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Automated production of [^{11}C]acetate and [^{11}C]palmitate using a modified GE Tracerlab FX$_{C\text{-}Pro}$

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ABSTRACT

As researchers explore new applications for positron emission tomography radiopharmaceuticals, the demand for effective and readily available radiopharmaceuticals continues to increase. The syntheses of two such radiopharmaceuticals, [^{11}C]acetate and [^{11}C]palmitate, can be automated on the GE Tracerlab FX$_{C\text{-}Pro}$ by utilizing Grignard reactions. Radiochemical purities of the [^{11}C]acetate and the [^{11}C]palmitate products were high ($>98\%$ and $>99.9\%$, respectively) with average non-corrected yields of 18% ($n=3$) and 10% ($n=5$), respectively. These data comprise the validation trials for site qualification of clinical production of both radiopharmaceuticals.

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1. Introduction

Two radiopharmaceuticals which have gained great interest from researchers searching for less expensive and more accessible positron emission tomography (PET) radiopharmaceuticals are [^{11}C]acetate and [^{11}C]palmitate. Although the viability of [^{11}C]acetate as a PET radiopharmaceutical was first described more than 25 years ago (Pike et al., 1982), its application to myocardial imaging has continued to be of interest ever since (Brown et al., 1987; Timmer et al., 2010). Nonetheless, myocardium was quickly discovered to be only a single facet of the applicability and versatility of PET imaging with [^{11}C]acetate because the advantage to utilizing [^{11}C]acetate resides in the mechanism by which it is incorporated into target cells. By entering the Krebs cycle in the form of the acetyl group in acetyl coenzyme A (acetyl CoA) (Kornberg and Krebs, 1957) cells undergoing more or less cellular respiration relative to the surrounding cells are easily identifiable. Thus, recent studies have reported higher uptake of [^{11}C]acetate than [^{18}F]FDG in meningiomas (Liu et al., 2010), high specificity and selectivity of [^{11}C]acetate in renal carcinomas (Maleddu et al., 2009), as well as diagnostic applications for liver and prostate tumors (Ho et al., 2003; Schoder and Larson, 2004; Ho et al., 2007; Bouchelouche et al., 2009). However, the considerable uptake of [^{11}C]acetate in various organs (Song et al., 2009) may afford [^{11}C]palmitate specific advantages in imaging of the myocardium.

In the 1970s, investigators began experimenting with fatty acids in studies of the myocardium and, more specifically, myocardial metabolism (Weiss et al., 1977; Klein et al., 1979; Goldstein et al., 1980). Fatty acids were known to be utilized differently by the heart and, in fact, were shown to supply 60–70% of the primary energy source for myocardial ATP production (Neely and Morgan, 1974). Therefore, [^{11}C]palmitate was identified as a valuable radiopharmaceutical for the assessment of myocardial metabolism and function (Kong and Friedberg, 1971; Weiss et al., 1976; Machulla et al., 1978). However, although the success of [^{11}C]palmitate in myocardial imaging has been well documented, a void remains in the literature as very few descriptions of its production and synthesis exist (Lerch et al., 1981; Padgett et al., 1982; Welch et al., 1983; Jewett et al., 1985). Neither the Molecular Imaging & Contrast Agent Database (MICAD), 2010 managed by the National Institutes of Health, nor the U.S. Pharmacopeia [USP-32, NF-27, 2009] report any information on the synthesis, production, or utilization of [^{11}C]palmitate for use in human studies. While the automated production of [^{11}C]acetate has been described on multiple occasions recently (Oberdorfer et al., 1996; Moerlein et al., 2002; Roeda et al., 2002; Le Bars et al., 2006; Soloviev and Tamburella, 2006; Lodi et al., 2007; Cheung and Ho, 2009), a detailed description of the synthesis and production of [^{11}C]palmitate has not been published for more than 15 years (Iwata et al., 1995). Although the synthetic steps may not have changed since the most recent description, improvements in synthesis module design, automation, efficiency, versatility, and product yield continue to be noteworthy for the continued progress of radiopharmaceuticals.

