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Synthesis procedure for routine production of [*carbonyl*-^{11}C]desmethyl-WAY-100635 ☆

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Abstract

An improved one-pot synthesis procedure for routine production of [*carbonyl*-^{11}C]desmethyl-WAY-100635 ([^{11}C]DWAY) is described. An efficient purification of the crude product has also been developed and was accomplished by C-18 reversed-phase semi-preparative HPLC using 55/45 EtOH–NaH_2PO_4 buffer (20 mM, pH = 6.5) as the eluent. The desired product fraction was collected in a 2.0–2.5 mL volume and formulated with 11 mL of 0.9% saline. The radioligand was ready for human use in 45 min (EOB). The product was obtained with a radiochemical yield of $11.1 \pm 1.8\%$ (EOB, $n = 15$) with a radiochemical purity of >99%. Specific activity was 133.2–185.0 GBq/μmol (3.6–5.0 Ci/μmol, EOS, $n = 2$) when ca. 37.0 GBq (ca. 1.0 Ci) of starting [^{11}C]CO_2 was used. Unlabeled mass of [^{11}C]DWAY was found to be 0.15–0.24 μg/mL and the precursor was present in less than 50 ng/mL in final production solution.

Keywords: [*carbonyl*-^{11}C]Desmethyl-WAY-100635; 5-HT_{1A} receptors; PET imaging; 1,2-Dichloroethane

1. Introduction

The positron emission tomography (PET) radioligand [*carbonyl*-^{11}C]*N*-(2-(1-(4-(2-methoxyphenyl)piperazinyl))ethyl))-*N*-(2-pyridinyl) cyclohexanecarboxamide ([^{11}C]WAY-100635 or [^{11}C]WAY), is commonly used for quantitation of 5-HT_{1A} receptors in the human brain. However, the desmethyl analogue [*carbonyl*-^{11}C]*N*-(2-(1-(4-(2-hydroxyphenyl)piperazinyl))ethyl))-*N*-(2-pyridinyl)cyclohexanecarboxamide ([^{11}C]DWAY-100635 or [^{11}C]DWAY), which is a metabolite of [^{11}C]WAY, has been suggested to be superior to [^{11}C]WAY. Its higher brain uptake compared to [^{11}C]WAY and fewer labeled metabolites that cross the blood–brain barrier were reported to result in improved counting statistics and modeling (Andrée et al., 2002; Pike et al., 1998).

Although there are a number of studies describing the synthesis and use of [^{11}C]WAY for imaging 5-HT_{1A} receptors, to date, only one synthesis procedure for

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[^{11}C]DWAY, which is based on the methods developed earlier for the synthesis of [^{11}C]WAY by the same group (McCarron et al., 1996), is available in the literature (Pike et al., 1998). This general method utilizes a three step reaction sequence (Fig. 1): (1) [^{11}C]carboxylation of cyclohexylmagnesium chloride with [^{11}C]CO_2, (2) conversion to [*carbonyl*-^{11}C]cyclohexanecarbonyl chloride with $SOCl_2$, and (3) condensation of the resulting labeled acid chloride with the precursor amine. Two method variations were used for the initial stages of the reported preparations. The first method (method A) is based on a single-pot process for the formation of labeled acid, subsequent transformation to the acid chloride and condensation with the precursor amine (13.0 mg, 41 μmol). The method yielded an average of 500 MBq (2.0–2.5%, end of beam, EOB, presumably from 93.0–110.0 GBq of [^{11}C]CO_2) of [^{11}C]DWAY at end-of-synthesis (EOS) with a specific activity of 75.0 GBq/μmol (EOS, $n = 3$). With the second method variation (method B), the [^{11}C]cyclohexanecarboxylic acid was generated by carboxylation with [^{11}C]CO_2 of cyclohexylmagnesium chloride immobilized in a polypropylene tube. The labeled acid was then eluted with $SOCl_2$ (5 μL) in tetrahydrofuran into a reaction vial and was subsequently condensed with the precursor amine (3.5 mg). Using this method, an average of ca. 1.2 GBq (5–6%, EOB) of [^{11}C]DWAY was obtained with specific activity of 105.0 GBq/μmol (EOS, $n = 4$). Synthesis time for both the methods was 45 min. Finally, for both method variations, [^{11}C]DWAY was isolated by sample enrichment followed by reverse-phase HPLC purification using a mixture of 0.1 M ammonium formate–methanol–triethylamine (20:80:0.2 v/v) and, after rotary evaporation, was formulated with sterile saline. Preparations purified in this way were reported to contain low levels of the precursor amine DWAY-100634 (average ~4.0 μg/mL) (Pike et al., 1998).

