Efficient Synthesis of 2-Bromo-1-[^{18}F]fluoroethane and its Application in the Automated Preparation of ^{18}F-fluoroethylated Radiopharmaceuticals

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Introduction:
^{18}F-Fluoroalkylation is an effective way to introduce a no-carrier-added (nca) ^{18}F-fluorine label into molecules comprising hydroxy-, amino- or amido-moieties. In comparison to a direct ^{18}F-fluorination of relevant precursors, this method is not negatively affected by acidic groups which are often found in complex molecules.

The most common ^{18}F-fluoroalkylating agent is 2-[^{18}F]fluoroethyltosylate ([^{18}F]FETos) introduced first by Block et al. [1]. 1-Bromo-2-fluoroethane (BFE, [^{18}F]BFE) in comparison has slightly better alkylating properties in dipolar aprotic solvents than [^{18}F]FETos and might diminish purification problems by generally using acetonitrile [2]. There are several examples in the literature for the synthesis of [^{18}F]BFE starting from different precursors [3]. All methods include a final distillation of the [^{18}F]BFE from the reaction vessel into a receiving flask, which makes an integration into an automated synthetic system difficult. For that reason, [^{18}F]BFE has not been applied often as a secondary labelling precursor yet, although the quality of bromide as a leaving group in nucleophilic substitutions in dipolar aprotic solvents like DMSO, DMF and acetonirile is slightly better than the tosylate leaving group [4]. Thus [^{18}F]BFE could become an alternative for the use as a ^{18}F-fluoroethylating agent in automated radioactive syntheses of ^{18}F-labelled pharmaceuticals.

As as examples for the easy and effective use of [^{18}F]BFE we chose the syntheses of 1-(2-[^{18}F]fluoroethyl)-4-benzylpiperidine and benzyl-(2-[^{18}F]fluorethylamine in acetonitrile and compared it with 2-[^{18}F]fluoroethyltosylate.

Results and discussions:
The radiolabelling of [^{18}F]BFE for the non-automated applications was performed via the reaction of 1,2-dibromoethane and the [^{18}F]fluoride/Kryptofix®2.2.2/ carbonate-complex in acetonitrile using a 1 ml septum sealed reaction vial.
1,2-Dibromoethane (2-5 mg) was added and the mixture was stirred for 2 min at a reaction temperature of 70°C. The mixture was diluted with 20 ml water and passed through a LiChrolute®EN-cartridge. The fixed product was eluated with acetonitrile (1 ml) and immediately passed through an Alumina®B-cartridge into a receiving flask.
The whole preparation time was 10 min and the overall radiochemical yield was between 60-70% (uncorrected). The radiochemical purity was >98% (fig.1).
This procedure was easily integrated into an automated system developed for the routine ^{18}F-fluoroalkylation of eligible precursors with [^{18}F]BFE.

To analyse its chemical purity, the concentration of 1,2-dibromoethan after purification of the crude radioactive reaction product with the combined EN- and AluminaB-cartridges was determined. An HPLC calibration curve (UV at 254 nm) for 1,2-dibromoethan was measured within concentrations of 1,2-dibromoethan ranging from 1-27 mmol/l. However, the UV-chromatogram of [^{18}F]FBE after the purification using the Alumina®B-cartridge demonstrated a total absence of 1,2-dibromoethane, at least below our minimum detectable limit of 1-2 mmol/l.

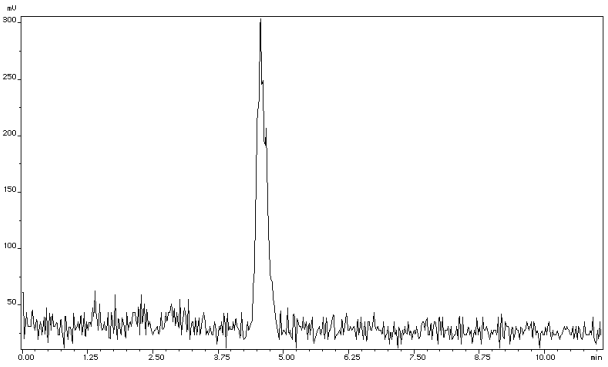

Fig 1: HPLC-chromatogram of pure [^{18}F]BFE obtained after the purification procedure

Conclusion:
The [^{18}F]BFE can be used for further labelling reactions directly and on line, i.e. without destillation or purifications using HPLC. This might be a significant advantage compared to the purification required for [^{18}F]FETos.

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