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ARTICLE

Continuous-flow synthesis of [^{11}C]raclopride, a positron emission tomography radiotracer, on a microfluidic chip

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Abstract: ^{11}C-labelled radiotracers such as [^{11}C]raclopride are produced in a process that can take between 45 and 60 min to complete. These conventional approaches can consume upwards of 75% of the ^{11}C ($t_{1/2}$ = 20 min) due to radioactive decay alone, even more if synthesis losses are considered. To compensate, a large starting quantity of radioactive precursors such as [^{11}C]methyl iodide is required to produce an adequate amount of the tracer for injection. In this investigation, a continuous-flow microchip is explored for the purpose of synthesizing ^{11}C radiotracers in a shorter time by exploiting the favorable reaction kinetics of using smaller reaction volumes. To enhance the mixing of reagents within the microchannel, a micromixer "loop" design was used in fabricating various polydimethylsiloxane chip styles. With a loop design implemented in an abacus-style chip for the production of nonradioactive raclopride, shorter reaction times, reduced precursor use, and improved yields were possible when compared with the use of a simple serpentine design (no loop-style chip). However, when performing the equivalent radiochemical reaction, the results were not as favorable. Using the loop design in a full loop-style chip, parameters such as premixing the reagents, reducing flow rate, and varying reagent concentrations were explored to improve the yields of [^{11}C]raclopride (in terms of relative radioactivity) formed. The full loop chip design produced the best results, and future work will see the polydimethylsiloxane prototype chip design translated into a glass chip for further optimization.

Key words: microfluidic reactor, positron emission tomography (PET) imaging, radiotracer, raclopride, polydimethylsiloxane (PDMS) chip.

Résumé : Les traceurs radioactifs marqués au ^{11}C, tel le [^{11}C]raclopride, sont produits selon un procédé pouvant durer de 45 à 60 min. Il arrive que ces méthodes conventionnelles consomment jusqu'à 75 % du ^{11}C ($t_{1/2}$ = 20 min.) rien que par désintégration radioactive, et davantage si l'on tient compte des pertes de synthèse. Pour compenser ces pertes, on doit utiliser une grande quantité initiale de précurseurs radioactifs, comme l'iodure de [^{11}C]méthyle, afin de produire une quantité adéquate de traceur pour l'injection. La présente étude porte sur l'emploi d'un microréacteur à flux continu pour synthétiser plus rapidement des traceurs radioactifs marqués au [^{11}C] en tirant parti de la cinétique de réaction favorable due à l'utilisation de plus petits volumes de réaction. Pour améliorer le mélange des réactifs dans les microcanaux, on a utilisé un dessin de micromélangeur à « boucles » pour fabriquer divers styles de puce en polydiméthylsiloxane. L'utilisation du dessin à boucles dans une puce de style abaque pour produire du raclopride non radioactif a permis de réduire les temps de réaction ainsi que la consommation de précurseurs et d'augmenter le rendement comparativement à l'utilisation d'un simple dessin en serpentin (puce de style sans boucles). Cependant, lors de l'exécution de la réaction radiochimique équivalente, les résultats n'ont pas été aussi encourageants. En se servant du dessin à boucles dans une puce de style entièrement en boucles, on a examiné des paramètres tels que le prémélange des réactifs, la réduction du débit et diverses concentrations de réactifs en vue d'améliorer le rendement en [^{11}C]raclopride (mesuré par la radioactivité relative). La puce entièrement en boucles est celle qui a donné les meilleurs résultats, et dans le cadre de futurs travaux, le prototype en polydiméthylsiloxane sera converti en une puce en verre afin de poursuivre l'optimisation. [Traduit par la Rédaction]

Mots-clés : réacteur microfluidique, tomographie par émission de positrons (TEP), traceur radioactif, raclopride, puce en polydiméthylsiloxane (PDMS).