As described by Pike et al. (1998), even the preferred method (method B) (a) is unsuitable for the production of usable quantities of [^{11}C]DWAY when starting with 37.0–48.0 of [^{11}C]CO_2 normally produced by lower energy (11 MeV) accelerators, (b) the HPLC purification method described, which resulted in the contamination of the final radiopharmaceutical preparations with the precursor amine (DWAY-100634), would have to be improved, (c) the components such as ammonium formate and triethylamine, present in purification buffer, are not suitable for human use, even after complete evaporation of methanol (these components were not removed from the radiopharmaceutical preparations in the published manuscripts and techniques would have to be devised to eliminate their presence), and (d) moreover, removal of the HPLC eluent by rotary evaporation is also a time consuming and cumbersome process. We, therefore, sought a radiosynthesis procedure of [^{11}C]DWAY that would provide higher radiochemical yields along with an efficient HPLC purification procedure for routine clinical studies.

Hwang et al. (1999) reported several refinements to the synthesis (McCarron et al., 1996; Pike et al., 1998) that have resulted in an improved one-pot preparation of [^{11}C]WAY which provided this related tracer in usable quantities (1.1 ± 0.5 GBq, EOS) and with higher specific activity (133.2 ± 70.3 GBq/μmol, EOS) starting from 48.1 GBq of [^{11}C]CO_2. The desired product, after HPLC purification using an acetonitrile/ammonium formate eluent, was further processed with a C-18 Sep-Pak extraction to remove noninjectable components (formate and acetonitrile) before formulation. We report further modifications of this procedure (Hwang et al., 1999) and applied to the synthesis of [^{11}C]DWAY which minimized the formation of unwanted by-products, simplified the purification of the crude product and increased the overall radiochemical yield significantly. In addition, changes to the HPLC purification buffer eliminated the need for additional C-18 extraction.

2. Experimental

2.1. Materials and methods

All chemicals and solvents (HPLC grade) were purchased from either Aldrich-Sigma (USA) or Fisher Scientific (USA) and were used without further

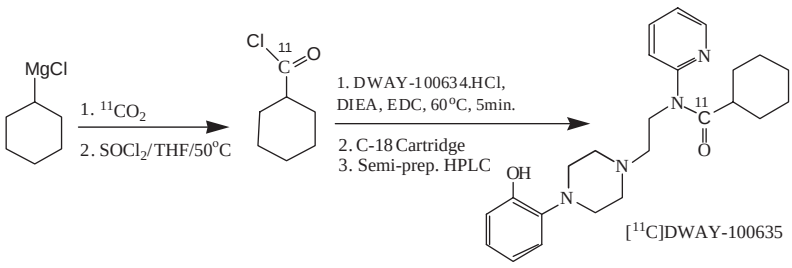

Fig. 1. Modified one-pot radiosynthesis of [*carbonyl*-^{11}C]DWAY-100635.

