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Original Article

Optimization and comparison of [^{18}F]FET synthesis on two distinct automated radiochemistry systems

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Abstract: *O*-(2-[^{18}F]Fluoroethyl)-$_L$-tyrosine ([^{18}F]FET) is a promising amino acid PET tracer for assessment of malignant brain tumors. Herein, we report optimized production of [^{18}F]FET for clinical use on two commercial radiochemistry systems: Sofie ELIXYS and GE FASTlab 2. While the Sofie ELIXYS procedure requires high performance liquid chromatography (HPLC) purification, the GE FASTlab 2 method uses solid-phase extraction (SPE) purification. In both cases, [^{18}F]FET met release specifications for clinical investigation laid out in the United States Pharmacopeia (USP) and/or European Pharmacopeia (Ph. Eur.). The radiochemical yield of [^{18}F]FET was 35-55% and 30-55% decay corrected to start of synthesis (SOS) for Sofie ELIXYS and GE FASTlab 2, respectively. The overall synthesis time was 75-85 and 70-80 min from SOS for Sofie ELIXYS and GE FASTlab 2, respectively. The radiochemical purity was > 99%, and the molar activity (A_m) was 340-464 GBq/μmol at end of synthesis (EOS).

Keywords: *O*-(2-[^{18}F]Fluoroethyl)-$_L$-tyrosine ([^{18}F]FET), radiosynthesis, automation, quality control (QC), positron emission tomography (PET), brain tumor imaging

Introduction

O-(2-[^{18}F]Fluoroethyl)-$_L$-tyrosine ([^{18}F]FET) is a widely used amino acid radiotracer for PET imaging, particularly in neuro-oncology [1-3]. The uptake of [^{18}F]FET is mediated by system *L* amino acid transporters (LATs), primarily LAT1, which is highly expressed in many malignancies resulting in high tumor to background contrast. Unlike [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), [^{18}F]FET is not significantly taken up by inflammatory cells making it a valuable tool for distinguishing tumor from treatment-related changes such as radiation necrosis. Furthermore, dynamic [^{18}F]FET PET imaging provides important kinetic parameters, which can further aid in distinguishing low-grade from high-grade gliomas based on differential uptake patterns. The ability to assess amino acid metabolism in vivo makes [^{18}F]FET an attractive option for evaluating tumor biology and potential therapeutic targets. Given its favorable properties and increasing clinical evidence, [^{18}F]FET PET is now regarded as a crucial imaging tool in the management of patients with primary and recurrent brain tumors. The United States (US) Food and Drug Administration (FDA) granted fast track designation for [^{18}F]FET (TLX101-CDx, Pixclara) in 2024. [^{18}F]FET is produced under an expanded access IND (investigational new drug) authorization in our radiochemistry facility for hybrid [^{18}F]FET PET/MRI (magnetic resonance imaging) to assess patients with malignant brain tumors [4].

Building upon our experience with [^{18}F]FET preparation on an in-house built radiochemistry module (IU) [5, 6], herein we describe our implementation of [^{18}F]FET synthesis on the Sofie ELIXYS radiosynthesizer [7] using a final reversed-phase high performance liquid chromatography (RP-HPLC) purification and on the GE FASTlab 2 cassette-based synthesis module using a final solid-phase extraction (SPE) purification.

Materials and methods

General

Solvents and silica gel 60 F_{254} TLC plates 50×100 mm were purchased from Sigma-Aldrich (St. Louis, MO) or Fisher Scientific (Hampton, NH) and used without further purification. The radiolabeling precursor *O*-(2-tosyloxyethyl)-*N*-trityl-$_L$-tyrosine *tert*-butylester (TET) and reference standard *O*-(2-fluoroethyl)-$_L$-tyrosine (FET) hydrochloride, as well as *O*-(2-hydroxyethyl)-$_L$-tyrosine ($_L$-HET) were obtained from ABX advanced biochemical compounds (Radeberg, Germany). USP saline (0.9% sodium chloride) and sterile water were purchased from McKesson Medical-Surgical (Urbancrest, OH), and anhydrous ethanol from Decon Labs (King of Prussia, PA). Deionized water (DI, 18.2 MΩ cm at 25°C) was produced using a Milli-Q Advantage A10 Water Purification System (Millipore Sigma, Billerica, MA). ELIXYS cassettes were purchased from ON-SITE ENGR LLC (Placentia, CA). [^{18}F]FET FASTlab cassettes and all related materials including reagents, Tetrabutylammonium Hydrogen Carbonate (TBA·HCO_3) solution (1.05 mL) and TET precursor (4.0 mg) were purchased from ABX (Radeberg, Germany).

