

Synthesis of ¹⁸F-L-FDOPA via Nucleophilic Pathway on IBA's Synthera®

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Objectives

¹⁸F-L-FDOPA (FDOPA) is a diagnostic tracer used in the imaging of Parkinson disease, head and neck cancers and, most recently, Neuroendocrine Tumors (NET). The aim of this work is to describe the fully automated synthesis of FDOPA on IBA's Synthera® platform via the nucleophilic method.

Materials/Methods

The process, based on the nucleophilic method developed by Coenen et al [1] (Figure 1) using the new non-carrier-added precursor (ABX 1336), takes place within a set of disposable cassettes (IFP). The synthesis includes trapping, elution and drying of the fluoride, nucleophilic ¹⁸F-fluorination, oxidation of the intermediate and hydrolysis. The purification is carried out in a set of cartridges and the final product is formulated in citrate buffer.

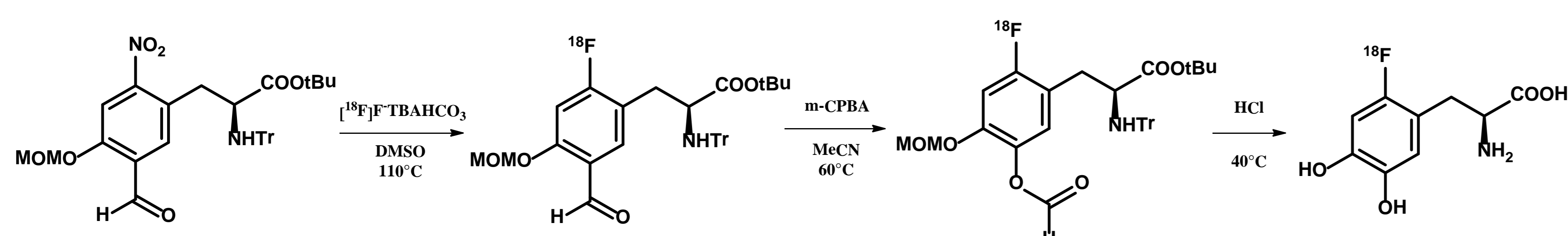


Figure 1: Radiosynthesis of ¹⁸F-L-FDOPA



Synthera® Platform
designed for a GMP
environment



IFP™ cassette
(Integrated Fluidic
Processor)

Results

The trapping of fluoride on the anion exchange cartridge, its elution with Tetrabutylammoniumhydrogen carbonate (TBA) solution followed by azeotropic drying and fluorination of the precursor in DMSO are accomplished on IFP#1 (Figure 2). The intermediate compound is then purified on a reversed-phase cartridge and eluted with m-Chloroperoxybenzoic acid (m-CPBA) in acetonitrile to IFP#2, where the oxidation takes place at 60°C for 20 min. The hydrolysis is performed with HCl at 40°C. The crude mixture is diluted with the citrate buffer (pH 4.5-5.5) and purified via solid phase extraction. Total synthesis time is < 90 minutes and the quality control is within Eur. Pharmacopoeia limits.

