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

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ABSTRACT

There is an increasing interest in ^{18}F-radipharmaceuticals especially in ^{18}F-FDG, which is used in Nuclear Medicine for brain, heart and tumor studies. This report describes the routine production and quality control of ^{18}F-FDG at IPEN-CNEN/SP.
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 %). The synthesis is achieved by a nucleophilic substitution of mannose triflate reaction in the automatic module (Coincidence - GE). Thin layer chromatography system was carried out for radiochemical and chemical determination. Sterility and pyrogen tests were performed by the microbiology procedures outlined in the pharmacopoeias and by the "in-vitro" Limulus test, respectively.
Typical protons irradiation of 110-120 minutes, at energy of 18 MeV and current of 30 μA, produces about 3,700 mCi/batch of $^{18}F^-$[fluoride] and about 98 % of this activity was recovered in the QMA filter. The radiochemical and radionuclide purities of ^{18}F-FDG were better than 97 %. The Kriptofix level was below of the detection limit of color spot test. Sterility and pyrogen tests were negative in all the delivered vials. In 20 productions during 2005, the Radiopharmacy Center has produced about 1,850 mCi/batch of ^{18}F-FDG (End Of Synthesis) and distributed in four months 1,424 doses (64,742 mCi).

1. INTRODUCTION

Fluorine-18 has been used in several inorganic chemical forms as a tracer for experimental study involving a variety of organs for over three decades [1]. Since the introduction in 1977 of 2-[^{18}F]fluor-2 deoxy-D-glucose (^{18}F-FDG) by Ido [2, 3] the compound has provided a valuable tool for the study the glucose metabolism in both normal and disease tissue in conjunction with positron emission tomography (PET) for brain, heart and tumors studies as well as research [4]. The $^{18}F^-$[fluoride] can be obtained with very high specific activity (no-carrier-added), from the nuclear reaction of ^{18} O (n,p)^{18}F using an oxygen-18 (^{18}O) enriched water target. Several methods of successful nucleophilic syntheses of ^{18}F-FDG have been reported in the literature. A large-scale production requires the handling of radioactivity in the range of thousand of mCi 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 [5], the semi-automated [6-7] and the fully automated synthetic procedures are available for production, the main advantages of these methods are the high purity of the final product, the reduced synthesis time and decrease radiation exposition. Recently there has been a significant

increase in the number of automatic module for synthesis of ^{18}F-FDG [8-9]. 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.

2. MATERIALS AND METHODS

The $^{18}F^-$[fluoride] is obtained by the nuclear reaction $^{18}O(p,n)^{18}F$ in a typical protons irradiation of 110-120 minutes, at energy of 18 MeV and current of 30 μA at Cyclone-30 (IBA), using 2 ml of enriched $H_2{}^{18}O$ (95.2 %) Cambridge. At the end of bombardment the fluoride is transferred directly to the automatic Module (GE TRACERlab MX_{FDG} Synthesizer Module) by helium pressure. All the reagents are packaged ready to use and contains all chemicals required for the nucleophilic radiosynthesis with ultra-pure degree and provided as a "reagents kit" (ABX) that must be fit 15 - 20 minutes before the start of the synthesis. The automatic synthesis is achieved in 25 minutes by a nucleophilic substitution using mannose triflate. The impurities are trapped automatically and the labeled precursor is washed away. The labeled precursor is hydrolyzed under basic medium to eliminate the protecting group and sterilized by 0.22 μm Millipore filter. The resulting neutral eluent (16 ± 0.6) ml of ^{18}F-FDG is dispensing in a sterile glass vial.
Thin layer chromatography system is carried out for radiochemical and chemical determination of Kriptofix, 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)º C. The apirogenicity is evaluated using the "in-vitro" Limulus test (LAL).

3. RESULTS

The yield of the target (Y_0) and the yield at saturation (A_S) for proton-integrated currents of (59,0±2,3) μAh are given in table 1, and are (62,2±1,4) mCi/μAh and (234±4) mCi/μA, respectively. These values were obtained from 20 routine productions. The yield of the target is an important practical parameter because it defines the irradiation time necessary to produce a desirable activity of ^{18}F-FDG.
The activity of $^{18}F^-$ (A_0) and ^{18}F-FDG (A_{FDG}) obtained in 20 batches during the year 2005, given in table 1, are (3,667±114) mCi/batch and (1,846±187) mCi/batch, respectively. A_0 corresponds to the value measured at the end of bombardment and A_{FDG} at the end of synthesis.

Table 1. Typical values of productions in 2005.

	Dose (μAh)	A_o (Target) $^{18}F^-$ (mCi)	Y_o (Target) (mCi/μAh)	A_s (Target) (mCi/μA)	A_{FDG} (mCi)	Yield (%) (Not-corrected)
M	**59.0**	**3667**	**62.2**	**234**	**1846**	**50.9**
SD	**2.3**	**114**	**1.4**	**4**	**187**	**5.0**
(n = 20)						

Figure 1 shows the activity of the ion F^- (A_0) obtained and the target yield (Y_0). The fluctuations of the data around the average value are 3.1% and 2.3%, respectively, which represents a very good stability of the target. This stability can be seen also in figure 2: the fluctuation in the yield at saturation (A_S) is 1.7%.
It is important to emphasize the activities obtained during the runs are determined in function of demands or the activities ordered by the nuclear medicine service. Figure 3 shows a comparison between these parameters. The fluctuations of the data around the average value are 3,1% and 10,1%, respectively.

