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Short Communication

IMPACT OF PROLONGED REDUCED-PRESSURE CONDITION PRIOR TO PRECURSOR LABELING ON THE LABELING EFFICIENCY OF F-18 FLUOROCHOLINE SYNTHESIS

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ABSTRACT

Objective: The goal of this preliminary work was to observe the impact of the prolonged reduced-pressure condition prior to labeling stage on the F-18 Fluorocholine labeling yield at the end of synthesis.

Methods: At this present work, the condition inside the reactor vial prior to labeling stage was manipulated. In the first technique of syntheses of F-18 Fluorocholine, the condition inside the reactor vial was set at 0 atmospheric pressure (0 atm) while in the second technique the condition inside the reactor was set at reduced-pressure (between-0.65 to-0.85 bars) with the delay time of 120 seconds. At the end of the synthesis, the impact of the prolonged reduced-pressure condition prior to precursor labeling was measured in terms of labeling yield of F-18 Fluorocholine.

Results: With the second technique, the labeling yield of F-18 Fluorocholine was elevated from 9.7% (the first technique) to 24.3%.

Conclusion: This preliminary work indicates that delay in a reduced-pressure condition prior to labeling step has greatly improved the labeling yield of F-18 Fluorocholine at the end of synthesis. Using this approach, the labeling yield of F-18 Fluorocholine was elevated from 7.5% to 24.3%.

Keywords: Azeotropic drying, F-18 Fluorocholine, Labeling yield, Reduced-pressure

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N-methyl-(C-11) choline (C-11 choline) was the first choline derivative labeled with positron emitter isotopes [1]. Since then, C-11 choline proved to be an effective marker in various tumors located in brain, lungs, urinary bladder, and most significantly in prostate [1-5]. However, due to the short half-life of radioisotope carbon-11 compared to radioisotope fluorine-18, it becomes a limiting factor to those centres which are not cyclotron-bounded. For this reason, fluorinated labeled choline, *N,N-dimethyl-N-(F-18)-fluoromethyl-2-hydroxyethyl ammonium* or known as F-18 Fluorocholine, has been developed as a substitute for choline derivatives in Positron Emission Tomography (PET) imaging technique [6-8]. Due to its high positron emission abundance, low positron energy, the small ion radius and its ease of production, fluorine-18 (F-18) become the most extensively used radioisotope for PET imaging technique. In addition, the half-life of fluorine-18 is relatively long enough to allow for multistep synthesis and transportation to remote hospitals without an on-site cyclotron [9-10].

In 2001, DeGrado had successfully synthesised F-18 Fluorocholine using the reactive intermediate, F-18 fluorobromomethane (F-18 CH_2Br) [11-13]. DeGrado's work was followed by Iwata in 2002 but using F-18 fluoromethyl triflate, a different reactive intermediate [14]. In 2008, Kryza and co-workers had successfully synthesised F-18 Fluorocholine using a similar approach as DeGrado but eliminated the use of semi-preparative HPLC column for purification [15].

In this attempt, F-18 Fluorocholine were synthesised in accordance with Kryza method on an automated synthesis platform, GE TracerLab MX_{FDG} [15]. It is known the limiting factor that affects the F-18 Fluorocholine production around the globe, is due to its relatively low yield. Therefore, this preliminary works attempt to investigate whether a prolonged reduced-pressure condition prior to labeling step will affect the yield of F-18 Fluorocholine.

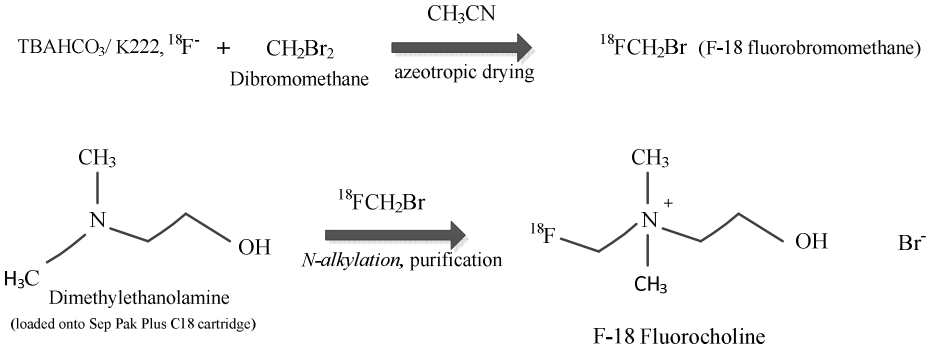

Fig. 1: Synthesis of F-18 fluorocholine

At the present works, two techniques were employed to observe the impact of the prolonged reduced-pressure condition on the yield of F-18 Fluorocholine. In the first technique, during the syntheses of F-18 Fluorocholine (*n = 3*), succeeding to F-18 ions elution to reactor vial, the condition inside the reactor was set at 0 atmospheric pressure (0 atm). Meanwhile, in the second

technique, the condition inside the reactor was set at reduced pressure (between-0.65 to-0.85 bars) with 120 seconds of additional time.

