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Ethanollic Carbon-11 Chemistry: the Introduction of Green Radiochemistry

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Abstract

The principles of green chemistry have been applied to a radiochemistry setting. Eleven carbon-11 labeled radiopharmaceuticals have been prepared using ethanol as the only organic solvent throughout the entire manufacturing process. The removal of all other organic solvents from the process simplifies production and quality control (QC) testing, moving our PET Center towards the first example of a green radiochemistry laboratory. All radiopharmaceutical doses prepared are suitable for clinical use.

Keywords

PET chemistry; green chemistry; positron emission tomography; carbon-11; radiopharmaceutical synthesis

1. Introduction

In simple terms, green chemistry is the design of products or processes that minimize or eliminate the use, generation, or disposal of hazardous chemical substances (Anastas and Warner, 1998; Horváth and Anastas, 2007; Li and Trost, 2008; Sheldon, 2012; Zhang and Cur Jr., 2012). Achieving this goal may include design of better synthetic pathways, use of alternative reaction conditions, and/or invention of safer (non-toxic) chemicals. Successful application of green chemistry in the chemical and pharmaceutical industries provides rewards both economically and in environmental safety.

In a novel application, we have found that the principles of green chemistry can be extended to the field of Nuclear Medicine, and specifically to the preparation of radiopharmaceuticals for clinical Positron Emission Tomography (PET) imaging. The use of PET imaging to non-

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invasively image biochemical processes in living human subjects is being increasingly applied to personalized medicine in the academic setting (Pither, 2003), and to drug discovery in the pharmaceutical industry (Matthews et al., 2012). Patients receive an injection of a radiopharmaceutical (i.e. a bioactive molecule typically radiolabeled with a short half-life radionuclide, such as carbon-11 (Scott, 2009) or fluorine-18 (Littich and Scott, 2011)) followed by PET imaging of the radioactivity distribution in the body. Reflecting the increasing global demand for access to PET imaging, sophisticated reactions for the synthesis of radiopharmaceuticals continue to be developed (Ametamey et al., 2008; Miller et al., 2008).

Radiopharmaceuticals labeled with carbon-11 are amongst the most prevalent due to the ubiquitous presence of carbon in pharmacologically active molecules. However, the art and science of radiopharmaceutical synthesis with carbon-11 present the radiochemist with some unique challenges. First and foremost, the short half-life (20.38 min) demands fast and efficient radiochemical syntheses, frequently in an academic radiochemistry laboratory adjacent to the hospital PET scanner as the timescales involved prohibit transport. Secondly, radiopharmaceutical doses must be formulated and the quality control procedures finished rapidly, as administration to a patient occurs typically within 1 hour following end of synthesis (EOS). Therefore streamlined quality control (QC) is also an essential aspect of carbon-11 labeled radiopharmaceutical production. Despite these challenges, a large number of carbon-11 labeled radiopharmaceuticals have been developed for human studies, and our laboratory manufactures many of these daily for imaging applications in neurology, oncology, and cardiology.

Each of the radiopharmaceuticals we prepare, and indeed nearly all routinely used for human studies, are synthesized by methylation of a heteroatom (N, O or S) of the corresponding precursor using a one-carbon reagent, usually [^{11}C]methyl iodide ([^{11}C]MeI) or [^{11}C]methyl triflate ([^{11}C]MeOTf). The syntheses of all of these radiopharmaceuticals were developed using alkylation reactions in organic solvents, such as *N,N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), 3-pentanone, methyl ethyl ketone (MEK), *n*-propanol (*n*PrOH), acetone, and acetonitrile (MeCN). However, in response to increasing scrutiny over supply and disposal of such solvents, as well as simplifying radiopharmaceutical quality control (use of such solvents in human radiopharmaceutical preparations requires testing of doses for residual solvent concentrations using gas chromatography before a dose can be released for use), we had an interest in entirely eliminating all hazardous solvents from our carbon-11 labeled radiopharmaceutical manufacturing program and replacing them with an alternative reaction solvent. The most obvious replacement was ethanol (EtOH) as it is often a component of purification and formulation systems. From an HPLC perspective, ethanol is a desirable semi-preparative mobile phase component in radiopharmaceutical syntheses as it frequently negates the need for a reformulation step and, reflecting this, new developments continue to be reported (Lehel et al., 2009; Zhang et al., 2012). Moreover, in keeping with the green chemistry focus of the present paper, ethanol has been demonstrated as a suitable greener substitute for acetonitrile in HPLC mobile phases (Welch et al., 2009), although its higher viscosity and UV absorbance cutoff should be kept in mind when making the switch. In our hands,

