A COMPACT MICROWAVE SYSTEM FOR RAPID, SEMI-AUTOMATED RADIOSYNTHESES

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Introduction

Microwave irradiation has long been used to increase the rate of reactions, generate better, cleaner materials, and to help accelerate transformations that will not occur by any other means. Nowhere, however, does microwave irradiation have a larger potential impact than in radiochemistry. For the short-lived radionuclides, reduction of the reaction time can serve to increase the yield of the final product significantly. Herein we describe the integration of a compact microwave system into a remote-controlled radiochemical synthesizer and utilize it to improve the overall synthetic processes for two ^{18}F-labeled compounds.

[^{18}F]FDG. Production of 2-[^{18}F]fluorodeoxyglucose is used as a benchmark process for any radiochemical synthesizer due to its extremely wide spread use in clinical practice. Its quality control and evaluation are routine procedures. A repeatable, rapid, high-yield synthesis is demonstrated.

[^{18}F]SFB. A novel repeatable, one-pot radiosynthesis of N-succinimidyl-[^{18}F]fluorobenzoate has been developed and is described in poster **P066**: Convenient N-succinimidyl-[^{18}F]fluorobenzoate ([F-18]SFB) Synthesis and Labeling of Biomolecules. Compared with conventional heating, the use of microwave irradiation greatly accelerated this three-step process, resulting in a 30 minute reduction of reaction time alone.

Methods

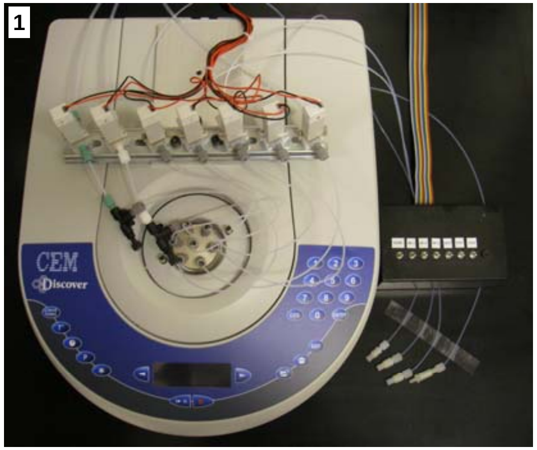
In the first part of this work, a full-sized CEM Discover microwave system (**Figure 1**) was modified so that a 5-mL Wheaton V-vial, equipped with a magnetic stir bar and PEEK adapter lid for tubing connections, could be placed into the irradiation cavity. A remote-controlled radiosynthesizer was constructed based on this microwave module. Seven electrically-controlled solenoid valves were connected to the V-vial via the seven-port PEEK adapter through 1/16" Teflon tubing. Three ports were used for reagent delivery and one port permitted venting of the vial. Another port served as a solution output, where the tubing is extended to the bottom of the vial, and the final two ports were connected to pressurized nitrogen (to transfer product out of the reactor) and a vacuum pump (for evaporations), respectively. Control of the CEM Discover system was accomplished using the Synergy software.

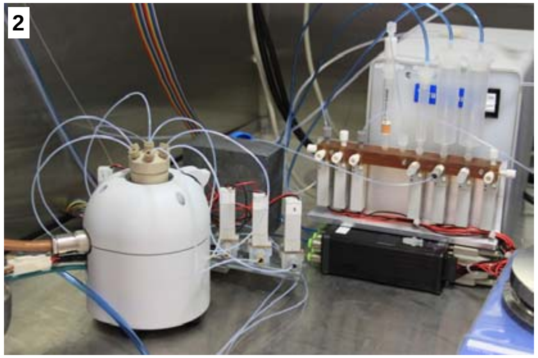
In the second part of this work, the microwave system (**Figure 2**) was miniaturized by decoupling the cavity from the microwave electronics and by shrinking the cavity to the minimum size which can still accommodate a 5-mL vial. A second remote-controlled radiosynthesizer was constructed by adding remote-controlled valve controls for fluid handling and a custom, standalone cartridge purification system.

