Radiopharmaceutical proposal and synthesis overview: $[^{18}F]$Fluorodeoxyglucose

Marco Nieto Pérez
Investigation Department, Innova Physics UPV.

Abstract

A short (up to 250 words) summary of the main contributions of the paper and the context of the research. Full length papers discuss and illustrate methods, challenges, and limitations in the creation, collection, management, access, processing, or analysis of data in humanities research, including standards and formats. These aspects must not necessarily be discussed with reference to a specific dataset (or collection thereof) but, if your paper focusses on particular datasets, we advise to add the dataset metadata under the section 'Dataset description'. This template provides a general outline for full length papers and authors can adapt the headings and include subheadings as they find appropriate. Please delete or replace the blue text with your own text in black.

1 Context and motivation

The most used radiopharmaceutical nowadays is $[^{18}F]$Fluorodeoxyglucose [1], a molecule who acts analogously to glucose [2] (Conformed by a glucose molecule with a displaced hydroxyle group, substituted by a fluorine-18 atom). This compound can be handy when dealing with tumors thanks to their high glucose metabolism, known as 'Warbug Effect' [3] However, the usage of $[^{18}F]$FDG is not suitable for every case, because not all of them consumes glucose as primary energy source. That's why this radiopharmaceutical is a good option but there might be other alternatives.

2 $[^{18}F]$Fluorodeoxyglucose synthesis

2.1 Fluorine-18 ion synthesis

The reaction used to synthetize Fluorine-18 is called $^{18}O(p,n)^{18}F$ [4][5][6], which consists in bombing 97% ^{18}O enriched water ($H_2^{18}O$) with protons carrying a kinetic energy of 17.5 MeV. The solution of enriched water has to be stored in a standard recipient for cyclotrons conformed by Ag or Ti and a Havar Foil window.
The resulting bombed solution has to be filtered through an Ion Exchange Cartridge, where the negative charged ^{18}F ions replace the negative counterparts of the cartridge, remaining sticked to it and letting the ^{18}O enriched water pass through, which has to be recovered in as much as possible quantity due to its high cost.
Then, ^{18}F is removed from the cartridge introducing a CO_3^{2-} solution, potassium carbonate (K_2CO_3). The finished product is a mixture of K ions and ^{18}F.

Possible impurities: Although the enriched water has a very high ^{18}O proportion, there are some remaining ^{16}O atoms in it, which produce ^{13}N atoms through the $^{16}O(p,\alpha)^{13}N$. The bombarded recipient is conformed by a Ag or Ti body and a Havar Foil window, produced using a Cobalt alloy. In case that the proton beam incides in any of the previously mentioned elements, the following impurities will be produced: ^{56}Co, ^{57}Co, ^{58}Co, ^{52}Mn, ^{54}Mn. A silver container body will produce ^{109}Cd atoms and a titanium one ^{48}V atoms.
Last but not least, the production of ^{19}F atoms shall not be discarded, chemically identical to the expected ^{18}F, thus reducing the efectivity of the radiopharmaceutical.

Requirements for the ^{18}F:

- Must be anhydridous. Any water presence will lead in Fluorine and Hidrogen interactions, reducing the efectivity of the compound. One effective way of removing the water is a 100^{o}C destillation. This process can be performed with the aid of an azeotrope compund, in order to lower the boiling point of the mixture.
- The K and ^{18}F mixture must be treated, as the high stability between the ions prevent the ^{18}F to interact as expected in the following reaction steps. We use a compound called 'Cryptand', which acts as a cage for the positive potassium ions, augmenting the fluorine ions reactivity. The chosen cryptand is the 2.2.2-Cryptand. To perform the reaction, we heat the mixture of K and ^{18}F ions along with the cryptand in an acetonitrile solution. Once the reaction has finished, acetonitrile must be removed.

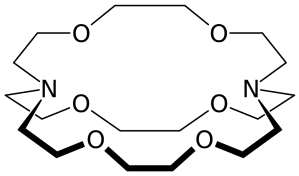

Figure 1: Schematic representation of the 2.2.2 Cryptand molecule.

2.2 Production of an intermediate compound between ^{18}F and the [^{18}F]FDG

Once ^{18}F ions have been produced with all the previous requisites, we can start the reaction with the precursor 1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-Dmannopyranose (abbreviated as mannose triflate). It has the peculiarity of being identical to the glucose, except for the carbon 2 which is inverted.

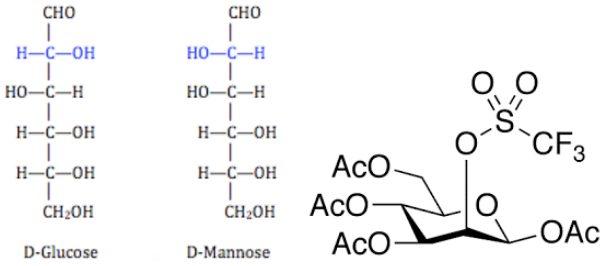

Figure 2: Difference between glucose and mannose molecules (left) and schematic representation of the mannose triflate molecule(right)

We seek the ^{18}F atom to join the second carbon of the molecule (the front centered one that contains the triflate group). The bond between the triflate and the carbon is polarized, because the triflate is highly electronegative, thus its a group that tends to leave the molecule and get replaced by the ^{18}F ion. As a nucleofilic reaction has been produced, there has been an inversion in the stereochemistry of the carbon two, transforming the molecule in a glucose analogue.

2.3 Elimination of the mannose triflate's acetyle groups

This step can be performed following two different paths. On the one hand, a reaction with a base producing acetate can be done. On the other hand, the compound can also be heated in an acid medium producing acetic acid.

2.4 Purification of the mixture containing the [^{18}F]FDG

The impurities that can be present in the mixture are:

- ^{18}F ions that have not reacted at the step 2.2

- Mannose triflate molecules that have not been hydrolized in step 2.3
- 2.2.2-Cryptand and acetonitrile from step 2.1
- Acid or basic compounds from the 2.3 step
- Bacteria and microbes

All impurities and their elimination process can be found at the following figure.

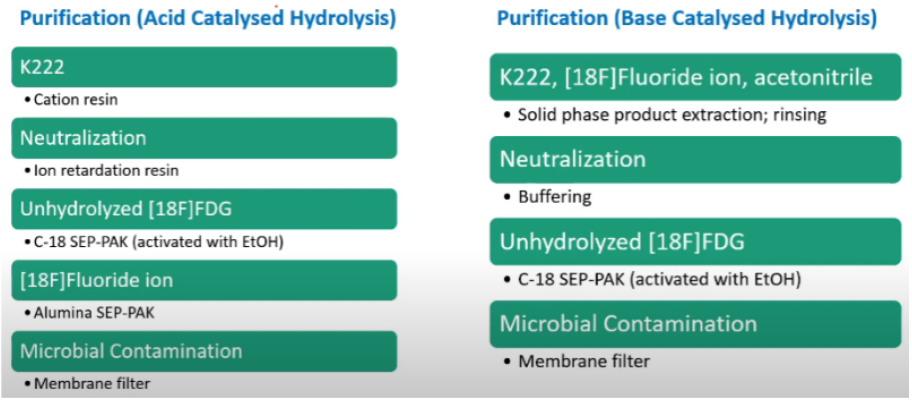

Figure 3: Steps needed to eliminate the impurities for the acid catalysed hydrolisis (left) and base catalysed hydrolisis (right)

References