moving to ethanol-based mobile phases has had only negligible or positive effects on peak shape, but retention times were frequently off set by a minute or two. Finally, ethanol can be purposefully added to radiopharmaceutical formulations to inhibit oxidative radiolysis (Bogni et al., 2003; Fawdry, 2007; Fukumura et al., 2004a; Fukumura et al., 2004b; Scott et al., 2009).

The above reasons made a compelling case for moving towards ethanolic radiochemistry. Historically however, alcohol solvents have always been considered incompatible with methylating agents such as [^{11}C]MeOTf, as alkyl perfluoroalkanesulfonate esters are particularly prone to solvolysis (Effenberger, 1980). Moreover, protic solvents are generally considered to retard $\text{S}_{\text{N}}2$ reactions because of unfavorable solvation of the nucleophilic component. Nevertheless, in an initial report involving the syntheses of [^{11}C]4-[2-[(di(methyl)amino)methyl]phenyl]sulfanylbenzonitrile ([^{11}C]DASB) and [^{11}C]raclopride, we demonstrated that this was not the case with the low solvent volumes and fast reactions times associated with carbon-11 loop chemistry (the radiochemical equivalent of flow chemistry), and ethanol served the only organic solvent throughout the entire manufacturing process, including preparatory cleaning of the automated synthesis apparatus, product purification by preparative HPLC, and formulation for injection (Shao et al., 2013). With the principles of green chemistry firmly in mind, and the goal of moving our facility towards the first example of a green radiochemistry laboratory, the scope of ethanolic carbon-11 chemistry has now been extensively refined and expanded to include numerous additional radiopharmaceuticals.

2. Material and Methods

2.1 General Considerations

All reagents and solvents were commercial products used without further purification. Precursors and standards were commercially available, unless otherwise indicated, and purchased from Aldrich (choline, carfentanil (contract synthesis)); ABX Advanced Biochemicals (DASB, HED, PiB, Raclopride); Fluka (methionine); Monomerchem (DTBZ precursor (contract synthesis)); or SRI (DTBZ standard (contract synthesis)). PBR28, PMP and OMAR standards and precursors were synthesized in house. Ethanol, United States Pharmacopeia (USP) was acquired from American Regent; ethanol, USP (used for HPLC as dedicated ethanol for HPLC often contains methanol) was obtained from Decon Labs, Inc.; Sterile Water for Injection, USP and 0.9% sodium chloride, USP were purchased from Hospira; iodine was acquired from EMD; phosphorus pentoxide was purchased from Fluka; ammonium acetate, sodium dihydrogen phosphate and molecular sieves were purchased from Fisher Scientific; Shimalite-Nickel was purchased from Shimadzu. Other synthesis components were obtained as follows: sterile filters were obtained from Millipore; sterile product vials were purchased from Hollister-Stier; C18-light Sep-Paks, CM-light Sep-Paks and Porapak Q were purchased from Waters Corporation. C2 and C18 Extraction discs were obtained from 3M. Sep-Paks and extraction discs were flushed with 10 mL of ethanol followed by 10 mL of sterile water prior to use.

2.2 Preparation of TBA Salts of Precursors

The desmethyl precursor (10 mg $\pm$ 0.2 mg) was dissolved in ethanol (100 μ L) and water (50 μ L) in a bullet vial by vortexing for 30 sec. 1M Tetrabutylammonium hydroxide (100 μ L in methanol) was added and the vial was vortexed for an additional 30 sec. The resulting solution was diluted with water (6 mL) and passed through a C18 extraction disk (preconditioned with ethanol (5 mL) and water (10 mL)). The disk was washed with additional water (2×5 mL) and dried under a nitrogen stream. The product was then eluted into a new vial with ethanol (2 mL), and the resulting eluent was dispensed into 10 bullet vials (1 mg precursor in 200 μ L ethanol per vial). The vials were placed in a vacuum dessicator and evaporated to dryness overnight under vacuum. Vials were stored in the refrigerator and used within 30 days of production.