Introduction

Positron emission tomography (PET) is a sensitive technique used for the in vivo monitoring of biochemical and physiological processes. This nuclear imaging technique uses short-lived positron emitting isotopes such as carbon-11 (^{11}C) ($t_{1/2}$ = 20 min) in synthesized radiotracers that are administered to patients for research or diagnostic purposes. PET has demonstrated uses in various areas of medicine, e.g., [^{11}C]raclopride ([^{11}C]Rac) is used in psychiatry for dopamine receptor imaging, [^{11}C]meta-hydroxyephedrine is used in cardiology for adrenergic receptor imaging, ^{11}C-labelled Pitsburgh compound B ([^{11}C]PiB) is used in neurology for amyloid plaque imaging, and L-[methyl-^{11}C]-methionine ([^{11}C]MET) is used in oncology for tumor imaging.[1–3]

Currently, the challenge with C-11 radiotracer production is in developing a rapid, efficient, and safe radiolabelling platform.[2] Since the radiolabelled precursors are short-lived, any production processes completed within 2–3 half-lives can result in over 75%–88% radioactivity loss through radioactive decay.[4] Therefore, large amounts of initial activities are needed to compensate for the loss in decay and excess amounts of expensive precursor (10^2–10^6 mol difference between the precursor and ^{11}C-labelled methyl iodide ([^{11}C]MeI)) are used to accelerate the radiolabelling process.[5] Re-

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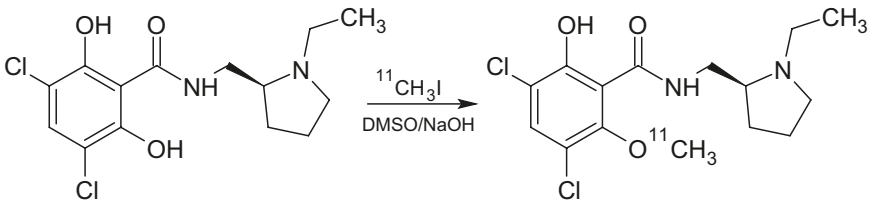
Scheme 1. [^{11}C]Rac synthesis using [^{11}C]MeI.[5,31,33]



cently, microfluidic reactors have shown improved synthesis performance and product purities over conventional processes.[6,8–11] This is attributed to the enhanced mass and heat transfer because of the increased surface area to volume ratio in the microchannels (up to 50 000 m^2/m^3 compared with conventional laboratory reactors at 1000 m^2/m^3).[4,7,12–21] The microfluidic reactor geometry facilitates the optimization of reaction conditions such as temperature, flow rate, and residence time.[17–21] For example, Ratner et al. used a simple serpentine microfluidic reactor to explore a glycosylation reaction where the product stereochemistry is dependent on temperature, solvent choice, stoichiometry, and concentration.[12,22] Using the microfluidic reactor, they were able to reduce reagent quantities compared with conventional methods and efficiently handle microlitres of volume. Also, using a single batch of reagents usually used for one conventional experiment, they were able to carry out up to 44 experiments at varied experimental conditions. Furthermore, maximum conversions were achieved within a short residence time (26–213 s).[22] With an enclosed system and controlled reaction conditions, they were also able to retrieve data that improved their understanding of the reaction kinetics.[12,22]

The development of a quick process using microfluidics for PET radiotracer production has attracted a great deal of attention.[12,23–28] Miniaturization of PET radiolabelling processes has the potential of reducing probe precursor amounts as well as providing better fluid handling and control over reaction conditions.[4,6,29] In addition, the small chip dimensions can reduce workspace and facilitate safer and more localized shielding requirements.[4,7,11,23] ^{11}C radiolabelling examples in the literature have shown reaction times and radiochemical yields (RCY) that are similar to the conventional methods. For example, Lu et. al. were able to radiolabel a carboxylic ester using [^{11}C]MeI on a continuous-flow T-shaped microchip that is 200 μm wide and 60 μm deep with a total volume capacity of 0.2 μL. The precursors 3-(3-pyridinyl)propionic acid and [^{11}C]MeI were both introduced through separate inlets, and at a 1 μL/min flow rate, they were able to achieve RCYs as high as 88%.[14] This was completed using reduced reagent amounts in a residence time of 12 s and total processing time of 10 min at room temperature. However, to the best of our knowledge, there have been no investigations of [^{11}C]Rac synthesis on a microfluidic chip.