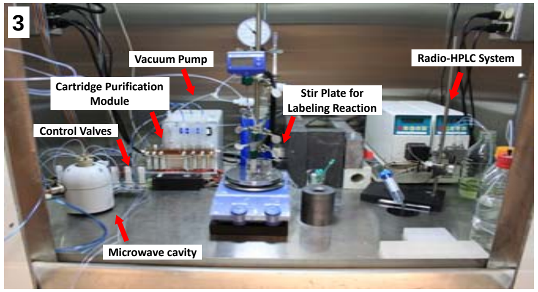
In both microwave reactors, stirring of the reaction mixture with magnetic stir bar is possible, and the reaction vial can be cooled by a stream of gas.

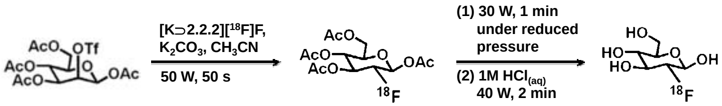
Results

As a proof of principle for the capabilities of the system, [^{18}F]FDG was synthesized. In addition, the radiosynthesis of [^{18}F]SFB was performed by a novel one-pot process. Both processes start from aqueous [^{18}F]fluoride solution. Importantly, the aqueous [^{18}F]fluoride solution was directly dried in the microwave reactor (30W for 3 min x2), simplifying automation of the overall system. Furthermore, the use of microwave irradiation shortened the total reaction time, especially for three-step synthesis of [^{18}F]SFB, from over 30 min to 4 min. The schematic illustration of [^{18}F]FDG production is shown below (radiofluorination, CH_3CN removal and deprotection). Radiochemical yields were about 75% after 15 min of reaction and purification starting from aqueous [^{18}F]fluoride solution. The radiochemical purity of >95% was determined by radio-TLC.

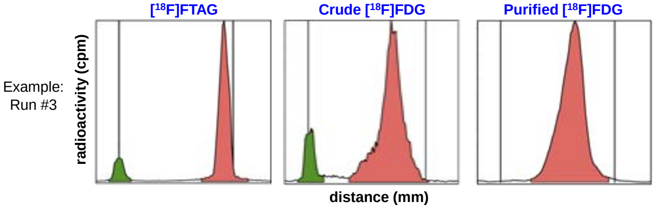








Run #	[^{18}F]FTAG	Crude [^{18}F]FDG	Purified [^{18}F]FDG
1	84%	78%	66.7%
2	85%	85%	70.9%
3	87%	86%	75.4%
4	87%	-	74.7%
5	82%	-	81.3%
6	-	-	84.0%



For [^{18}F]SFB, the one-pot radiosynthesis takes about 40 min from direct drying of aqueous [^{18}F]fluoride solution to the final product. [^{18}F]SFB can be obtained in RCY of 40-60% with >95% radiochemical purity. These results are comparable with conventional automated radiosynthetic production routes, however the setup here is much simpler and the entire process is significantly shorter.

The second-generation microwave system with a miniaturized cavity isolated from megatron and controller takes far less space than the original full-sized CEM Discover module. With a footprint just over 10 cm^2, it could easily fit inside a hot cell or mini-cell, along with analytical equipment, fluid handling system, and cartridge purification system (**Figure 3**). The small size could also be leveraged to implement additional reactors for multi-vessel microwave-assisted syntheses.

Conclusion

Two microwave radiochemical synthesizers were assembled and syntheses of [^{18}F]FDG and [^{18}F]SFB were demonstrated. The compact microwave system enables versatile and speedy one-pot radiochemical syntheses. Further work in our laboratories involves the integration of the miniature cavity into a low-cost, modular radiosynthesizer platform we are developing. These reagent handling, reaction, and purification modules can easily be reconfigured to perform diverse chemical/radiochemical syntheses.