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SYNTHESIS AND QUALIFY CONTROL OF ^{18}F-FDG AT IPEN-CNEN/SP

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ABSTRACT

In this paper the procedure developed at IPEN-CNEN/SP and some results of the 18F- FDG production and quality control during the year are presented.

Keywords: fluorine-18 fluorodeoxyglucose, positron emission tomography, radiofluorination.

I. INTRODUCTION

Fluorine-18 has been applied to biomedical investigation for over three decades, during that time it has been used in several inorganic chemical forms as a tracer for experimental study involving a variety of organs (1). Since the introduction in 1977 of 2-[^{18}F]fluor-2 deoxy-D-glucose (^{18}F-FDG) by Ido et. al (2-3) the compound has provided a valuable tool for the study the glucose metabolism in both normal and disease tissue (4) in conjunction with positron emission tomography (PET), ^{18}F-FDG is the most important radiopharmaceutical, which has been used in Nuclear Medicine for brain, heart and tumors studies.

The ^{18}F[fluoride] can be obtained with very high specific activity nca (no-carrier-added), from the nuclear reaction of ^{18}O (n,p) ^{18}F using an oxygen-18 (^{18}O) enriched water target. This reaction can be carried out with a small 10 MeV proton accelerator (5 - 6). The cost of the highly enriched material is such that the recovery of [^{18}O] water, subsequent to the extraction of ^{18}F from an irradiated target solution, is desirable. The efficient recovery of the water would allow larger volumes of water to be used in the target.

Many successful nucleophilic syntheses of ^{18}F-FDG are published. One based upon the replacement of the triflate group of methyl 4,6-*O*-benzylidine-3-*O*-methyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranoside by ^{18}F$^-$, and the other on the reaction of ^{18}F$^-$ with methyl 4,6-*O*-benzylidine-2,3-*O*-sulfuryl-β-D-mannopyranoside. The substitution of the triflate group proceeds with a yield of about 30 %, but the difficulty in removing the methyl group from de 3-*O*-position reduced the overall yield significantly (~ 10 %) The method developed by Tewson leads to an excellent incorporation of ^{18}F$^-$ into de cyclic sulfuryl-compound (90 %), but the hydrolysis of the glycoside resulted in a considerable reduction of the radiochemical yield to about 40 % or less. (7). The goal of the study was to use the triflate as a precursor and the aminopolyether potassium complex [K/2.2.2]$^{+}$^{18}F$^-$ as a phase transfer catalyst. This complex has been shown to allow a mild and efficient nucleophilic fluorination at a nca level. (8)

This has dictated the need to investigate alternative synthesis, with the ultimate objectives of providing higher radiochemical yields, while at the same time reducing overall synthesis time and the complexity of the processing system.

A large-scale production requires the handling of radioactivity in the range of hundred of MBq to produce sufficient amount of labeled compound. There are various established methods for large-scale production. The manual synthesis, without adequate protection, inevitably increases the radiation burden of the chemist (9), the semi-automated (10) and the fully automated synthetic procedures available for production, reduce synthesis time and decrease the radiation exposition. Recently there has been a significant increase in the number of automatic module for synthesis of ^{18}F-FDG. It permits production of large quantities of radiopharmaceuticals for clinical use and is safe, reliable and efficient.

The purpose of this work is to describe the procedure developed at the Radiopharmacy Center for the production and quality control of ^{18}F-FDG.

II. MATERIALS AND METHODS

The ^{18}F$^-$ (fluoride) is obtained by the nuclear reaction ^{18}O (p,n) ^{18}F in the Cyclone-30 (IBA), using 2 ml of enriched $H_2{}^{18}O$ (95.2 %). At the end of bombardment the fluoride is transferred directly to the automatic Module (IBA) by helium pressure. In a typical production, a 40 – 60 minutes bombardment at energy of 18 MeV and current of 25 – 40 μA produces 75,000 – 90,000 MBq of [^{18}F] - fluoride. After [^{18}F$^-$] fluoride retention in QMA filter, under

