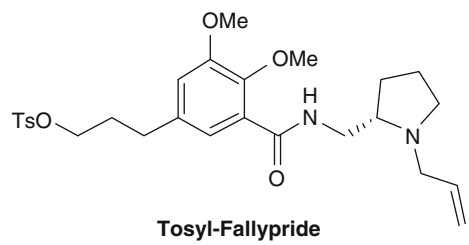


Fig. 6.9 'Tosyl-Fallypride' as precursor for one-step ^{18}F-labelling of [^{18}F]fallypride

6.1.1.10 [^{18}F]Fallypride

This ^{18}F-labelled derivative of benzamide neuroleptics has a high affinity (reversible binding) to dopamine D$_2$ receptors. [^{18}F]Fallypride is widely used as PET radiopharmaceutical for investigations of the dopamine D$_2$ receptor system and allows PET imaging of both striatal and extrastriatal dopamine D$_2$ receptors [84–88]. The ^{18}F-radiolabelling using the 'Tosyl-Fallypride' precursor (see Fig. 6.9) is a one-step ^{18}F-labelling procedure and provides [^{18}F]fallypride in good RCY of 20–40% [89].

6.1.2 *^{11}C-Labelled PET Radiopharmaceuticals and Their Precursors*

Carbon-11 is particularly suited for labelling compounds with short biological half-lives. Compared to fluorine-18, the short physical half-life of ^{11}C permits repeated investigations in the same subject and within short intervals. Labelling is mainly by isotopic

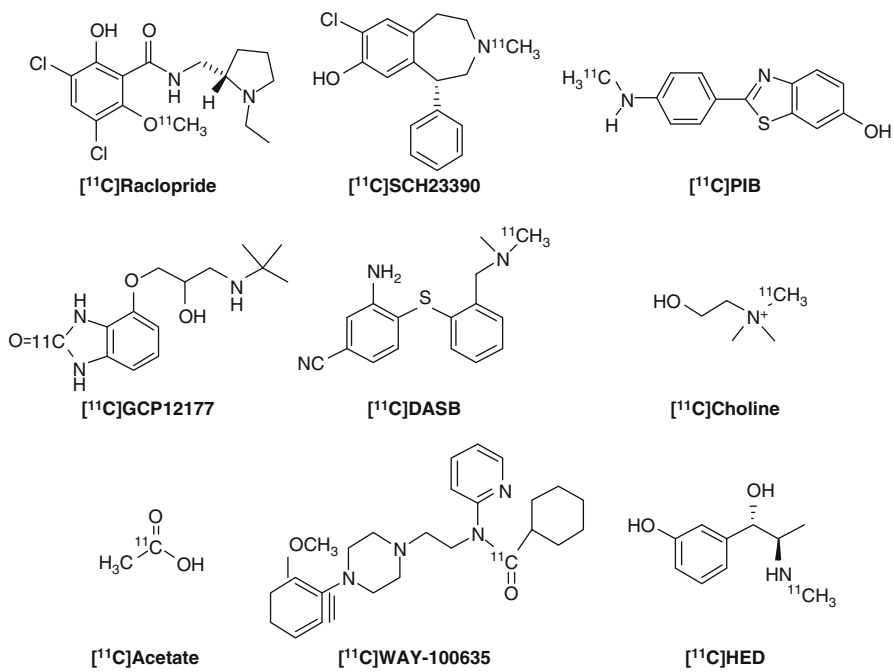


Fig. 6.10 Examples of commonly used and clinically established ^{11}C-labelled PET radiopharmaceuticals

substitution, but unlike ^{18}F labelled radiopharmaceuticals, carbon-11 labelled compounds can be prepared and used only in PET centres with a cyclotron and radiochemistry facility. As such carbon-11 labelled compounds are not commercially available. In Fig. 6.10, the structures of some established and commonly used carbon-11 labelled radiopharmaceuticals are shown, which have found routine application in clinical PET studies. All the compounds are prepared starting from the commercially available desmethyl or normethyl precursors. A large number of carbon-11 labelled radiopharmaceuticals have been reported in the literature, but only a handful of these have been shown to have clinical utility (see Chap. 5, Table 5.1). Procedures for the preparation of some representative examples of these radiopharmaceuticals are described.

