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Optimization of the automatic synthesis of 16α-[18F]fluoroestradiol in the SYNTHRA RNplus Research Module

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Introduction: 16α-[18F]-fluoroestradiol ([18F]FES) is used for estrogen receptors imaging in breast cancer diagnosis and follow up. Although reported methods use similar labelling procedures, optimal hydrolysis and purification conditions may be different according to the module used. No data referring SYNTHRA RNplus Research Module were found in the literature.

Objective: The aim of the present study was the optimization of the automatic synthesis of [18F]FES using the SYNTHRA RNplus Research platform.

Methodology: Synthesis of ([18F]FES) was achieved by reaction of 1 mg of 3-O-methoxy-methyl-16β-epiestriol-O-cyclic sulfone in 1 ml of anhydrous acetonitrile with 37 GBq of [18F]F at 100℃ for 10 min (Fig. 1). The product was hydrolyzed at 100℃ for 12 minusing different conditions: 1) 1.0N HCl, 2) 2.0N HCl in acetonitrile: water (3.0 ml, 9:1 v/v) and 3) 0.5N H2SO4 in ethanol: water (3.0 ml, 9:1 v/v). Purification was performed by HPLC using a C18 column (VP250/10 SynthraReeperbahn, 5 μm) flow rate: 2.0 ml/min, λ=280 nm, using either a) Ethanol: water 50:50 or b) Water: Etanol: Acetonitrile (50:25:25) as mobile phases. The peak was either diluted with 0.9% NaCl (a) or with 50 ml of water and purified with a Sep-Pak C18 Plus-Light cartridge (b).
The radiochemical purity (RCP) was determined by HPLC using a Phenosphere column (ODS 80 A, 250x4.6 mm, 5 μm), flow 1.5 ml/min. and a gradient of acetonitrile in water (acetonitrile 10% to 90% from 0 to 10 min) and λ=280 nm.

Results and discussion: The module contains a reduced volume reactor (7 mL, conical shape) to perform the labelling and a standard reactor for the hydrolysis.
Synthesis of ([18F]FES) was developed by a standard procedure and the labelling yield (aprox. 25%) was similar to reported data.
Hydrolysis and purification are the critical steps and different conditions were assayed in order to optimize the RCP of the product. Hydrolysis can be performed either using HCl or H2SO4. The use of H2SO4 led to the formation of less impurities and consequently was selected for further experiments. Purification was developed by preparative HPLC. The selection of ethanol as only organic solvent offers the advantage of the simplicity of the final conditioning. However, this condition led to poor RCP (<90%). The use of a mixture of ethanol and acetonitrile, on the other hand, required an additional step of solid phase extraction but rendered a RCP of aprox. 100%
In all the syntheses, the pH was in the range 5.0-6.0, the residual Kryptofix® was below the limit and the residual solvents (acetone, acetonitrile and ethanol) met the specifications.

Conclusion: The synthesis of [18F]FES was optimized in a SYNTHRA RNplus Research platform. The best hydrolysis condition was the use of 0.5N H2SO4 in ethanol: water (3.0 ml, 9:1 v/v) and the purification by HPLC using Water: Etanol: Acetonitrile (50:25:25) as mobile phase followed by solid phase extraction to remove acetonitrile.
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