In this work, we investigate the radioactive synthesis of a ^{11}C radiotracer, [^{11}C]Rac. This is an important compound for brain research due to its high binding affinity and selectivity as a dopamine D2/3 receptor antagonist.[7] Currently, [^{11}C]Rac is synthesized in a methylation reaction using [^{11}C]MeI (see Scheme 1).[14] The reaction consumes up to 1.7 mg of expensive precursor (desmethyl raclopride (DMR)) with a total production time of up to 45 min, limiting the commercial availability of [^{11}C]Rac.[5,30–34] Our goal is to explore the use of a continuous-flow microreactor chip for the rapid, efficient, and safe radiosynthesis of [^{11}C]Rac. A continuous-flow microfluidic reactor system involves the continuous pumping of fluids into the microchannels and collection of product from the outlets (plug-flow).[10] This type of microreactor is found to shorten the reaction time, reduce the precursor consumption, and allow for safe and remote operation of a disposable microreactor chip.

Experimental

General

Rac was purchased from ABX GmBH (Radeberg, Germany) and the free base DMR precursor was purchased from JML Biopharm Inc. (Vancouver, British Columbia). Both reagents were stored at –20 °C until use. The SU-8 50 photoresist and SU-8 developer solution used in the microchip molding master fabrication were purchased from MicroChem (Newton, Massachusetts). Sylgard 184 crosslinking silicone prepolymer and the curing agent used to make the polydimethylsiloxane (PDMS) chips were acquired from Dow Corning (Midland, Texas). HPLC-grade acetonitrile (MeCN) was purchased from Caledon (Georgetown, Ontario). Extra dry sure-sealed bottle solvents DMSO and MeCN used as reaction solvents were purchased from Sigma Aldrich (Oakville, Ontario).

Fabrication of polymer–glass microfluidic chip

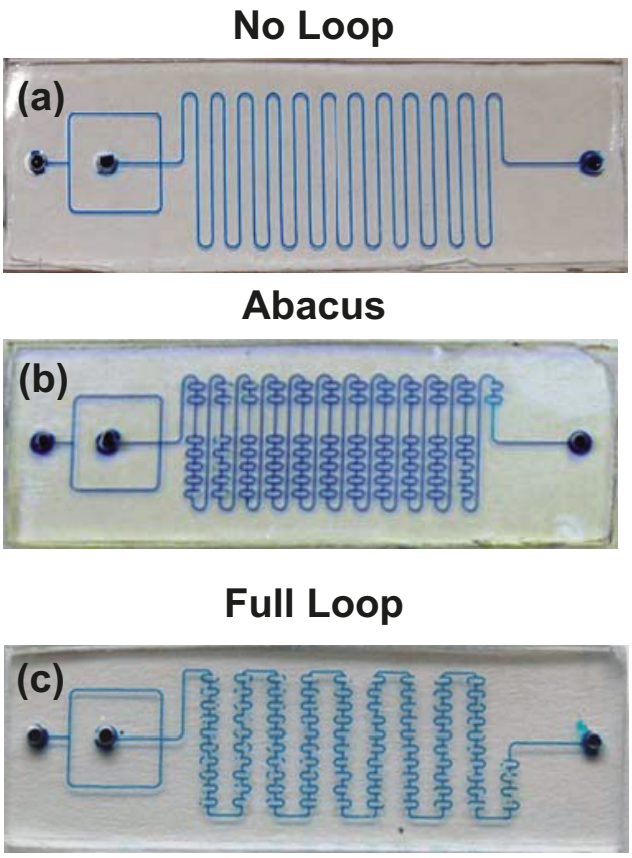
A micromixer design, initially explored by Garstecki et al.[35] for the purpose of mixing samples, was adopted for the radioactive synthesis of [^{11}C]Rac in this work. It was anticipated that the micromixer loop design would induce more mixing as compared with a serpentine or a T-shaped microfluidic reactor chip, previously used for radiolabelling.[6,14,28,29,36–38] Three microchip designs (shown in Fig. 1) were made: no loop (or serpentine, no micromixer loop designs were incorporated), abacus (a combination of micromixer loop design and serpentine design was incorporated in the microchannel), and full loop (the micromixer loop design is incorporated throughout all of the microchannels). The split and recombine design of the microreactor loop design is expected to induce passive mixing through splitting and recombining the fluid streams. Therefore, the full loop chip that has more microreactor loops is expected to have more efficient mixing and high yield. PDMS was used to prototype the microreactor design using a single-layer mold to fabricate the chip.[39–40] Once the PDMS mold (1.2 mm thick) was created, it was bonded permanently to a glass wafer (0.6 mm) using O_2 plasma treatment. The dimensions of the PDMS–glass microchips were 45 mm (length) × 15 mm (height) × 1.8 mm (thickness) with a channel depth of 100 μm. Along with its fast prototyping time, the polymer (PDMS) material was used due to its low cost of fabrication and its compatibility with the solvents (DMSO and MeCN) used in the [^{11}C]Rac synthetic process.

