Short Note

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Utility of commercial radiosynthetic modules in captive solvent [^{11}C]-methylation reactions

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The utility of commercial radiosynthetic modules to prepare [^{11}C]-radiotracers using the captive solvent 'LOOP' method is demonstrated with the common radiosynthons [^{11}C]-iodomethane and [^{11}C]-methyl triflate. Several widely utilized radiotracers are prepared by this technique to demonstrate the versatility of the method.

Keywords: methylation; PET; carbon-11; methyl triflate; captive solvent

Introduction

Captive solvent [^{11}C]-methylation reactions have proved extremely efficacious for the radiosynthesis of [^{11}C]-radiotracers from either [^{11}C]-iodomethane or [^{11}C]-methyl triflate.[1–14] A common implementation involves trapping the [^{11}C]-methylating synthon in a standard HPLC injection loop, which has been pre-coated with a small amount of precursor in (usually) a dipolar aprotic solvent such as DMF, DMSO, or ketone.[1] The technique is attractive because of its simplicity (no heating, no cooling required), its ease of automation, its reliability, and its efficiency (no transfer losses). The original description of the apparatus required in-house assembly of commercially available components,[1,15] and subsequently a commercial dedicated apparatus has become available (Auto-Loop^{TM}, Bioscan).

The advantages of [^{18}F]-radiotracers (principally their ability to be shipped off-site) over [^{11}C]-radiotracers have led to the widespread use of versatile modules capable of producing a variety of [^{18}F]-radiotracers over and above [^{18}F]-FDG. Such modules often include HPLC purification and formulation components. We demonstrate here that such modules can easily be adapted to produce [^{11}C]-radiotracers by the captive solvent [^{11}C]-methylation technique. Successful implementation of this technique has allowed us to increase our production of [^{11}C]-radiotracers using existing equipment. In addition, this expansion of the module's capability has allowed us to produce two different [^{11}C]-radiotracers simultaneously by splitting the [^{11}C]-methylation synthon stream.[16,17]

Many laboratories, which at present do not have dedicated captive solvent [^{11}C]-methylation apparatus, can now use their radiotracer modules to carry out such reactions.

Results

A variety of [^{11}C]-radiotracers in general use were successfully synthesized using the FX_{FN} module from either [^{11}C]-iodomethane or [^{11}C]-methyl triflate (Table 1). Our in-house 'LOOP' apparatus and the FX_{FN} box gave very similar outcomes, i.e. times of syntheses, radiochemical yields, and specific activities were within 15% of each other. Splitting of the stream to allow delivery of the [^{11}C]-methylation synthon to both our in-house 'LOOP' apparatus and the FX_{FN} module allowed the simultaneous production of two different [^{11}C]-radiotracers.[16,17] The stream splitting also had no effect on the outcome of either process, apart from the reduced overall quantities produced by the reduction in starting radioactivity in each module.

In all the cases residual solvent was less than ICH guidelines for injectables.[18] Final solutions were sterile, pyrogen-free, with a pH of 6–8. Several radiotracers ([^{11}C]-PIB, [^{11}C]SB-13, [^{11}C]-PE2I) required the addition of ascorbic acid to solutions to prevent radiolysis during formulation.[4,19] For the sake of conformity, we use ascorbic acid for all formulations.

Discussion

Many commercial modules for the production of short-lived radiotracers (including those designed for either [^{18}F] or [^{11}C]) are equipped with HPLC purification capabilities, including the ability to load crude material onto an injection loop, monitor the chromatogram, collect the appropriate fraction, and formulate the purified radiotracer into an appropriate form for animal or human studies. All that is required to adapt the modules to [^{11}C]-captive solvent methylations is to plumb the line carrying the stream of [^{11}C]-iodomethane or [^{11}C]-methyl triflate into a clean, dry HPLC injection loop. An ability to detect radioactivity build-up in the injection loop is advantageous, but not critical. The built-in capabilities of the module essentially take care of the rest. The results summarized in Table 1 clearly demonstrate that standard radiosynthesis modules are readily adaptable to the production of a variety of PET radiopharmaceuticals using