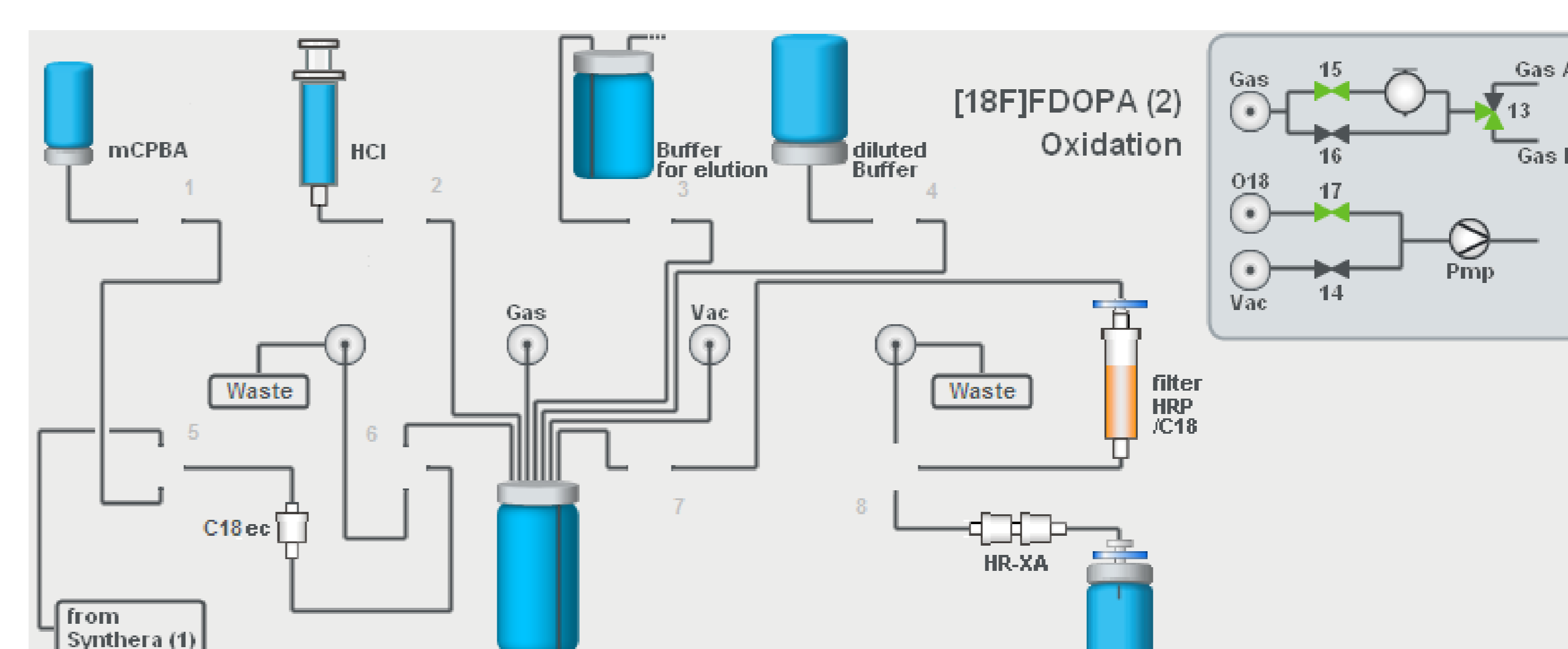
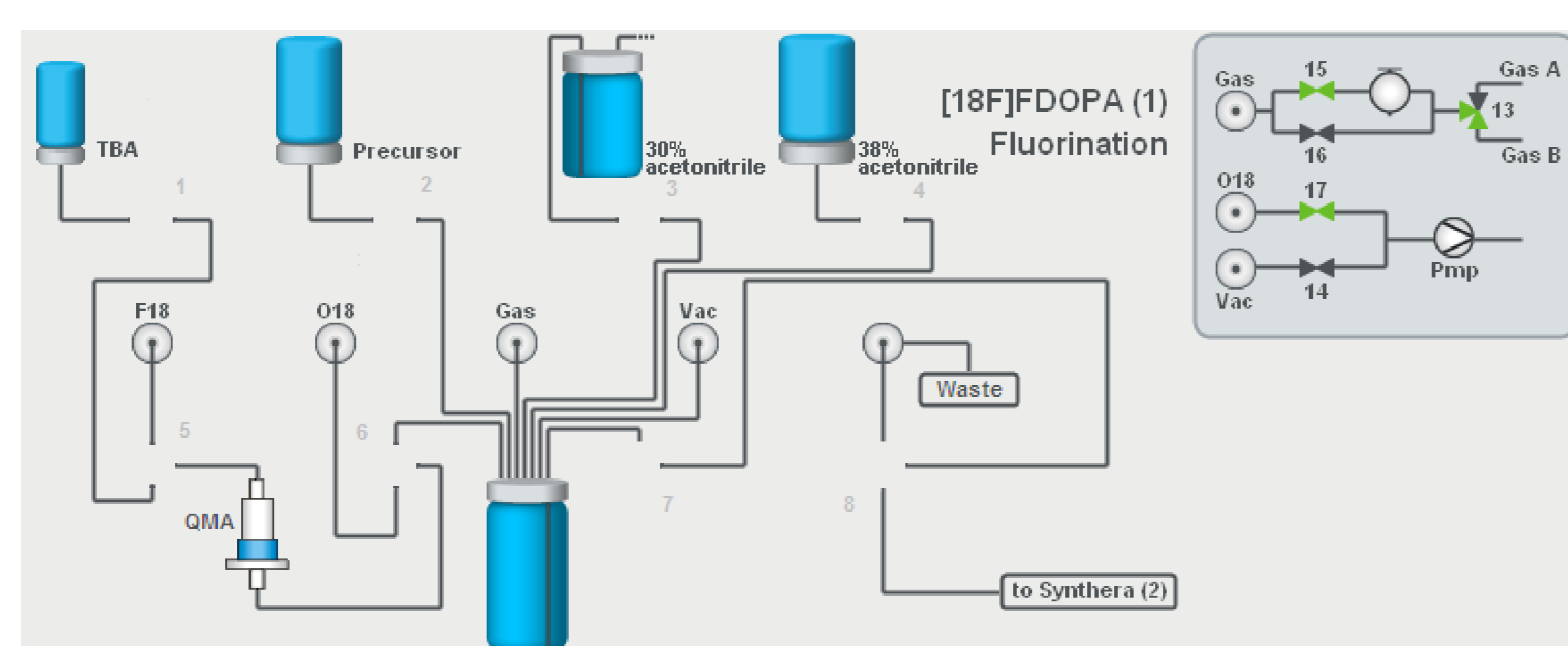