2.3 Radiochemistry

2.3.1 Production of Carbon-11—Carbon-11 was produced with a General Electric PETTrace cyclotron via the $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$ reaction as $[^{11}\text{C}]\text{CO}_2$. ~ 3 Ci (111 GBq) of $[^{11}\text{C}]\text{CO}_2$ was delivered to the TRACERlab FX_{C-Pro} synthesis module and initially converted into ~ 900 mCi (33.3 GBq) of $[^{11}\text{C}]\text{MeI}$ as previously described (Shao et al., 2011a). $[^{11}\text{C}]\text{MeI}$ was then subsequently converted into $[^{11}\text{C}]\text{MeOTf}$ in $>90\%$ conversion.

2.3.2 General Procedure for Loop Syntheses—The TRACERlab FX_{C-Pro} synthesis module was configured for loop chemistry as previously described (Shao et al., 2011a). The appropriate precursor (1.0 mg) was dissolved in ethanol (100 μ L) and loaded into the 2 mL steel HPLC loop and conditioned with nitrogen gas for 20 seconds at 10 mL/min. In the event that a reformulation was involved, additional set-up was as follows: Vial 4: Sterile water for injection, USP (7 mL); Vial 5: Ethanol (0.5 mL); Vial 6: 0.9% NaCl for Injection, USP (9.5 mL); Round-bottomed Dilution Flask: Milli-Q Water (20–50 mL). $[^{11}\text{C}]\text{MeOTf}$ was passed through the HPLC loop at 40 mL/min for 3 minutes. Following reaction, the mixture was purified by semi-preparative HPLC. The product peak was collected either directly for injectable mobile phases, or reformulated into ethanolic saline. The final formulation was then passed through a 0.22- μ m filter into a sterile dose vial and submitted for QC testing.

2.3.3 General Procedure for Reactor Syntheses—The TRACERlab FX_{C-Pro} synthesis module was configured for reactor syntheses with HPLC or SPE purification as previously described (Shao et al., 2011a). The appropriate precursor (1.0 mg) was dissolved in ethanol (100 μ L) (or an ethanol/water mixture) and loaded into the reaction vessel of the synthesis module. In the event that a reformulation was involved, additional set-up was as follows: Vial 4: Sterile water for injection, USP (7 mL); Vial 5: Ethanol (0.5 mL); Vial 6: 0.9% NaCl for Injection, USP (9.5 mL); Round-bottomed Dilution Flask: Milli-Q Water (20–50 mL). $[^{11}\text{C}]\text{MeOTf}$ or $[^{11}\text{C}]\text{MeI}$ was bubbled through the precursor solution in the reactor at 15 mL/min for 3–5 minutes. Following reaction, the mixture was purified by semi-preparative HPLC (DTBZ, HED and PMP), SPE (carfentanil) or by simple evaporation of the solvent (methionine). Final formulations were then passed through a 0.22- μ m filter into a sterile dose vial and submitted for QC testing.

2.3.4 Ethanolic Purification Conditions— $[^{11}\text{C}]$ Carfentanil was purified by SPE. The crude reaction mixture was transferred to the dilution flask containing 5 mL of 1% ammonium hydroxide. This mixture was passed through a 3M Empore C2 extraction disk where the $[^{11}\text{C}]$ carfentanil was trapped. 3 mL of 20% ethanol followed by 7 mL Milli-Q water were then passed through to remove impurities from the disk. The disk was then dried by passing helium gas through for 1.0 minute and the $[^{11}\text{C}]$ carfentanil was eluted off with ethanol (0.5 mL) and diluted with sterile water for injection (9.5 mL). Note: USP saline is not used for elution, as it elutes an unknown chemical impurity of the extraction disk.