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Table 1. Synthesis of [^{11}C]-radiotracers using captive solvent techniques on the FX_{FN} module

Radiotracer	Reaction time (min)	Solvent	Base	Precursor amount (mg)	Radiochemical yield (%)
PE2I	1.5	DMF	TBAOH (1 N in MeOH, 2 μL)	0.9–1.1	15–20
PIB	1	2-Butanone	None	0.4–0.5	7–9
Raclopride	3	DMSO	NaOH (5 N, 3 μL)	1.0–1.2	9–14
DASB	5	DMF	None	1–1.1	15–20
SB-13	1	2-Butanone	None	0.5–0.6	6–8
DTBZ	1	DMF	TBAOH (0.5 N in MeOH, 3 μL)	0.4–0.5	12–15
Harmine	1	DMF	TBAOH (1 N in MeOH, 3.5 μL)	1–1.2	15–16
SKF 82957	3.5	DMF	$NaHCO_3$ (1 N, 10 μL)	0.8–1.1	12–16

Yields are uncorrected from trapped [^{11}C]-CO_2, ca. 900 mCi, and refer to the final formulated product. All radiochemical purities were greater than 95%. All precursors were used as the free base except for SKF 82957(SKF 81297 hydrochloride). PIB and SB-13 required [^{11}C]-methyl triflate – all others are derived from [^{11}C]-iodomethane. Radiosynthesis times, including purification and formulation, were 25–30 min from end of bombardment, while specific activities were routinely greater than 1500 mCi/μmol (at end of synthesis).

the captive solvent methylation 'LOOP' technique. Indeed during the course of this work, Shao demonstrated that a different module could be used to prepare [^{11}C]-raclopride and [^{11}C]-carfentanil by essentially the same techniques.[20]

Methods

Set-up: A General Electric Medical Systems (GEMS) TRACERlab FX_{FN} module was prepared for use as a captive solvent module by the following steps (refer to Figure 1):

(1) With the HPLC valve in the 'Load' position, the HPLC loop is cleaned and dried by passing acetone through it followed by drying with a stream of N_2 for 5 min.
(2) The inlet nut on the HPLC valve (position ♯1) is replaced by a needle injection port (Valco ♯VISF-2).
(3) The precursor solution (80 μL[1]) is loaded onto the clean and dry injection loop.
(4) The needle injection port is replaced by a PTFE line (1/16 in OD, 1/32 in ID) that delivers the [^{11}C]-methylation synthon: either [^{11}C]-iodomethane or [^{11}C]-methyl triflate.

Only the stability of the precursor solution limits the timing of the above steps. For example, for [^{11}C]-DASB, the precursor solution of which is quite stable, the steps could be performed hours before end of bombardment (EOB) – whenever it is convenient. For [^{11}C]-PE2I, the less stable precursor solution is optimally loaded onto the HPLC loop 5 min before EOB.

Implementation: Upon completion of the above steps, the module is ready to receive the synthon, either [^{11}C]-iodomethane or [^{11}C]-methyl triflate:

(i) Trapping of radioactivity in the HPLC injection loop is monitored by viewing the background signal increase in the built-in HPLC radiation detector. This signal is quite noisy as the detectors used with this specific GEMS system are insensitive GM tubes; however, the signal obtained is quite sufficient to observe the process (Figure 2). A solid-state detector close to the HPLC loop would offer an improvement, however, especially if working with low levels of radioactivity.
(ii) Upon maximal trapping of the radioactivity, the N_2 stream carrying the [^{11}C]-methylation synthon is stopped and the reaction occurs for a pre-determined time interval (1–5 min usually).
(iii) The contents of the HPLC loop is injected onto the purification column by switching the position of the HPLC injection valve.
(iv) Standard executable 'time lists' are then employed for fraction collection and solid-phase formulation on the FX_{FN} module.[21]

