Improvements in Quality Assurance of 2-[Fluorine-18]Fluoro-2-deoxy-D-glucose

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Introduction

2-[^{18}F]Fluoro-2-deoxy-D-glucose („[^{18}F]2-FDG") is a widely used radiopharmaceutical for various PET investigations. Because of the relatively long half-life of ^{18}F (109 min), it can be distributed also externally. At PSI, [^{18}F]2-FDG is produced for the in-house PET use as well as for some external users. The results of about 3 years experience in quality assurance for the production of [^{18}F]2-FDG (1988-1990) are given.

Isotopic Enrichment of Target Water [^{18}O]H_2O

^{18}F is produced at PSI via the nuclear reaction

$$^{18}O(p,n)^{18}F$$

by irradiation of ^{18}O enriched water with 72 MeV protons which are degraded to 15 MeV before entering the target capsule. The details of our production process, particularly the silver target, are described elsewhere [1]. The target material ([^{18}O]H_2O and [^{18}O]D_2O, resp.) is recovered after the synthesis by microdistillation (10 % or 0.4 ml loss per distillation). Fig. 1 shows the yield of ^{18}F in some consecutive production runs in the same target chamber, starting with 80 % enriched material. At the end of this series, the material had 78 % enrichment. The overall yield loss, consequently cannot be explained by isotope dilution only. Obviously, there are some changes in the surface of the target chamber. After heating the target chamber, or leaving it for several weeks, the yield of ^{18}F is again at the original high level.

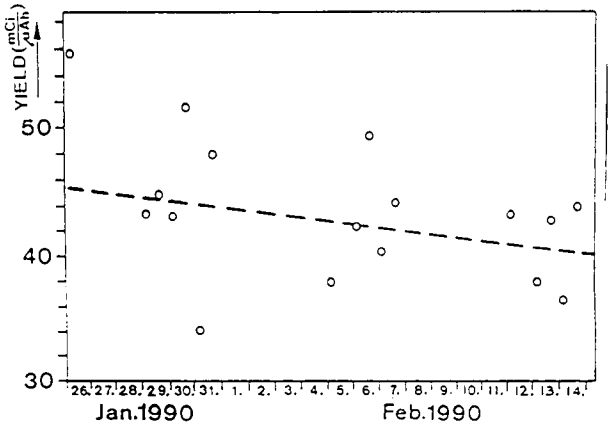
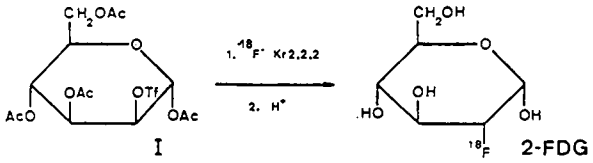


Figure 1. Yield of [^{18}F]2-FDG in Some Consecutive Runs

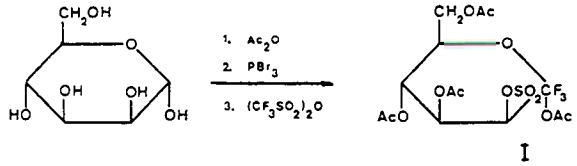
We found that, after the irradiation, the target water is of brownish colour. It could be cleaned by filtration; the precipitate consisted mainly of silver oxide. We found however, that a clear solution after the irradiation showed poor yields in [^{18}F]2-FDG synthesis, likewise a too strong black precipitate. The maximum of [^{18}F]2-FDG yield was obtained by a middle-brown solution. Although this effect to a certain content was reproducible, it could not be explained.

Synthesis

Purity of the Precursor. For the preparation of [^{18}F]2-FDG, we used the well-known method of aminopolyether-supported nucleophilic substitution, first published by HAMACHER *et al.* [2]:



Some charges of the commercially available precursor, 1,3,4,6-Tetraacetyl-2-triflyl-mannopyranose (I), obviously were not of sufficient quality. They were of yellow-brownish colour, smelled of acetic acid, and we suspected a yield reduction of [^{18}F]2-FDG. For retaining the conditions with regard to a correct educt hygiene, we synthesized the precursor (I) in our laboratory by classical procedures [3,4]:



We obtained each charge in the pure crystallized form without smell. The compound was stable over more than one year. Afterwards, we had no problems with educt hygiene at all.

