First single-use cassette for the automated high-output production of $^{[11]}$CCholine


$^{*}$ Trasis S.A. – Rue Gilles Magnée 90, 4430 Ans (Belgium)
$^{a}$ Hôpital Erasme – Service de Médecine Nucléaire – Route de Lennik 808, 1070 Bruxelles (Belgium)

INTRODUCTION

Carbon-11 is metabolically the best nuclide for PET. The dominant use of Fluorine-18 is essentially due to a more convenient half-life time for commercial distribution (110 minutes for $^{18}$F vs only 20 minutes for $^{11}$C) and a low $\beta$ energy. Choline, which is an essential nutrient involved among others in cell-membrane signaling after phosphorylation in phosphorylcholine, is compelling for cellular proliferation, especially for malignant tumors in which cellular growth is high. Nowadays, $^{[11]}$CCholine is mostly used as a PET radiopharmaceutical for imaging tumors in the brain, esophagus, rectum, prostate and urinary bladder. In contrast to $^{[18]}$FFDG, the uptake of $^{[11]}$CCholine is negligible in the brain and urinary tract resulting in highly sensitive imaging of tumors near those benign structures. This compound, however, had never been automated on an easy-to-use disposable system. This first easy-to-use cassette-based system for the synthesis of $^{[11]}$CCholine (Figure 1) is entirely automated on the Trasis AllinOne synthesizer and requires no preparation prior to production or preventive cleaning. It operates on ready-to-use consumables, does not require HPLC purification and facilitates implementation of GMP.

![Figure 1. General layout used for the synthesis of $^{[11]}$CCholine on the AllinOne synthesizer](image1.png)

METHODS

The synthesis is completed in three steps utilizing the standard « wet » chemistry method for the preparation of $^{[11]}$CCH$_3$C (Figure 2) through simple carbon chemistry. The $^{[11]}$CCH$_3$C produced by bombardment of protons on a N$_2$/O$_2$ mixture is directly converted within the cassette by bubbling in LiAlH$_4$ (step 1) followed by treatment with HI at high temperature to form the desired methyl iodide (step 2). The latter is distilled and transferred to a CM cartridge pre-loaded with DMAE precursor to form $^{[11]}$CCholine (step 3). $^{[11]}$CCholine is washed with NH$_4$OH solution, ethanol and water, eluted with a phosphate buffered saline, passed through a 0.22 $\mu$m filter into a sterile dose vial and finally ready for quality control testing.

$^{[11]}$CCH$_3$O$_2$ $\xrightarrow{\text{LiAlH}_4}$ $^{[11]}$CCH$_2$OH $\xrightarrow{\text{HI (97%)}}$ $^{[11]}$CCH$_3$I

Figure 2. Synthetic pathway of $^{[11]}$CCholine through direct conversion of $^{[11]}$CCH$_3$O$_2$ to $^{[11]}$CCH$_3$I on the cassette-based system using standard « wet » method

RESULTS

The AllinOne synthesizer allows the routine production of the tracer of interest with a non-decay corrected yield >20% after 16 minutes only (n > 10). Quality control procedures for $^{[11]}$CCholine provide results in compliance with the European Pharmacopoeia (Table 1).

<table>
<thead>
<tr>
<th>Test</th>
<th>Acceptance criteria</th>
<th>Experimental data (n &gt; 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield, uncorrected (%)</td>
<td>NA</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>Appearance and color</td>
<td>clear and colorless</td>
<td>clear and colorless</td>
</tr>
<tr>
<td>Radiochemical purity (%)</td>
<td>≥ 95</td>
<td>≥ 98</td>
</tr>
<tr>
<td>Specific activity (Ci/µmol per Ci at 50µg)</td>
<td>NA</td>
<td>up to 2.5</td>
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<tr>
<td>pH</td>
<td>4.5-8.5</td>
<td>7.2 ± 0.2</td>
</tr>
<tr>
<td>Residual DMAE (mg/V)</td>
<td>1.0</td>
<td>&lt; 0.75</td>
</tr>
</tbody>
</table>

Table 1. Representative quality control data

$^{*}$ PA/Ph/Exp. 14/T (07) 24 CDM – Monograph N°2462 (draft)
Eur. Ph. Fluorocholine “F” Injection 07/2016:2793
$^{a}$ Specific activity achieved without any special precaution

CONCLUSION

Using the “wet” method for the production of $^{[11]}$CCH$_3$C, a rapid and simple synthesis of $^{[11]}$CCholine has been implemented on the AllinOne synthesizer from Trasis. This production of $^{[11]}$CCholine is ready for routine clinical work. Furthermore, mastering the production of $^{[11]}$CCH$_3$C offers new opportunities to easily synthesize other $^{[11]}$C tracers by applying this method with LiAlH$_4$ ($^{[11]}$C-L-Methionine,...) or other reagents such as Grignard reagent ($^{[11]}$C-Acetate,...) and even other methylating agents ($^{[11]}$CCH$_3$OTf,...). Extrapolation of SA to 3 Ci of $^{[11]}$CCH$_3$C indicates that SA of $^{[11]}$CCH$_3$C ≥ 10 Ci/µmol can be achieved.