Automated radiosynthesis of O-(2-[^{18}F]fluoroethyl)-O-(4-nitrophenyl)methylphosphonate: a PET tracer surrogate of VX

Thomas R. Hayes, Joseph E. Blecha, Tony L. Huynh, Charles M. Thompson, John M. Gerdes, Henry F. VanBrocklin

Introduction:

Organophosphate esters (OP) are a class of compounds that include insecticides and chemical warfare agents (CWAs). CWAs such as the V- (e.g. VX) and G-agents (e.g. sarin, soman) are non-discriminating poisons that pose a threat to both military and civilian populations. Human toxicity occurs through the inactivation of acetylcholinesterase (AChE), an enzyme responsible for the hydrolysis of the neurotransmitter acetylcholine. While countermeasures do exist for OP poisoning (2-pyridine aldoxime methyl chloride and atropine) the development of new more effective treatments remains an ongoing objective. Herein the multistep nucleophilic synthesis has been automated on the Sofie Biosciences ELIXYS to reliably provide reproducible quantities of [^{18}F]VX for use in development of new countermeasures for OP chemical agent poisoning.

Methods:

We employed the Sofie Biosciences ELIXYS FLEX/ CHEM module with minor modifications the previously reported manual synthetic procedure. [^{18}F]Fluoride ion was produced in the UCSF GE PETtrace cyclotron. The [^{18}F]fluoride ion was passed through a K_2CO_3 washed QMA light cartridge connected to the ELIXYS module using forward pressure. The trapped fluoride ion was eluted with 12 mg of kryptofix [2.2.2] and 1 mg of $KHCO_3$ in water/acetonitrile. Azeotropic drying was performed with additional acetonitrile (2 x 1 mL) added to remove trace water. Ethylene sulfite (15 µL) in acetonitrile was then added and the solution was reacted for 20 min at 90 °C. After cooling, a solution of DBU (2 µL) and precursor phosphonate (5-6 mg) in acetonitrile was added and the solution was reacted for 5 minutes at 35 °C. The reaction solvent was removed and the solution was resuspended in 400 µL acetonitrile for purification by reverse phase semi-preparative HPLC. After isolation, the tracer was diluted to 30 mL of 5 mM pH 6.8 phosphate buffer and passed through a C-18 Sep-pak. The tracer was then eluted with acetonitrile as pure [^{18}F]VX and formulated with pH 6.8 PBS.

Results:

The original manual synthesis of [^{18}F]VX, utilizing 2 separate reaction vessels and 2 solid phase cartridges, took 65 mins and produced 8 ± 2% radiochemical yield (n=6) from starting [^{18}F]fluoride. The new automated synthesis uses a single reaction vessel and one solid phase purification cartridge. The automated synthesis is still being optimized but currently produces 2.0 ± 1.1% yield in 80 mins. Automation of the reaction greatly reduced handling and exposure times.

Conclusions:

[^{18}F]VX was synthesized using a SOFIE ELIXYS FLEX/CHEM module. Due to differences in solvent volumes and transfer into the HPLC, lower yields were observed compared to the manual synthesis method, however, sufficient quantities for imaging studies can be obtained with minimal handling. Continued optimization to improve transfer efficiencies and rapid neutralization may lead to increased yields.

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Figure: