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Novel, Simple and Fast Automated Synthesis of ^{18}F-Choline in a Single Synthera Module

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Abstract. The aim of this work is to develop a method to produce ^{18}F-Fluorocholine in a single Synthera module with high yield, quality and reproducibility. We give special importance to the details of the drying and distillation procedures. After 5 syntheses we report a decay corrected yield of (27 ± 2) % (mean ± S.D.). The radiochemical purity was > 95%, and the other quality control parameters were within the specifications. Product ^{18}F-fluorocholine was administrated to 17 humans with no observed side-effects.

Keywords: Radiochemistry, PET, radiopharmaceuticals, radiosynthesis
PACS: 87.57.un

INTRODUCTION

Choline is a precursor of phosphatidylcholine, a phospholipid required for cell membrane synthesis. Since carcinogenesis is characterized by increased cell proliferation in tumor tissues, ^{18}F-fluorocholine uptake *in vivo* should correlate with increased cell proliferation, suggesting the use of this radiotracer in diagnostic imaging studies of oncological pathology. Positron emission tomography / computed gomography (PET/CT) with ^{18}F-Fluorocholine is a useful and sensitive tool with high potential to differentiate between local, regional or systemic recurrences with a high potential impact on patient management.

Taking into account that ^{18}F-Fluorcholine has been recently approved for human use in countries like Germany and France, we decided to supply this important radiopharmaceutical to the Argentine market. Until now, its synthesis has been carried out with different modules. The published synthesis to obtain this molecule with the Synthera module requires the utilization of two modules connected in series.[1,2] In the present work we utilized a totally automatic synthesis using only one module.

MATERIALS AND METHODS

Reagents and Columns

We used the commercial kits supplied by ABX for the synthesis of ^{18}F-Choline. The used reagents were: Kryptofix solution, dibromomethane in dry acetonitrile 20%v/v (DBM), dimethylaminoethanol (DMAE), NaCl 0,9%, ethanol and water for

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injection. The used columns are: Sep-Pak Light Accell Plus QMA (130 mg), Sep-Pak Plus Silica cartridge (690 mg), Oasis HLB Plus Sep-Pak Cartridge (225 mg) and Sep-Pak Plus Accell Plus CM cartridge (360 mg). The Integrated fluidic processor (IFP) was also supplied by ABX. We used an IFP for FDG synthesis with some modifications (Figure 1). The enriched water was supplied by Nukem GmbH (Germany).