purification unless otherwise mentioned. Desmethyl-WAY-100634 was obtained from ABX Advanced Biochemical Compounds (Germany) as the monohydrochloride salt. Tetrahydrofuran (THF) was distilled over lithium aluminum hydride under an argon atmosphere prior to use. 1,2-Dichloroethane (EDC) was distilled over P_2O_5 and stored over 4Å molecular sieves. Diisopropylethylamine (DIEA) and triethylamine (TEA) were dried over CaH_2. Radiosyntheses were performed remotely in a lead-lined hot cell (Von Gahlen) using a synthesis module designed and built in-house (Fig. 2). $[^{11}C]CO_2$ was produced by the $^{14}N(p,\alpha)^{11}C$ reaction with 11 MeV protons in a CTI RDS-112 cyclotron using a commercial aluminum target filled to 13.3 bar (200 psi) with 1% O_2 in N_2, and it was purified using a column (66 cm or 108 cm long) made of copper tube (3.2 mm o.d, 1.65 mm i.d.), packed with carbosphere (0.9–1.5 g, 60–80 mesh, Alltech) to separate oxygen and other gaseous impurities (Mock et al., 1995). For product concentration prior to semi-preparative HPLC, an on-line metal cartridge (Alltech, 50 × 4 mm) packed with C-18 silica gel (Waters Associates, 200 mg) was used instead of a conventional injector loop on the injector valve (Fig. 2). Reversed phase semi-preparative high-performance liquid chromatography (Millipore) was done using a Waters 510 pump, remote injector (Rheodyne), C-18 Column (LUNA, 10 μm, 250 × 10 mm, Phenomenex) and in-line gamma detector (LND). Analytical HPLC system (Millipore) consisted of a Waters 510 pump, injector (Rheodyne), column (LUNA, 5 μm, 250 × 3.0 mm, Phenomenex), UV detector (Waters 486) and a sodium iodide scintillation detector (Ortec). The quality control and semi-preparative HPLC were performed using 55/45 CH_3CN-buffer (5 mM KH_2PO_4, pH = 6.5) and 55/45 EtOH-buffer (20 mM NaH_2PO_4, pH = 6.5), respectively. The mass of DWAY in the formulated dose was determined (UV 254 nm) by comparison of peak area to a standard solution containing both the product (5 μg/mL) and the precursor (1 μg/mL). Thin-layer chromatography (TLC) was performed using the following systems: (A) C-18 silica gel plates (Alltech, 250 μm, 5 × 20 cm); solvent: chloroform–methanol (85:15),

