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Studies of the mechanism of the in-loop synthesis of radiopharmaceuticals

Andrei R. Studenov*, Salma Jivan, Michael J. Adam, Thomas J. Ruth, Kenneth R. Buckley

TRIUMF, PET Group, 4004 Wesbrook Mall, Vancouver, British Columbia, V6T 2A3, Canada

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Abstract

A series of experiments were performed to better understand the mechanism of the In-loop [^{11}C]CH$_3$I-methylation. The timing of [^{11}C]CH$_3$I delivery is critical for the high yield of radiolabeling since in-loop radioactivity trapping is reversible. Trapped radioactivity escapes faster from a Tefzel loop compared to a PEEK- or stainless steel loop. Up to 50% of delivered radioactivity may be concentrated at the loop origin (representing 8.1% of the total loop volume). A five-fold reduction of the reaction solvent volume and/or precursor amount may lead to a decrease of the product radiochemical yield either by lowering the in-loop radioactivity trapping or by diminishing conversion of [^{11}C]CH$_3$I into the product.

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1. Introduction

In many radiosyntheses with the short-lived radionuclide carbon-11 the radioactive agent, in a gas phase, is introduced into the solution of the precursor as [^{11}C]CH$_3$I or [^{11}C]methyl triflate. In some cases, these reactions could be conveniently carried out in a thin (0.75–1 mm i.d.) tubing loop typically attached to the HPLC injector (Wilson et al., 2000; Iwata et al., 2001, 2002). Methylation with [^{11}C]CH$_3$I is by far the most widely used reaction in the synthesis of carbon-11 PET radiotracers. However, little is known about the details of in-loop [^{11}C]CH$_3$I-methylation such as the distribution of radioactivity in the loop and the limit for the amount of the precursor and solvent necessary for the success of the radiosynthesis. Only the use of DMF and DMSO as the solvent for in-loop [^{11}C]CH$_3$I-methylation have been reported.

To partially fill the gap in the understanding of in-loop [^{11}C]CH$_3$I-methylation (Table 1) we studied the dynamics of radioactivity distribution in a Tefzel tubing loop placed in a PET scanner using the synthesis of [^{11}C]carfentanil as a model reaction. The radioactivity distribution pattern was further verified by separately eluting the origin (containing 8.1% of the loop volume) and the rest of the tubing; different loop materials: Tefzel, PEEK and stainless steel (ss) were compared. An assessment of the longitudinal distribution of radioactivity along the segments of the tubing loop at the end of the radiosynthesis was done using a radio TLC scanner. The possibility of decreasing the amounts of the solvent and/or the precursor in the radiosyntheses of [^{11}C]carfentanil and [^{11}C]SCH23390 was probed. The use of DMF, DMSO and acetonitrile as the solvents for the in-loop synthesis of [^{11}C]DTBZ ([^{11}C]dihydrotetrabenazine) was compared.

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*Corresponding author. Tel.: +1-604-222-7534; fax: +1-604-222-1074.
E-mail address: studenov@triumf.ca (A.R. Studenov).

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Table 1
Overview of the experiments performed to study in-loop [^{11}C]CH$_3$I-methylation

	Research tool/ method	Tubing material	Tracer	Key findings
A. In-loop radioactivity distribution				
A.1	PET scanner	Tefzel	Car[a]	It is critical to keep the volume of [^{11}C]CH$_3$I delivery gas to a minimum as trapping of [^{11}C]CH$_3$I is reversible. A big portion of delivered radioactivity is concentrated at the loop origin.
A.2	Loop with a separately eluted origin	Tefzel, PEEK, stainless steel	Car, Sch[b]	Up to 50% of delivered radioactivity may be concentrated at the loop origin (containing 8.1% of the total loop volume). Trapped radioactivity escapes faster from Tefzel loop compared to the PEEK and stainless-steel loop.
A.3	Radio TLC scanner	Tefzel, PEEK	Car	No sharp spikes (for example, associated with the individual droplets of the solvent) of radioactivity along the tubing were found. Wave-shape radioactivity distribution along the tubing body was detected.
B. Small amounts of the precursor and/or solvent vs. radiochemical yield				
	Five-fold precursor/solvent decrease	Tefzel, stainless steel	Car, Sch	The volume of the solvent and/or the precursor mass used for the in-loop radiosynthesis cannot be considerably reduced since decreasing the solvent volume leads to reduction of in-loop [^{11}C]CH$_3$I trapping. Lowering of the precursor concentration below some limit while keeping the same solvent volume may lead to a drop in the ^{11}C-methylation yields.
C. The use of the CH$_3$CN as a reaction solvent				
	Comparison of reaction in CH$_3$CN, DMF and DMSO	Stainless steel	DTBZ[c]	The use of DMF and DMSO resulted in poor specific radioactivity of the product. In the case when acetonitrile was used for in-loop synthesis of [^{11}C]DTBZ, the results were highly variable.