No-carrier-added aqueous [^{18}F]fluoride was produced by the nuclear reaction ^{18}O(*p*, *n*)^{18}F through proton irradiation of enriched [^{18}O]H_2O (95%, Rotem, Topsfield, MA) in the

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Siemens Radionuclide Delivery System (RDS-111) Eclipse cyclotron. Semi-preparative purification on the ELIXYS module was conducted on a RP-HPLC system with a HITACHI Primaide 1110 pump associated with a KNAUER K-2520 UV detector and PIN diode γ-detector. The radioactivity was measured using CAPINTEC CRC-55tR radioisotope dose calibrator (Galway, Ireland).

Analytical quality control (QC) analyses were performed on a RP-HPLC Waters ACQUITY Arc UHPLC System equipped with a Waters 2998 Photodiode Array (PDA) Detector (Milford, MA, USA), and a Carroll & Ramsey single channel high sensitivity radiation detector (Knoxville, TN, USA). 10 µL of sample were injected on a Phenomenex Gemini C18 column (150×4.6 mm, particle size 5 µm, 100 Å) with isocratic eluent 7% ethanol/93% 50 mM KH_2PO_4/K_2HPO_4 buffer (pH = 6.9) as mobile phase at a flow rate of 1.0 mL/min and detection at a wavelength of 220 nm. $_L$-FET and $_L$-HET were detected and analyzed based on their UV absorbance at 220 nm. [^{18}F]FET and [^{18}F]impurities were analyzed by the in-line radiation detector connected in series with PDA detector. Data analysis was performed using Empower 3.0 software (Waters). Gas chromatography (GC) was conducted on Agilent 8890 gas chromatography system with a flame ionization detector (FID).

Synthesis of [^{18}F]FET on Sofie ELIXYS module

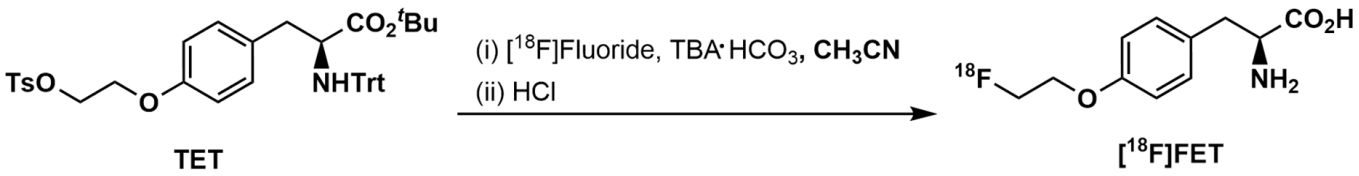
Aqueous [^{18}F]fluoride was delivered from the cyclotron into a glass V-vial. Upon starting the ELIXYS FET production sequence, the radioactivity from the vial was trapped on a preconditioned Accell™ QMA cartridge and further eluted with 200 µL TBA·HCO_3 (0.075 M solution) in 1 mL acetonitrile into the reaction vial. After three azeotropic distillations at 120°C with acetonitrile under vacuum and a stream of nitrogen, 4 mg of TET precursor, dissolved in 1.0 mL acetonitrile, was added and heated at 120°C for 15 minutes. Upon cooling to 50°C, 1.0 mL of 2 N aqueous hydrochloric acid is added followed by acid hydrolysis at 100°C for 4 minutes. Following the acid hydrolysis, the acetonitrile was evaporated under a stream of nitrogen at 100°C for 3.5 minutes. The reactor was then cooled to 30°C and its contents neutralized by 0.4 mL 4 N NaOH solution followed by 1.5 mL water, and 0.6 mL 50 mM sodium phosphate buffer. The reaction vial mixture was then transferred onto the injection loop for RP-HPLC purification (Phenomenex Gemini C18 column, 5 µM, 10×250 mm with an eluent of 12% EtOH/88% 50 mM NaH_2PO_4/Na_2HPO_4 buffer (pH = 6.9) at a flow rate of 4.0 mL/min and wavelength of 220 nm). The product elutes at approximately 9 minutes, and the [^{18}F]FET fraction is collected into a gross-dilution reservoir containing 20 mL sterile saline solution (0.9% sodium chloride for Injection, USP grade). The content of the gross dilution reservoir, containing the [^{18}F]FET fraction (1.5-3.5 mL) eluate mixed with 20 mL of saline solution was then transferred out to a sterile intermediate product collection vial. The total synthesis time is around 85 minutes, with no manual intervention until the intermediate product vial is removed for terminal sterilizing filtration and subsequent patient dose dispensing and QC testing.

