Routine production in a GMP environment of multiple ^{18}F-radiopharmaceuticals on a disposable-based fully automated platform

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Introduction

PET modality is one the most rapidly growing areas of medical imaging thanks to the availability of innumerous clinical centers with their own biomedical cyclotrons. To be able to cover the growing clinical demands a flexible, reliable platform (IBA Synthera) was developed for a (c)GMP environment. Well-known conventional chemistry steps were fully automated allowing the synthesis of multiple ^{18}F-radiopharmaceuticals beyond FDG.

Synthera® Platform designed for a GMP environment

IFP™ cassette (Integrated Fluidic Processor)

Materials/Methods

The platform consists of a synthesizer and a HPLC. The synthesizer employs a disposable system (IFP=integrated fluidic processor) where the entire synthesis takes place. The IFPs are named after conventional synthesis steps they are designed to perform: nucleophilic, chromatography, alkylation, distillation, and reformulation. One IFP only is needed for a single synthesis, but they can be connected in series for multi-step processes.

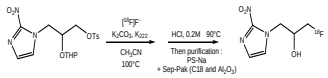
Results

In this work, several ^{18}F-labeled tracers were synthesized by nucleophilic fluorination: direct fluorination (S_N2 and S_NAr) and synthon chemistry. The former can be performed in one step (^{18}F-FP-DTBZ[1], ^{18}F-fallypride[1]) or in two steps; fluorination followed by removal of protective groups (^{18}F-FDG, ^{18}F-FMISO[1], ^{18}F-FAZA[2], ^{18}F-FHBG[1], ^{18}F-FAcetate[3], ^{18}F-F-A85380[1], ^{18}F-ML-10, florbetaben). Synthons like^{18}F-FBM (fluorobromomethane), ^{18}F-SFB[4] (succinimidylfluorobenzoate) were also synthesized and they may be coupled to adequate precursor via acylation, alkylation or amide formation. For instance, ^{18}F-FCH[5] synthesis; ^{18}F-FBM synthon produced in the first step N-alkylates the precursor resulting in ^{18}F-FCH. This example shows the system is be able to carry out multi-step process.

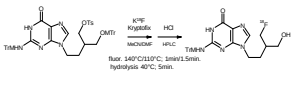
Synthera® Platform: Synthera synthesizer & Synthera® HPLC

^{18}F-NaF yield: 97% d.c.**

^{18}F-FMISO yield: 64% d.c.**

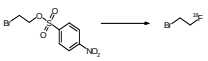


^{18}F-FHBG* yield: 9 % d.c.

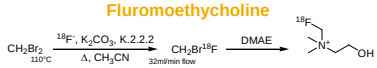


Ref. [1] Schmitz A, Freifelder R [2011] ISRS 2011 Poster 367 & Blykers A, Vaneycken I, Xavier C, Everaert H, Cavelliers V, [2011] ISRS 2011 Poster 347

^{18}F-FBE yield: 23.7% d.c.**

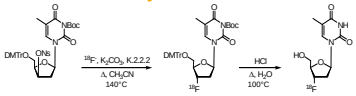


^{18}F-FCH yield: 28 % d.c.**
Fluromoethycholine

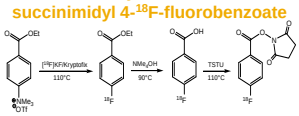


Ref. [5] Kryza D, Tadino V, Filannino M A , Villeret G, Lemoucheux L [2008] Nuclear Med. & Bio. 35: 255

^{18}F-FLT* yield: 26.5% d.c.

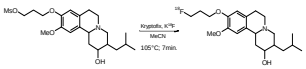


^{18}F-SFB yield: 82.5% d.c**
succinimidyl 4-^{18}F-fluorobenzoate

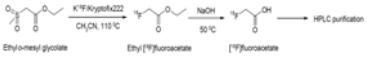


Ref. [4] Ackermann U, Yeoh S D, Sachinidis J I, Poniger S S, Scott A M, Tochon-Danguy H J [2011] J. Label Compd. Radiopharm, 54(10): 671-673

^{18}F-FP-DTBZ* yield: 6% d.c.

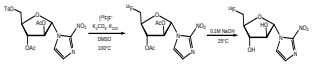


^{18}F-Facetate* yield: 62 % d.c.



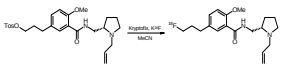
Ref. [3] Mori T, Arai R, Lambert B, Gameiro-Paris C, Kosuga T, Asai T, Fujibayashi Y, Okazawa H, Kiyono Y [2011] ISRS 2011 Poster 332

^{18}F-FAZA* yield: 28% d.c;

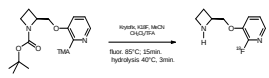


Ref. [2] Horti A G, Kiseleve M Y, Revert H T, Wahl R L, Dannals R F [2007] ISRS 2007 Poster 039 .

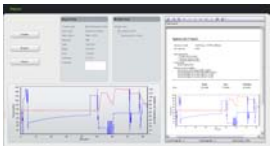
^{18}F-Fallypride* yield: 36.2% d.c.



^{18}F-F-A85380* yield: 34.3% d.c.



Synthera® & Synthera® HPLC Main page: fluidic pathway scheme, time counters ; signal recording window for real-time monitoring
Report Page: report information can be customized, (from left to right)



Discussion/Conclusion

In most cases, the crude synthesis product required HPLC purification (*) while for the others cartridge purification (**) was sufficient. In every synthesis parameters were optimized with respect to precursor amount, reaction time, temperature and concentration. In the majority of the cases synthesis time was < 60 min. even when HPLC purification was included. Good synthesis yields and > 95 % radiochemical and chemical purity were obtained and were superior when compared to manual synthesis (yields at least doubled). Less radiation exposure, shorter synthesis time and stable yields are the other advantages versus manual synthesis. By simply adapting the recipe and by using adequate IFP the automated platform was able to consistently produce several tracers in high yields and suitable for human injection.