6.1.2.1 [^{11}C]Raclopride

Of all benzamide derivatives reported to date, ^{11}C-raclopride is the most widely used PET ligand for the investigation of postsynaptic striatal D2/D3 receptors in humans. It has been used to image D2/D3 receptors in patients with Parkinson's disease, Huntington's disease, and schizophrenia, for determining receptor occupancy of antipsychotic drugs as well as for the indirect measurement of dopamine concentrations in the synaptic cleft. Raclopride can be labelled by O-methylation with ^{11}C-methyl iodide or ^{11}C-methyl-triflate (see Chap. 5, Fig. 5.24). Another approach involves N-ethylation with ^{11}C-ethyl iodide; however, due to the longer reaction time and a lower specific radioactivity, O-methylation is the preferred method for routine synthesis [90]. O-methylation was performed by using 5 M NaOH as the base in dimethylsulfoxide at 80°C for 5 min. ^{11}C-raclopride is purified by reversed phase HPLC using a μ-Bondapak C-18 column (Waters, 300 × 7.8 mm, 10 μm) with acetonitrile/0.01 M phosphoric acid (30/70) as the mobile phase. After formulation, the product is filtered through 0.22 μm Millipore membrane filter to give a sterile and pyrogen-free product. The total synthesis time is around 40–45 min and specific activities are in the range of 20–100 GBq/μmol depending on the synthesis method and the production route of ^{11}C-methyl iodide (i.e. 'wet' or 'dry' method).

6.1.2.2 [^{11}C]Flumazenil

^{11}C-labelled flumazenil is routinely used in clinical PET studies for the visualisation of central benzodiazepine receptors. It has high affinity for the

$GABA_A$ receptors and has been employed in PET studies mainly for the localisation of epileptic foci. ^{11}C-flumazenil has been labelled with carbon-11 by N-methylation with ^{11}C-methyl iodide or esterification with ^{11}C-ethyl iodide. For routine synthesis, N-methylation with ^{11}C-methyl iodide is the method of choice (Chap. 5, Fig. 5.24). [^{11}C]flumazenil is purified by reversed phase HPLC using a μ-Bondapak C-18 column (Waters, 300 × 7.8 mm, 10 μm) with acetonitrile/0.01 M phosphoric acid (25/75) as the mobile phase [91]. After formulation, the product is filtered through 0.22 μm Millipore membrane filter to give a sterile and pyrogen-free product. The total synthesis time is around 40–45 min and specific activities are in the range of 20–100 GBq/μmol.

6.1.2.3 L-[S-Methyl-^{11}C]Methionine

Methionine, labelled in its methyl position and named L-[S-methyl-^{11}C]-methionine, is a widely used amino acid for the detection of tumours using PET imaging. The uptake of L-[S-methyl-^{11}C]-methionine reflects several processes including transport, protein synthesis and transmethylation.

A number of synthetic pathways leading to L-[S-methyl-^{11}C]-methionine have been reported [92, 93]. The most simple and commonly used synthetic approach utilises the L-homocysteine thiolactone method. This method involves the in situ ring opening of L-homocysteine thiolactone by sodium hydroxide and the subsequent alkylation of the sulphide anion of L-homocysteine with ^{11}C-methyl iodide or ^{11}C-methyltriflate (Chap 5, Fig. 5.24). The final product is purified by HPLC, formulated and filtered through a 0.22 μm Millipore membrane filter to give a sterile and pyrogen-free product. The total synthesis time is around 40–45 min and although, unlike brain receptors, high specific radioactivities are not required, practical values obtained after the radiosynthesis are in the range of other ^{11}C-labelled compounds (Table 6.1).