Synthesis of [^{18}F]FET on GE FASTlab 2 module

Aqueous [^{18}F]fluoride was delivered from the cyclotron into the FASTlab 2 cassette conical activity vial and trapped on a preconditioned Accell™ QMA Light cartridge and further eluted with TBA·HCO_3 (0.075M solution) into the reaction vial. After two azeotropic distillations at 125°C with acetonitrile, 4 mg of TET precursor, dissolved in 1.0 mL acetonitrile, was introduced and reacted at 135°C for 10 minutes. The reactor was then cooled to 110°C. The acetonitrile was then evaporated under a stream of nitrogen at 125°C for approximately 3-4 minutes. Acid hydrolysis was performed at 130°C for ~9 minutes, using 1.3 mL of 1 N hydrochloric acid solution followed by reactor cooling to 60°C and dilution with 3.0 mL sterile water. SPE purification was performed using one Oasis® WAX Plus cartridge (Waters), two Oasis™ HLB Plus cartridges (Waters) and one Accell™ CM Plus cartridge (Waters). FET was trapped on the HLB cartridges which were subsequently rinsed 3 times with sterile water. The product was then eluted in three steps from the HLB cartridges using a total of 20 mL of 5% EtOH in water and transferred to the intermediate product vial. Then 3.3 mL of citrate buffer was transferred directly to the intermediate product vial. The synthesis time was approximately 80 minutes, requiring no manual intervention until the intermediate product vial was removed for terminal sterilizing filtration and subsequent patient dose dispensing and QC testing.

Quality control

[^{18}F]FET tests [5, 8] included: 1) visual inspection for color and clarity; 2) pH test by spotting on a narrow-range pH indicator strip; 3) radiochemical identity, radiochemical purity and molar activity (A_m, spike method, [9]) determination by analytical RP-HPLC above mentioned; enantiomeric purity determination by analytical chiral HPLC using a Chirex® 3126 (D)-penicillamine column (4.6×150 mm) with an eluent of 15% *i*-propanol/85% 2.0 mM $CuSO_4$ at a flow rate 1.0 mL/min and wavelength of 220 nm; 4) residual solvent analysis by GC; 5) residual TBA·HCO_3 by a color spot test: the content of TBA·HCO_3 was determined by applying 2.5 µL sample to aluminum backed thin-layer chromatography (TLC) plates sprayed with commercial iodoplatinate [10]; 6) radionuclidic identity analysis by testing radioactivity half-life; 7) filter integrity test by bubble point procedure; 8) bacterial endotoxins analysis by a Charles River Laboratories Endosafe Portable Testing System (PTS) unit; and 9) sterility test by direct inoculation method. Five-hour tracer stability tests following sterilization by terminal filtration was performed to check the radiochemical, enantiomeric purity and pH value using the above-described methods.



Scheme 1. Radiosynthesis of [^{18}F]FET.