The microchip was mounted in an in-house built Al microchip holder for interfacing to the fluid delivery system. The fluidic connections were made using polyetheretherketone (PEEK) (Fisher Scientific, Ottawa, Ontario) tubing (outside diameter = 1.6 mm) with an inlet tubing inside diameter of 175 μm and an outlet tubing inside diameter of 400 μm. The larger outlet tubing inside diameter was used to avoid pressure buildup (see Fig. 2).[6]

Microfluidic nonradioactive synthesis

Two solutions were made for Rac synthesis: (1) 0.8 mg of DMR (2.4 μmol), unless otherwise noted, was dissolved in 400 μL of DMSO and mixed with 7 μL of 5 mol/L NaOH solution and (2) 120 μmol of MeI added to HPLC-grade MeCN (750 μL). Both solutions were loaded on two separate syringes and the experiment was carried out using a setup similar to the one shown in Fig. 2. A flow rate of 8 μL/min on each pump (16 μL/min total for both) was used.

Fig. 1. Images of the microchips of three micromixer designs (45 mm × 15 mm): (*a*) no loop chip (total channel length = 272 mm, volume = 2.7 μL), (*b*) abacus chip (length = 437 mm, volume = 4.4 μL), and (*c*) full loop chip (length = 356 mm, volume = 3.6 μL). All channels (100 μm wide and 100 μm deep) were filled with blue dyed solutions.



The microchip with the microchip holder was placed on a hot plate, with the temperature monitored using a calibrated thermocouple. During collection of product with a volume of 40 μL (or 80 μL, depending on the collection time), it was immediately quenched using 100 μL (or 200 μL) of 0.1 mol/L ammonium formate ($HC(O)ONH_4$) solution. Multiple runs at various temperatures were carried out.

The product samples were then analyzed using HPLC (Agilent 1100; Agilent Technologies Canada Inc., Mississauga, Ontario). The nonradioactive Rac yield was then quantified using an internal standard (IS), 2,4-dihydroxybenzoic acid.

Microfluidic radioactive synthesis

The radioactive synthesis of [^{11}C]Rac was conducted in the setup shown in Fig. 2. In this case, an in-house made aluminum rotating collection vial holder, capable of holding 12 vials, was used to facilitate vial switching during consecutive collections and to decrease radiation exposure due to reduced contact with vials by the user. DMR (0.8 mg or 2.4 μmol, unless otherwise noted) was dissolved in 250 μL of extra dry DMSO in a reaction vial and mixed with 7 μL of 5 mol/L NaOH. On the other hand, 50–80 mCi of [^{11}C]MeI, which varied by the different amounts of [^{11}C]CH_4 supplied by the cyclotron, was trapped in 250 μL of extra dry MeCN. With a specific activity of 10 Ci/μmol, the radioactivity of [^{11}C]MeI translated to 5–8 nmol.[5] For each batch of DMR, multiple runs were conducted using various flow rates and collection times. A 100 μL (or 200 μL) amount of 0.1 mol/L ammonium formate ($HC(O)ONH_4$) solution was added to each collection vial so that the product sample of 40 μL (or 80 μL) could be quenched immediately after collection.

HPLC product analysis was carried out on a UV-RAD Waters HPLC instrument (Waters 200E; Waters Limited, Mississauga, Ontario).

Results and discussion

Rac nonradioactive synthesis

Initially, the nonradioactive synthesis was explored on two prototypes of the PDMS–glass microchips (i.e., no loop and abacus). Although glass chips are the preference for organic synthesis, we used PDMS chips in this work because of the advantage of fast chip prototyping. The plan is to translate the best design onto a glass chip for future work.