Table 6.1 Established ^{11}C-labelled PET radiopharmaceuticals and their clinical applications

^{11}C-radiopharmaceutical	Target	Reference
[^{11}C]Flumazenil	Central benzodiazepine receptors	[94]
[^{11}C]WAY-100635	5-HT_{1A} receptors	[95]
[^{11}C]PIB	Amyloid deposits	[96]
[^{11}C]raclopride	D2-receptor occupancy	[97]
[^{11}C]SCH23390	D1-receptor occupancy	[98]
[^{11}C]DASB	SERT	[99]
[^{11}C]methionine	Amino acid uptake	[100–102]
[^{11}C]choline	Cell membrane synthesis	[97]
[^{11}C]acetate	Oxygen metabolism	[103]
[^{11}C]HED	Presynaptic uptake-1 and storage	[104, 105]
[^{11}C]GP 12177	β-Adrenoceptors	[104, 105]

6.1.3 ^{15}O- and ^{13}N-Labelled PET Radiopharmaceuticals

Oxygen-15 ($T_{½}$ = 2 min) has been used mainly for the labelling of oxygen, water and butanol. Of all these three compounds, ^{15}O-labelled water and butanol have found widespread application as myocardial and brain perfusion imaging agents.

6.1.3.1 [^{15}O]Water

A number of nuclear reactions exist for the production of oxygen-15, but the most commonly used method is the ^{14}N(d,n)^{15}O nuclear reaction [106]. The target material is aluminium and the target content is a mixture of nitrogen and 0.2–1.0% of oxygen. [^{15}O]water is then produced by reacting hydrogen with [^{15}O]O_2 (formed from the exchange reaction with carrier oxygen) over palladium-alumina catalyst at 200°C. The [^{15}O]water vapour formed is trapped in sterile isotonic saline and filtered through a 0.22 μm Millipore membrane filter.

6.1.3.2 [^{15}O]Butanol

n-[^{15}O]Butanol is prepared by the reaction of tri-n-butyl borane with [^{15}O]O_2 produced via the ^{14}N (d,n)^{15}O nuclear reaction. Alumina is used as a solid support

for the tri-n-butyl borane. After the reaction, the labelled product is washed from the cartridge with water. Further purification is achieved by passing the product through a C-18 cartridge and eluting over a sterile filter with 10% ethanol/saline [107].

6.1.3.3 [^{13}N]Ammonia

Nitrogen-13 ($T_{½}$ = 10 min) is prepared via the ^{16}O(p,α)^{13}N nuclear reaction [108]. The material is usually aluminium, but targets made of nickel or titanium are in use. Of all compounds labelled with nitrogen-13, [^{13}N]ammonia is most commonly used for PET studies. Two methods exist for its production. The first method involves the reduction of ^{13}N-labelled nitrites/nitrates, formed during the proton irradiation, with either titanium(III) chloride or hydroxide or Devarda's alloy in alkaline medium [109]. After distillation, trapping in acidic saline solution and sterile filtration, [^{13}N]ammonia is ready for human application. The second method prevents the in situ oxidation of ^{13}N to ^{13}N-labelled nitrites/nitrates through the addition of ethanol as a radical scavenger to the target content [109]. Thereafter, the target content is passed through a small cation exchanger. [^{13}N]ammonium ions trapped on the cartridge are eluted with saline and the solution containing the product is then passed through a sterile filter. [^{13}N]Ammonia is used mainly for myocardial perfusion studies.

6.1.4 Other PET Radiopharmaceuticals

As an alternative to carbon-11 and fluorine-18, the most commonly used PET radionuclides, metallic positron emitters have gained acceptance also as radionuclides for the labelling of biomolecules. Apart from ^{64}Cu, most of the metallic positron emitters including ^{82}Rb, ^{68}Ga and ^{62}Cu are generator-produced isotopes. An advantage of generators is the fact that PET studies can be performed without an on-site cyclotron.

Rubidium-82 ($T_{½}$ = 1.3 min) is produced from the strontium-82 (^{82}Sr)-^{82}Rb generator system. The ^{82}Sr-^{82}Rb generator system (Cardiogen-82®) is commercially available from Bracco Diagnostics, Princeton, NJ. [^{82}Rb]RbCl is used in clinical routine for cardiac perfusion measurements.