[a] [^{11}C]carfentanil,
[b] [^{11}C]SCH23390,
[c] [^{11}C]dihydrotetrabenazine.

2. Materials and methods

All chemicals were acquired from Aldrich or Acros Organics except where noted. The precursor of [^{11}C]SCH23390 in free base form was obtained from JML Biopharm (Vancouver, BC, Canada) Macherey–Nagel polygram sil G/UV$_{254}$ plastic-back TLC plates (4 × 8 cm) were purchased from Bodman Industries (Aston, PA). In all experiments 1/16" Tefzel- (Upchurch Scientific) or stainless steel (ss) tubing of 0.040" (1.0 mm) i.d. or PEEK tubing of 0.030" i.d. were used (total loop volume was always 2 ml). Analyses of the radioactive mixtures were performed with a Waters 600 HPLC pump and controller, Waters 2487 dual λ absorbance detector (set at 229 nm for [^{11}C]carfentanil, 280 nm for [^{11}C]SCH23390 and [^{11}C]DTBZ), and a NaI radioactivity detector with associated electronics and rate meter (Canberra). A short wavelength UV lamp and radio TLC scanner (Bioscan Automatic TLC Linear Analyzer™) were used as UV and radioactivity detectors for TLC analysis. The same scanner was used for measurements of the radioactivity distribution in the tubing loop. The radiochemical purity was determined by radio TLC and analytical radio HPLC.

2.1. Trapping, transfer, storage and release of [^{11}C]CH$_3$I

[^{11}C]CH$_3$I was produced from [^{11}C]CH$_4$ generated in target (Buckley et al., 2000) using an automatic gas-phase synthesizer following a standard synthetic route (Larsen et al., 1995; Link et al., 1995, 1997). The labeled compound was transferred using a stream of helium (flow rate, 15 ml/min) and trapped (at room temperature) on a cartridge (made from stainless steel and fitted with Teflon/silicon septa on both ends) filled with Poropak N (100 mg). The cartridge, in a similar fashion as with all other radiopharmaceuticals produced in our laboratory, was transported in a plastic "rabbit" to the UBC Hospital (where the ECAT 953B PET scanner is located) through a 2.4 km pneumatic line (Burgerjon et al., 1979). After the radioactivity trapped on the cartridge decayed to a level suitable for introducing into the tomograph field of view (20–30 mCi), the [^{11}C]CH$_3$I was released in a stream of helium (flow rate, 5 ml/min) when the cartridge was heated to 80°C (using a metal block heater built to accommodate the Poropak N cartridge, thermocouple and a heating element).

