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Technical note

Specific activity of [^{11}C]CH_3I synthesized by the "wet" method: Main sources of non-radioactive carbon

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ABSTRACT

Positron emission tomography (PET) is a powerful molecular imaging technique based on the administration and detection of radioactive (positron emitting) species. In some applications, the concept of specific activity becomes especially important in order to prevent undesired pharmacological and/or toxic effects after injection of the radiotracer. Problems to obtain high specific activities are found when ^{11}C-labeled compounds are prepared by methylation following the so called "wet" method, which consists of a simple route but usually yields radiotracers highly diluted with the stable specie. In the present work, the main sources of contamination by stable carbon in the [^{11}C]CH_3I synthesis following the "wet" method have been analyzed and their individual contribution has been quantified. The results show that the most relevant contamination of CO_2 is generated during the bombardment process.

1. Introduction

Positron Emission Tomography (PET) is a powerful molecular imaging technique which produces a three-dimensional image or map of functional processes in a biological system. It is based on the administration and detection of radioactive tracers, and has been widely used in the last decades with the aim of obtaining *in vivo* biological and physiological information at a cellular and/or molecular level. Recent advances concerning PET applications are associated to an increasing demand for innovative and more specific radiotracers labeled with short-lived isotopes, mainly ^{18}F ($t_{1/2}$ = 109.8 min) and ^{11}C ($t_{1/2}$ = 20.4 min) (Mason and Mathis, 2003).

In some applications, such as *in vivo* studies approaching the behaviour of bioactive or toxic molecules and the visualization of low-density receptors in the brain (Noguchi et al., 2003), the concept of specific activity (or molar activity) becomes specially relevant, provided that the quantity of injected tracer can definitely produce undesired pharmacodynamic and/or toxic effects, as well as receptors saturation.

Among the extensive variety of PET radiotracers, those which are labeled with ^{11}C show several advantages, such as the possibility to perform multiple PET studies per day in the same subject (Lodi et al., 2007) and the capability to achieve radiotracers indistinguishable from the non-labeled molecule within the biological system (Noguchi et al., 2003). Although several routes for ^{11}C-labelling have been already described in the literature (Rahman et al., 2004 and references therein), the most widely used strategy is based on the so called "wet" method (Langstrom and Lundqvist, 1976) in which the methylating agent ([^{11}C]CH_3I) is produced following four steps: (i) production of [^{11}C]CO_2 in a cyclotron by bombardment of N_2/O_2 mixture with high energy protons through the ^{14}N(p,α)^{11}C nuclear reaction; (ii) reduction of [^{11}C]CO_2 with lithium aluminum hydride solution ($LiAlH_4$); (iii) treatment with hydriodic acid (HI) and (iv) distillation of [^{11}C]CH_3I under continuous flow of an inert gas. Despite its simplicity, one of the major drawbacks of this method is that radiotracers coexist with a reasonable high quantity of the non-radioactive specie, leading to low specific (or molar) activities. The formation of the non-radioactive specie is due to the presence, incorporation and/or *in situ* generation of [^{12}C]CO_2 before the treatment with HI. The low specific activity obtained by using the "wet" method has promoted the development of alternative procedures, like the "gas phase" method, which exploits the conversion of [^{11}C]CH_4 (produced from [^{11}C]CO_2) into [^{11}C]CH_3I by free radical iodination vapour at high temperature in the gas phase (Larsen et al., 1995; Link et al., 1995). The radioactive specie [^{11}C]CH_4 can also be produced directly in the cyclotron by bombardment of a 5% H_2/N_2 target gas mixture (Buckley et al., 2000; Helus et al., 1986). In this last case, specific

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activity of the final radiotracer is extremely improved (Noguchi and Suzuki, 2003; Noguchi et al., 2003).

Although an increase in the specific activity of the radiotracers obtained by following the "wet" method is highly desirable, up to now and from the early 1980s only a few works have evaluated the factors that potentially affect the presence of non-radioactive specie and thus contribute to decrease the specific activity of ^{11}C-labeled radiotracers. Iwata et al. (1988) concluded that carrier carbon dioxide was originated in methanol formed from a trace of THF remaining in the $LiAlH_4$ after the evaporation step, and could be decreased to 0.2 μmol by reducing the amount and concentration of the $LiAlH_4$/THF solution. In more recent works (Zhang and Suzuki, 2005), $LiAlH_4$ solution has been found to be again the major source of ^{12}C, while others (Ermert et al., 2008; Matarrase et al., 2003) state that the major contribution seems to come from $[^{11}C]CO_2$ production process in the cyclotron. This historical disagreement suggests that the sources of contamination are extremely dependent on the particular configuration of the systems involved in the production process of each particular site (e.g. quality of the reagents, target material, synthesis box, etc.).

In the present work, the sources of ^{12}C which, in our particular case, contribute to decrease the specific activity of $[^{11}C]CH_3I$ synthesized by the "wet" method have been determined and its individual contribution has been quantified. Finally, some general procedures to be performed in order to improve the specific activity are suggested.

2. Experimental

2.1. Materials and reagents

$LiAlH_4$ (0.1 M solution in dry THF) and HI (57% aqueous solution) were purchased from ABX (Advanced Biochemical Compounds, Radeberg, Germany). Soda lime (ACS reagent, granular, +100 mesh), water (HPLC grade), acetonitrile (HPLC grade), active charcoal (purum, granulated) and methyl iodide (⩾99%, GC quality) were obtained from Panreac Química (Madrid, Spain). Molecular sieve (powder) was purchased from Sigma-Aldrich. All reagents were used as received without further purification.