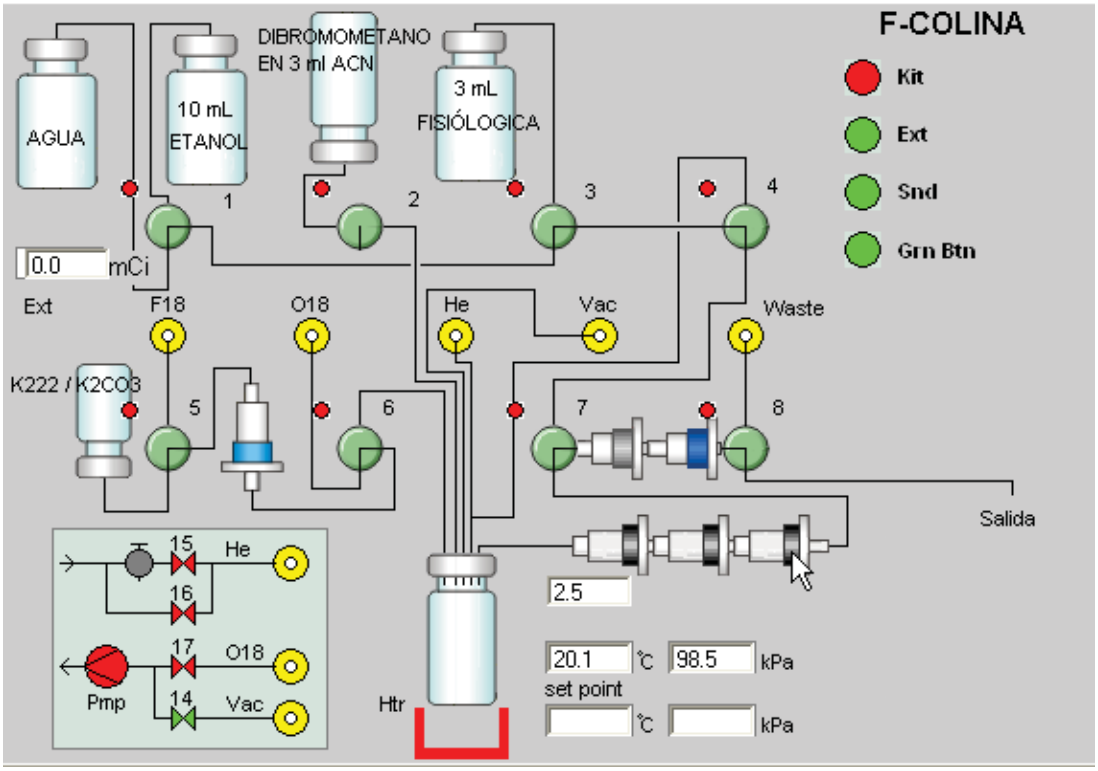

FIGURE 1. Synthera® graphical user interfaces screen-shots for 18F-Choline

Labeling Protocol and System Description

The ^{18}F was produced by the $^{18}O(p,n)^{18}F$ nuclear reaction with an IBA Cyclone 18/9 cyclotron. The fluoride is passed through a QMA column and eluted afterwards with the Kryptofix solution followed by an azeotropic evaporation to dryness. Drying is performed at 95ºC during the first 45s with vaccum and continues an additional 4 minutes with pulses of nitrogen at 70ºC in order to stimulate the evaporation of occluded solvents. Next, the DBM solution is added to the closed vial at 110 ºC during 5 minutes for a reaction during which the ^{18}F-fluoride, assisted by Kryptofix, attacks the dibromomethane, forming an the intermediate product ^{18}F-fluorobromomethane. The reaction solution is subsequently distilled at 60 ºC for 20 minutes using nitrogen pulses in order to keep the pressure close to 125 kPa. Even though 10 minutes of distillation time are enough, we add an extra minute in order to ensure that the process is complete.[3] (Figure 2).

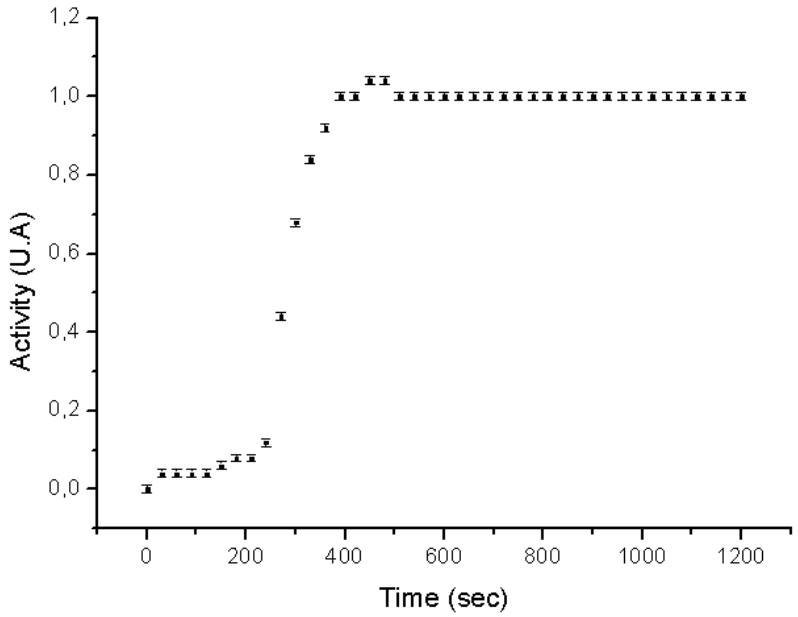

FIGURE 2. Measurement of the activity of ^{18}F-Fluorbromomethane in HLB column during the distillation

Then the product is passed through the silica columns and reacts with the DMAE on the surface of the HLB column, on which the DMAE was previously charged. Afterwards the column is eluted with ethanol. The obtained ^{18}F-fluorocholine passes from the HLB to the CM column where it is retained and washed with 9 mL of water. Finally the solution is eluted with 3 mL of NaCl 0.9%. The duration of the synthesis is 53 minutes.

Quality Control

A radio TLC was used for identifying the radiopharmaceutical and checking its radiochemical purity. It was developed on silica-based TLC with H_2O/acetone/ propionic acid (6:4:2, v/v) saturated with NaCl as mobile phase (R_f = 0.65 for ^{18}F-fluorocholine).[4]

The residual solvents were analyzed with a gas chromatograph (Varian, Star Cx3400) using a J&W Scientific DB-Wax column (60m x 0.25 mm). Oven, detector and injector temperatures are ramped from 50ºC to 110ºC, 220ºC and 210ºC respectively. Assays to determine radionuclidic identity, chemical purity and other requirements for injection were performed as described elsewhere[5].

RESULTS

After 5 syntheses we report a decay corrected radiochemical yield of (27± 2) % (Figure 3).