Figure 2: IFP#1 configuration (left) and IFP#2 configuration (right)

Quality control of a typical production is represented in the table on the right. The radiochemical and chemical purity was checked on Waters X-Terra RP C18 5µm 4.6x 250 mm column; mobile phase: 1% HOAc/acetonitrile gradient, flow of 1 mL/min; γ-detector and UV at 254 and 283 nm. For the enantiomeric purity, the final product was analyzed with chiral HPLC using the following conditions: Crownpak® CR+ 5 µm 4 x 150 mm; mobile phase: 20 mM perchloric acid, isocratic flow of 1 mL/min; γ-detector and UV at 283 nm. Gas chromatography was performed with liquid injection (conditions: HP-Fast Residual Solvent, 30 m, 0.53 mm, 1.00 µm, 5 inch cage; gradient: 30°C up to 100°C; 15 min.; FID; Helium carrier gas and flow 3.0 mL/min), for residual solvent determination (acetonitrile, ethanol and DMSO).

Test	Specifications	Results
Appearance	Clear, colorless solution	Comply
pH after dilution	4.0 to 5.5	4.6
Chemical purity		
TBA	< 2.75 mg/10 mL	Comply
Total peak of 6-fluoro-L-DOPA	< 15 mg/10 mL	Comply
Radiochemical purity		
Identification	Retention time of major peak corresponds (± 15%) to the retention time of FDOPA reference standard	Comply
Total peak area of [18F]6-fluoro-L-DOPA	> 95.0%	99.2%
Radionuclidic purity		
Radionuclidic identification (energy of photons)	The only gamma photons have an energy of 511 keV. A sum peak of 1.022 MeV can be observed	Comply
Half-life	105 to 115 min	109.2
Enantiomeric purity		
Total peak of [18F]6-fluoro-L-DOPA	> 98.0%	99.2%
Total peak of [18F]6-fluoro-D-DOPA	< 2.0%	0.8%
Concentration		
Radioactive concentration at calibration time	166.5 to 203.5 MBq/mL	192.5 MBq/mL (20 min)
Residual solvents		
Ethanol	≤ 2500mg/10mL	114
Acetonitrile	≤ 4.1mg/10mL	2.4
DMSO	≤ 50mg/10mL	0.5

Conclusion

Reproducible and reliable FDOPA production via the nucleophilic route is achieved on commercial automated synthesizer resulting in final product of high radiochemical and chemical purity (> 95%) and high enantiomeric purity (> 98%) with n.d.c. yields > 10%.

References: [1] F. M. Wagner, J. Ermert, H.H. Coenen, J.Nucl.Med. 2009,50, 1724-1729