Microscale One-pot Radiosynthesis of 18F-Labeled Probes

VI. 3. Microscale One-pot Radiosynthesis of ^{18}F-Labeled Probes

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Radiochemistry of no-carrier-added [^{18}F]fluoride (nca [^{18}F]F^-) with high molar activity (specific activity) is essentially microchemistry defined as “chemistry with minute quantities of material”. For instance, the carrier amount of 10 GBq [^{18}F]F^- having a molar activity of 100 GBq/μmol is only 0.1 μmol. Therefore, to better exploit this feature the idea of microreactors was introduced for the radiosynthesis of ^{18}F-labeled probes as an advanced tool allowing the reduction in quantities of reagents as well as rapid and efficient reactions. This concept has been partly exploited in microfluidics, where reactions take place in microchannels filled with flowing reagents However, because of this continuous flow, the overall solvent volume often exceeds several hundred μL, i.e. a volume comparable to that is the same level with a conventional automated radiosyntheses carried out in a glass vessel. Consequently, in such cases the scale reduction advantages associated to microreactors is clearly lost.

One-pot radiosynthesis is a batchwise method for carrying out two consecutive procedures of labeling and deprotection in one reaction vessel. We thought the use of a microreactor to be better suitable to this way of operating and to lead to several advantages over conventional scale radiosynthesis, such as reduction in amount of precious/toxic reagents; increase in precursor concentrations (and thus in radiochemical yields); easier and faster purification. For this purpose we successfully minimized the amount of K.222/$KHCO_3$ needed for an efficient recovery of [^{18}F]F^-. In this report we describe a new microscale method for the one-pot radiosynthesis of two widely used ^{18}F-labeled probes: [^{18}F]fallypride, a dopamine D2/D3 radioligand and *O*-(2-[^{18}F]fluoroethyl)-L- tyrosine ([^{18}F]FET), a positron emitting tyrosine analog for tumor imaging.

[^{18}F]Fallypride and [^{18}F]FET were prepared according to the synthesis schemes shown in Fig. 1. Their precursors, tosyl-fallypride (2 mg) and TET (12 mg), were obtained from ABX and dissolved in 1 mL of either DMSO or MeCN. Using the 20 mM K.222/$KHCO_3$-MeOH containing K.222/K[^{18}F]F (Solution A), which was prepared by eluting [^{18}F]F^- retained by an Oasis MAX cartridge with 20 mM K.222/$KHCO_3$-MeOH (see the present CYRIC Annual Report for details), the following 3 methods were performed to develop microscale one-pot radiosynthesis.

- Method 1: a 5-50 μL portion of the 20 mM K.222/$KHCO_3$-MeOH containing K.222/K[^{18}F]F (Solution A) was put in a small glass vial (300 μL) and evaporated to dryness at 85°C with He (200 mL/min). To the residue was added the same volume as Solution A of precursor solution (DMSO for [^{18}F]fallypride or MeCN for [^{18}F]FET) and then heated for the reaction.
- Method 2: a 5-50 μL portion of Solution A in a glass vial was brought to 300 μL with MeOH and evaporated to dryness at 85°C with He (200 mL/min). The same volume of precursor solution (DMSO for [^{18}F]fallypride or MeCN for [^{18}F]FET) was added to the residue and then heated for the reaction.
- Method 3: a 5-50 μL portion of Solution A in a glass vial was brought to 300 μL with MeOH followed by addition of 5-50 μL of DMSO. The MeOH was carefully evaporated and to the remaining DMSO was added the same volume of a MeCN solution of precursor. MeCN was quickly removed by evaporation and the vial was capped and heating was continued.

For [^{18}F]FET 2 M HCl was added to the reaction solution and the mixture was heated at 120°C for 10 min. The reaction solution was cooled in an ice bath and then diluted with KF (1 M). RCYs were determined by HPLC analysis of the crude solution (column: InertSustain C18, 4.7 x 150 mm; Solvent: MeCN/20 mM NaH_2PO_4/MeCN 40:60, 2.0 mL/min for [^{18}F]fallypride, MeCN/10 mM H_3PO_4 10:90, 2.0 mL/min for [^{18}F]FET). These analytical conditions were also applied to the purification of the crude product.

The radiochemical yields (RCYs) obtained for both probes with the three methods were compared. Method 1 was not practical because only a part of the total volume of the MeOH eluate was used but an ideal procedure to provide the highest RCYs at a given solvent volume, whereas Method 2 was a simulation of a practical procedure which started from the same volume of the MeOH with that eluted from the MAX cartridge (300 μL).

Figure 2 indicates that RCYs for the two probes in Method 1 gradually decreased by decreasing the solvent volume down to 20 μL, with a drastic drop beyond this point. On the other hand, RCYs in Method 2 were more markedly affected by the volume reduction, suggesting that this straightforward approach could not be adopted to practical microscale radiosynthesis due to its low RCYs. The decrease in the RCYs for Method 2 might be caused mainly by deposition of K.222/K[^{18}F]F on the vessel walls that could not be reached by the reaction solvent. In Method 3 addition of DMSO, which was expected to catch and concentrate K.222/K[^{18}F]F during MeOH evaporation, considerably improved the RCYs of both [^{18}F]fallypride and [^{18}F]FET. Although RCYs did not exceed those obtained by Method 1, Method 3 seems to be promising for further improvement in developing practical microscale radiosynthesis.

Figure 3 demonstrates that HPLC purification of the crude products obtained by microscale radiosynthesis was conveniently performed with an analytical column. The purifications were finished within 5 min for [^{18}F]fallypride and 4 min for [^{18}F]FET.