2.2. Pet studies of in-loop radioactivity distribution

The synthesis of [^{11}C]carfentanil was accomplished by [^{11}C]CH$_3$I-methylation of the ammonium salt of the carboxylic acid precursor in DMF in the presence of base [1 equivalent of tetrabutylammonium hydroxide (TBAOH)] as previously described (Dannals et al., 1985; Jewett, 2001; Studenov et al., 2003). The stock solution/suspension of [^{11}C]carfentanil precursor was prepared by adding TBAOH (2.6 μl of 1 M solution in methanol) to the precursor (1 mg, 2.6 μmol) suspended in DMF (100 μl). The reaction loop (Tefzel) was shaped in the form of the planar spiral (max ∅ 20 cm, 1.2–1.5 cm steps) with the inlet axially extruding (7 cm) from the center (Fig. 1). Cartridges (Alltech Associates, Extract Clean Empty Reservoirs fitted with Alltech Syringe Adaptors) filled with cotton wool (50 mg) and Poropak N (200 μl) were subsequently attached at the end of the tubing to capture eluted reaction solvent (DMF) and retain [^{11}C]CH$_3$I that escaped from the loop. The spiral was positioned in-plane inside of the PET camera with the inlet extending axially in the center of the rings. [^{11}C]CH$_3$I was introduced into the spiral tubing preloaded with the solution of the precursor (100 μl). The scanner data acquisition was started simultaneously with the start of the flow of helium (flow rate, 5 ml/min) through the [^{11}C]CH$_3$I cartridge. The scanning protocol consisted of 12 frames of 15 s duration, followed by 4 frames of 30 s, finishing with 5 frames of 120 s. The partial transparency of Tefzel tubing and reservoirs allowed visual observation of solvent movement. In the first PET scanner experiment the flow of carrier helium was maintained for 4 min, and in the second experiment the flow was stopped after the radioactivity trapped in the loop reached maximum (at 1.5 min).

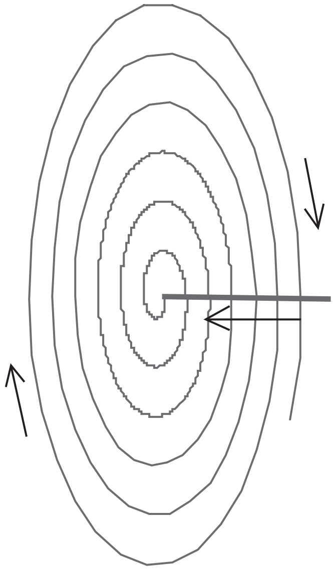

Fig. 1. Schematic representation of the Tefzel tubing spiral used for the study of radioactivity distribution during delivery of [^{11}C]CH$_3$I using a PET scanner . The loop is in the plane of the camera and the inlet proceeds axially.

2.3. General procedure for in-loop radiosynthesis

The precursor solution (100 μl) was loaded into a Tefzel-, PEEK- or ss loop. [^{11}C]CH$_3$I in a stream of helium (flow rate, 15 ml/min) was passed through the loop, and escaped radioactivity was retained on a Poropak N trap, which was positioned ~20 cm from a photodiode radiation probe (Zeisler et al., 1993) used to detect arrival of [^{11}C]CH$_3$I. (Probe sensitivity to γ-radiation decreases proportionally to the square of distance.) The probe was originally positioned against the origin of the tubing; in the later experiments the tubing was tightly wrapped around the probe to assess total trapped radioactivity. After 5 min, the product was purified using either HPLC or an Empore™ HD 10 mm (3 M, St. Paul, MN) extraction disc.

2.4. Separate elution of the loop origin and assessment of the radioactivity distribution along the segments of tubing

In the experiments performed to compare radioactivity distribution in tubing made from three different materials the loop was divided into two segments connected with a 3-way valve; the first segment represented 8.1% of the total length. The whole loop (except a tail attached to the Poropak N trap) was tightly wrapped around the radiation probe. The flow of helium delivering [^{11}C]CH$_3$I was stopped when the probe reading reached a plateau or started to decline. After 5 min, up- and downstream segments of the loop were separately washed with 3 ml of 1:1 ethanol: water, and, in some experiments, the eluate was analyzed (see Section 2.5).

To assess the radioactivity distribution along the tubing after [^{11}C]CH$_3$I-methylation was finished the tubing was counted on a radio TLC scanner. Because of the high flexibility, the segments of Tefzel tubing could be separately counted on the intact loop. PEEK tubing was cut into 20 cm pieces for measurements, while it was impossible to make ss tubing straight enough for the scanning once it was wrapped around the probe. To keep Tefzel and PEEK tubing straight during the measurements it was affixed on the support of the TLC scanner using Transpore™ surgical tape (3 M, St. Paul, MN). This tape leaves no trace of glue once it is removed from the surface after the measurements are complete.