Table 1. A comparison of [^{18}F]FET radiosynthesis in Two different modules

[^{18}F]FET	ELIXYS	FASTlab 2
Module structure	Cassette, fixed flow path, and valve	Cassette
Phase transfer catalyst	TBA·HCO_3	TBA·HCO_3
Precursor TET (mg)	4	4
Reaction solvent	CH_3CN	CH_3CN
Solvent evaporation	Yes	Yes
Acid hydrolysis	2.0 N HCl	1.0 N HCl
Neutralization	NaOH	Citrate buffer
Purification	HPLC	SPE
Overall synthesis time (min)	75-85	70-80
Radiochemical yield	35-55%	30-55%

Results and discussion

As shown in **Scheme 1**, the fully-automated synthesis of [^{18}F]FET was achieved by a two-step one-pot strategy using two different commercially available ^{18}F-radiosynthesis modules including the Sofie ELIXYS and GE FASTlab 2, which included [^{18}F]fluoride receiving, azeotropic distillation, labeling reaction, acid hydrolysis, purification and formulation steps. The ELIXYS [^{18}F]FET synthesis sequence is developed based on our previous work [5, 6], and the FASTlab 2 [^{18}F]FET synthesis sequence is developed by ABX. A summarized comparison is listed in **Table 1**. Both ELIXYS method and FASTlab 2 method gave similar radiochemical yield, radiochemical purity and molar activity. [^{18}F]FET production method on the ELIXYS module has cleaner product with less cold mass, but it is labor intensive with longer overall synthesis time due to HPLC purification. [^{18}F]FET production method on the FASTlab 2 module is facile with shorter overall synthesis time, because of the use of SPE instead of HPLC, but it also provides higher cold mass, as the SPE method is not as effective as the HPLC method to separate cold FET and synthesis related impurities.

Our initial development of [^{18}F]FET on the ELIXYS utilized 3 cassettes [11]. All chemistry in the Initial development of [^{18}F]FET on the ELIXYS module took place in cassette two. The crude product was transferred to reactor three (cassette three) via a 0.45 µm filter. The crude reaction mixture is then transferred to the HPLC for purification directly from reactor three. The [^{18}F]FET fraction (retention time tR ~ 8 min) is collected into an external recovery vial containing sterile saline for injection. The final formulated product is transferred to the final vial using the push gas from cassette one (**Figure 1**).

While this original method for the production of [^{18}F]FET was able to produce the desired product in good yield and high molar activity, supply chain issues during the Covid-19 pandemic coupled with an increase in the number of patients enrolled on our expanded access IND study of [^{18}F]FET required an alternative that would use fewer cassettes per production. As all of the chemistry took place in a single cassette, we sought to eliminate the need for the other 2 cassettes. This was accomplished by utilizing a Hamilton Modular Valve Positioner (MVP) equipped with a 6-way distribution valve.

The cassette is set up in an identical fashion to the 3-cassette method with the exception of the diptube. The diptube is connected to the common position of the MVP valve. This allows for distribution of the contents of the reactor vial as well as use of the push gas from this position. At the end of the synthesis, the crude reaction mixture is transferred to the HPLC loop through a 0.45 µm filter via position 1 of the MVP valve. While the HPLC is running the MVP valve is changed to position 2 and the diptube line is rinsed with sterile water (2×6 mL) to waste. Finally, when the HPLC fraction is collected, the MVP valve is switched to position 3 where the push gas from the diptube is used to push the product to the final vial. This method has reduced the number of cassettes required for [^{18}F]FET production from 3 to 1 with no impact on yield or molar activity. This method [12] also affords a modest time savings of approximately 5 minutes compared with the previous method. The 1-cassette ELIXYS module layout and reagent map for [^{18}F]FET production are shown in **Figures 2** and **3**, respectively.