argon pressure of 0.5 bar, the ^{18}FK is recovery in 0.3 ml of K_2CO_3 solution. The recovery process runs in about 7 minutes. All the reagents are of ultra-pure degree, anhydrous and should be prepared 30 minutes before the start of the synthesis. The ^{18}FK eluted are transferred into the labeling vessel containing 26 mg kriptofix in 0.8 ml of acetonitrile, during evaporation acetonitrile is added automatically 2 times. The synthesis is achieved by a nucleophilic substitution by addition of mannose triflate followed by evaporation to dryness at 85° C, under vacuum and argon flow; ether is added and the solution passed through silica cartridges. The impurities are trapped and the labeled precursor is washed away The labeled precursor is hydrolyzed under acid medium to eliminate the protecting group and the final product is purified by anionic resin, Aluminum and C_{18} cartridges (Waters) and sterilized by 0.22 μm Millipore filter. The resulting neutral eluent is dispensing in a sterile glass vial containing 1.5 ml of pH 7.5 buffer phosphates.

The enriched water used in the production is recycled after distillation, twice in quartz distillatory.

Thin layer chromatography system is carried out for radiochemical and chemical determination, in ITLC-SG (AL) (2 x 10 cm), using acetonitrile:H_2O (95:5) and NH_4OH: MeOH (1:9) as solvents, respectively. The radionuclide purity is determined by γ-ray spectroscopy using hipper-pure Ge-detector. Sterility and pyrogen tests are performed by the microbiology procedures outlined in the pharmacopoeias in different culture medium (sodium tioglicolate and Soybean casein tripticase broths) incubated at room temperature and at (35 ± 2)°C. The apirogenicity is evaluated using the "in-vitro" Limulus test (LAL).

III. RESULTS

Table 1 shows typical values obtained in 10 batches of radiochemical, chemical and microbiological purity of ^{18}F-FDG. The radiochemical purity is (98,57 ± 0,47)% and it can be seen that in all runs we didn't find Kriptofix in final product.

TABLE 1. Radiochemical, Chemical and Microbiological purity of ^{18}F-FDG

Batch	Radiochemical (%) *	Kriptofix	Sterility / Pyrogen
1	98.83	negative	negative
2	98.81	negative	negative
3	98.94	negative	negative
4	98.66	negative	negative
5	97.86	negative	negative
6	98.40	negative	negative
7	98.42	negative	negative
8	99.34	negative	negative
9	98.54	negative	negative
10	97.87	negative	negative

*** Average = (98.57 ± 0.47) %**

Table 2 and Figure 1 show the number of runs classified in terms of activity range of ^{18}F-FDG obtained during the year 2001. It is important to emphasize the activities obtained during the runs are not the maximum but is determined in function of the users or demands.

The uncorreted yield in function of the irradiation dose is shown in Table 3. The average value obtained from 14 productions is (27.2 ± 1.63) mCi / μAh. This value is an important practical parameter because it defines the irradiation time necessary to produce a desirable activity of ^{18}F-FGD.

TABLE 2. Activities of 18F-FDG (EOS) Produced in 2001

No. Events	Activity (mCi)*	(%)
10	230 - 293	11,2
11	305 - 341	12,3
11	348 - 392	12,3
24	**401 - 496**	**26,5**
23	**502 - 597**	**25,8**
8	605 - 697	08,9
2	706 - 770	02,2

*

Range of activities from 8,510 to 28,490 MBq

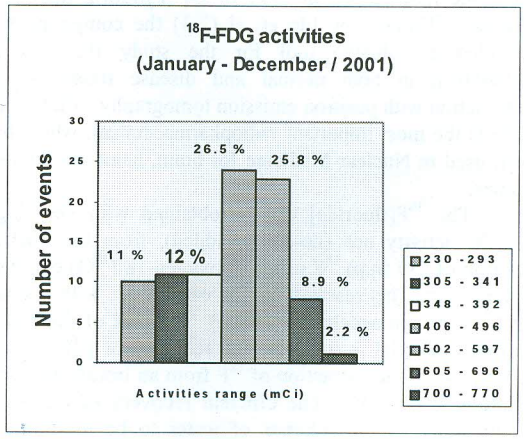

Figure 1 – Range of activities produced during 2001 at IPEN-CNEN/SP

TABLE 3. Uncorrected yield in function of irradiation dose

Batch	i (μA)	Dose (μAh)	^{18}F-FDG activity (EOS) (mCi)	*Yield (mCi / μAh)
1	23.8	15.9	432	27.2
2	25.7	15	339	26.6
3	24.9	17	469	27.8
4	26.6	13.3	365	27.4
5	26.4	18.5	486	26.3
6	26.2	8.3	245	29.5
7	25.6	8.1	203	25.1
8	27.4	20	507	25.3
9	25.9	10.8	305	28.4
10	27.4	18.3	453	24.7
11	26.5	18.1	505	27.9
12	26.4	20.7	549	26.5
13	27.5	11	335	30.4
14	26.3	19.3	538	27.9