Gallium-68 ($T_{½}$ = 68 min) is produced from the ^{68}Ge-^{68}Ga generator system. The generator is made up of a matrix of Sn(IV), Ti(IV) and Zr(IV) oxides in a glass column. The ^{68}Ga is eluted from the column with 0.005 M EDTA or 1 M HCl (mostly). When, however, the ^{68}Ga is eluted with EDTA, prior dissociation of the [^{68}Ga]EDTA complex is necessary, provided [^{68}Ga]EDTA is not the desired radiopharmaceutical. [^{68}Ga]EDTA is used mainly for brain tumour imaging as perfusion agent. For other ^{68}Ga-based radiopharmaceuticals, the ^{68}Ga needs to be available for chelating and thus the acidic elution with HCl is more favourable [110]. The most prominent examples of clinically used ^{68}Ga-radiopharmaceuticals are [^{68}Ga]DOTA-TOC and [^{68}Ga]DOTA-NOC, which have found application as imaging agents for somatostatin receptor-positive tumours [111, 112].

Copper-62 ($T_{½}$ = 10 min) is produced from the ^{62}Zn-^{62}Cu generator system. In this generator system, ^{62}Zn is loaded on a Dowex 1 × 10 anion exchange column and the ^{62}Cu is eluted with 2 M HCl. Two well-known copper-62 radiopharmaceuticals are [^{62}Cu]ATSM (Diacetyl-bis(N^4-methylthiosemicarbazone)) and [^{62}Cu]PTSM (Pyruvaldehyde-bis(N^4-methylthiosemicarbazone)). [^{62}Cu]ATSM is being used in the clinic as a hypoxia imaging agent [113–115]. [^{62}Cu]PTSM has found application as a myocardial and brain perfusion PET imaging agent [116].

6.2 Automated Radiosyntheses – Modules

Semi-automated and automated processes have always been part of radiochemical methods or syntheses. This is due to the fact that one major concern in radio- and nuclearchemistry is to keep the radiation dose to personnel at a minimum. Accordingly, automation is favourable and generally preferable as many of these automated operations process large amounts of radioactivity which are excluded for a direct manual handling. Particularly,, for short-lived radionuclides such as carbon-11, nitrogen-13, oxygen-15 and fluorine-18, the required amounts of radioactivity in routine productions are very high and call for fully remote-controlled operations. Furthermore, automated reaction steps or procedures are generally more reliable and thus more reproducible than manual

radiosyntheses. In addition, automated processes save time and therefore enhance product yields and efficiency. Today, the radiosyntheses of almost all routine PET radiopharmaceuticals are fully automated and are performed in so-called modules.

The first radiosynthesis modules were self-constructed and made of several remote-controlled valves, solvent reservoirs, radiation detectors and reactors or heating systems. The components were connected by tubes and lines from conventional HPLC systems. The radiosyntheses were carried out by manual switching of the valves. Today, the modules are computer-controlled, and the reaction steps of a radiosynthesis are programmed, while the basic concept of the hardware has not changed much [117].

After a module is equipped with precursor, solvents and reagents, the radionuclide is transferred directly from the target into the module and the radiosynthesis is started. During the procedure, (radio)detectors and other probes in the module monitor the course of radioactivity, temperature, pressure and further reaction parameters which are all usually recorded by the computer.

Depending on the system, different radiosyntheses can be programmed. If they are all based on the same radiochemical principle (e.g. a two-step radiosynthesis consisting of a radiolabelling step and a subsequent deprotection step), only basic parameters such as temperature and time need to be re-programmed. For more complex radiosyntheses, more changes are required and the radiosynthesis module has to be technically adapted to meet the demands of the new procedure. Consequently, in routine productions for clinical use on daily basis, each PET radiopharmaceutical is produced in a specifically designed module.