Synthesis Without the Amino Polyether? The phase transfer catalyst Kryptofix (2.2.2), which is used in the synthesis of [^{18}F]2-FDG, is a toxic compound (LD_{50} in rodents 32-35 mg/kg [5]). Consequently, we tried to run the synthesis without this catalyst. The results of a series of test syntheses by varying the ^{18}F activity, but otherwise under identical conditions, are shown in Fig. 2.

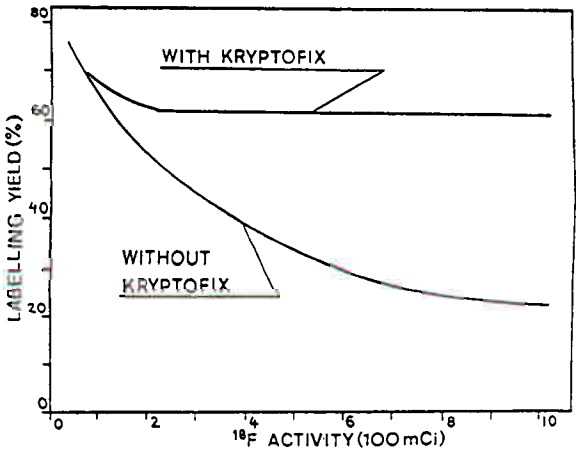


Figure 2. Yield of [^{18}F]2-FDG vs. ^{18}F starting activity, with and without the phase transfer catalyst.

It was found that the yield in syntheses without the addition of the aminopolyether decreased dramatically with increasing starting activities. In order to obtain large amounts of [^{18}F]2-FDG, we continued the syntheses with Kryptofix. In some test samples, however, we checked the amount of Kryptofix spectrophotometrically via its Pb^{++} complex [6]. No higher concentration than 90 µg/ml of Kryptofix 2.2.2 in the final injectable solution was found.

The spectrometric test is rapid, inexpensive and obviously more sensitive than the TLC method commonly used for this purpose [7].

Quality Control

Radiochemical Quality Control. Thin layer chromatography (TLC), as proposed by the most authors, separates 2-FDG from fluoride ion, Kryptofix 2.2.2 and several other impurities. The precursor and non-hydrolyzed fluorinated products, however, are not separated from 2-FDG.

In order to follow and to improve both labelling and hydrolysis yields, we separated 2-FDG and its non-hydrolyzed precursor by HPLC. Carbohydrate columns (two in series) proved to be superior to the RP-18 column, since the 2-FDG peak appears behind the educt and the non-hydrolyzed precursor, and not in front of it (Front peaks are often contaminated in a non-controllable way).

A typical HPLC chromatogram of [^{18}F]2-FDG, obtained by a Carbohydrate column, is shown in Fig. 3. In our opinion, for estimation of chemical purity, and consequently of the specific activity, HPLC separation seems to be mandatory.

Additionally, the amount of glucose was measured by an enzymatic test kit (BOEHRINGER MANNHEIM).

Until 10 hours after EOS, no radiolytic decomposition of [^{18}F]2-FDG was found.

Quality Control Routine Procedure. Based on the results demonstrated above, a quality control procedure has been settled as outlined in Table 1. It was accepted by the Swiss Regulatory Agency (Bundesamt für Gesundheit).

