10 Micro-reactors for PET Tracer Labeling

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Abstract. Miniaturization of PET radiosynthesis devices (micro-reactors or microfluidic systems) is an emerging area that has the potential to deliver many advantages, such as more efficient use of hot-cell space for production of multiple radiotracers; use of less non-radioactive precursor for saving precious material and a reduced separation challenge; highly controlled, reproducible and reliable radiotracer production; and cheap, interchangeable, disposable and quality-assured radiochemistry processors. Several ‘proof of principle’ examples along with basics of micro-reactor flow control, mixing principle and design, and device fabrication are discussed in this chapter.
10.1 Introduction

Positron-emission tomography (PET) is a radionuclide imaging modality that is used to provide quantitative information on physiological and biochemical phenomena in animals and human subjects in vivo (Phelps and Mazziota 1985; Phelps 1991, 2000). As such, PET is highly valuable for clinical research (Wagner 1991) and drug development (Comar 1995; Pike 1997; Burns et al. 1999). The biochemical scope and specificity of PET is determined by the available array of positron-emitting radiotracers (Iwata 2004), which are generally labeled with positron-emitters such as carbon-11 \((t_{1/2} = 20.4 \text{ min})\) or fluorine-18 \((t_{1/2} = 109.8 \text{ min})\) at high (no-carrier-added; NCA) specific radioactivity.

Because of their short half-lives, these radiotracers must be produced as needed from cyclotron sources of carbon-11 and fluorine-18, which are usually \([^{11}\text{C}]\)carbon dioxide, \([^{11}\text{C}]\)methane and \([^{18}\text{F}]\)fluoride ion (Fowler and Wolf 1982, 1997, Stöcklin and Pike 1993; Elsinga 2002; Welch and Redvanly 2003). \([^{11}\text{C}]\)Carbon dioxide and \([^{18}\text{F}]\)fluoride ion may be used directly in labeling reactions. Otherwise, primary cyclotron products are converted into useful secondary labeling agents, such as \([^{11}\text{C}]\)iodomethane (Crouzel et al. 1987; Larsen et al. 1997; Link et al. 1997) or \([^{18}\text{F}]\)2-fluoroethyl tosylate (Block et al. 1987; Studenov and Berridge 2001). In a typical labeling procedure, a very large \((10^2 \text{ to } 10^4\)-fold) excess of the non-radioactive reactant (precursor) is used to promote rapid and efficient incorporation of the radioisotope into the target radiotracer. The reaction volume is typically 0.3–1.0 ml with the vessel sealed and heated. These conditions necessitate rapid separation of a low quantity of radioactive product (\(\sim \mu\text{g}\)) from a large excess of unreacted precursor (\(\sim \text{mg}\)) that is usually achieved with single-pass high-performance liquid chromatography (HPLC) on a semi-preparative size column. Moreover, in practice, efficient transfers of radioactive product to HPLC are not always possible, since they may require intervening concentration of the reaction mixture by evaporation or solid-phase extraction. In addition, the reliable and regular production of PET radiotracers must be performed in a lead-shielded hot-cell with remotely controlled and preferably automated equipment that is capable of (a) synthesis of the radiotracer from high initial levels of radioactivity (up to 5 Ci; 1 Ci = 37 GBq), (b) purification of the radiotracer and