Several commercial module-based synthesis systems have been marketed so far. The first systems were available for [^{18}F]FDG and have clearly contributed to the success and commercialisation of [^{18}F]FDG [117–119]. Some examples of manufacturers and vendors of radiosynthesis modules and their corresponding synthesis modules for [^{18}F]FDG productions are outlined in Table 6.2.

Automated radiosynthesis devices are commercially available for almost every clinically relevant PET radiopharmaceutical such as [^{18}F]FDG, [^{18}F]FLT, [^{18}F]F-DOPA, [^{11}C]CH_3I or [^{13} N]NH_3. Furthermore, systems which are more flexible and adaptable for different radiosyntheses have been developed. The so-called modular systems offer a broad adaptability and high flexibility towards more complex radiosyntheses and individual method development. Various small components, generally designed for certain processes or reaction steps, are combined and assembled according to the desired radiosynthetic route. In contrast, the so-called 'black boxes', which generally allow only one type of radiosynthesis, need more service and maintenance, for example, cleaning procedures and the radiosyntheses have to be programmed and developed by the customers.

Table 6.2 Examples of vendors of automated radiosynthesis apparatuses and their systems for [^{18}F]FDG

Company	Radiosynthesis module for [^{18}F]FDG
CTI Molecular Imaging/ Siemens Healthcare	CPCU (chemistry process control unit)
GE Medical Systems (Nuclear Interface Module)	TRACERlab Fx_{FDG}
Raytest Isotopenmessgeräte GmbH	SynChrom F18 FDG
Eckert & Ziegler Strahlen- und Medizintechnik AG	Modular-Lab for FDG
EBCO Industries Ltd./ Advanced Cyclotrons	Radiochemistry modules (FDG synthesis)
Bioscan	FDG-plus synthesiser

Recently, new approaches using micro-reactors and microfluidic systems have emerged in the field [120, 121]. Such microscale reactions benefit from very small amounts of precursors while they still give high yields after very short reaction times. The first systems have proven applicability and have shown satisfying results for the production of some ^{11}C-labelled [122–124] and ^{18}F-labelled [122] PET radiopharmaceuticals. As [^{18}F]FDG is the most widely employed PET radiopharmaceutical in nuclear medicine, the radiosynthesis of [^{18}F]FDG is commonly used as a benchmark test for those microfluidic systems. The development of these systems is still in its infancy, but the proof-of-principle has been made.

6.3 Quality Control of PET Radiopharmaceuticals

As PET radiopharmaceuticals are administered to humans, they need to fulfil certain test criteria before

Table 6.3 Quality control tests for PET radiopharmaceuticals

Quality control test	Criteria or subject of test	Test method
Biological tests		
Sterility	Injected volume needs to be sterile	Incubation over 2 weeks (bacteria growth)
Pyrogenicity	Batch needs to be apyrogenic	Limulus amebocyte lysate (LAL) test[a]
Physicochemical tests		
Appearance	Colour/clarity–turbidity	Visual inspection
Isotonicity	Injected volume needs to be isotonic	Osmometry (cryoscopy)
pH	7.4 (ideal) and slightly lower or higher	pH meter
Radionuclidic purity	Radionuclides must be pure prior to use	γ-spectroscopy and further radioanalytics
Chemical purity	Impurities or solvent traces need to be removed or proved to be harmless	Chemical analytics, frequently HPLC or GC
Radiochemical purity	Individual limits[b]	Radiochromatography (HPLC and TLC)

[a]Quick test for pyrogens based on coagulation of the lysate of amebocytes from the blood of the horseshoe crab (Limulus Polyphemus).
[b]Generally, for PET radiopharmaceuticals, there are individual limits/specifications set by the national pharmacopeia or the authorities of the corresponding country.

they are authorised for administration. In comparison to normal drugs, some test results cannot be obtained before administration due to the short half-lives of the radionuclides used for PET radiopharmaceuticals. In such cases, so-called dry runs for validation are performed. The full batch of a PET radiopharmaceutical production is used for tests and thereby, the method and procedure of production can be validated. In general, all productions, methods and test procedures have to be validated in accordance with GMP guidelines.