- **Average = (27.2 ± 1.6) mCi / μAh**

IV. DISCUSSION AND CONCLUSION

The advantage of the synthetic method in automatic module presented in this work is the high yield (max. 55 % corrected) as EOB of non-carrier-added ^{18}F-FDG, based on the phase-transfer-mediated substitution of triflate. The stereochemical specificity of the nucleophilic displacement combined with a rapid hydrolysis of the acetylated sugar derivative makes it possible to synthesize pure and larger quantities of ^{18}F-FDG in 55 minutes.

In more than 80 productions during 2001, the Radiopharmacy Center has produced 18,500 MBq / batch of ^{18}F-FDG at the end of synthesis (EOS). About 98 % of the activity were recovered in the QMA filter and the radiochemical and radionuclide purities of ^{18}F-FDG were better than 98 %. The Kriptofix level was below of the detection limit of color spot test which is 50μg /ml according to FDA recent revision (11). From our experience, the recovery of [^{18}O] water by distillation is very convenient and economical and can be used for further production of $^{18}F^-$.

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REFERENCES

[1] Blau, M.; Nagler, W. and Bender, M.A. F-18. **A new isotope for bones scanning.** J. Nucl. Med. 3: 332 – 334, 1962

[2] Ido, T.; Wan, C.N.; Fowler, J.S. and Wolf, A.P. **Fluorination with F_2. A conventionent synthesis of 2-deoxy-2-fluor-D-glucose.** J. Org. Chem. 42: 2341 – 2342, 1977

[3] Ido, T.; Wan. C.N.; Casella, V. and Wolf, A.P. **Labeled 2-deoxy-D-glucose analogs. ^{18}F-labeled 2-deoxy-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose, and ^{14}C-2-deoxy-2-fluor-D-glucose.** J. Label. Comp. Radiopharm. 14: 175 – 183, 1978

[4] Phelps, M.E.; Mazziotta, J.C.; Huanc, S.C. **Study of cerebral function with positron computed tomography.** Cereb.Blood Flow Metab. 2: 113 – 162, 1982

[5] Kilbourn, M.R.; Hood, J.T.; Welch, M.J. **A simple ^{18}O water target for ^{18}F production.** Int. J. Appl. Radiat. Isot. 2: 111 – 115, 1985

[6] Wieland, B.W; Hendry, G.O.; Schidt, D.G.; Bida, G. and Ruth, T.J. **Efficient small-volume O-18 water targets for producing 18F fluorine with low energy protons**. J. Label. Compd. Radiopharm. 23: 1338 – 1340, 1986

[7] Tewson, T.J. **Synthesis of no-carrier-added fluorine-18-2-fluoro-2-deoxy-D-glucose.** J. Nucl. Med. 24: 718 – 721, 1983

[8] Hamacher, K.; Coenen, H.H. and Stöclin, G. **Efficient stereo specific synthesis of no-carrier-added 2-[^{18}F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution** J. Nucl. Med. 27: 235 – 238, 1986

[9] Fowler, J.S.; Mac Gregor, R.R.; Wolf, A.P.; Farrell, A.A.; Karlstrom, K.I. and Ruth, T.J. **A shielded synthesis system for production of 2-(^{18}F)-2-fluoro-deoxy-D-glucose.** J. Nucl. Med. 22: 376 – 380, 1981

[10] Barrio, J.R.; MacDonald, M.S.; Robinson Jr., G.D.; Najafi, A.; Cook, J.S. and Kuhl, D.E. **Remote, Semiautomatic production of F-18-labaled 2-deoxy-2-fluoro-glucose.** J. Nucl. Med. 22: 372-375, 1981

[11] Ma, Y.; Huang, B.X.; Channing, M.A. and Eckelman, W.C. **Quantification of Kriptofix 2.2.2 in 2-[18F]-FDG and other radiopharmceuticals by LC/MS/MS.** Nucl. Med. and Biol. 29: 125 – 129, 2002