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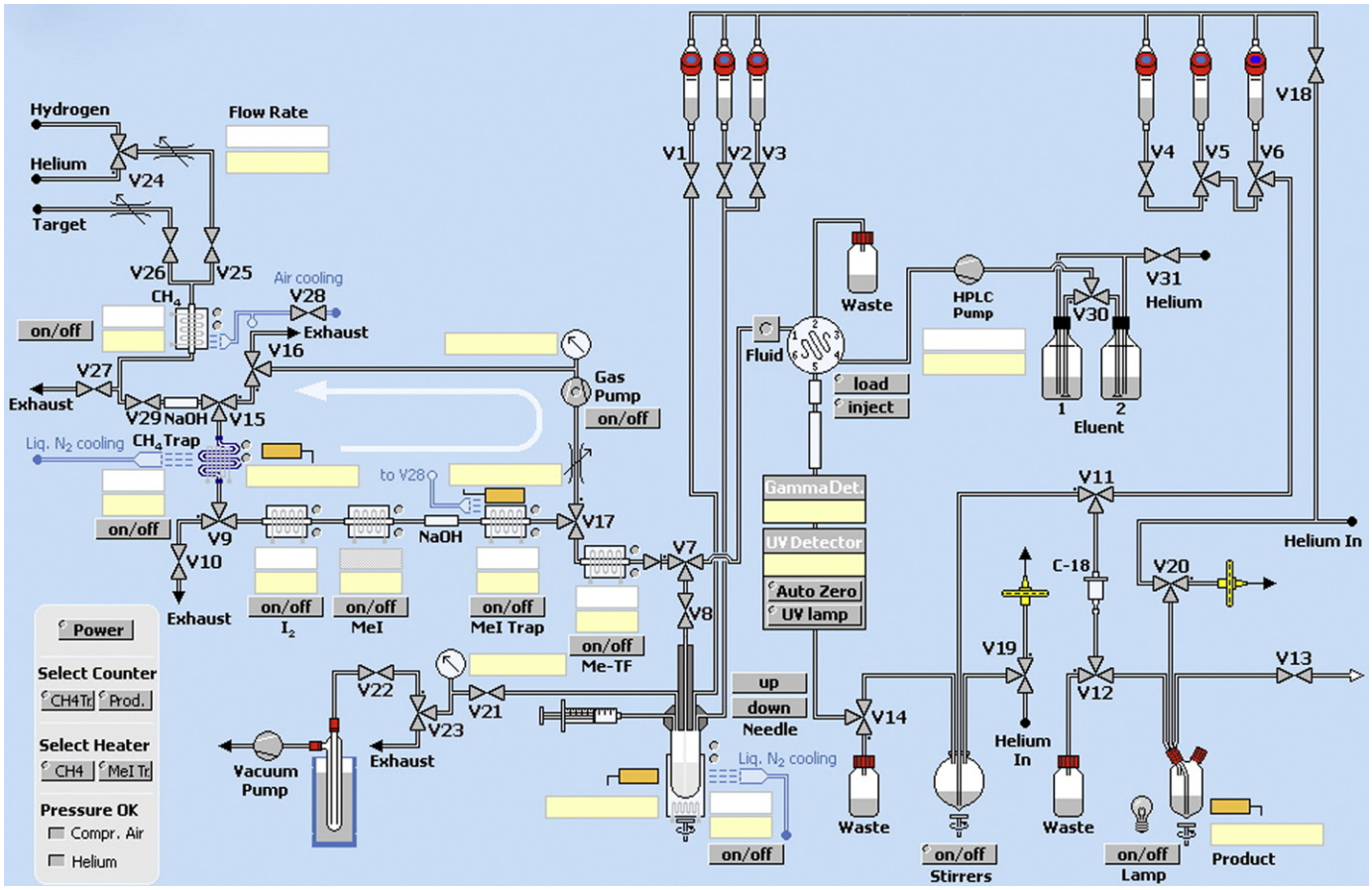

Fig. 1. The GE Tracerlab $FX_{C\text{-}Pro}$.

Recent years have yielded significant improvements to automated radiochemical synthesis modules such as the General Electric (GE) Tracerlab $FX_{C\text{-}Pro}$ (Fig. 1). The main advantage of such improved synthesis modules is that they allow for the rapid and fully automated production of a variety of radiopharmaceuticals, while requiring minimal time and effort between production runs. However, the modules are set up for "routine" radiopharmaceutical production using standard radiochemical techniques. Therefore preparation of radiopharmaceuticals via non-standard radiochemical reactions is frequently not trivial, and often involves synthesis module reconfiguration. To allow for the expedited, fully automated, production of carbon-11 radiopharmaceuticals such as [^{11}C]acetate (Fig. 2) and [^{11}C]palmitate (Fig. 3) that are derived from Grignard reagents, simple modifications were made to the GE Tracerlab $FX_{C\text{-}Pro}$. These modifications were easily implemented, documented appropriately in the synthesis module logbook, and did not compromise the radiochemical yield of the product nor increase the difficulty of synthetic steps. The modifications to the module, the synthetic steps, and analytical results of the final products are presented herein.

2. Materials and methods

2.1. Materials

NaCl, 0.9% USP, sterile water for injection, USP, and sodium phosphates, Inj. USP were purchased from Hospira Inc. Chromafix PS-H$^+$ and Chromafix PS-Ag$^+$ Sep-Pak cartridges and Millex® sterile filters were purchased from Macherey-Nagel Inc. and Millipore, respectively. Sterile product vials were obtained from Hollister-Stier. Glacial acetic acid (CH_3CO_2H), 6 M HCl, ethyl ether, and sodium acetate, >99% were purchased from Fisher Scientific Inc. Grignard reagents – 3.0 M methyl magnesium chloride in tetrahydrofuran (P/N: 38096JJ) and 0.5 M pentadecyl magnesium bromide in ether (P/N: 68196DJ) – anhydrous THF, and palmitic acid, 99% were obtained from Sigma-Aldrich Inc. The [^{11}C]CO_2 required for both of the following protocols was produced according to the nuclear reaction $^{14}N(p,\alpha)^{11}C$ in the presence of oxygen on a PETtrace cyclotron (16.5 MeV protons). The target was irradiated for 30 min at 40 μA to yield approximately 3 Ci which was delivered directly to the GE Tracerlab $FX_{C\text{-}Pro}$ module.

2.2. Modifications to GE Tracerlab $FX_{C\text{-}Pro}$: [^{11}C]acetate

The modifications made to the $FX_{C\text{-}Pro}$ module are shown in Fig. 2. The activity was delivered from the target and trapped on the first molecular sieve column (**MSC1**). Two three-way valves (**3W-1** and **3W-2**) were inserted into the system between **V27** and **V30** and controlled via an external switch. Once the three-way valves had been switched to the normally closed (**NC**) position, **V27** was opened and the activity was released from **MSC1** by heating to 350 °C. The gas then flowed through the second molecular sieve column (**MSC2**) placed in the MeI Trap position, and to **V31**. To improve the efficiency and adaptability of the $FX_{C\text{-}Pro}$, **V30** and **V31** have been adapted to function as three-way valves as opposed to being dedicated HPLC eluent valves. The activity was then released from **MSC2** by heating to 250 °C

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