2.2. General method for the production of $[^{11}C]CH_3I$

$[^{11}C]CH_3I$ was produced according to literature (Gómez et al., 2008) following five steps: (i) $[^{11}C]CO_2$ was generated in an IBA Cyclone 18/9 cyclotron via the $^{14}N(p,\alpha)^{11}C$ nuclear reaction. The target system consisted of an aluminum 6061 body (irradiated volume = 40 cm^3) covered with aluminum 6061 foil (thickness = 500 μm). The target gas [N_2 (99.99% purity)/0.5%O_2, pressure = 21 bar before bombardment] was irradiated with 18 MeV protons (effective beam energy = 15 MeV) and the beam current was maintained at 24 μA (pressure in the range 35–40 bar) during bombardment. (ii) The target content was transferred by spontaneous expansion to the synthesis module (MeI-Plus Methyl Iodide Production System, Bioscan Inc., Washington, USA; see Fig. 1 for scheme) through a stainless-steel tube (0.8 mm ID) and $[^{x}C]CO_2$ ($[^{12}C]CO_2$+$[^{11}C]CO_2$) was trapped in a molecular sieve column at room temperature (Mock et al., 1995). (iii) The reactor (see Fig. 1) was filled with $LiAlH_4$ (0.1 M solution in dry THF, 250 μL). (iv) $[^{x}C]CO_2$ was released from the molecular sieve by heating at 250 °C under continuous nitrogen flow (15 mL/min, t = 2 min) and trapped in the reactor. (v) After complete trapping, solvent was evaporated to dryness (T = 115 °C, continuous nitrogen flow at 15 mL/min, t = 2 min) and HI (57% aqueous solution, 150 μL) was added. $[^{x}C]CH_3I$ was distilled by heating under continuous nitrogen flow (T = 115 °C, flow = 15 mL/min, t = 1.5 min), circulated through a soda-lime solid phase extraction (SPE) cartridge and bubbled into a vial pre-charged with ice cold acetonitrile (0.5 mL). The vial exhaust was connected to an active charcoal trap. After distillation was completed, 0.5 mL of cold water was added and the activity of the vial and the charcoal trap were measured in a dose calibrator (Capintec CRC®-25 PET, New Jersey, USA) to determine the percentage of the radioactivity trapped in the vial (only in *hot* tests).

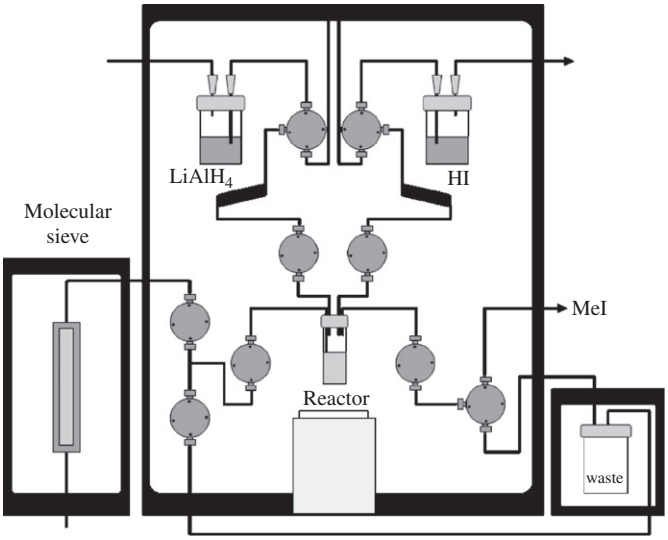

Fig. 1. Scheme of MeI-Plus Methyl Iodide Production System.

In all cases, the synthesis box was cleaned with ethanol, acetone and diethyl ether and carefully dried under nitrogen continuous flow before use. The system was pressurized with nitrogen between runs to avoid external contamination. Just before the first run of each series, the molecular sieve column was heated at 250 °C for 60 min under continuous nitrogen flow (50 mL/min) to remove traces of stable CO_2. Before hot tests, three pre-irradiations were carried out (target current = 24 μA, integrated current = 1 μA h) and discarded. For cold tests, when appropriate (scenario 3, see below), the target was loaded and unloaded three times before running the experiments.

2.3. General method for the quantification of $[^{x}C]CH_3I$

The final solution ($[^{x}C]CH_3I$ contained in 1 mL of 1:1 acetonitrile/water mixture) was analyzed without dilution by means of high performance liquid chromatography using an Agilent 1100 series HPLC system with a multiple wavelength detector (λ = 220 nm) and an isotopic detector. A Mediterranean Sea RP-18 column (4.6 × 150 mm, 5 μm) was used as stationary phase and water/acetonitrile (1:1) was used as mobile phase at a flow rate of 1 mL/min. Integrated areas in the UV chromatogram were compared to areas obtained after injection of standard solutions to determine the amount of $[^{x}C]CH_3I$.

2.4. Search for the source of $[^{12}C]CO_2$: partial runs

In order to find the sources of non-radioactive carbon and to assess their individual contribution, different partial runs were carried out under the following scenarios:

Scenario 1: Syntheses were carried out by executing steps (iii) and (v) of the general procedure; hence, bombardment, transfer of