Quality control tests for PET radiopharmaceuticals can be divided into two subtypes: biological tests and physicochemical tests [125]. A list of required tests for PET radiopharmaceuticals is outlined in Table 6.3 (see Chap. 4).

In general, the biological tests need prolonged time and cannot be analysed before the administration of the PET radiopharmaceutical. These tests are performed 'after the fact' or for validation of the production process in dry runs.

The quality control tests for PET radiopharmaceuticals in clinical routine are regulated by the national law of the corresponding country. Responsible authorities usually provide guidelines such as pharmacopeia with clear specifications for routine productions of PET radiopharmaceuticals in clinical use.

6.4 PET Radiopharmaceuticals in Drug Development

During the development of new drugs, many questions and decisions have to be answered and made, respectively. Some of them are crucial and serve as knock-out criteria for the drug candidates. In pharmaceutical industry and the drug development field, three main concepts are classified: 'Proof of Target (POT),' 'Proof of Mechanism (POM)' and 'Proof of Concept (POC)' [126]. The available methods to give such proofs are limited and the field of PET imaging offers great opportunities for that. However, only a few examples can be found where PET radiopharmaceuticals have been employed as biomarkers in drug development.

Examples for the use of a PET tracer for the POT can be found in the development of therapeutics for neurodegenerative diseases. In the development of a new dopamine D2 receptor antagonist (ziprasidone, CP-88,059-01), the receptor occupancy of a dopamine D2 receptor antagonist, ziprasidone (CP-88,059-01) was determined using [^{11}C]raclopride [127]. In the same manner, the dopamine D_2 and D_3 receptor occupancy were studied by PET imaging using [^{11}C]raclopride during the development of a potential

antipsychotic drug (aripiprazole, OPC 14597) [128]. In both studies, the displacement of the radiolabelled receptor ligand by the drug candidates gave the proof of target interaction. If, in a later stage, PET imaging results correlate with the clinical outcome, it could be further used as proof of concept.

In oncology, PET imaging is commonly used for the diagnosis and staging of cancers and has also shown potential in therapy monitoring. PET imaging using [^{18}F]FDG can visualise changes in tumour metabolism and thus can show therapy effects at a very early stage. Consequently, [^{18}F]FDG PET imaging can give the proof of mechanism as it can provide information of the tumour response to a new drug. This has been demonstrated in patients with gastrointestinal tumours treated with new kinase inhibitors as the [^{18}F]FDG uptake into the tumours was significantly reduced already after one cycle of treatment [129, 130].

Most information can be obtained if the drug candidate itself is radiolabelled. This strategy is not always adaptable and limited to structures which allow the authentic introduction of a radionuclide. However, a radiolabelled drug candidate gives information about the full pharmacokinetics and can answer many crucial questions at once.

PET imaging is particularly suitable for several questions in drug development. However, PET imaging has been used in drug development only to a small extent until now, but it is gaining more and more acceptance. Besides neurosciences and oncology, the use of PET imaging in drug development can be expected to grow further and also to emerge in other fields of drug development.

6.5 Conclusions

[^{18}F]FDG is the best clinically known and the most successful PET radiopharmaceutical. Due to the clinical utility of [^{18}F]FDG, PET imaging has grown rapidly and PET has become a powerful imaging technique. It is one of the leading technologies in molecular imaging. Besides [^{18}F]FDG, a number of PET radiopharmaceuticals have also found application as routine imaging agents in the clinic. Most of these radiopharmaceuticals can be produced in automated synthesis modules and quite a number of ^{18}F-labelled radiopharmaceuticals are commercially available for those clinics lacking an on-site cyclotron or radiochemistry facility. Nonetheless, for a vast majority of new targets there are currently no PET imaging probes. Radiochemists are therefore challenged to develop appropriate imaging probes for these new targets. The hope is also that those PET radiopharmaceuticals currently under development and in preclinical evaluation will find their way very rapidly into the clinics.

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