$[^{11}\text{C}]$ DASB was purified by semi-preparative HPLC (column: Phenomenex Luna CN, 150 $\times$ 10mm, mobile phase: 5 mM NaOAc in 80% ethanol, pH: 5.0, flow rate: 4 mL/min). The product peak (t_{R} ~7 min) was collected into 50 mL of water. The solution was then passed through a C18 Sep-Pak, and washed with 7 mL sterile water. The product was then eluted with 0.5 mL of USP ethanol followed by 9.5 mL of USP saline.

$[^{11}\text{C}]$ DTBZ was purified by semi-preparative HPLC (column: Phenomenex Luna C8(2) 10 $\times$ 100 mm; mobile phase: 20mM NaH_2PO_4 85/15 water/ethanol; flow rate: 3 mL/min). The product fraction (~3 mL) was collected (t_{R} ~10–11 min) into the product collection vial where it was simultaneously diluted with isotonic saline (7 mL).

$[^{11}\text{C}]$ HED was purified by semi-preparative HPLC (column: Phenomenex Luna C8(2) 10 $\times$ 150 mm; mobile phase: 1 mL of 20mM NH_4OAc in 99/1 water/ethanol; flow rate: 4 mL/min). The product fraction (~8 mL) was collected (t_{R} ~12 min) into the product collection vial where it was simultaneously diluted with isotonic saline (2 mL).

$[^{11}\text{C}]$ Methionine was purified by evaporation of the residual $[^{11}\text{C}]\text{CH}_3\text{I}$ at 55 $^\circ\text{C}$ under a helium gas stream for 5 min. The product was then diluted in 0.9% sodium chloride for Injection, USP (1.0 mL) and passed into the round-bottomed flask charged with 45 mM sodium phosphates, USP (0.5 mL) and additional 0.9% sodium chloride for Injection, USP (8.0 mL).

$[^{11}\text{C}]$ OMAR was purified by semi-preparative HPLC (column: Phenomenex Luna C-5, 100 $\times$ 10mm, mobile phase: 20 mM NH_4OAc in 45% ethanol, flow rate: 3 mL/min). The product peak (t_{R} ~15 min) was collected into 50 mL of water. The solution was then passed through a C18 Sep-Pak, and washed with 7 mL sterile water. The product was then eluted with 0.5 mL of USP ethanol followed by 9.5 mL of USP saline.

$[^{11}\text{C}]$ PBR28 was purified by semi-preparative HPLC (column: Phenomenex Luna C-5, 100 $\times$ 10mm, mobile phase: 20 mM NH_4OAc in 40% ethanol, flow rate: 3 mL/min). The product peak (t_{R} ~10 min) was collected into 50 mL of water. The solution was then passed through a C18 Sep-Pak, and washed with 7 mL sterile water. The product was then eluted with 0.5 mL of USP ethanol followed by 9.5 mL of USP saline.

$[^{11}\text{C}]$ PMP was purified by semi-preparative HPLC (column: Phenomenex Luna C18, 150 $\times$ 10mm, mobile phase: 50 mM NH_4OAc in 5% EtOH, flow rate: 4 mL/min). The product peak was collected (t_{R} ~12–14 min) for 2 min (8 mL), diluted with USP saline (2 mL) to provide a final ethanol concentration <5%.

2.3.5 Quality Control Testing—Quality control testing of radiopharmaceuticals was conducted according to the guidelines outlined in the U.S. Pharmacopeia using the standard tests as previously described (Shao et al., 2011a), and key data are highlighted in Table 1. Testing included visual inspection, pH, chemical and radiochemical purity (RCP), specific activity (SA), sterile filter integrity, bacterial endotoxin analysis, and sterility testing. All doses prepared using this new methodology met or exceeded all requisite QC testing confirming their suitability for clinical use.