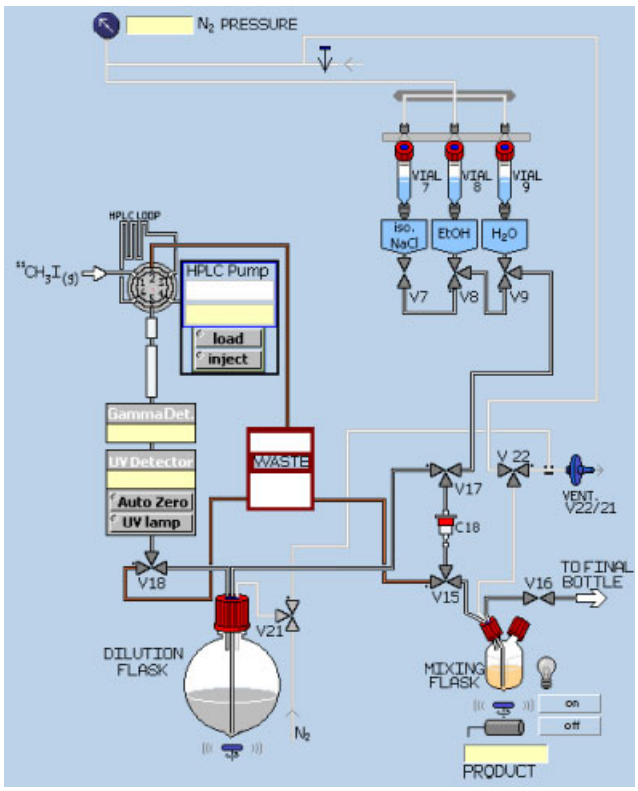

Figure 1. Plumbing diagram of the FX_{FN} module modified for [^{11}C]-methylations by the captive solvent technique. Only the relevant part of the FX_{FN} module is shown. This figure is available in colour online at www.interscience.wiley.com/journal/jlcr.

As an example specific conditions are described below for the radiosynthesis of [^{11}C]-PIB on a GE FX_{FN} module (refer to Figure 1).

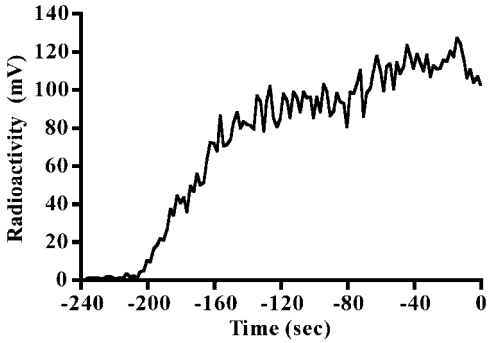

Figure 2. Trapping of [^{11}C]-iodomethane in the HPLC loop monitored by the built-in GM tube. Loop contents were injected onto HPLC at t=0.

Radiosynthesis of [^{11}C]-PIB[4,22]

1. Vials 7, 8, and 9 of the module were charged with saline (10 mL plus 0.25 mL of 4% ascorbic acid in sterile water), ethanol (1 mL), and sterile water (5 mL plus 0.25 mL of 4% ascorbic acid in sterile water), respectively.
2. The dilution vessel was charged with 23 mL sterile water, 2 mL aq. 1 N $NaHCO_3$, and 2 mL of 4% ascorbic acid in sterile water.
3. A solution of the normethyl precursor[4,22] (0.4 mg) in dry 2-butanone (80 μL) was loaded onto the HPLC loop of the FX_{FN} module.
4. [^{11}C]-methyl triflate[23] was delivered to the HPLC loop in a stream of N_2 gas (20 mL/min).
5. One minute after trapping of maximal radioactivity in the loop, its contents were injected (by switching the HPLC valve) onto the HPLC column (Phenomenex Luna2 C18 10 μm, 250 × 10 mm) and eluted with 40% CH_3CN:60% H_2O+0.1 N NH_4HCO_2, 9 mL/min.
6. The fraction containing the product (t_R = 9 min) was collected in the dilution vessel, trapped on a tC18 plus Sep-Pak (Waters), and washed with water from vial 9. The product was eluted from the Sep-Pak by ethanol from vial 8 into the mixing vessel, followed by saline from vessel 7. The contents of the mixing vessel were then passed through a 0.22 μm sterile filter into the final bottle, pre-charged with 1 mL of sterile 1 N $NaHCO_3$.

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