After the microchip synthesis, product mixtures were analyzed using HPLC. As shown in Fig. 3, the peaks of Rac, DMR, and the IS are well separated. The IS was used to determine the peak area ratios of Rac/IS, and these together with the amount of the limiting reagent DMR were used to calculate the Rac yield. As shown in Table 1, at the same temperature of say 82 °C, the abacus chip produced a yield of 5.8%, which was higher than that of the no loop chip. It was thus confirmed that the microchip that incorporated the micromixer loop design gave higher yields compared with the serpentine or no loop microchip reported in the literature. It is believed that the micromixer loop design induces mixing through the split–recombine path of the reagent streams. Furthermore, the continuous-flow microchip allowed us to explore the effect of temperature through multiple runs using a single batch of DMR and MeI, indicating that the Rac yield increased with temperature.

The microchip Rac synthesis process was also compared with the conventional technique. As shown in Table 2, an experiment on the abacus microchip showed a Rac yield of 5.8%, which is comparable with that of the conventional method, conducted at a slightly lower temperature using a previously reported procedure.[5,41] More importantly, the microchip method was achieved in a shorter time (one third), with a reduced amount of MeI (~1/20) needed.

Microchip radioactive synthesis of [^{11}C]Rac

After investigating the nonradioactive synthesis on the microchip, the abacus chip, but not the no loop chip, was selected to conduct radioactive synthesis. Figure 4 shows the UV-HPLC and RAD-HPLC results. On the lower trace, a Rac cold (^{12}C) mass peak was not observed, indicating that the concentrations were below detectable levels in each product sample. Meanwhile, on the inverted RAD-HPLC trace, the corresponding radiolabelled products [^{11}C]Rac and unreacted [^{11}C]MeI were observed.

As substantial ^{11}C side products were formed and the yield (now based on the limiting reagent [^{11}C]MeI) was not optimized, we adopted the relative activity of [^{11}C]Rac (as defined in eq. 1) for comparison purposes.

The [^{11}C]Rac relative activity equation accounts for ^{11}C activity used to make [^{11}C]Rac from [^{11}C]MeI:

$$[1] \qquad [^{11}\text{C}]\text{Rac relative activity (\%)} = \frac{[^{11}\text{C}]\text{Rac RAD-HPLC peak area}}{\text{Total RAD-HPLC peak areas}} \times 100$$

As shown in Table 3, three consecutive experiments were conducted at a flow rate of 10 μL/min (with a residence time of 13 s). The relative activities of [^{11}C]Rac in the three runs are quite reproducible, giving rise to 2.0%. This low value is in part due to the underutilization of [^{11}C]MeI, resulting in substantial relative activity of unreacted [^{11}C]MeI. Nonradioactive MeI was, however, undetected in UV-HPLC due to the low UV absorbance of MeI.

Fig. 2. Microchip synthesis reaction setup in which two syringe pumps are used to deliver the precursor solution (DMR in DMSO) and [^{11}C]MeI solution ([^{11}C]MeI in MeCN).

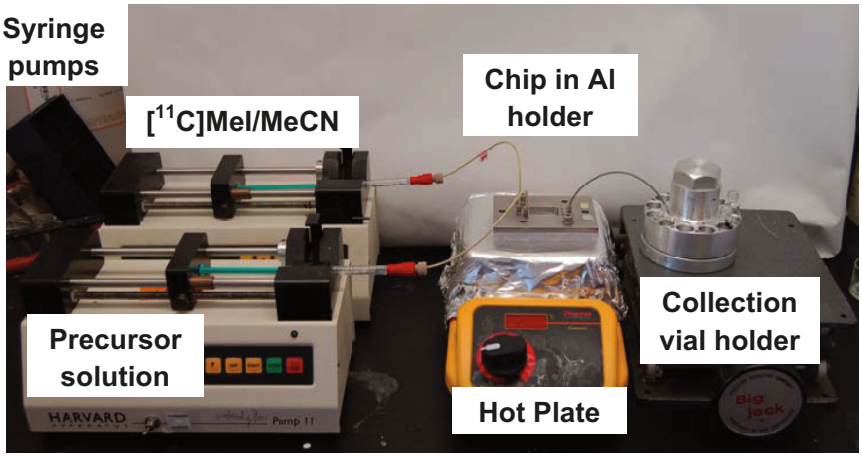


Fig. 3. UV-HPLC chromatogram of a standard mixture containing 2,4-dihydroxybenzoic acid (IS) – DMR – Rac standard solution. The IS, DMR, and Rac concentrations used were 130, 523, and 480 μmol/L, respectively. The HPLC conditions employed a C18 column (Zorbax, 4.6 mm × 150 mm, Agilent) and a UV detector (λ = 240 nm). The mobile phase composition for analysis was 5 mmol/L sodium dihydrogen phosphate buffer (pH ~ 3.0) and MeCN (70:30).

