Radiochemical Synthesis of ^{18}F-labelled Compounds Using the H-Cube® Advance Reactor

INTRODUCTION

Radiochemistry has great importance in research and diagnosis, but working with radioactive materials requires **special processes** and a high level of **safety regulations**. Currently, the involvement of **PET** (positron emission topography) in medical examinations is a generally accepted methodology, which often needs the generation of **^{18}F-labelled compounds**. This isotope has a short, approximately **110-min half-life**, which creates a real challenge for chemists when they are trying to provide a suitable compound and synthetic route that can be easily performed in the shortest time possible. Harvard Medical School, in cooperation with the Massachusetts General Hospital, has developed an efficient, rapid, and reproducible flow chemistry-based methodology for the synthesis of a radiotracer used in PET scans.

INSTRUMENTATION

All reactions were carried out in a combined flow-based system containing:

1. **Nanotek® microfluidic device** from Advion Inc. for the **^{18}F-labelling**
2. **H-Cube® Advance** from ThalesNano for the **hydrogenation** of **labelled compounds**. The products were then purified by a **semi-preparative HPLC** before the formulation for injection by **GE TRACElab FX$_{F-N}$**.

MODEL REACTION

Fluorine-18 labelled fluoroanilines, as building blocks of different radiotracers used in PET, were chosen for the model reaction. First, the **fluorination** of **1,4-dinitrobenzene** with **[^{18}F]Et$_4$NF** was optimized resulting in the ^{18}F-labelled compound in **92% radiochemical conversion** at **180 °C** using a flow rate of **80 µL/min** and **CH$_3$CN** as a solvent. The reaction was carried out in **5 min**.

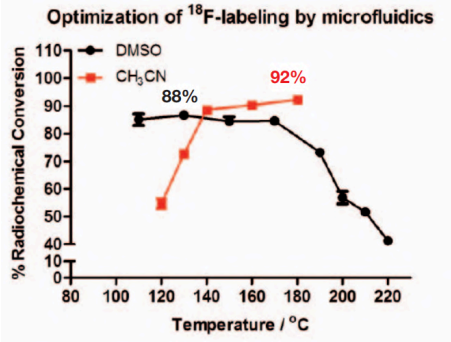

Figure 1: *Optimization of the fluorination step*

During the optimization of the **nitro group hydrogenation**, all parameters – the solvent, the flow rate, the reaction temperature, and the pressure – were screened *(Table 1)*.

A **90% conversion** was achieved in **3 min** at the optimum conditions using **THF** as solvent, **1 mL/min** flow rate, **20 bar** reaction pressure, and **60 °C** reaction temperature respectively. The **Pd/C**-filled cartridges were changed after **15 uses** without any degradation observed.

Finally, the automated isolation resulted in the final compound in **32 ± 5%** (n=3) decay-corrected radiochemical yield with specific activity **>1.2 Ci/µmol**. The whole process required an overall reaction time of **40 min**.

No	Solvent	Temperature (°C)	H_2 pressure (bar)	Radiochemical conversion (%) (n=3)
1	CH_3CN/MeOH (1:1)	30	1	64.3 ± 2.0
4	CH_3CN/MeOH (1:1)	60	1	47.1 ± 2.3
5	CH_3CN	50	10	57.5 ± 1.3
6	CH_3CN	50	20	61.7 ± 1.2
7	THF	50	10	86.7 ± 1.5
8	THF	60	20	90.5 ± 2.9
10	THF	80	50	84.6 ± 4.7

Table 1: *Reaction conditions and results of hydrogenation using a Pd/C catalyst and 1 mL/min flow rate*

SYNTHESIS OF [^{18}F]CABS13

After the model reaction proved the usefulness of applying flow synthesis, the next attempt was the synthesis of **[^{18}F] CABS13**, the radiotracer designed to explore the „metal hypothesis of Alzheimer's disease". Upon performing the same reaction series in **batch**, **30% yield** was achieved. The simplification of the reactions with the combined microfluidic and flow hydrogenation system first required the optimization of the fluorination reaction. Although **DMSO** resulted in a **90% conversion**, **acetonitrile** was chosen as the solvent so that the final material could be produced in one flow without having to involve and additional solvent exchange step for the hydrogenation. However, it should be noted that ThalesNano does not recommend acetonitrile as a solvent because of its susceptibility to hydrogenation.

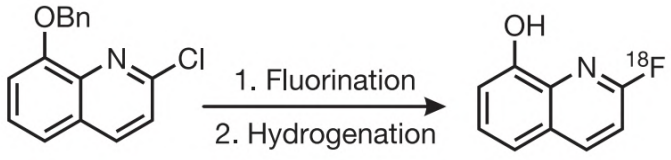

Figure 2: *Synthesis of [^{18}F]CABS13, a PET radiotracer*

Applying a **180 °C** temperature and **10 µL/min** flow rate resulted in the fluorinated compound in **57%**. The ***O*-debenzylation** step was then performed in the **H-Cube® Advance**, and although **10% Pd/C** usually provides high yield for this type of transformation, in this case, only **50-60% conversion** was achieved.

The change to **20% Pd(OH)$_2$/C** catalyst in **THF** at **70 °C**, **1 mL/min**, and **20 bar** could improve the hydrogenation step to a near quantitative yield within **3 min**. After purification, the final compound was isolated with **12 ± 3%** (n=3) decay-corrected radiochemical yield with specific activities **>1.4 ci/µmol** within **45 min** from **dried [^{18}F]fluoride**.

CONCLUSION

It was demonstrated that hydrogenation is not a limiting factor in radiochemical applications anymore. Compared to conventional batch methods, the **H-Cube® Advance** reactor offers many advantages in hydrogenation, enabling the discovery of **new radiopharmaceutical labelled compounds** with short-lived positron emitting radionuclides.

REFERENCE

S. Liang, T. Collier, B. Rotstein, R. Lewis, M. Steck, and N. Vasdev.; Chem. Com., 2013; 49 (78); 8755 – 8757

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