Nucleophilic Labeling Reactions on Synthera: A Multipurpose Synthesis Platform

Alexander Schmitz & Richard Freifelder
University of Pennsylvania, Department of Radiology

Introduction

In the clinical environment, FDG accounts for the vast majority of clinical PET radio-pharmaceuticals. However, when one considers the research side of PET the pallet of options open to the researcher is much broader than FDG.

Home made synthesis units are quite often used because they can be put together in a flexible manner and on a quick time scale. There are also a number of commercial units now available that claim the ability to manufacture multiple compounds with only modest changes in the kits and chemicals (Bioscan, IBA-Molecular, GE, etc.).

At the University of Pennsylvania we have focused on Synthera from IBA-Molecular. In collaboration with IBA-Molecular we have been using the Synthera synthesis unit for a number of 18F radiotracers with very positive results. This solution was chosen for a number of reasons, small size, ready to synthesize FDG, flexibility for other radiotracers. So far we have produced eight compounds with our unit.

Objective

To adapt the manual synthesis method of the aforementioned ^{18}F-radiotracers to our automated Synthera synthesis unit, we evaluated and implemented each synthesis step into the automated synthesis as accurately as possible. Commercially available IFP Nucleophilic™ for the Synthera box were used for all compounds and experiments.

Goal was to make a minimum of changes to the existing setup to achieve highest convenience while still providing satisfying yields and results. The method and setup should also allow multiple synthesis runs of different radiotracers per day.

Synthesis methods for new radiotracers are to be developed on Synthera according to the goals listed above and results should comply with USP/FDA guidelines.

Methods

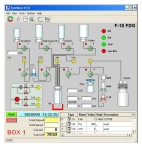
Based on test experiments, alterations to the synthesis script and method were made to ensure best results and yields with respect to the desired radiotracer. Due to the set goals changes were limited to the variation of parameters like reaction time, temperature and flow rates and the use of different cartridges and solvents, respectively reagents.

After achieving the best parameters for each compound, the script and method was written and saved to the Synthera control computer, several test runs were made to ensure consistent result. SOPs were written and used to follow USP/FDA guidelines.

Except ^{18}F-FDG all productions runs were single dose syntheses and yielded 10-50mCi (eos) depending on radiotracer.

Software and IFP™

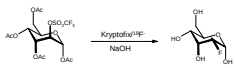
The graphical interface shows current state of valves, heater and pressure settings.



Methods and scripts can be saved and loaded. The software tests the system and can give warnings if necessary.

We always used IFP™ Nucleophilic synthesis kits. They are individually packed and sealed. The kit is disposable and should only be used once. It is recommended to check the IFP for before use.

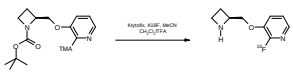
^{18}F-FDG



Synthesis of FDG with Synthera proved to be consistent, reliable and with yields of 80-85% d.c. on average.

The synthesis is compliant with USP and cGMP standards and the resulting FDG was used for human clinical scans at the Hospital of UPenn.

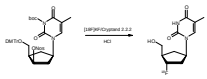
^{18}F-F-A85380[7]



The ^{18}F-F-A85380 production method was immediately developed on Synthera as a one-pot two-step synthesis. Yields were at 34% (d.c.) on average.

The resulting ^{18}F-FA85380 will be for human use and animal scans .

^{18}F-FLT[1]



Synthesis of ^{18}F-FLT with Synthera was done with an in house method on Synthera, which was adapted from a previously used manual synthesis method. Yields were at 13% (d.c.) on average and were improved significantly.

The resulting ^{18}F-FLT was used for human clinical scans at the Hospital of UPenn and for animal scans.

^{18}F-Fluoromisonidazole (FMiso)[5]

The ^{18}F-FMiso production method was immediately developed on Synthera as a one-pot two-step synthesis. Yields were at 31% (d.c.) on average.

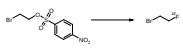
The resulting ^{18}F-FMiso was used for cell studies and animal scans.

^{18}F-FHBG[2]

Synthesis of ^{18}F-FHBG with Synthera was done with an in house method adapted from the previously used manual setup. The one-pot two –step synthesis yielded 9% (d.c.) on average and improved significantly.

The resulting ^{18}F-FHBG was used for animal scans and cell studies.

^{18}F-BFE[6]



The ^{18}F-Bromofluoroethane production method was immediately developed on Synthera as a one-pot synthesis. Yields were at 23% (d.c.) on average. The single-step one-pot synthesis required a minor change of the IFP™, an additional valve/cartridge was added.

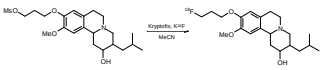
The resulting ^{18}F-BFE was then transferred to another synthesis setup for ^{18}F-Fluroethyl-Labeling.

^{18}F-Fallypride[4]

Synthesis of ^{18}F-Fallypride on Synthera showed improvement to the previously used manual setup. Yields for this one-step one-pot reaction were at 36% (d.c.) on average.

The resulting ^{18}F-Fallypride was used for cell studies and animal scans.

^{18}F-FP-DTBZ[3]



Synthesis of ^{18}F-FP-DTBZ with Synthera showed no improvement to previously used manual setup. This single-step one-pot reaction yielded 6% (d.c.) on average. However, the precursor used was not certified and up to the usual standard.

The resulting ^{18}F-FP-DTBZ was used for cell studies.

Yields and Improvements

	FDG	FLT	FHBG	FP-DTBZ	Fally-pride	BFE	FMiso	F-A85380
Production runs	50	62	8	2	10	7	6	5
Average yield at EOS [%dc]	75	13.6	9	6	36.2	23.7	31.4	34.3
Improvement to previous method	similar	Yield doubled	Yield doubled	similar	Yield 60% increased	*	*	*
Failed runs	1	1	0	0	0	0	0	0

* No previous method, synthesis developed on Synthera

Discussion and Conclusions

Besides FDG routine production, four ^{18}F-radiotracers (FLT, FHBG, Fallypride and FP-DTBZ) were synthesized at UPenn by a manual synthesis set-up. The Synthera synthesis unit offers a convenient and flexible way to synthesize these compounds under remote conditions. BFE was successfully synthesized with Synthera as an intermediate for fluoroethylation. Synthesis of FMiso and F-A85380 were directly developed on Synthera with great success. Yields were high and consistent and the Synthera unit performed very reliably.

Huge advantages of the Synthera syntheses in comparison to the previously done manual syntheses are less exposure, shorter synthesis duration and improved yields. Our focus was on the use of the commercially available IFP™ Nucleophilic and straight forward adaptation and development of radiotracer syntheses to this setup. Synthera showed great flexibility even with a preset synthesis kit. Changes to script and method are quickly and easily done.

Another advantage of the Synthera unit is to be able to switch between compounds within hours. For a center with both an active clinical and research program this kind of flexibility is crucial. For the FDA, the Synthera unit fulfills necessary regulatory requirements and can be used for human use radiotracer production.

References

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Acknowledgments

Thanks to IBA Molecular for providing the Synthera Synthesis box and technical advice.
Also thanks to Ben LeGeyt for running the Cyclotron and delivering ^{18}F and Peggy Nowak and Rahul Poria for performing the QC tests.
All precursors were purchased from ABX Chemicals (except DTBZ), thanks for providing immaculate quality compounds.