2.5. Dependence of radioactivity trapping and ^{11}C-methylation yields on the amounts of precursor and solvent

2.5.1. [^{11}C]Carfentanil

The radiotracer was prepared as described in Section 2.2. Two further conditions were investigated, a five-fold decrease in both precursor and solvent, and a five-fold decrease in precursor mass only. In all cases the proportion of precursor: base remained unchanged. In the small solvent volume-small precursor mass experiment, an aliquot (20 μl) of the stock solution was injected (using 25-μl HPLC syringe) into the entrance of the Tefzel loop, and the tubing was connected to the remotely controlled reaction system. In the small precursor mass- usual solvent volume experiment an aliquot (20 μl) of the precursor/base stock solution was diluted with DMF (80 μl). The efficiency of in-loop [^{11}C]CH_3I trapping was measured by comparing radioactivity in the product and waste to the radioactivity that escaped from the loop and trapped on the Poropak N. Labelling of [^{11}C]CH_3I to the product was measured by comparing radioactivity contained in the product to the sum of the radioactivity in the product and in waste. To validate the measurements, in some experiments the product and waste samples were analyzed by radioTLC or/and radioHPLC. HPLC, Phenomenex, Synergi Max-RP, 4 μm, 250 × 4.6 mm column; eluent: 30 mM ammonium acetate–70% CH_3CN at 2 ml/min; t_R ([^{11}C]carfentanil) 3.5 min. TLC: 5% triethylamine-(1:1 ethyl acetate: hexane), Rf ([^{11}C]carfentanil) 0.48.

2.5.2. [^{11}C]SCH23390

The synthesis was followed the literature (Halldin et al., 1986; Ravert et al., 1986) except the reaction was conducted in a ss loop according to the following procedure. A solution of desmethyl precursor (free base form, 0.5 mg, 1.8 μmol) in DMF (100 μl) was used. At the end of reaction (5 min), the mixture was injected onto the HPLC, Phenomenex, Ultremex, Silica, 5 μm, 250 × 10 mm column run with 4 mM $(NH_4)_2HPO_4$–80% acetonitrile at a flow rate 5 ml/min; t_R ([^{11}C]SCH23390) 6.0 min. The radiotracer quality control was performed using the HPLC, Waters, Resolve Spherical Silica, 5 μm, 3.9 × 150 mm column with eluent, 4 mM $(NH_4)_2HPO_4$–65% acetonitrile at a flow rate 2 ml/min; t_R 2.0 min.

2.6. Use of acetonitrile as a solvent for in-loop [^{11}C]CH_3I-methylation

2.6.1. [^{11}C]DTBZ ([^{11}C]dihydrotetrabenazine)

The compound was prepared using previously described chemistry (Kilbourn et al., 1995; Jewett et al., 1997; Adam et al., 1999). A solution of nor-precursor (0.15 mg, 0.49 μmol) and tetrabutylammonium fluoride (0.42 mg, 1.6 μmol) in acetonitrile (100 μl) was introduced into the ss loop. At the end of the synthesis (5 min), the radiotracer was purified by HPLC, Waters, Nova-Pak, Prep HR C18, 7.8 × 300 mm column using 0.1 M ammonium formate, 0.5% acetic acid–17% acetonitrile eluent at a flow rate 4 ml/min; t_R ([^{11}C]DTBZ) 8.0 min. Product quality control was performed using HPLC, Waters, Nova-Pak C18, 3.9 × 150 mm column with 0.1 M ammonium formate, 0.5% acetic acid–22% acetonitrile eluent at a flow rate 1 ml/min; t_R 4.0 min.