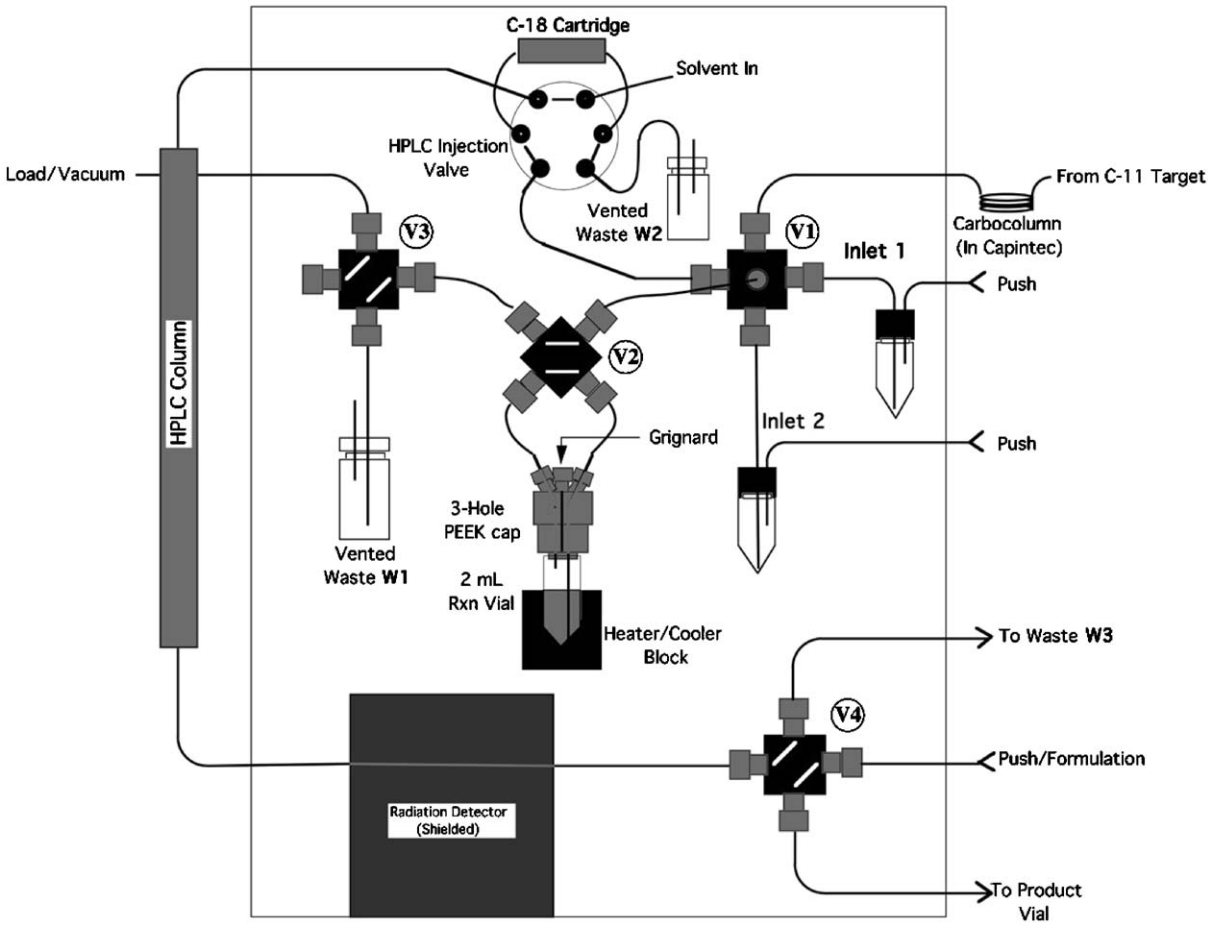

Fig. 2. Schematic diagram of synthesis module for [*carbonyl*-^{11}C]DWAY-100635 preparation.

(B) silica gel plates (Whatman, LK6DF, 5 × 20 cm) (Ma et al., 2003); solvent: chloroform–methanol–diisopropylamine (95:4:1) or (C) silica gel plates (Whatman, K6F, 250 μm, 5 × 20 cm); solvent: chloroform–methanol (9:1). Following development, the radioactivity was detected using a radio-TLC scanner (Bioscan). The yields of the products reported here were decay corrected from the amount of $[^{11}C]CO_2$ introduced into the Grignard solution. The total preparation time was 45 min from EOB. A schematic diagram of our synthesis module, to which references are made in the synthesis descriptions, is shown in Fig. 2.

2.2. Preparation of [carbonyl-^{11}C]cyclohexanecarboxylic acid

The carbosphere column was activated at 120 °C for about 1 h under the flow of helium (40 cm^3/min). It was brought to room temperature under the flow of helium and placed inside a dose calibrator for monitoring the radioactivity (Fig. 2). After proton bombardment, target gas containing $[^{11}C]CO_2$ was passed through the carbosphere column in a stream of helium at room temperature for 1 min 45 s. The helium flow was then reduced (to 25 cm^3/min), and the temperature of the column was increased to 80 °C over 3 min. The helium flow from the column was initially diverted (Fig. 2, V2) past the Grignard reaction vial to the waste (Fig. 2, W1, V3). When the elution of radioactivity from the column was first observed, the reaction vial was opened (V2) to allow $[^{11}C]CO_2$ to bubble (over 1.5–2 min) into the solution of cyclohexylmagnesium chloride (50 μL of 2 M in ether, 100 μmol) dissolved in dry THF (350 μL) at 25 °C.

2.3. Preparation of [carbonyl-^{11}C]cyclohexanecarbonyl chloride

Immediately after the introduction of $[^{11}C]CO_2$, a solution of $SOCl_2$ (20 μL, 274 μmol) in THF (150 μL) was added (Inlet 1) and mixed well with a flow of argon. The vial was closed (Fig. 2, V2) and warmed to 50 °C. After 4 min, the mixture of THF and $SOCl_2$ was evaporated (W1) to dryness at 75 °C, with gradual increments of argon flow (Inlet 1) to 1300 cm^3/min (2–2.5 min). A vacuum (55–60 cm Hg) was then applied (V3, 30 s) followed by argon flow (inlet 1, 950 cm^3/min, 30 s) to remove any remaining traces of $SOCl_2$.