The synthesis time for F-18 Fluorocholine was 50±5 min. The labeling yield of F-18 Fluorocholine at the end of synthesis for both techniques was found to be significantly different (table 1).

Table 1: Overview of F-18 fluorocholine RCY (%)

Synthesis (Technique)	1	2	3
1st technique	7.5	9.1	9.7
2nd technique	19.8	19.8	24.3

For Technique 1, the highest labeling yield was only 9.7% (decay not corrected) and was found to be lower than the average labeling yield for Group 2, 21.3%.

In most of the published works, the F-18 Fluorocholine had a relatively low yield, between 5 to 15%. It was acknowledged that the yield of F-18 Fluorocholine is not largely dependent upon the initial amount of fluorine-18 activity transferred from cyclotron [15]. Nevertheless, the yield relied upon the fluorination conditions of dibromomethane [15]. However, the amount of dibromomethane added into the reactor did not certainly increase the yield as similar yield was noticed when the amounts of dibromomethane used varied from 200 to 400 µl [15].

At the present work, the highest yield for F-18 Fluorocholine when the reactor at 0 atm was only 9.7%. Though it was still within the range of 5 to 10% in most of the studies, the labeling yield has been greatly improved when the conditions inside the reactor prior to labeling stage was set at reduced-pressure with an additional time of 120 seconds. The F-18 Fluorocholine yield was elevated at 24.3%.

When the conditions inside the reactor vial prior to labeling stage was set at a reduced-pressure (-0.65 to-0.85 bars) with an additional time of 120 seconds, there was a possibility that prolonged azeotropic drying condition led to F-18 ions to be properly dried and allowed for removal of excessive water in form of residues that might possibly still present in acetonitrile solution even after successive azeotropic drying cycles. As a result, only the very reactive F-18 ions in evaporated acetonitrile were left inside the reactor prior to precursor labeling.

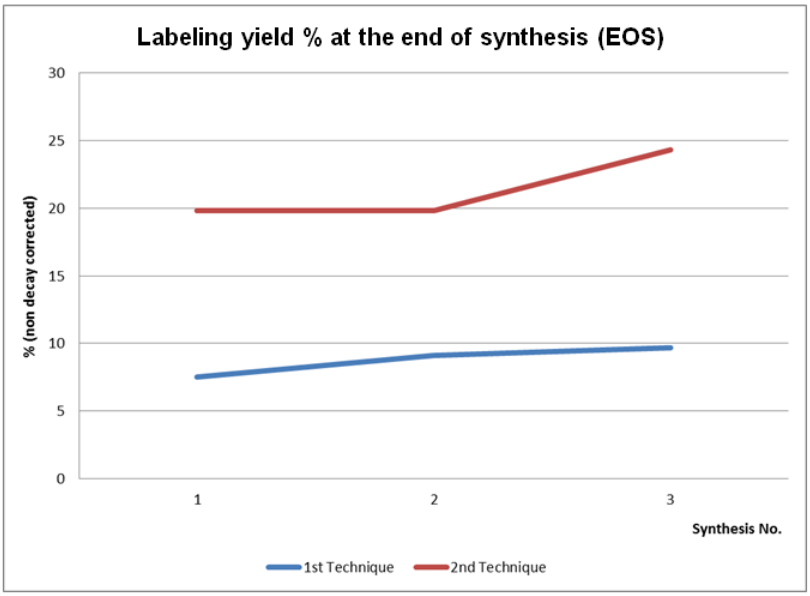

Fig. 2: Percentage of labeling yield of F-18 fluorocholine

In a work presented by Lasne on 2002 and later was supported by Cai on 2008, both agreed that in the presence of water although in the form of residue will make the F-18 ions are highly solvated and hydrogen bonded [16-17]. This, in turn, decreases the nucleophilicity of F-18 ions and making it unreactive [16-17]. Thus, it shows that prolonged reduced-pressure prior to labeling of dibromomethane with F-18 ions greatly affect the labeling yield of F-18 Fluorocholine. Using this approach, the labeling yield of F-18 Fluorocholine was elevated from 7.5% to 24.3%. However, additional work is needed to understand whether this technique is applicable to other F-18 radiolabeling syntheses.

Limitations of the study

As the F-18 Fluorocholine in this preliminary work was syntheses in limited number, hence the extent of the present work may be conducted on a large scale and also to include the quality control analysis, particularly the radiochemical purity analysis.

AUTHORS CONTRIBUTIONS

Author's contributions are as follows, Hishar H: design of the work, data collection, data analysis and writing the manuscript, Hanafi MH: grant publication (Putra-IPS 9458000), Fathinul Fikri AS generating the research idea and critical comments.

CONFLICT OF INTERESTS

All authors state that they have no conflict of interest to declare.

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