Automated Synthesis of [11C]Meta Hydroxyephedrine, a PET Radiopharmaceutical for Studying Sympathetic Innervation in the Heart

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Abstract

PET imaging of the sympathetic innervation of the heart can involve the labelling of catecholamine analogues as [^{11}C]meta-hydroxyephedrine ([^{11}C]MHED) which allows the study of adrenergic neurons in heart diseases. Aim of this study was the development of an automatic synthesis program for [^{11}C]MHED using a computer-assisted [^{11}C]methylation module which provides the production and the purification of this radiopharmaceutical with reproducible radiochemical yield for cardiological studies in clinical PET. Radiochemical yield of [^{11}C]MHED was 12 ± 1% (n=5) (decay corrected referred to the end of bombardment) with an average production of 3.1 GBq for patient administration. Radiochemical purity was always higher than 99%. These preliminary results show that this computer-assisted approach for the synthesis of radiopharmaceuticals represents a reliable tool for [^{11}C]MHED production in clinical PET.

1. Introduction

PET imaging of the sympathetic innervation of the heart can involve the labelling of catecholamine analogues (false neurotrasmitters) which allow the study of adrenergic neurons in heart diseases [1]. [^{11}C]meta-hydroxyephedrine ([^{11}C]MHED) (Figure 1) is a norepinephrine analogue which accumulates in nerve terminals as the parent compound but is not metabolized by catechol−O−methyl transferase (COMT) and is also resistant to oxidative deamination by monoamine oxidase (MAO) [2, 3]. Due to its charateristics, [^{11}C]MHED seems to be a putative radiopharmaceutical for non invasive assessment of the sympathetic neuronal integrity of the heart in clinical PET [4].

The synthesis of [^{11}C]MHED is performed in PET centers with on-site cyclotron because of the short half-life of carbon-11 (20.4 minutes) by means of computer-assisted modules which provide automation of all the processes because of the high activites needed for clinical productions.

The synthesis consists in [^{11}C]methylation of a precursor metaraminol using [^{11}C]CH_3I as methylating agent [3]. The latter is obtained from the cyclotron produced [^{11}C]CO_2.

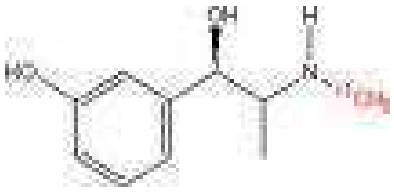

Figure 1: Chemical structure of [^{11}C]MHED.

Aim of this study was the development of an automatic synthesis process for [^{11}C]MHED by using a computer-assisted [^{11}C]methylation module which provides the production of this radiopharmaceutical with reproducible radiochemical yield for cardiological studies in clinical PET.

2. Methods

2.1. Production of [^{11}C]CO_2

[^{11}C]CO_2 was produced using standard $^{14}N(p,\alpha)^{11}C$ nuclear reaction in a PETtrace 16.5 MeV cyclotron (G.E. Healthcare). The target body was in alluminium (78 cm^3),

with 2 front Havar foils 25 µm thikness. The target was filled at 150 psi with a mixture of nitrogen (N60 purity grade) and 1% oxygen.

2.2. Synthesis of [^{11}C]MHED

[^{11}C]MHED synthesis was performed in a computer-assisted [^{11}C]methylation module TRACERlab FX$_C$ (GE Healthcare). A program which automatically performed every steps of the synthesis was developed by means of dedicated software (GE Healthcare) and a graphical process panel of the process was also present (Figure 2). The software also provided the registration of operative parameters as temperature, pressure and activity in the module during the synthesis (Figure 3).

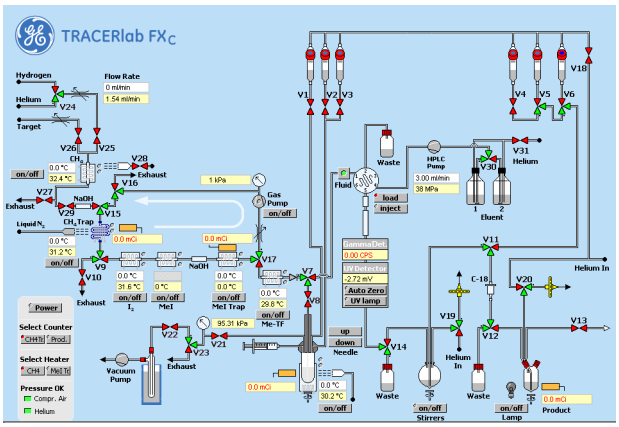

Figure 2. Graphical process panel of the module.

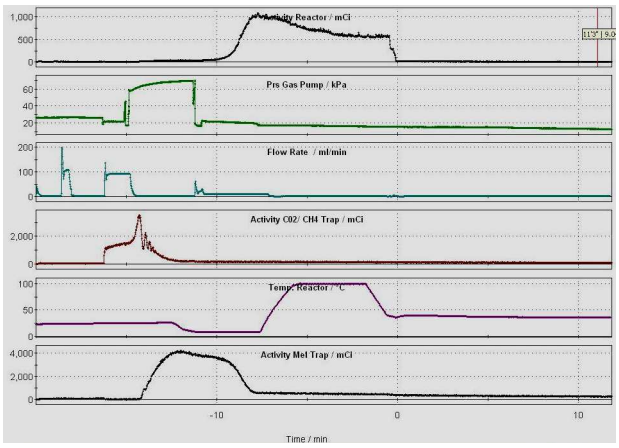

Figure 3. Graphical registration of the [^{11}C]MHED synthesis parameters.