Every charge is documented in 3 sheets:
- Control sheet for Galenics
- Control sheet for synthesis
- Data sheet for the user

Results

From August 1988 to November 1990, 178 syntheses

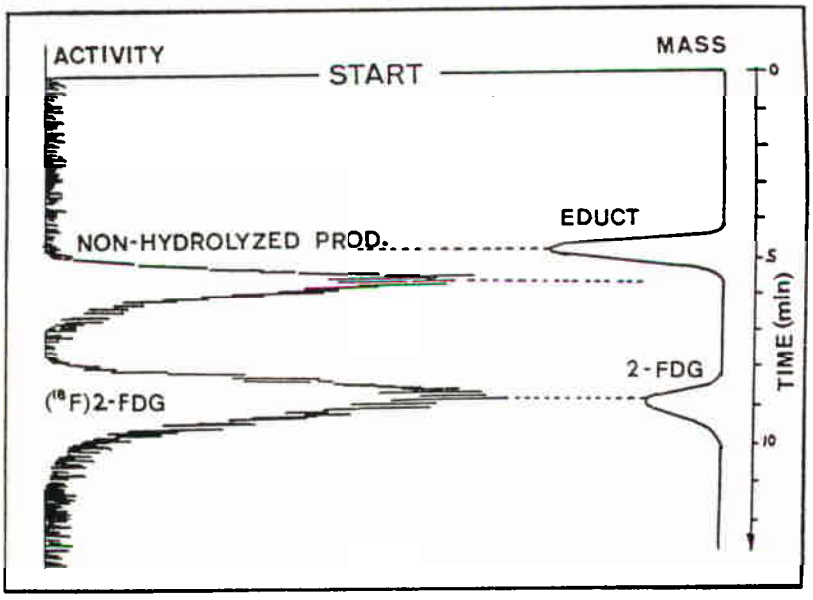


Figure 3. HPLC chromatogram of a low-yield hydrolyzed [^{18}F]2-FDG charge.

Test	Procedure
Activity[1]	Ionization chamber
Radiochemical and chemical purity[1]	(1) TLC. Si 60 plates, ethylacetate/ethanol 7:3, Rf about 0.8 (2) HPLC. Carbohydrate Analysis Column WATERS P/N 84038, 2 in series, acetonitrile/water 9:1, Mass (RI), Activity (NaI well type).
Apyrogenity[1]	Limulus test
Sterility test[1]	
Isotopic enrichment of $[^{18}O]H_2O$[2]	Mass separation
Amount of K/2.2.2[2]	Pb^{++} complex, spectrophotometrically, 250 nm
Glucose amount[2]	Enzyme Kit, BOEHRINGER MANNHEIM

[1] Mandatory, for each charge
[2] Spot tests, not for each charge

Table 1. Quality Control Procedure for [^{18}F]2-FDG at PSI

of [^{18}F]2-FDG were carried out by request of three groups:

- PSI In-House Medical PET group
- Department of Nuclear Medicine, Inselspital, Berne
- Department of Nuclear Medicine, University Hospital, Geneva.

The following observations were made:

- The produced ^{18}F activity ranged from 400 to 1000 mCi (15-37 GBq) EOB per batch.
- The radiochemical yield ranged from 50 to 65 % EOS, decay corrected.
- The product was of no-carrier added quality (1700 Ci/µmol).
- The radiochemical purity generally was > 98 %.
- The chemical purity ranged from 94 to 98 %. The main contaminant was D-glucose.
- The amount of Kryptofix 2.2.2 in the final solution generally was <90 µg/ml (< 300 µg per run).

Table 2 shows the development of the process with the exact documentation of failures. At the end of 1990, the development of the procedure was finished, and the synthesis with all items was transferred to the radiopharmacy production department at PSI.

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Time Section	Number of Syntheses	Number of Deliveries to PSI-PET	Berne	Geneva	Failures Numbers	Rate	Reasons
8/88 - 12/88	19	25	7	-	5	21 %	No beam (3), Chemistry(2)
1/89 - 12/89	58	137	27	18 (F^-)	6	10 %	Beam (4), Beam Station (2)
1/90 - 11/90	101	180	32	13	3	2 %	Beam Station (3)

Table 2: Processing Development of the Routine Synthesis of [^{18}F]2-FDG at PSI