3. Results and Discussion

Initially we adapted the ethanol-based syntheses to radiopharmaceuticals previously prepared using the loop method, a type of thin-film chemistry that serves to minimize solvent volumes (Shao et al., 2011a; Shao et al., 2013; Wilson et al., 2009; Wilson et al., 2000); examples are [^{11}C]OMAR, [^{11}C]Pittsburgh Compound B (PiB) and [^{11}C]PBR28 (Table 1), in addition to [^{11}C]raclopride and [^{11}C]DASB reported earlier (Shao et al., 2013). One concern remained about the scope of our methodology, and if it was applicable beyond the confines of loop chemistry. Loop chemistry is a special case in which a solution of the precursor is loaded into the semi-preparative HPLC loop and then [^{11}C]MeOTf is blown rapidly through the loop to promote reaction, which could be the reason solvolysis is not a competing process. The contents of the loop are then injected onto the HPLC column for purification. However, many radiopharmaceuticals are more efficiently prepared using other methods and so we wanted to explore the scope of this new methodology further. For example, our previously reported solid-phase synthesis of [^{11}C]choline also employs only ethanol (Shao et al., 2011a; Shao et al., 2011b). Many other carbon-11 labeled radiopharmaceuticals are synthesized in the reaction vessel of a radiochemical synthesis module (or a vial), where [^{11}C]MeOTf is bubbled through a solution of the precursor. Therefore we set about evaluating whether our ethanol-only approach to radiochemistry was also compatible with reactor-produced radiopharmaceuticals.

Five radiopharmaceuticals that we prepare routinely were chosen to test suitability of ethanol for reaction-vessel based syntheses: 1-[^{11}C]methylpiperidin-4-yl propionate ([^{11}C]PMP) and [^{11}C]meta-hydroxyephedrine ([^{11}C]HED) as examples of N-alkylation; [^{11}C]dihydrotetrabenazine ([^{11}C]DTBZ) and [^{11}C]carfentanil as examples of O-alkylation; and [^{11}C]methionine as an example of S-methylation. Precursors were dissolved in 100 μL of ethanol (in certain cases solubility could be improved by preforming the corresponding tetrabutyl ammonium (TBA) salt) and either [^{11}C]MeI or [^{11}C]MeOTf was bubbled through the reaction mixture for 3 – 5 minutes. All reactions were conducted at temperature and, following purification (using ethanol/water based purification strategies – see Section 2.2 for details), the five radiopharmaceuticals were generated in suitable quantities for clinical imaging (4.4 – 6.8% non-decay-corrected radiochemical yield at EOS based upon 3 Ci (111 GBq) of [^{11}C]CO₂). The radiochemical yields were as good or better than the organic-solvent based syntheses (Table 1), supporting compatibility of our green methodology with both loop and reactor-based syntheses.

Encouraged by the high yields obtained in some of the syntheses, we next considered extending the concept further to test the tolerance of [^{11}C]MeOTf for water, and determine

if we could eliminate ethanol from the synthesis step. Using [^{11}C]DTBZ and [^{11}C]HED as test compounds, to our astonishment the reactions proceeded in 80:20 ethanol:water without significant impact on yield. Challenging the scope of the chemistry further, we found that the synthesis of [^{11}C]DTBZ proceeded in 50:50 ethanol:water without any obvious loss of yield. [^{11}C]HED could also be synthesized in 50:50 ethanol:water, although there was a ~40% decrease in yield that we attribute to precursor solubility issues (Table 2). This tolerance of water removes the requirement to use of vials of absolute ethanol, which have been previously employed in the synthesis step, as well as the need for extra dry glassware and synthesis equipment. The latter is significant from a green chemistry point of view, because it allows elimination of acetone from synthesis module cleaning and drying protocols (although synthesis modules should still be appropriately cleaned and disinfected).

To date, eleven carbon-11 labeled radiopharmaceuticals have been prepared using ethanol as the only organic solvent for module cleaning and disinfection, radiopharmaceutical synthesis, purification and reformulation. All reactions were conducted at temperature, and ethanolic carbon-11 radiochemistry is compatible with the loop method, reactor syntheses, and reactions conducted on Sep-Pak cartridges. The removal of all other organic solvents from the process simplifies production and QC as it eliminates the need to purchase, inventory, handle and properly dispose of other hazardous solvents.