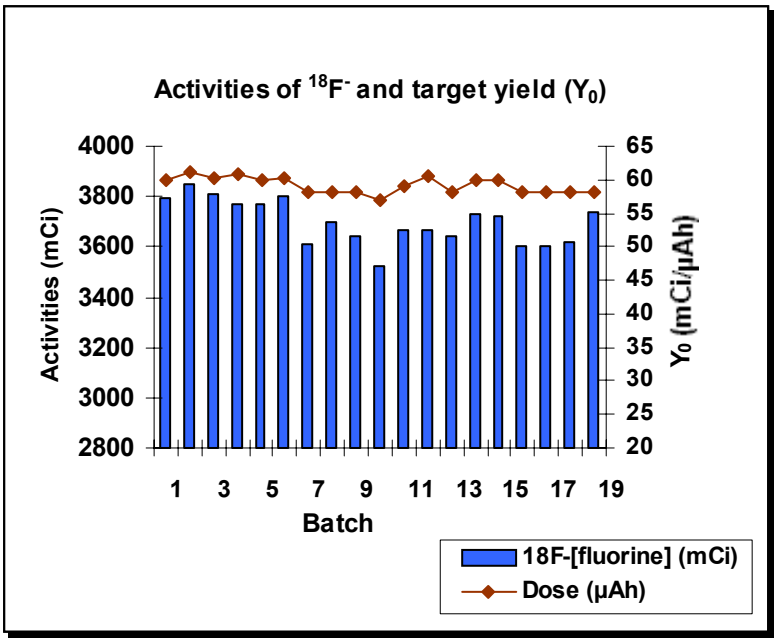

Figure 1. The average value (20 batches) obtained of ^{18}F-(fluorine) in function of integrated current

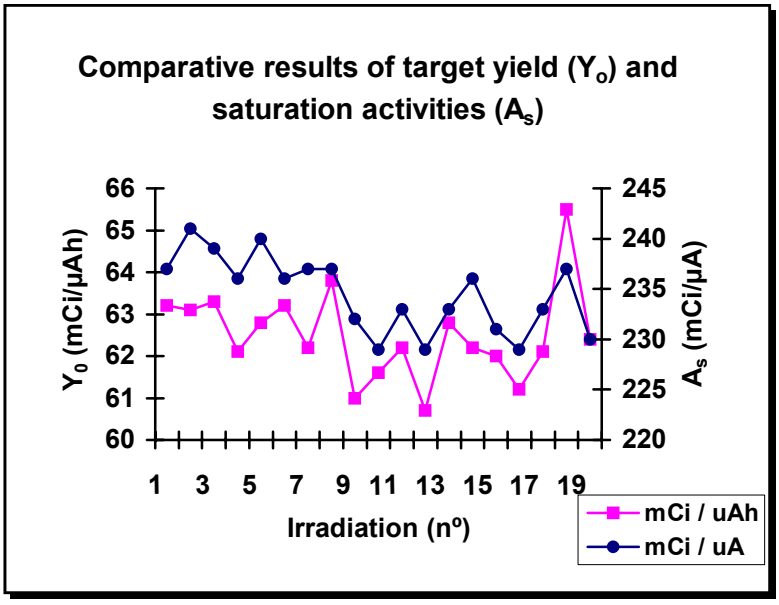

Figure 2. Comparative values of yield (Y_o) and saturation activities (A_s) of target.

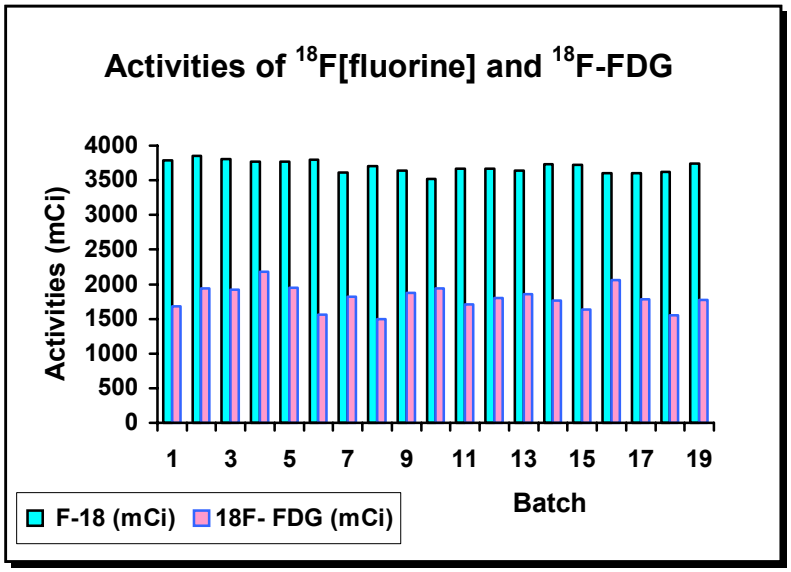

Figure 3. Activities of ^{18}F- and ^{18}F-FDG obtained in 2005 *(n = 20).*

Figure 4 shows typical values obtained of radiochemical purity of ^{18}F-FDG determined by paper chromatography system. The average value is (99.37±0.18)%. The Kriptofix level was below of the detection limit of color spot test which is 50 µg/ml according to FDA recent revision [10]. Sterility and pyrogen tests were negative in all the delivered vials.