2.4. Synthesis of [^{11}C]DWAY

The free base of desmethyl-WAY-100634 was generated in situ from hydrochloride (3–4 mg, 9–12 μmol) with DIEA (10–20 μL, 58–116 μmol) in EDC (500 μL). The resulting homogeneous amine solution (vortexed) was added (Fig. 2, Inlet 2) to the reaction vial containing the dry [*carbonyl*-^{11}C]cyclohexanecarbonyl chloride reaction mixture. The vial was closed (V2), and the light yellow suspension was heated at 60 °C for 5 min with frequent mixing by briefly opening V2 (argon flow, Inlet 2). The reaction mixture turned into a bright yellow solution. The solvent was then evaporated at 90 °C with gradual increments of argon purge flow to 1300 cm^3/min (2.5–3.0 min) and brought to room temperature.

2.5. Purification of ^{11}C-DWAY

The crude radioactive residue was then suspended in 50% aqueous ethanol (400 μL) followed by the addition of aqueous HCl (1 M, 600 μL). The resulting solution was then loaded onto an on-line metal C-18 cartridge (Fig. 2, preconditioned with ethanol followed by water) attached to an HPLC injection valve in place of the customary sample loop. The cartridge (V3 + V2 + V1) was then washed with 12 mL of 20/80 EtOH- NaH_2PO_4 buffer (20 mM, pH = 6.5) to remove most of the unreacted precursor, polar radioactive impurities (radio-TLC) and inorganic salts which were collected in the waste vial (W2). The flow (3 mL/min) of the purification buffer (55/45 EtOH-20 mM NaH_2PO_4, pH = 6.5) was then diverted through the on-line metal C-18 cartridge (*vide supra*) onto the semi-preparative HPLC column (LUNA). After 2.5 min, buffer flow through the cartridge was discontinued. The elution of the radioactivity was monitored by a flow-through radiation detector. Pure product ([^{11}C]DWAY) was eluted at ~11.0 min and was collected in an intermediate sterile vial for 40–50 s (2.0–2.5 mL). The product solution was formulated by diluting with 0.9% saline (11 mL) and collected in a sterile dose vial after passing through a sterile 0.2 μm nylon filter (Cole-Parmer Instruments, USA).

3. Results and discussion

3.1. Synthesis of [carbonyl-^{11}C]cyclohexanecarbonyl chloride

The synthesis of [*carbonyl*-^{11}C]cyclohexanecarboxylic acid was performed according to the published one-pot method (McCarron et al., 1995, 1996; Hwang et al., 1999) in THF. Like Hwang et al. (1999), we used a carbosphere column as described by Mock et al. (1995) for separation of oxygen from $[^{11}C]CO_2$. We have observed that the yield of the labeled acid improved by increasing the length of the column from 66 to 108 cm. The decay-corrected radiochemical yield of the [*carbonyl*-^{11}C]cyclohexanecarboxylic acid was 70–75% (EOB, 55–60% using the 66 cm carbosphere column). The yield was determined in a separate experiment after decomposition of the $[^{11}C]CO_2$-Grignard adduct with dilute

phosphoric acid (12%, 0.5 mL) followed by nitrogen purge to remove unreacted [^{11}C]CO_2 and [^{11}C]carbonates. Radiochemical purity was >99% as indicated by radio-TLC (system B or C, $R_f = 0.30-0.35$).

Since radio-TLC could not be used directly to determine whether the conversion of the acid to the acid chloride was complete due to the reactivity of the acid chloride and its easy hydrolysis to the acid, this was determined in a separate experiment. An aliquot (2 μL) of the radioactive reaction mixture was added to a solution containing DWAY-100634 hydrochloride (1 mg) with DIEA (5 μL) in EDC (100 μL). Radio-TLC examination of the radioactive solution (system C) showed that the major radioactive peak ($R_f = 0.3$) was essentially converted to product ($R_f = 0.57$) after 20 min at room temperature. Using this method to monitor the status of the chlorination reaction under various reaction conditions, the conversion to the acid chloride was shown to be complete at 50 °C in 4 min.