3. Results and discussion

While several methods could be suggested to study dynamics of the linear radioactivity distribution in a tubing loop, we chose to use a PET scanner as a "whole column radiation detector" (Link and Synovec, 1999). Although primarily used for clinical studies and biomedical research, PET scanners were also recently applied in geology (Maguire et al., 1997) and studies of paper formation (Martinez et al., 2001). As a final step of the gas phase synthesis of [^{11}C]CH_3I, the compound is selectively extracted from the circulating gas using Poropak N trap, and later released in a stream of helium when the trap is heated (Larsen et al., 1995; Link et al., 1995, 1997). Further extending this process we used sorption-desorption on Poropak N to trap, transport (via pneumatic line), store and release [^{11}C]CH_3I.

In principle, the linear distribution of radioactivity along the tubing loop should not significantly depend on the presence of the precursor because [^{11}C]CH_3I could be trapped on the solvent-only loaded loop (Wilson et al., 2000). However, to bring the system to the radiosynthesis-like conditions we used in-loop synthesis of [^{11}C]carfentanil as a model reaction. Since our presumptive hypotheses was that the [^{11}C]CH_3I is predominantly adsorbed within a few centimeters from the origin of the tubing, we extended the inlet of the loop axially while keeping the rest of the tubing in-plane folded in a radially spreading spiral (Fig. 1). Upon the start of the gas flow (5 ml/min) an initial single bolus of solvent divided into many small droplets that drifted along the Tefzel tubing moving back and forth driven by gravity and the flow of helium. At the end of the first PET scanner experiment, more than 90% of delivered radioactivity escaped from the loop. This made it clear that the amount of gas used to deliver [^{11}C]CH_3I into the loop is a critical parameter because trapping of [^{11}C]CH_3I is reversible. Analysis of the radioactivity distribution indicated that maximum radioactivity was trapped in the loop 1.5 min after the start of the helium flow, while most of the radioactivity left the loop after 2 min.

In the next experiment the flow of helium carrying [11C]CH_3I was stopped once the radioactivity counts in the PET scanner reached maximum. Analysis of the axial radioactivity distribution (Fig. 2) at the end of [11C]CH_3I trapping showed that the radioactivity is almost evenly distributed among the two regions: the first representing the inlet 7 cm of tubing extending from the spiral and the second containing the rest of the tubing (folded in a spiral). The observation that the distribution of radioactivity in the tubing loop is very uneven was further confirmed by selectively eluting the first 20 cm (8.1% of the total loop volume or 162 μl) and the last 226 cm of the Tefzel tubing preloaded with radioactivity from the gas-phase [11C]CH_3I system. We found that the first segment contains about one third of the total radioactivity trapped in the loop. Standard uptakes (defined as a percentage of radioactivity concentrated in the tubing segment divided by the percentage of the segment length) were 3.8 ± 0.4 for the first 20 cm and 0.75 ± 0.03 ($n = 4$) for the rest of the tubing when the flow (15 ml/min) of carrier helium was stopped after 87 s. The in-loop radioactivity distribution did not depend on whether [11C]carfentanil or [11C]SCH23390 precursors were used. Decreasing the amount of [11C]carfentanil precursor 20 times also did not affect the distribution of the radioactivity.

Although a PET scanner is indispensable for many applications, in our case selective elution of the loop segments and counting of the total radioactivity trapped in-loop provided information that is more detailed. Spatial and temporal resolution of the PET scanner is insufficient to match the small diameter of the tubing and fast kinetics of radioactivity distribution, which results in a low accuracy of measurements. However, PET provided the necessary information to design subsequent experiments.

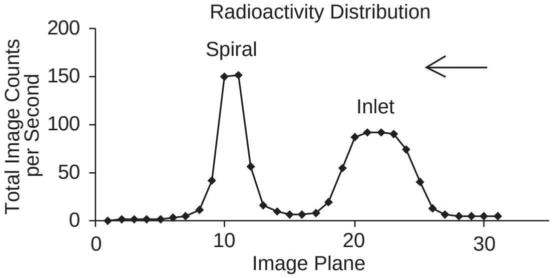

Fig. 2. Axial view of radioactivity distribution in the spiral (Fig. 1). The ECAT 953B PET scanner produces 31 transaxial images each 3.375 mm thick in the axial direction. The data are obtained by placing a large region of interest on each of the 31 axial planes. The loop entrance was between planes 27–17 and contained 54% of the radioactivity trapped in the loop. The spiral was viewed in planes 15–7 and contained 42% of the radioactivity.