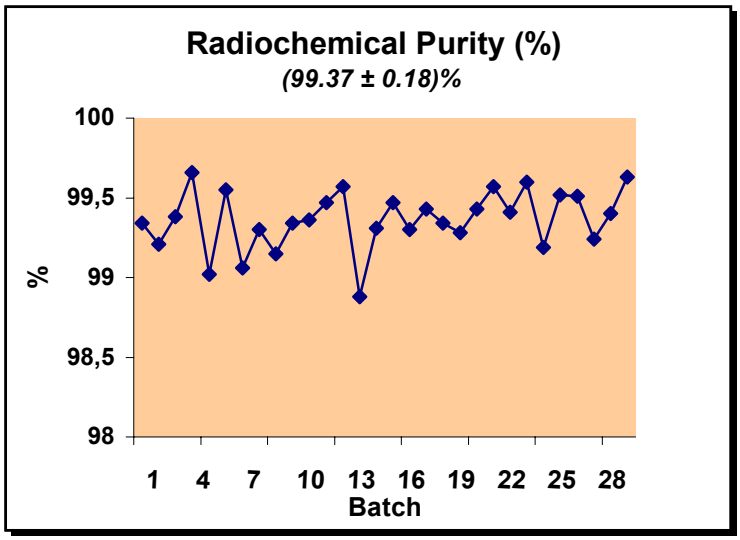

Figure 4. Radiochemical purity of ^{18}F-FDG in ITLC-SG (Al) system, using acetonitrile:H_2O (95:5) as a solvent *(n=30).*

Figure 5 shows the uncorrected yield of synthesis, which means the relationship between the activities of ^{18}F-FDG obtained at the end of synthesis and the activity of the ion $^{18}F^-$ obtained at the end of bombardment (A_{FDG}/A_0). The average value obtained is (50.9±5.0)%, in good agreement with the supplier of the equipment.

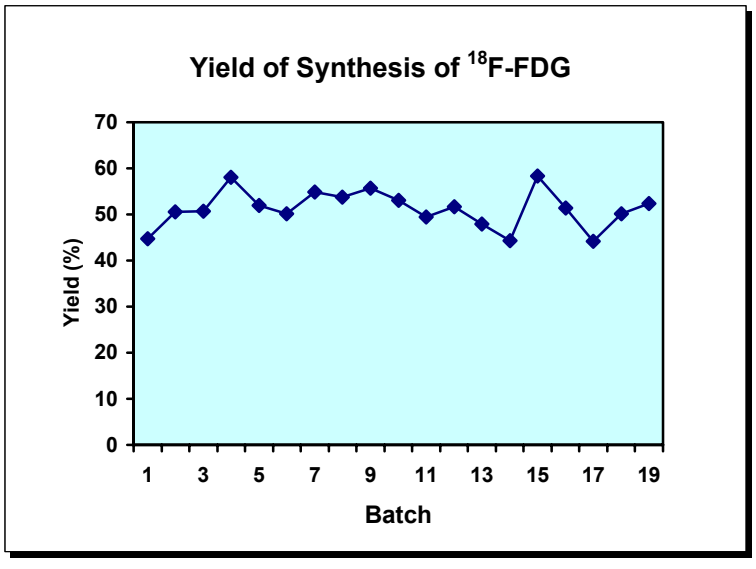

Figure 5. Yield of synthesis in Module of "Coincidence"-GE

4. CONCLUSIONS

The synthetic method in automatic module (Coincidence-GE) presented in this work showed an uncorrected yield of (50.9±5.0)% of no-carrier-added ^{18}F-FDG, based on the phase-transfer mediated substitution of triflate. The stereochemical specify 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 25 minutes.
In 20 productions during 2005, using protons integrated currents of (59,0±2,3) μAh, the activity of $^{18}F^-$ (A_0) and ^{18}F-FDG (A_{FDG}) obtained were (3,667±114) mCi/batch and (1,846±187) mCi/batch, respectively. About 99 % of the activity of $^{18}F^-$ was recovered in the QMA filter and the radiochemical and radionuclide purities of ^{18}F-FDG were better than 97 %. The Kriptofix level was below of the detection limit of color spot test which is 50μg /ml according to FDA recent revision. The Radiopharmacy Center has produced about 1,850 mCi/batch of ^{18}F-FDG (End Of Synthesis) and distributed in four months 1,424 doses (64,742 mCi) in São Paulo, Rio de Janeiro and Brasilia.

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