Radio-TLC (system C) analysis following reaction with $SOCl_2$, complete evaporation to dryness at 75 °C and re-dissolution in EDC revealed that, in addition to the desired product ($R_f = 0.30$), one or more nonpolar radiochemical impurities were also invariably formed ($R_f > 0.70$). The thermal polymerization and/or decomposition of acid chloride during the reaction and the $SOCl_2$ removal process may have contributed to the formation of those nonpolar radiochemical impurities. Indeed, the relative amount of those impurities were increased (up to 37% of the total radioactivity) when excessive heat was used for the reaction (75 °C for 5 min) and the evaporation of the excess $SOCl_2$ (complete evaporation at 75 °C), as described by Hwang et al. (1999) prior to the next reaction. To circumvent this problem, we carried out the reaction at lower temperature (50 °C for 4 min), reduced the $SOCl_2$ evaporation time (from 5 to 2.5 min at 75 °C), and applied a moderate vacuum and argon purge successively in the later stages of the $SOCl_2$ removal process. By thus minimizing the heat applied during the chlorination reaction, the nonpolar radiochemical impurities formed during the synthesis of the [^{11}C]acyl chloride were reduced from 35–37% to <20%. However, a 20–35% loss of radioactivity as volatile species was observed during this process. Hwang et al. (1999) also reported a 20–30% loss at this step. Nevertheless, strict removal of all traces of $SOCl_2$, with minimal heating, helped us to limit the amount of precursor amine (3–4 mg) required and to increase the yield of the subsequent condensation reaction by reducing those nonpolar impurities.

We did not use dry HCl (in ether) to decompose excess of Grignard reagent before proceeding for chlorination, as described by Hwang et al. (1999). In our preliminary experiments, we found that the chlorination proceeded efficiently even without adding dry HCl using the same amount of $SOCl_2$.

3.2. Synthesis of [^{11}C]DWAY

In the previously described synthesis of [^{11}C]DWAY (Pike et al., 1998), it was not apparent whether the precursor amine was used as a free base or as its hydrochloride salt. In our synthesis, we have used the precursor amine as the monohydrochloride salt available from a commercial vendor. Initially, we used TEA (30 μL, 215 μmol) in THF for in situ generation of the precursor amine as the free-base, but a homogeneous solution could not be produced on mixing. Substitution of DIEA (20–35 μL) for TEA improved the homogeneity of the solution in THF. During the condensation reaction in THF using DIEA, however, an additional insoluble residue was formed which only partially dissolved upon heating during the reaction period. The presence of the insoluble residue in the reaction vial made complete removal of THF following the condensation reaction cumbersome.

Radio-TLC examination of the crude condensation reaction, when performed in THF using DIEA at 50 °C for 5 min, showed (Fig. 3A) the presence of several radioactive components which included one with an $R_f = 0.31$ corresponding to the unconverted [^{11}C]-acyl chloride (as the acid) and one ($R_f = 0.75$) corresponding to the nonpolar impurity(ies) formed during chlorination previously mentioned. We then examined the effect of temperature (from 40 to 70 °C in increments of 10 °C) and solvent on the condensation reaction. Radio-TLC examination of the condensation product using DIEA in EDC showed that the reaction proceeded satisfactorily at 60 °C for 5 min. Analysis of this crude reaction mixture by radio-TLC (Fig. 3B) revealed the presence of two major radioactive peaks ($R_f = 0.31$ and 0.57) in addition to few other minor peaks. The radioactive peak at $R_f = 0.57$ corresponds to the desired DWAY-100635. The percentage of the desired product in the crude reaction mixture was greatly improved when compared to the same reaction in THF. The polar product ($R_f = 0.31$), had the same retention factor as [*carbonyl*-^{11}C]cyclohexanecarboxylic acid and was later identified as unreacted [*carbonyl*-^{11}C]cyclohexanecarbonyl chloride (*vide supra*) in a separate experiment. The radioactive peaks having $R_f > 0.70$ were nonpolar impurities previously mentioned and the peak at $R_f = 0.49$ was not identified. However, the yield of the final product could not be improved significantly by increasing the amount (to 5.0 from 3 to 4 mg) of precursor in the synthesis. The percentage of nonpolar impurities sometimes increased significantly, in which case the product yield was lower than expected.