The FASTlab 2 simply employs a single cassette for synthesis with purification via SPE using Sep-Pak® cartridges [13, 14]. The FASTlab 2 layout is shown in **Figure 4**. The cassettes and reagent kits, as well as synthesis sequence, are commercially available from ABX. [^{18}F]FET was synthesized using the GE FASTlab 2 module based on the ABX kit. The precursor TET in CH_3CN was radiolabeled via a nucleophilic ^{18}F-fluorination with TBA[^{18}F]F, followed by a hydrolysis step with 1.0 N HCl, and purified

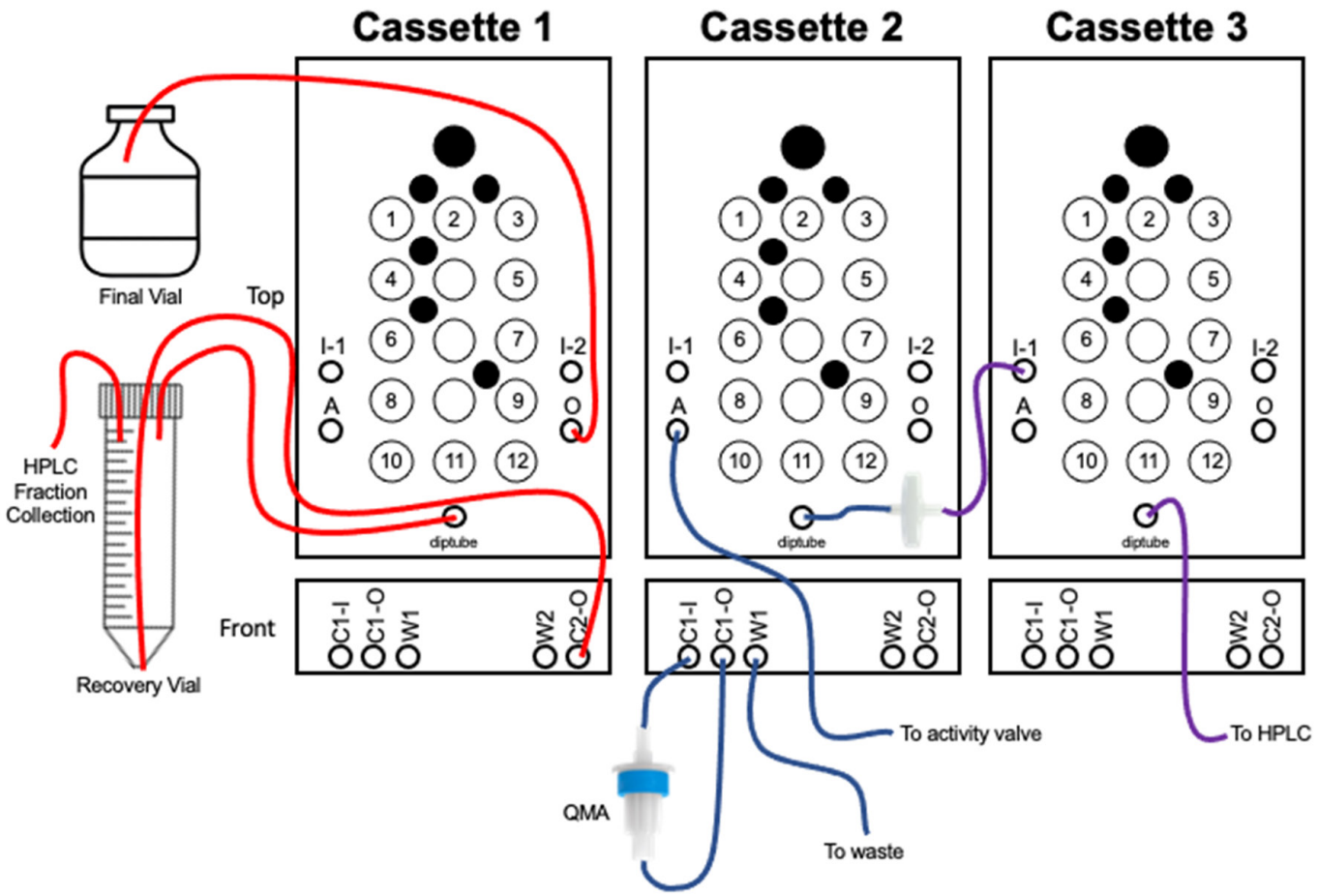


Figure 1. Sofie ELIXYS module 3-cassette layout for [18F]FET production.