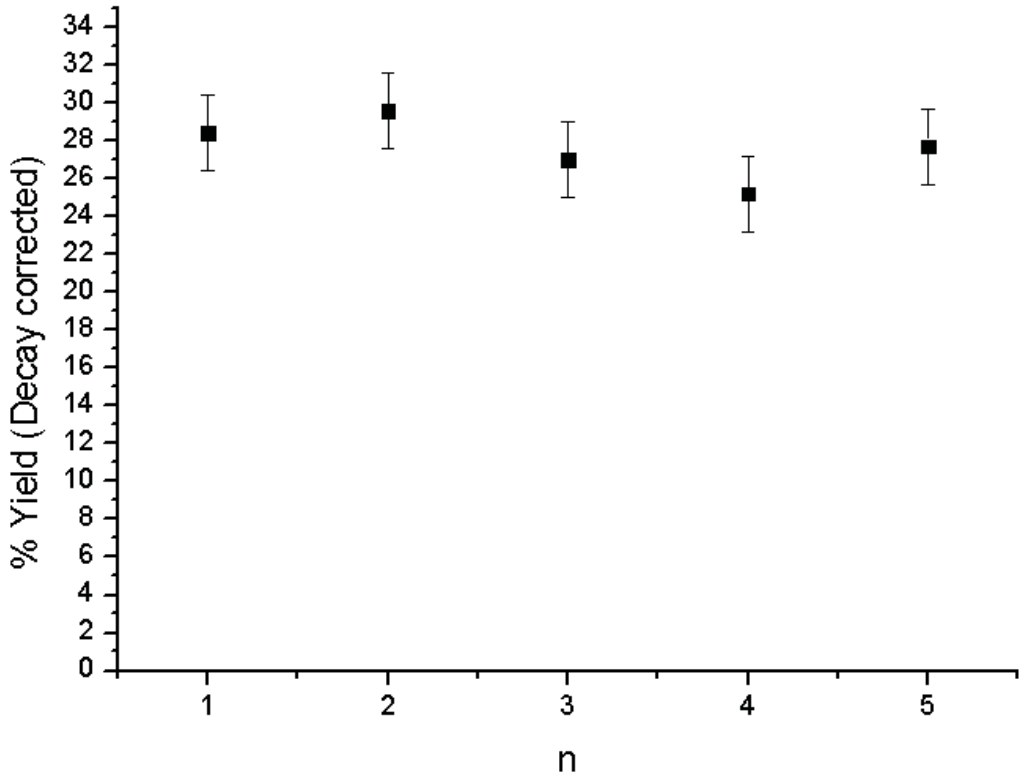

FIGURE 3. Decay corrected radiochemical yield for the synthesis of ^{18}F-Fluorcholine

The residual solvents and principle chemical impurities were below the limits established by USP 32th Ed[6] (Table 1). Seventeen patients were injected and no side effects were observed. In Figures 4 and 5 the images obtained in a 59 years old patient are shown. His diagnosis identified a prostate adenocarcinoma with a Gleason index of 8 in December, 2011; a radical prostatectomy was performed in February 2012, with negative ganglia (PSA 18 ng/ml (April/2012); 40 ng/ml (June/2012) and July, 2012: 49 ng/ml). PET/CT with ^{18}F-fluorocholine showed left inguinal adenomegaly.

TABLE 1. Residual solvents and main impurities content, n = 6

Solvent	Mean (ppm)	SD
Dibromomethane	< 0.5 ppm (Lower than detection limit)	-
Dimetilaminoethanol	47	41
Acetonitrile	6	3
Etanol	27	17

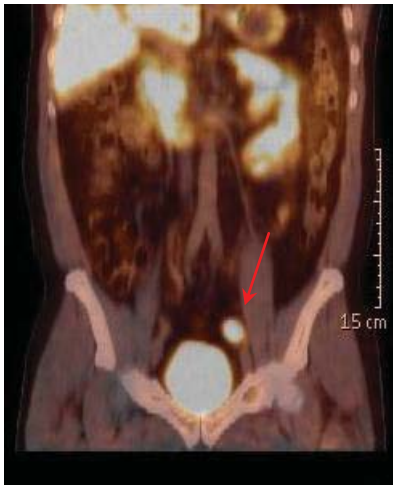

FIGURE 4. Image obtained 10 minutes after injection.

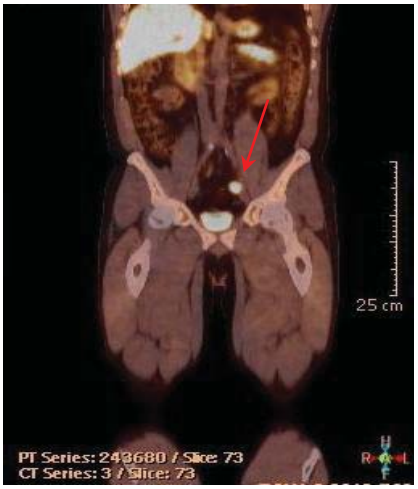

FIGURE 5. Image obtained 45 minutes after injection

CONCLUSION

The labeling of choline with ^{18}F instead of ^{11}C allows a successful application in satellite PET centers without access to localized radionuclide production. The synthesis reported here is advantageous for distribution thanks to its high yield and reproducible quality, as well as a decrease in the duration and cost over previously reported methods, easing its implementation as a routine production.

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