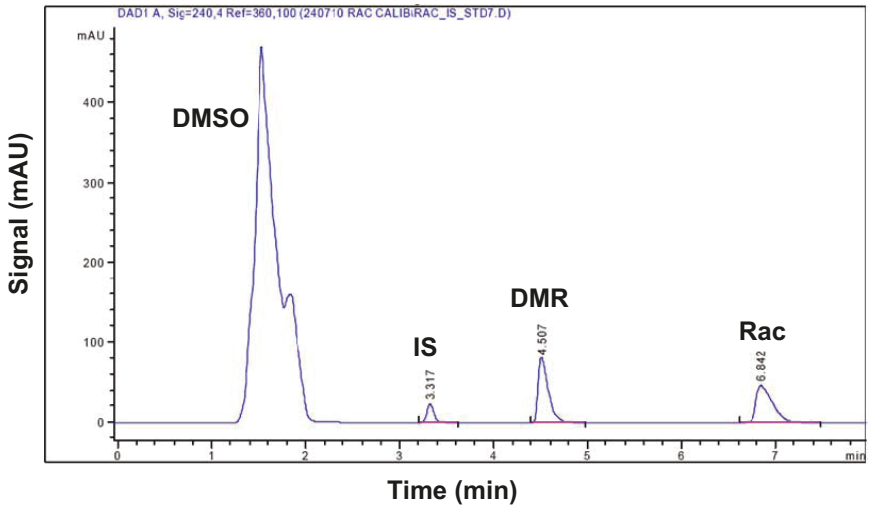


Table 1. Rac nonradioactive synthesis results on the no loop and abacus microchip designs using 2.4–3.9 μmol of DMR and 7.5 μL (120 μmol) of MeI in 750 μL of MeCN at 62–92 °C.

	Rac yield (%)	
Temperature (°C)	No loop[a]	Abacus[b]
62		2.8±0.7[c]
72	0.7	3.3±0.1[c]
82	1.3	5.8
92	2.2	

[a]3.9 μmol of DMR was used.
[b]2.4 μmol of DMR was used.
[c]Errors represent standard deviation of two or three experimental results. In other cases, errors are <0.7% according to the calibration curve.

Table 2. Rac reaction conditions and results comparison in the conventional and microchip nonradioactive synthesis.

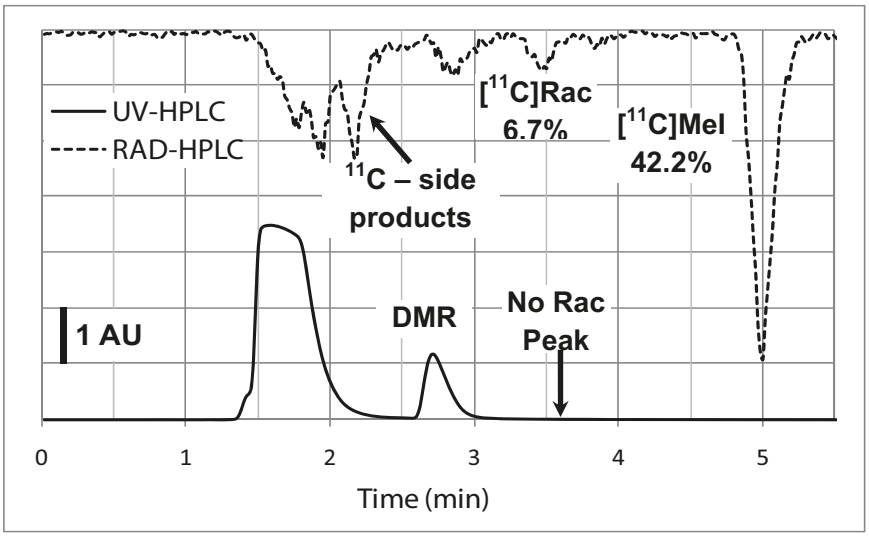
Parameter	Conventional	Abacus microchip
DMR (μmol)	4.2	0.2
MeI (μmol)	120	6.4
Reaction time (min)	15	5
Temperature (°C)	78	82
Rac yield (%)	4.6[a]	5.8

[a]Multiple runs (n = 2) for this conventional process showed a 4.4% ± 0.2% yield.