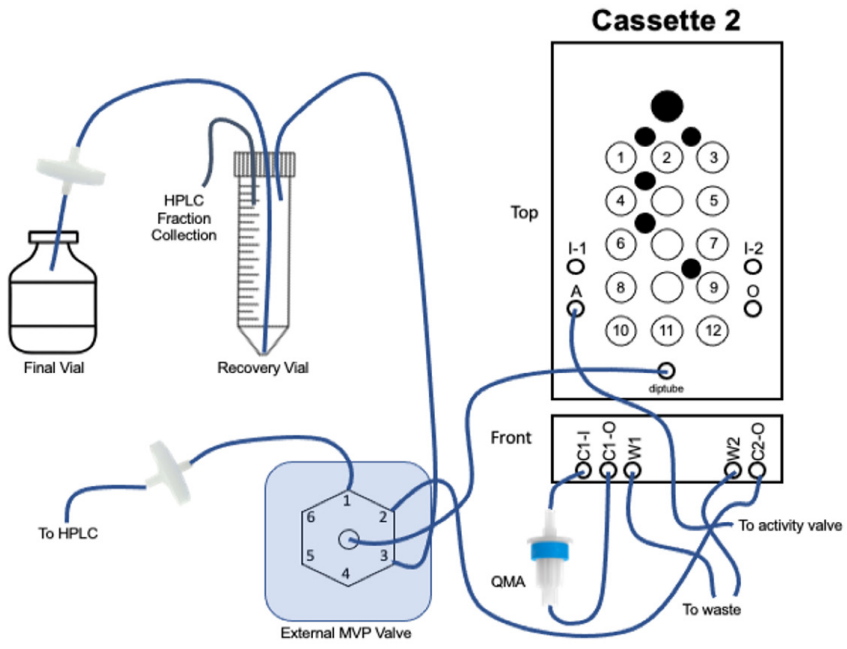


Figure 2. Sofie ELIXYS module 1-cassette layout for [18F]FET production.

by SPE method to give [18F]FET. Significant modifications of the ABX cassette-based procedure include decreasing the precursor amount from 15 mg to 4 mg. While decreasing the amount of precursor resulted in a small reduction in radiochemical yield of [18F]FET (approximately 5%), less precursor significantly improved the chemical purity of the final [18F]FET product. We also elected to remove the Alumina N Light cartridge which is normally used to remove any remaining unreacted [18F]fluoride. However, we found that removal of the Alumina N cartridge removed UV impurities and improved the final pH of [18F]FET product. We found no trace of free [18F] fluoride in the final product in the absence of the Alumina N cartridge as we believe this is removed in the rinsing steps of the SPE purification. The rationale for reducing the precursor amount and omitting the Alumina N cartridge is to improve the chemical purity of [18F]FET product, which has been detailed in our previous work [5, 6, 12]. These changes can reduce cold mass including both cold FET and other impurities.