The development of ethanol-based radiochemistry has the potential of simplifying workflow in PET radiopharmaceutical synthesis facilities by changing residual solvent analysis from a daily QC test of multiple different organic solvents to a single GC analytical method for ethanol that might, with regulatory approval, be relegated to a quarterly or annual test. All radiopharmaceutical doses prepared using ethanol radiochemistry are suitable for human administration (see supporting information for detailed QC data) and the described methods are now used for routine clinical production of these radiopharmaceuticals at the University of Michigan. The chemistry is readily adaptable to many different radiopharmaceuticals and appears limited only by the solubility of the precursor in ethanol.

4. Conclusions

By applying the principles of green chemistry to our carbon-11 drug manufacturing program, we have eliminated all organic solvents except ethanol from the radiosyntheses of many common radiopharmaceuticals in an effort to move our facility towards the first example of a green radiochemistry laboratory.

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Highlights

- We report application of the principles of green chemistry to a radiochemistry setting
- Radiopharmaceuticals are prepared using ethanol as the only organic solvent
- Green radiochemistry simplifies production and QC in busy clinical production labs
- Residual solvent analysis can be relegated to a quarterly or annual QC test.

Table 1

Synthesis and Quality Control Data

Product	n	Method	Precursor	Purification	RCY ^a	RCP ^b	SA ^c	pH
Carfentanil	2	[¹¹ C]MeOTf/Reactor	TBA salt	Sep-pak	6.8% (6.3%)	>95%	>30,000	5.5
Choline	10	[¹¹ C]MeI/Sep-pak	Free base	Sep-pak	7.3% (7.3%)	>95%	ND ^d	5.5
DASB	13	[¹¹ C]MeOTf/Loop	Free base	HPLC	3.0% (4.0%)	>95%	10,900	6.0
(+)-DTBZ	12	[¹¹ C]MeOTf/Reactor	TBA salt	HPLC	6.2% (2.8%)	>95%	31,400	5.5
HED	31	[¹¹ C]MeOTf/Reactor	Free base	HPLC	5.0% (2.9%)	>95%	10,100	6.0
Methionine	3	[¹¹ C]MeI/Reactor	Thiolactone + NaOH	Evap.	4.0% (8.0%)	>95%	ND ^d	6.0
OMAR	3	[¹¹ C]MeOTf/Loop	TBA salt	HPLC + Sep-pak	4.1% (3.1%)	>95%	4,900	6.0
PBR28	8	[¹¹ C]MeOTf/Loop	TBA salt	HPLC + Sep-pak	2.8% (4.0%)	>95%	5,700	6.0
PiB	3	[¹¹ C]MeOTf/Loop	Free base	HPLC	2.3% (1.6%)	>95%	11,000	5.5
PMP	26	[¹¹ C]MeOTf/Reactor	HCl salt + NaHCO ₃	HPLC	4.4% (3.0%)	>95%	Mass <LOD ^e	6.0
Raclopride	144	[¹¹ C]MeOTf/Loop	TBA salt	HPLC	3.6% (2.2%)	>95%	20,750	6.0

[a] RCY = non-decay-corrected radiochemical yield at end of synthesis (EOS) based upon 3 Ci of starting [¹¹C]CO₂ using ethanolic conditions (corresponding yields reported by our group using traditional organic solvents are given in parentheses (Shao et al., 2011a)),

[b] RCP = Radiochemical Purity,

[c] SA = Specific Activity in Ci/mmol determined at EOS,

[d] ND = Not Determined as there are no specific activity limits established for endogenous ligands,

[e] LOD = 25 µg/mL Limit of Detection for [¹¹C]PMP.

Table 2Solvent Effects on [^{11}C]Radiochemistry

Product	EtOH:H ₂ O	n	EOS	Yield (mCi)	SA (Ci/mmol)	RCP
DTBZ	100:0	6	150		10,117	>95%
	80:20	3	116		9,039	>95%
	50:50	3	130		12,998	>95%
HED	100:0	3	186		31,435	>95%
	80:20	3	159		17,824	>95%
	50:50	3	71		12,400	>95%