EFFICIENT SYNTHESIS OF 2-BROMO-1-[^{18}F]FLUOROETHANE AND ITS APPLICATION IN THE AUTOMATED PREPARATION OF ^{18}F-FLUOROETHYLATED RADIOPHARMACEUTICALS

S. Comagic, M. Piel, R. Schirrmacher, S. Höhnemann, F. Rösch

Institut für Kernchemie, Johannes Gutenberg University Mainz, Fritz-Strassmann Weg 2, D-55128 Mainz, Germany

Key words: ^{18}F-fluoroalkylation, automated synthesis, radiopharmaceuticals

Summary:
An efficient synthesis of 2-bromo-1-[^{18}F]fluoroethane from commercially available 1,2-dibromoethane and its integration into an automated preparation device was developed for the routine synthesis of ^{18}F-fluoroethylated radiopharmaceuticals. The precursor 1,2-dibromoethane was reacted with the [^{18}F]fluoride/Kryptofix®2.2.2./carbonate-complex in acetonitrile at 70°C for 3 minutes. The crude reaction mixture was diluted with water, loaded on a LiChrolute®EN-cartridge, eluated with acetonitrile and passed through an Alumina®B-cartridge. The method can provide 2-bromo-1-[^{18}F]fluoroethane with 98% radiochemical purity completely free of 1,2-dibromoethan within 10 min, thus avoiding a purifying distillation step. This method was easily integrated into an automated system for the routine synthesis of ^{18}F-fluoroalkylated radiopharmaceuticals.

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]. The disadvantage of this secondary labelling synthon is the inevitable HPLC purification step to avoid the transfer of 1,2-bistosyloxyethane which adversely affects the subsequent ^{18}F-fluoroalkylating step by decreasing the radiochemical yields of the product. Up to now there is no purification method of [^{18}F]FETos available which uses only a combination of cartridges.
Another detriment is the fact that fluoroalkylation reactions with [^{18}F]FETos often only work well in DMSO and DMF rather than in acetonitrile. However, DMF and DMSO can decrease the efficiency of the final HPLC purification step of the labelled product because of peak-tailing and -fronting. 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 practical examples for the effective and simple application 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 Alumina®B-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]BFE 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. We assume that either vinyl bromide with a boiling point of 16°C was formed under the basic reaction conditions within the basic column material, or the 1,2-dibromoethane was hydrolysed and retained on the cartridge.

It was shown in the literature that the elimination rate (E2) of 1,2-dibromoethane is significantly higher than the one of 1-bromo-2-fluoroethane under basic conditions, which supports our assumption [5]. Thus, [^{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.

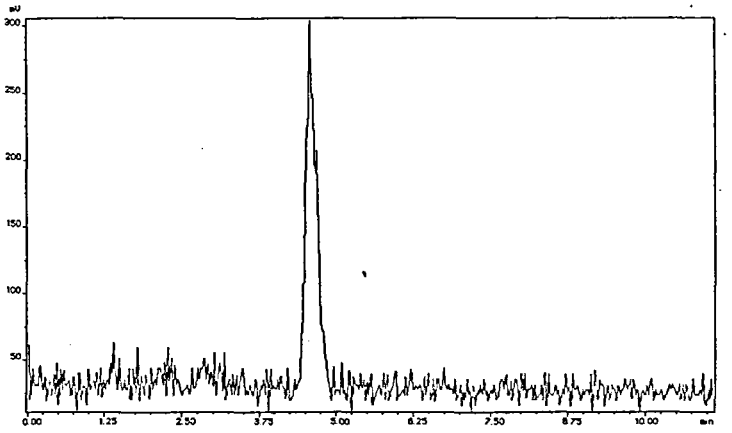

fig 1:
HPLC-chromatogram of pure [^{18}F]BFE obtained after the purification procedure

Conclusions:
A simple synthesis and purification of 1-bromo-2[^{18}F]fluoroethane [^{18}F]BFE via a combination of two cartridges (LiChrolute®EN-cartridge, Alumina®B) is reported. The integration of the described synthesis of [^{18}F]BFE and its purification via different cartridges into an automated system is straight forward. Within a total preparation time of 10 min this automated system can provide a solution of [^{18}F]BFE in acetonitrile for subsequent use in ^{18}F-fluoroalkylation reactions of eligible precursors. [^{18}F]BFE thus is suitable for routine radiopharmaceutical syntheses.

References:
[1] Block D. et al. J. Labelled Cpd. Radiopharm. 25: 201 (1988)
[2] Bunton C.A. Nucleophilic Substitution at a Saturated Carbon Atom. Elsivier, Amsterdam, London, New York
[3] Chie D. J. Org. Chem. 52: 658 (1987)
[4] Streitwieser jun A. Solvolytic displacement reactions. McGraw Hill Book Comp. New York (1962)
[5] Hine J. H. et al. J. Am. Chem. Soc. 78: 5002-5004 (1956)