BASIC HYDROLYSIS OF 2-[^{18}F]FLUORO-2-DEOXY-1,3,4,6-TETRA-O-ACETYL-D-GLUCOSE ON A SILICA C-18 SUPPORT IN THE PRODUCTION OF FDG

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In the preparation of 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) from [^{18}F]fluoride and 2-triflyl-1,3,4,6-O-acetyl-D-mannose, alkaline hydrolysis (1) (Figure 1, route a) of the intermediate, 2-[^{18}F]fluoro-2-deoxy-1,3,4,6-tetra-O-acetyl-D-glucose (FDTAG) offers a significant improvement over acid hydrolysis (2) (Figure 1, route b). Moreover, the technique is simple to introduce into existing automated FDG synthesis systems by substituting the 2M-hydrochloric acid required for the hydrolysis with 0.3M-sodium hydroxide and leaving the hydrolysis reaction vessel unheated. However, initial attempts to incorporate the alkaline hydrolysis into our automated synthesis apparatus were unsuccessful.

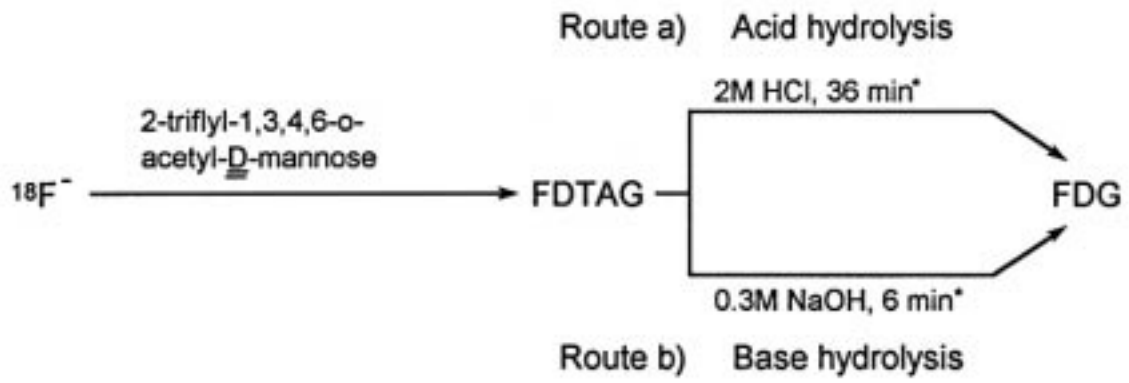

Figure 1. Acid (route a) and base (route b) hydrolysis of FDTAG in the synthesis of FDG.

Our apparatus is based on a single reaction vessel. After the initial >fluorination= step, the radioactive product is transferred from the reaction vessel to a C-18 Sep-pak cartridge for an acid wash (2). Ethanol is then used to elute the FDTAG back into the reaction vessel from the Sep-pak. The ethanol is then evaporated and 2M-hydrochloric acid is added for the hydrolysis stage.

The automated process was altered to add sodium hydroxide solution in the place of hydrochloric acid. However, after the evaporation of ethanol, the temperature of the reaction vessel had to be lowered to room temperature (*ca* <25 ^{0}C) to prevent the formation of FDG epimer ([^{18}F]2-fluoro-2-deoxy-D-mannose; FDM) (3). It was found that the time taken to cool the reaction vessel to a suitable temperature was too long: this negated any benefits introduced through the use of alkaline hydrolysis. This was a major drawback of the use of a single reaction vessel for the synthesis of FDG.

Various modifications to the apparatus to reduce the time taken to cool the reaction vessel were unsuccessful. Other possible solutions, for example, the addition of a second reaction vessel, required significant alteration of the apparatus. In addition, the apparatus was regularly used for the routine production of FDG for clinical experiments; significant alterations to the system could not be attempted.

It was decided to utilise alkaline hydrolysis of FDTAG while the product was bound to the C-18 Sep-pak

cartridge (4) by replacing ethanol reagent with sodium hydroxide for back elution (Figure 2). The generated FDG could then be passed directly onto the purification columns. Water, originally used to flush FDG from the purification columns, could also be used to flush the C-18 Sep-Pak.

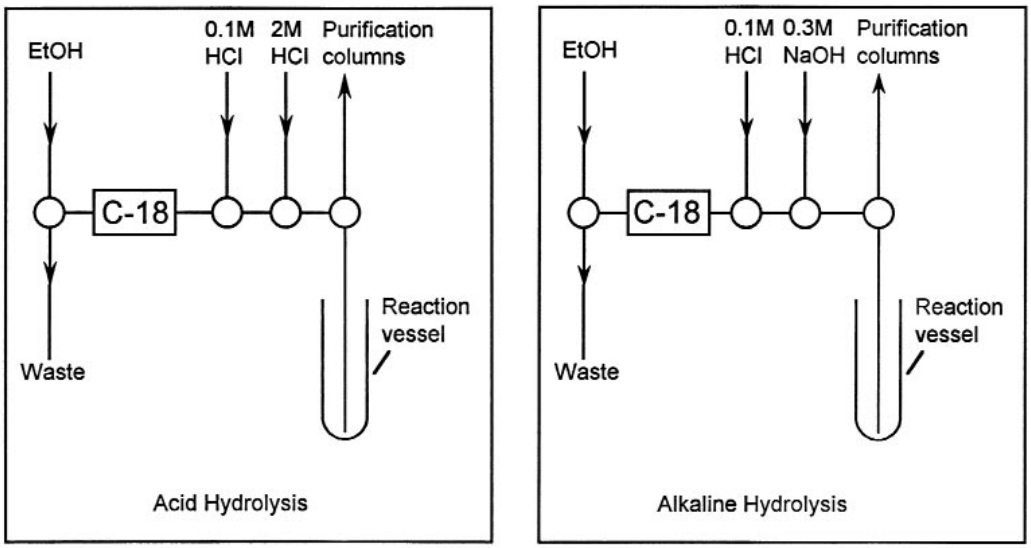

Figure 2: Diagram of the relevant modifications made to convert the automated FDG apparatus from the use of acid to base hydrolysis.

Of the FDTAG bound to the C-18 Sep-pak, 70% (decay-corrected) was converted into FDG in 6 min using alkaline hydrolysis (67% conversion). By comparison, the former method using acid hydrolysis converted 60% (decay-corrected) of the intermediate to FDG in 36 min (48% conversion). This represented a 19% improvement in the practical yield, which was comparable to that reported [20% (1, 4)].

Analysis of the final product has revealed the presence of an unknown stable impurity, which is believed to originate from the purification columns. Work is in progress to eliminate this impurity before the method is adapted to FDG production for PET experiments in human subjects.

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