ABX advanced biochemical compounds

FIRST SPE METHOD FOR ROUTINE PRODUCTION OF NUCLEOPHILIC [^{18}F]-L-DOPA

R. Martin, D. Baumgart, S. Huebner, S. Juettler, S. Saul, A. Clausnitzer, J. Mollitor, R. Smits, A. Hoepping, M. Mueller*
ABX advanced biochemical compounds, Radeberg, Germany

Introduction

6-^{18}F-Fluoro-3,4-dihydroxy-L-phenylalanine ([^{18}F]-L-DOPA) is an established radiotracer for diagnosis of the integrity and function of the nigrostriatal dopaminergic system by PET.[1] Moreover, recent studies have emphasized the usefulness of [^{18}F]-L-DOPA for diagnosis of neuroendocrine tumors[2] and several approaches for the synthesis of [^{18}F]-L-DOPA are known today. More recently, several nucleophilic approaches have been developed but, to the best of our knowledge, an automated production of [^{18}F]-L-DOPA including a cartridge-based purification process has not yet been reported.[3,4,5] Using a new developed precursor, we established an automated and remotely controlled process on the GE TRACERlab® MX, ORA Neptis® and Siemens Explora™ One modules which provided crude [^{18}F]-L-DOPA for HPLC purification.

Aim

Our aim was to develop a SPE purification method for the fully automated production of [^{18}F]-L-DOPA using the above-mentioned synthesizers.

General reaction conditions

This nucleophilic synthesis of [^{18}F]-L-DOPA is divided into three steps: (1) labelling, (2) oxidation and (3) hydrolysis. Labelling was carried out using [^{18}F]/TBA complex in DMSO. The labelled intermediate was trapped on a C18ec cartridge to remove DMSO and non-reacted [^{18}F]-fluoride. After elution with acetonitrile, the intermediate was oxidised with *m*-chloroperbenzoic acid. Hydrolysis was carried out with a mixture of ethanol and hydrochloric acid. After final purification, typical yields are in the range of 8-12% (non-decay corrected). The overall synthesis time is 100 min.

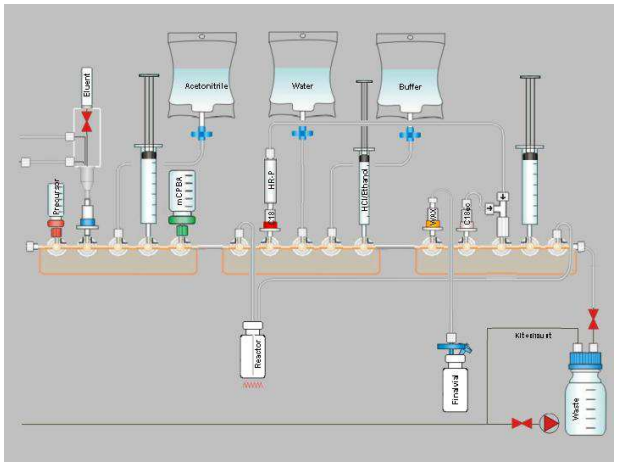

Figure 1: Configuration of the cassette

SPE purification

The crude product usually contains 60 – 70% of [^{18}F]-L-DOPA along with several side products (Figures 2 and 3). [^{18}F]-L-DOPA is a very polar compound which makes SPE purification challenging. As a consequence, trapping on a C18 or HLB cartridge as compared to other [^{18}F]-tracers is not possible. During preparative HPLC purification of [^{18}F]-L-DOPA it was observed that columns made of silica-based reverse-phase (RP) material show worse purification profiles as compared to columns made of polymer-based RP materials.[6] For this reason, we tested HR-P materials and cartridges provided from commercial sources. However, the material of pre-filled cartridges was too low which resulted in incomplete trapping. A custom-made HR-P cartridge finally allowed complete trapping of [^{18}F]-L-DOPA by concomitant removal of the rather large amount of hydrochloric acid. Furthermore, a Sep-Pak Plus C18 cartridge was installed for removal of non-polar by-products and solid impurities. In order to remove the rather non-polar impurity at ~10 min (Figure 3), an OASIS WAX cartridge was installed.

After transfer of the crude mixture onto the cartridges and rinsing with water, pure [^{18}F]-L-DOPA was eluted with citrate or phosphate buffer which contained 3% of ethanol and stabilizers. Using this procedure, [^{18}F]-L-DOPA was obtained in >95% radiochemical purity (Figure 4) and very high chemical purity (Figure 5). The final solution contains 3% ethanol and < 410 ppm acetonitrile. The enantiomeric purity exceeds 98% *ee*.