In an attempt to improve the yield of [^{11}C]Rac, we decreased the rate of fluid delivery into the microchannels or the liquid flow rate. It was believed that the decrease in flow rate increased the residence time, leading to more methylation products and less unreacted [^{11}C]MeI. For instance, a decrease in flow rate from 10 to 2 μL/min increased the residence time from 13 to 66 s and the relative activity of [^{11}C]Rac from 2.0% to 5.1%.

Although the relative radioactivity of unreacted MeI decreased from 84.0% to 51.8%, that of the undesirable ^{11}C side products increased from 14.0% to 43.1%. This suggested that the increased residence time also enhanced side product formation, possibly through other methylation processes or decomposition of the radiolabelled products.[25] The enhanced side product formation

Fig. 4. UV-HPLC and RAD-HPLC for [^{11}C]Rac synthesis on the abacus microchip at 82 °C and a flow rate of 1 μL/min in flow mix mode. The HPLC conditions are a C8 column (Zorbax-SD, 3.5 mm × 150 mm, Agilent) and UV detection at λ = 254 nm and a radioactivity detector (NaI(Tl)/PMT, FC-6106, photodiode). The mobile phase consisted of 5 mmol/L potassium dihydrogen phosphate buffer (pH ~ 2.8) and MeCN (63:37).



Note: The solvent DMSO was detected at ~1.8 min

Table 3. [^{11}C]Rac synthesis results using the abacus microchip where 0.8–1.0 μmol of DMR and [^{11}C]MeI are reacted at 82 °C at varied flow rates.

Flow rate (μL/min)	Calculated residence time (s)[a]	[^{11}C]Rac relative radioactivity (%)
10	13	2.0
		2.0
		2.0
5	26	4.0
2	66	5.1
1	131	6.7

[a]Residence time is calculated using the flow rate and the microchannel length.

indicates that the microchip flow mixing might be efficient for other fast and simple methylation syntheses, while not performing efficiently with the kinetically slower formation of [^{11}C]Rac, resulting in the low relative activity of [^{11}C]Rac.

For further investigation of the residence time effects, the reactant solutions (DMR and [^{11}C]MeI) were premixed before being introduced into the microchannels. This premix mode showed an increase in the [^{11}C]Rac relative activity with reduced levels of unreacted MeI in comparison with the flow mix mode. As shown in Table 4, at a flow rate of 10 μL/min, the [^{11}C]Rac relative activities increased by a factor of ~5 in the premix mode as compared with the flow mix mode. The highest relative radioactivity of 16% was observed when the reagents were flowed in at 2 μL/min. Premixing the reactants increases the interaction time of DMR and [^{11}C]MeI in the microchannel. Instead of the reactant molecules interacting for the first time at the T-junction, they are already interacting as they are introduced into the microchannel. Premixing the reagents may also prevent [^{11}C]MeI from being too concentrated, which can prevent it from reacting with the chip substrate rather than with DMR.

Another factor explored was the microchip design; we performed synthesis on the full loop chip in addition to the abacus chip. Results in Table 4 confirmed increased efficiency when premixing the reagents for the [^{11}C]Rac synthesis using the full loop microchip (25.6%) over the abacus design (16.0%) at a flow rate of 2 μL/min. This improvement was attributed to a higher ratio of micromixer loops to channel length (loop number/length in millimetres) in the full loop microchip (0.26 mm^{-1}) as compared with the abacus microchip design (0.18/mm). The higher relative activity obtained with the full loop chip is attributed to the better mixing and hence better utilization of [^{11}C]MeI, as quantified by the [^{11}C]Rac conversion defined by eq. 2. This parameter determines the efficiency of converting [^{11}C]MeI into ^{11}C compounds, not ^{11}C side products, and disregards the unreacted [^{11}C]MeI, i.e., a higher conversion indicates less side products formed. The highest conversion of 25.6% ± 0.6% was observed when the reagents were flowed in at 2 μL/min in the full loop chip. However, a conversion of 25.6% meant a side product level of 74.4%, most likely due to the radioactivity loss through the use of the PDMS polymer as the microchip substrate (*vide infra*).

