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Ethanolic carbon-11 chemistry: The introduction of green radiochemistry

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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 laboratories.
- Residual solvent analysis can be relegated to a quarterly or annual QC test.

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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.

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, 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-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.

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Second, radiopharmaceutical doses must be formulated and the quality control procedures finished rapidly, as administration to a patient occurs typically within 1 h 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, is 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 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 (nPrOH), 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 had only negligible or positive effects on peak shape, but retention times were frequently offset 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, 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 S_N2 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 disks were obtained from 3 M. Sep-Paks and extraction disks 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 ± 0.2 mg) was dissolved in ethanol (100 μL) and water (50 μL) in a bullet vial by vortexing for 30 s. 1 M Tetrabutylammonium hydroxide (100 μL in methanol) was added and the vial was vortexed for an additional 30 s. 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 μL 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 90 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}N(p,α)^{11}C reaction as [^{11}C]CO_2. ~3 Ci (111 GBq) of [^{11}C]CO_2 was delivered to the TRACERlab $FX_{C\text{-}Pro}$ synthesis module and initially converted into ~900 mCi (33.3 GBq) of [^{11}C]MeI as previously described (Shao et al., 2011a). [^{11}C]MeI was then subsequently converted into [^{11}C]MeOTf in >90% conversion.

2.3.2. General procedure for loop syntheses

The TRACERlab $FX_{C\text{-}Pro}$ 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 μL) and loaded into the 2 mL steel HPLC loop and conditioned with nitrogen gas for 20 s 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}C]MeOTf was passed through the HPLC loop at 40 mL/min for 3 min. Following reaction, the