Comparison of the three loop materials showed that the loss of the trapped radioactivity is much faster for the Tefzel- compared to PEEK- or ss loops. The amount of the total in-loop trapped radioactivity started to decrease immediately after it peaked at 1.5 min for Tefzel-, while it plateaued at 1.5–2.0 min for the PEEK- and ss loops (as indicated by the probe reading and the escaped radioactivity measurements). The fast release of the radioactivity from the Tefzel loop correlated with a much faster movement of the precursor solution though the tubing, which is due to poor wetability of perfluorinated polymers. [While no release of the solvent from the ss loop was observed after 10 min at 8 ml/min of nitrogen flow (Wilson et al., 2000), it took 3.3 and 0.75 min for the front of the DMF solution to get to the end of the Tefzel tubing when the helium flow rates were 5 and 15 ml/min.] A dependence of the radioactivity standard uptake in the first loop segment on the [11C]CH_3I delivery time (Fig. 3, all loop materials data are superimposed) showed an initial rise followed by a radioactivity clearance corresponding to the shifting of [11C]CH_3I peak along the tubing.

In experiments with the Tefzel loop, a visual inspection of the tubing at the end of the synthesis revealed that the origin of the tubing had almost no visible droplets of solvent, while there were a number of droplets scattered closer to the outlet. Scanning of a few randomly selected 20-cm segments of the tubing on the radio TLC scanner displayed wave-shape radioactivity distribution (with the distribution patterns different in each segment). In the middle and in the end of the tubing, the hills were 7–15 cm wide with the peak to valley ratios in the range of 2–15. No sharp spikes (for example, associated with the individual droplets of the solvent) of radioactivity along the tubing were found. The same pattern of linear radioactivity distribution was observed for PEEK tubing. Since the transfer of [11C]CH_3I in the stream of gas through the solvent-filled

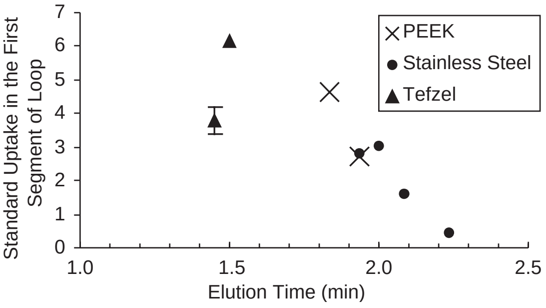

Fig. 3. Dependence of the radioactivity standard uptake (U) in the first segment (162 μl) of the 2-ml loop as a function of [11C]CH_3I delivery time and the loop material ($n = 4$ for the Tefzel error bar).

Table 2
An effect of decreased amounts of reagents on [^{11}C]CH$_3$I trapping and the yield of [^{11}C]CH$_3$I-methylation for in-loop synthesis of [^{11}C]carfentanil and [^{11}C]SCH23390

Synthesis	Radiosynthesis yield at the standard conditions[a]	Decreased precursor & solvent volume[b]		Decreased precursor,[b] unchanged solvent volume	
		Conversion of [^{11}C]CH$_3$I into product (%)	[^{11}C]CH$_3$I trapping (%)	Conversion of [^{11}C]CH$_3$I into product (%)	[^{11}C]CH$_3$I trapping (%)
[^{11}C]Carfentanil	70±12% ($n = 6$)	75	48	75	>85
[^{11}C]SCH23390	43±4% ($n = 3$)	47	53	20	>85

[a] Total decay corrected radiochemical yield, which is mostly determined by conversion of [^{11}C]CH$_3$I into the product since in-loop trapping of radioactivity is typically >85%, The "standard conditions" mass is 1 mg for [^{11}C]carfentanil- and 0.5 mg for [^{11}C]SCH23390 precursors.