Rac conversion accounts for the ^{11}C side products produced during the methylation process:

$$[2] \qquad [^{11}\text{C}]\text{Rac conversion (\%)} = \frac{[^{11}\text{C}]\text{Rac RAD-HPLC peak area}}{\text{Total RAD-HPLC peak areas} - \text{unreacted } [^{11}\text{C}]\text{MeI RAD-HPLC peak areas}} \times 100$$

From the relative activity of [^{11}C]Rac, we were able to calculate the absolute activity of [^{11}C]Rac (see Table 4). After starting with 7.48 mCi of [^{11}C]MeI, the actual [^{11}C]Rac activity was as high as 164 μCi (411 μCi after decay correction) for the abacus chip's premixed experiment at a flow rate of 10 μL/min. This absolute activity was obtained at a short time (3 min) and lower precursor amounts (~1/10 [^{11}C]MeI and ~1/20 DMR) as used in the conventional method. Although the specific activity cannot be evaluated due to the undetected levels of Rac cold mass, it is noted that the final activity is comparable with doses used in some [^{11}C]Rac animal studies in the literature.[42–44] For example, the study displayed in one article uses doses of 20 MBq (or 500 μCi) of [^{11}C]Rac

Table 4. [^{11}C]Rac conversion and absolute product radioactivity at varied flow rates using the abacus and full loop microchip in the premix mode at 82 °C.

Microchip	Flow rate (μL/min)	Calculated residence time (s)	[^{11}C]Rac relative radioactivity	[^{11}C]Rac conversion (%)	[^{11}C]Rac absolute activity (μCi)[a]
Abacus	10	13	10.0	20.5	411
	5	26	11.2	16.8	386
	2	66	16.0	16.9	330
Full loop[b]	2	53	25.6±0.6	25.6±0.6	441±138

[a]Decay-corrected.
[b]Errors for the full loop microchip represent a standard deviation of 4 (n = 4) experimental results.

activity to study the effect of amphetamine on the binding affinity of dopamine D2 receptors over a 90 min period.[42]

From the absolute radioactivity of [^{11}C]Rac and the initial radioactivity of [^{11}C]MeI, both decay-corrected, we can determine the RCY. In the case of the full loop chip at a flow of 2 μL/min, the RCY was found to be 8.9% ± 2.0%. Our RCY value is lower than the values of 17%–45% reported by conventional production methods,[5,45] which can be partially attributed to the use of PDMS as the chip substrate (see Supplementary material for activity loss measurement). Since the PDMS microchip is a prototype, there is room for improvement. Nevertheless, the finding that the full loop chip is a better design is an encouraging result that will lead us to future studies that involve the fabrication of the glass chip with the full loop design for evaluation of the microchip synthesis method.[46]

Conclusion

We have demonstrated that the use of a microchip maintains advantages through improved yields and shorter reaction times for the production of nonradioactive as well as [^{11}C]raclopride. Microfluidic synthesis has improved the nonradioactive synthesis results in comparison with the conventional process by reducing the reaction time by ~33% and required ~5% of the MeI used in conventional preparation. The abacus microchip was found to be a better design than the no loop or serpentine chip to provide a better yield.

For the [^{11}C]Rac synthesis, the full loop chip produced better results, demonstrating higher [^{11}C]Rac relative radioactivity and higher conversion of [^{11}C]MeI to [^{11}C]Rac than the abacus microchip. To evaluate the microchip method further, the reactants were premixed and it was found that the full loop chip still produced better results than the abacus chip, reinforcing the importance of a micromixer design for this process. We have also improved the [^{11}C]Rac synthesis by reducing the flow rate to 2 μL/min. Although we have demonstrated the advantages of lower precursor consumption and safer operation, this modification would not be the most efficient solution on a production scale, since a lower flow rate will decrease production speed. The fabrication of a glass chip with the micromixer design is underway for the full investigation and optimization of the microchip radiosynthesis of [^{11}C]Rac and other labelled compounds. In addition, the behavior of reagents in the microchannels is further explored in a computational fluid dynamics study.[46]

Supplementary material

Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0331.

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