The synthesis consists in 4 different steps:

1. Reduction of [^{11}C]CO_2 to [^{11}C]CH_4. Hydrogen gas reduction of [^{11}C]CO_2 to [^{11}C]CH_4 on nickel catalyst was obtained in a furnace that quickly reach 350°C, and cooled by compressed air. Trapping of produced [^{11}C]CH_4 was in a Carbosphere column cooled at –90°C by liquid nitrogen.

2. Synthesis of the methylating agent [^{11}C]CH_3I by converting [^{11}C]CH_4 with gas phase iodination method [5]. [^{11}C]CH_4, released by warming Carbosphere column at 80°C, was delivered in a iodine furnace at 734°C and [^{11}C]CH_3I produced was trapped in a Porapak Q column.

3. Reaction of [^{11}C]CH_3I with metaraminol. The Porapak Q column was warmed at 190°C and [^{11}C]CH_3I was delivered in a reactor containing the precursor solution in N,N-dimethylformamide. Reaction temperature was controlled by a heater.

4. Purification of [^{11}C]MHED. The reactor content was delivered in a built-in semi preparative HPLC which provides the purification of the final product. A fluid detector allowed an automatic HPLC injection of the reaction mixture. Peak detections were carried out by built-in UV/VIS as well as radiometric (NaI) detectors. A typical UV and radiometric chromatogram combination is shown in Figure 4.

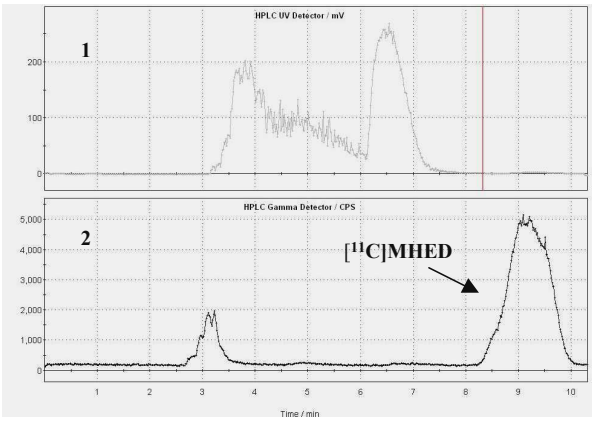

Figure 4. Semi preparative chromatogram of [^{11}C]MHED purification: 1) UV/VIS trace, 2) Radiometric trace.

In the end [^{11}C]MHED solution was sterilized by 0.22 µm membrane filter before clinical use.

3. Results

Radiochemical yield of [^{11}C]MHED was 12 ± 1% (n=5) (decay corrected, referred to the end of bombardment) with an average production of 3.1 GBq for patient administration.

Synthesis time was 33 min including HPLC purification.

Radiochemical purity determined by analytical Radio-HPLC was always higher than 99% (Figure 5).

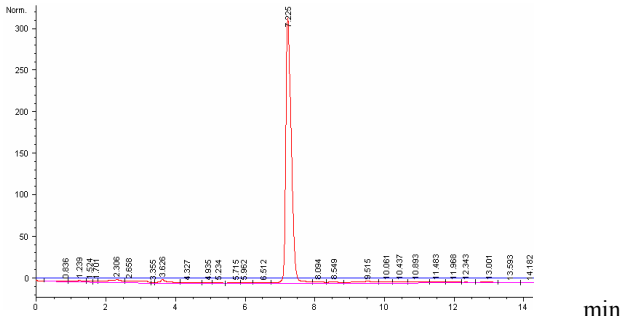

Figure 5. Analytical radiochromatogram of the final [^{11}C]MHED solution.

4. Discussion and conclusions

The developed synthesis program provides [^{11}C]MHED with reproducible radiochemical yield and high radiochemical purity. The activity produced was enough to study at least 2 patients with the same synthesis. Besides the radioprotection aspects, the computer-assisted approach provides the controls of the operating parameters of the process such as temperature, pressure, HPLC parameters and a real time process control.

The overall synthesis process can be followed by the operator on a very clear process panel which also allows manual procedures in case of needs. Moreover computer-assisted technology provides log-files and reports which guarantee the complete traceability of the process, an issue of utmost importance in radiopharmaceutical preparation.

Because of the system flexibility, all the methylation-based [^{11}C]radiophamaceuticals could potentially be synthesized by this system by writing appropriate time lists of the synthesis steps.

These results show that this computer-assisted approach for the synthesis of radiopharmaceuticals represents a reliable tool for [^{11}C]MHED production and opens interesting perspectives in the application of PET and molecular imaging in cardiology.

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