In conclusion, addition of DMSO to the MeOH eluate prior to its evaporation provided an efficiently concentrated solution of [^{18}F]F^{-} for microscale radiosynthesis of [^{18}F]fallypride and [^{18}F]FET. The present results were presented at International Symposium on 22nd Radiopharmaceutical Sciences, May 14-19, 2017 in Dresden (Germany).

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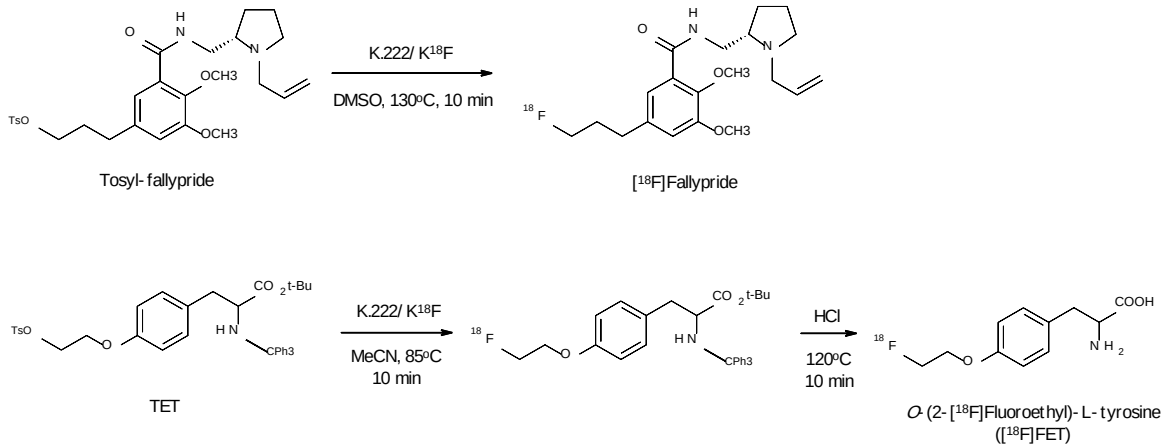

Figure 1. Synthesis schemes of [^{18}F]fallypride and [^{18}F]FET

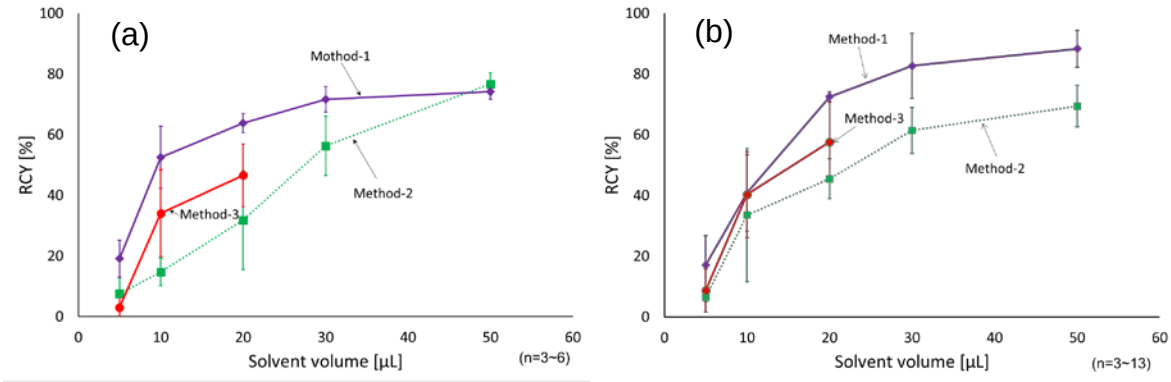

Figure 2. Dependence of RCY on solvent volume in the radiosynthesis of (a) [^{18}F]fallypride and (b) [^{18}F]FET.

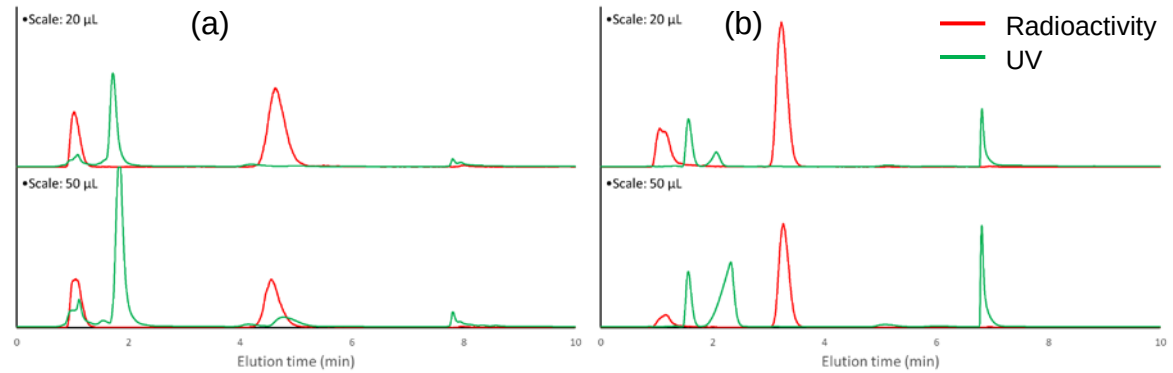

Figure 3. HPLC purification of (a) [^{18}F]fallypride and (b) [^{18}F]FET prepared in 20 and 50 μL scales.

HPLC conditions for [^{18}F]fallypride
- •Column: InertSustain C18 (4.6x150 mm)
- •Solvent: EtOH/20 mM NaH_2PO_4 (25/75)
- •Flow rate: 2.0 mL/min
- •UV: 254 nm

HPLC conditions for [^{18}F]FET
- •Column: InertSustain C18 (4.6x150 mm)
- •Solvent: EtOH/50 mM AcOH (10/90)
- •Flow rate: 2.0 mL/min
- •UV: 280 nm