3.3. Quality control and purification of ^{11}C-DWAY

After initial optimization of the condensation reaction using radio-TLC monitoring, we proceeded in the

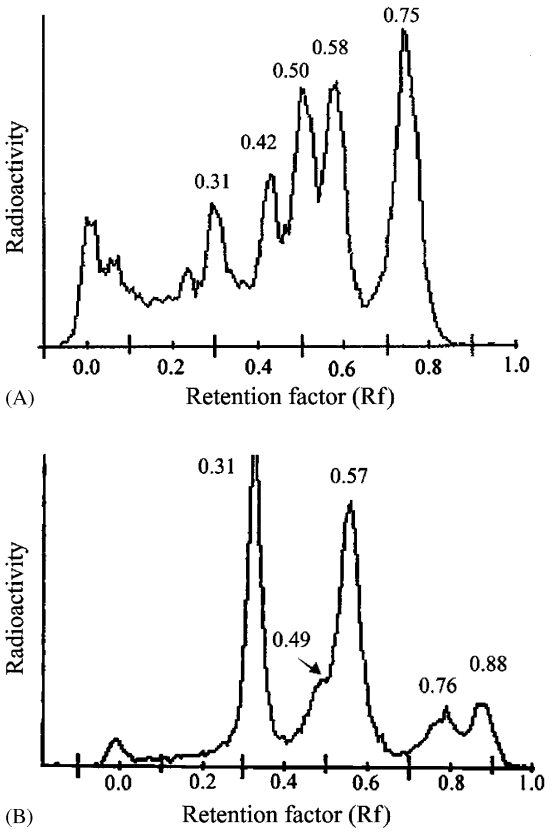

Fig. 3. (A) Thin layer radiochromatogram (system C) of the condensation reaction of DWAY-100634 with [*carbonyl*-^{11}C]-cyclohexanecarbonyl chloride in THF using DIEA. (B) Thin layer radiochromatogram (system C) of the condensation reaction of DWAY-100634 with [*carbonyl*-^{11}C]cyclohexanecarbonyl chloride in EDC using DIEA. The peaks with $R_f = 0.57$ corresponds to authentic DWAY, with $R_f = 0.31$ is unreacted [*carbonyl*-^{11}C]cyclohexanecarbonyl chloride and with $R_f > 0.7$ was referred as nonpolar compounds. The additional peak with $R_f = 0.49$ was not identified.

development of a quality control and a semi-preparative HPLC procedure. For analytical radio-HPLC of the formulated product, we used a C-18 reversed-phase column with 55/45 CH_3CN-buffer (5 mM KH_2PO_4, pH = 6.5) at a flow rate of 0.7 mL/min. Under these conditions, the precursor amine eluted at 3.0 min post-injection and the authentic product at 7.5 min. When this analytical radio-HPLC system was used to examine a sample of [^{11}C]DWAY after initial purification to remove extraneous radioactive impurities using C-18 Sep-Pak (Plus, Waters Associates), the presence of a radiolabeled impurity (20–25% of the total radioactivity) with a retention time (6.9 min) very close to that of the product (7.5 min) was revealed (Fig. 4). We have been able to minimize (to <5% of the total radioactivity) the formation of this impurity by reducing the amount of DIEA (10 μL) in the final condensation reaction (Maiti et al., 2004). However, the overall radiochemical yield of the purified product was not significantly improved by this reduction.

