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Use of tetrabutylammonium tosylate in conjunction with chiral NiII complex precursor for automated synthesis of [18F]FET

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Background and objectives Due to favorable characteristics in in vivo applications, high specificity and long half-life of 18F (109.8 min), the O-(2-[18F]fluoroethyl)-L-tyrosine ([18F]FET) has become an important tool for molecular imaging of cerebral tumors. In our previous studies we presented a convenient synthesis of [18F]FET via direct nucleophilic fluorination of a chiral NiII complex of an alkylated (S)-tyrosine Schiff base, Ni-(S)-BPB-(S)-Tyr-OCH2-CH2OTs (I) in the presence of K2.2.2 and K2CO3. After acidic hydrolysis [18F]FET was purified using reverse phase and strong cation exchange cartridges. The process was automated on the Scintomics Hotboxone synthesis module. However, when transferring this procedure to TRACERlab FX N Pro, commonly used 18F-radiolabeling platform, we observed two radiolabeled by-products that were not amendable to SPE purification procedure. Their formation may be a consequence of reaction vessel design (high volume/surface vs small amount of reaction mixture) and possible over-heating during vacuum drying of 18F-fluoride complex. As the construction of the heating block was amendable to modification, we have focused on improving fluorination process, substituting the K2.2.2/K2CO3 mixture with an alternate PTC - tetrabutylammonium tosylate (TBAOTs). The SPE purification protocol was also adjusted to better suite TRACERlab FX N Pro.

Methodology Aqueous [18F]fluoride solution (1.3 ml) was loaded on Waters QMA carbonate Plus light Sep-Pak cartridge (46 mg). The cartridge was rinsed with 5 ml of MeOH and dried using gas flow; the [18F]Fluoride was eluted with 700 µl of MeOH with 4 mg of TBAOTs.. After solvent removal 4 mg of I in 700 µl of MeCN was added, and reaction mixture heated to 80oC for 7 min. After acidic hydrolysis (0.5M HCl, 110 oC, 5 min) the reaction mixture was diluted with 11 ml of water and 2.5 ml of 0.1M NaOH. Resulting basic solution (pH 9) was passed through small filtration column and three tC18 Light cartridges connected sequentially. [18F]FET was eluted with 10 ml of sodium acetate solution (5 mM, pH 4) containing 3% of EtOH and further purified by passing through CM Plus cation exchange cartridge to removal any residual nickel.

Results and discussion Replacement of K2.2.2/K2CO3 with TBAOTs allowed us to substantially increase radiochemical conversion (RCC > 85%, radioTLC). Formation of radiolabeled by-products discussed earlier was not observed using gradient HPLC analysis. [18F]FET was obtained with radiochemical purity >99% and enantiomeric purity 94-95%. Decay corrected radiochemical yield was 50%, synthesis time ca. 35 min.

Conslusion Using non-aqueous solution of TBAOTs as an inert PTC allowed for substantial increase of fluorination efficiency while avoiding formation of radiolabeled by-products. The radioactivity loss on the inner surfaces, which is critical for the reaction vessel on the TRACERlab FX N Pro, was minimized. The proposed synthesis methodology appears to be well-suited for transfer to other automated synthesizers for nucleophilic synthesis of 18F-labeled radiotracers.

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