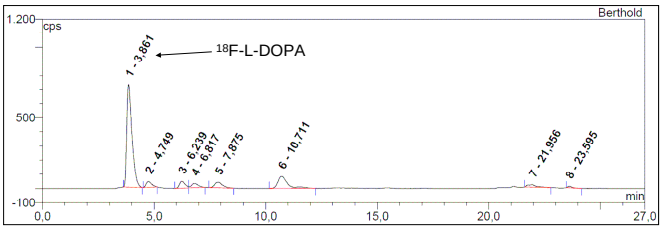

Figure 2: radiochemical purity of crude mixture after hydrolysis (~65% ^{18}F-DOPA, Rt = 3.86 min)

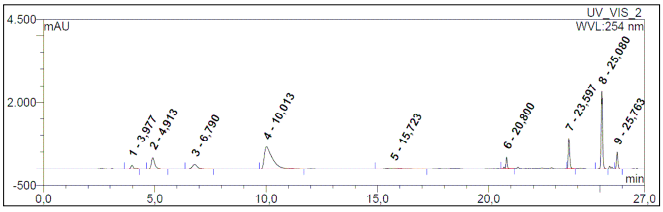

Figure 3: chemical purity of crude ^{18}F-L-DOPA

SPE purification

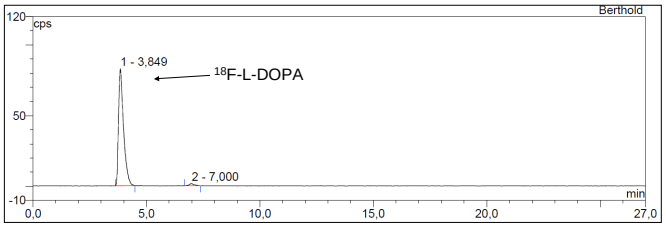

Figure 4: ^{18}F-L-DOPA in >95% radiochemical purity

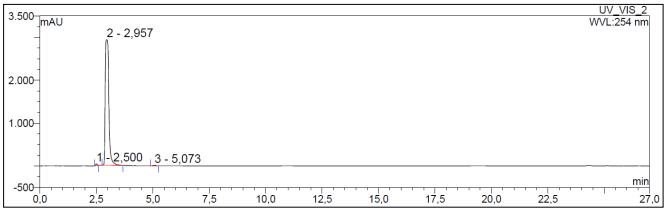

Figure 5: chemical purity

Quality control

Radiochemical/chemical purity: The purity was determined by HPLC using the following conditions: Waters X-Terra, 5 µm, 250 x 4.6 mm, eluent: 1% HOAc/ACN gradient, flow: 1 mL/min, 220, 254, 283 nm, gamma detector.

Enantiomeric purity: The enantiomeric purity of [^{18}F]-L-DOPA was analysed using a Daicel Crownpak® CR(+) chiral column, 5 µm, 150 x 4.0 mm, eluent: 20 mM perchloric acid, flow: 1 mL/min, gamma detector.

Conclusion

For the first time, [^{18}F]-L-DOPA has been successfully synthesized by a fully automated SPE process using the GE TRACERlab® MX_{FDG}, ORA Neptis® and Siemens Explora™ One modules. The one-pot nucleophilic production [^{18}F]-L-DOPA with high specific activity by simple cartridge cleaning is a reliable and convenient method for routine clinical production.

References [1] J. P. Seibyl, W. Chen, D. H. S. Silverman, *Semin. Nucl. Med.* **2007**, *37*, 440–450. [2] M.-Y. Lu, Y.-L. Liu, H.-H. Chang, S.-T. Jou, Y.-L. Yang et al., *J. Nucl. Med.* **2013**, *54*, 42–49. [3] F. M. Wagner, J. Ermert, H. H. Coenen, *J. Nucl. Med.* **2009**, *50*, 1724–1729. [4] K. Neumann, L. Qin, A. Vavere, S. Snyder, S. DiMagno, *J Nucl. Med.* **2012**, *53* (Supplement 1), 71. [5] L. C. Libert, X. Franci, A. R. Plenevaux, T. Ooi, K. Maruoka, A. J. Luxen, C. F. Lemaire, *J. Nucl. Med.* **2013**, *54*, 1154–1161. [6] F. Füchtner, P. Angelberger, H. Kvaternik, F. Hammerschmidt, B. Peric Simovc, J. Steinbach, *Nucl. Med. Biol.* **2002**, *29*, 477–481.