For the final purification, we have applied a 55/45 EtOH-NaH_2PO_4 buffer (20 mM, pH = 6.5) on a semi-preparative C-18 reversed-phase column. The crude reaction mixture was purified prior to semi-prep HPLC by loading onto an on-line metal C-18 cartridge (Fig. 2). The cartridge was then washed with 12 mL of 20/80 EtOH–NaH_2PO_4 buffer (20 mM, pH = 6.5) to remove most of the unreacted precursor, polar radioactive impurities and inorganic salts. The relatively pure product was then loaded onto the HPLC column by simply diverting the buffer flow through the cartridge, thus saving time for purification. As with the analytical radio-HPLC, a minor radioactive impurity was eluted at 10.0 min (6.9 min in QC system) from the semi-prep purification column, and the final product (11.0 min) was collected (over 40–50 s) in a 2.0–2.5 mL aliquot. Following dilution with 11 mL of normal saline solution, the pH of the formulated product was found to be 6.0–6.5. The radiochemical yield was 11.1 ± 1.8% (EOB, $n = 15$) and radiochemical purity was >99% by both radio-HPLC and radio-TLC (system A, $R_f = 0.50$) analysis. Specific activity was 38.9–65.5 GBq/μmol (EOS, $n = 13$) when 7.4–11.1 GBq of [^{11}C]CO_2 was used. However, specific activity increased to 133.2–185.0 GBq/mol (EOS, $n = 2$) when starting [^{11}C]CO_2 activity was increased to ca. 37.0 GBq. The mass of [^{11}C]DWAY was 0.15–0.24 μg/mL and the precursor was present in less than 50 ng/mL in final production solutions. The C-18 cartridge washings from the clean-up prior to final purification, which represent primarily unreacted acid (or from acid chloride) comprised 11.8 ± 4.0% (EOB) and combined radioactivity recovered from these fractions including the product represents ~25–30% of the initial [^{11}C]CO_2 activity, with the remaining activity lost as volatiles or unisolated nonpolar residues.

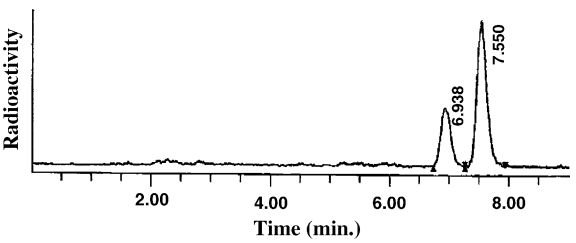

Fig. 4. Typical analytical radio-HPLC chromatogram of the condensation product after C-18 Sep-Pak purification. The peak with retention time of 7.5 min co-elutes with authentic DWAY, and the peak with retention time of 6.9 min is the radioactive impurity.

3.4. General

We have made an important alteration in the procedures previously published for [^{11}C]DWAY. In both the published (McCarron et al., 1996; Pike et al., 1998) methods (A or B), the [^{11}C]acyl chloride in THF was added or transferred to the vial containing precursor amine and TEA for the final condensation reaction. In our procedure, a homogeneous solution of commercially available DWAY-100634 (as the hydrochloride) and DIEA in EDC was added (reversed addition) to the [^{11}C]acyl chloride for condensation. This technique eliminated the loss of labeling agent due to transfer (as in method A, McCarron et al., 1996; Pike et al., 1998). We have substituted both the tertiary amine (DIEA vs. TEA) and the solvent (EDC vs. THF) in order to achieve desired homogeneity of the solution and also to minimize the formation of radioactive by-products in the condensation reaction (*vide supra*). Our in situ method for the generation of the precursor amine as the free-base, which eliminated any unnecessary handling of this moisture-sensitive reagent, likely added to consistency of our results.

4. Conclusion

We have described an improved one-pot synthesis procedure for the routine preparation of [^{11}C]DWAY for human use. The reaction parameters such as temperature and solvent were adjusted to minimize formation of radioactive by-products and to increase the decay-corrected radiochemical yield of [^{11}C]DWAY from ca. 6% (Pike et al., 1998) to 11%. The final purification procedure by HPLC was efficient and the precursor (DWAY-100634) was present in less than 50 ng/mL in desired radiopharmaceutical contrary to (average ~4.0 μg/mL) the published method for [^{11}C]DWAY. The ingredients used in the purification buffer are also compatible with human administration thus eliminating the need for further manipulation following HPLC isolation. The radiopharmaceutical was ready for human administration in 45 min (EOB). This approach should facilitate production of [^{11}C]DWAY-100635 for clinical studies.

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