[b] Decreased means reduced 5 times compared to standard conditions. At least two measurements were done for each data point.

tubing is a nonlinear process, unless the system reaches a diffusive equilibrium during the ^{11}C-methylation step, a uniform or monotonous distribution of radioactivity along the tubing cannot be expected.

The use of smaller reaction solvent volumes (<100 μl) could bring many advantages to [^{11}C]CH$_3$I-methylation such as use of smaller HPLC columns for product purification. Even with the standard reaction solvent volume, the use of a smaller amount of precursor in each run is also valuable because, in general, it leads to a higher purity of the final product along with saving resources allocated to precursor synthesis or purchase. Particularly, as little as 0.2 mg of precursor has been regularly used for the synthesis of some ^{11}C-tracers (Adam et al., 1999). In order to explore the lower limit for the amounts of solvent and precursor that can be used for in-loop [^{11}C]CH$_3$I-methylation, a series of experiments were conducted where either precursor amount was decreased [5 times, in order to bring it to a level used for the synthesis of some PET radiotracers (Adam et al., 1999)] while keeping the same solvent volume (100 μl), or both the amounts of the precursor and solvent were simultaneously decreased (5 times). The results of the studies (Table 2) indicated that simultaneous decrease of solvent volume (DMF) and precursor mass for both [^{11}C]carfentanil and [^{11}C]SCH23390 lead to 50% decrease of [^{11}C]CH$_3$I trapping, while the yield of the [^{11}C]CH$_3$I-methylation remained unchanged. A five-times decrease of precursor mass when the standard (100 μl) solvent volume was used, as expected, did not affect [^{11}C]CH$_3$I trapping. The yield of [^{11}C]CH$_3$I-methylation dropped by a factor of two for the synthesis of [^{11}C]SCH23390, while the yield of [^{11}C]carfentanil remained unchanged.

Only DMF and DMSO have been previously used as the solvents for [^{11}C]CH$_3$I-methylation (Wilson et al., 2000); however, sometimes these solvents are unsuitable for the radiosynthesis (Klein and Holschbach, 2001). In the case of [^{11}C]DTBZ (Kilbourn et al., 1995) the use of DMF and DMSO resulted in poor specific radioactivity of the product [ca. 1 Ci/μmol compared to 2.0–4.5 Ci/μmol ($n = 8$, EOS) when acetonitrile was used as a solvent]. Our application of acetonitrile as a solvent for in-loop synthesis of this radiotracer caused highly variable product yields [20–45% ($n = 8$) decay corrected radiochemical yield with respect to [^{11}C]CH$_3$I after 35 min total synthesis time]. Despite this, because of its simplicity and convenience, in-loop radiosynthesis was adopted for routine [^{11}C]DTBZ production. Variable product yields could be attributed to the low boiling point of acetonitrile, which leads to formation of no-solvent (no-reaction) zone(s) within the tubing.

4. Conclusions

In the in-loop syntheses with [^{11}C]CH$_3$I, it is critical to keep the volume of [^{11}C]CH$_3$I delivery gas to a minimum as trapping of [^{11}C]CH$_3$I is reversible. Upon delivery, about a third of the introduced [^{11}C]CH$_3$I is retained within the first 20 cm from the origin of the Tefzel tubing while the rest of the radioactivity is non monotonously distributed along the rest of the loop. A similar pattern of the radioactivity distribution was observed for PEEK and stainless steel tubing. Trapped radioactivity escapes faster from Tefzel loop compared to the PEEK and stainless steel loop. The volume of the solvent and/or the precursor mass used for the in-loop radiosynthesis cannot be considerably reduced since decreasing the solvent volume leads to reduction of in-loop [^{11}C]CH$_3$I trapping. Lowering of the precursor concentration below some limit while keeping the same solvent volume may lead to a drop in the ^{11}C-methylation yields. In the case when acetonitrile was used for in-loop synthesis of [^{11}C]DTBZ, the results were highly variable. Modern PET systems such as microPET or HRRT may provide a means for assessing the special/temporal distribution of reaction mechanisms in the loop to address the question further.

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