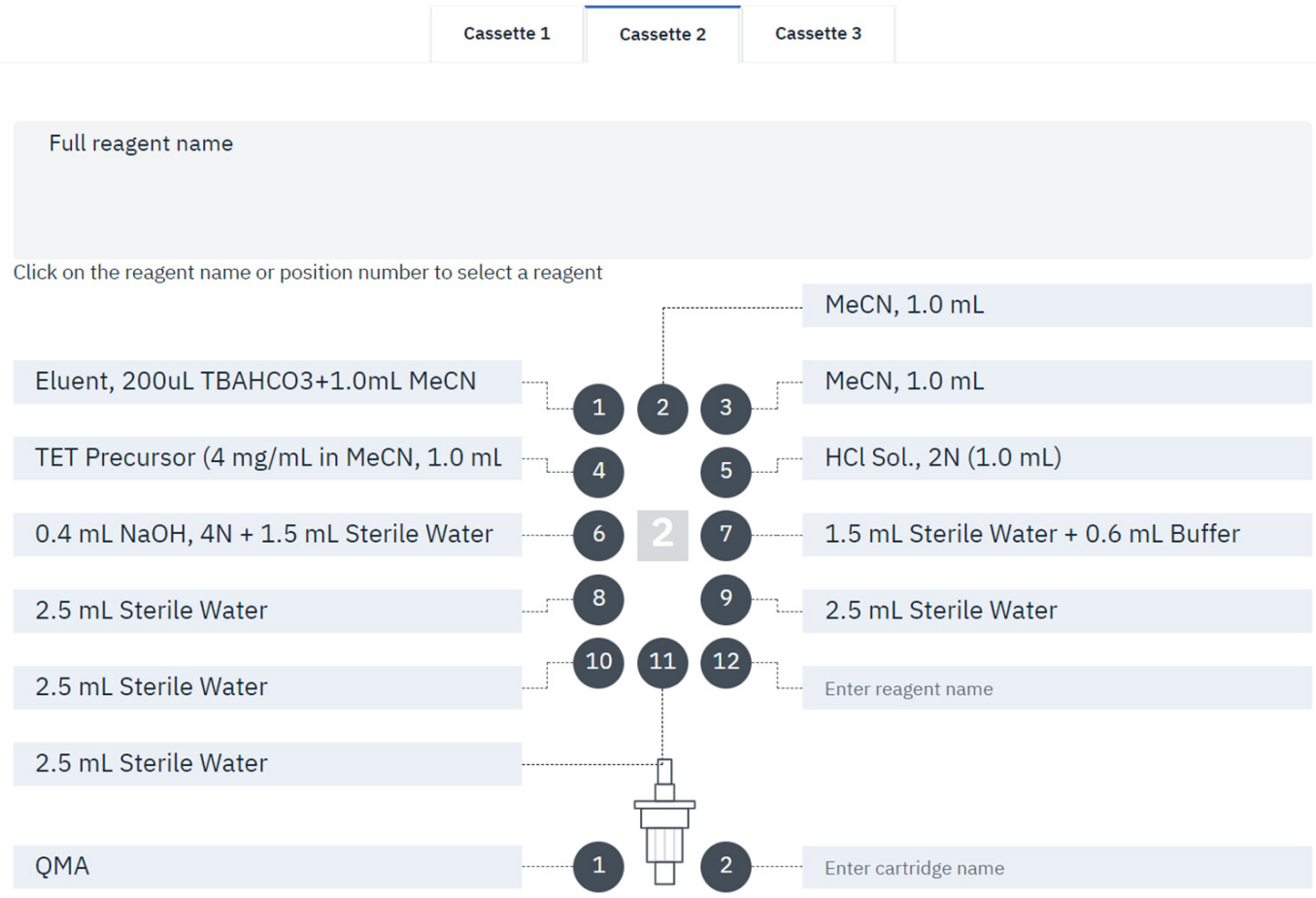


Figure 3. Sofie ELIXYS module 1-cassette reagent map for [18F]FET production.

The radiochemical yield of [18F]FET on the FASTlab 2 was 30-55% decay corrected to start of synthesis (SOS) based on H[18F]F, with an overall synthesis time of 80 min (**Table 1**). The radiochemical purity was > 99%, and the A_m was 340-464 GBq/μmol at end of synthesis (EOS) (**Table 2**).

The number of validation runs required for an IND submission isn't specified by a fixed number. For some well-characterized products like [18F]FET, three consecutive production batches are typically considered as a widely accepted standard for process validation within the pharmaceutical industry to ensure consistent quality and reproducibility of the manufacturing process, demonstrating the ability to reliably produce a drug candidate. In addition, three runs provide enough data to identify trends for a more robust statistical analysis. The [18F]FET produced in three validation runs met all release criteria for human use on both modules. The results using the ELIXYS module (data not shown) were similar to that of the [18F]FET dose produced in the IU module [5, 6], because both employed the same HPLC for purification. The results using the FASTlab 2 module are summarized in **Table 2**. The FASTlab 2 with ABX synthesis procedure employs nearly identical chemistry to what we currently utilize on our ELIXYS radiochemistry system. The only substantive differences are that the FASTlab 2 procedure uses a multi-cartridge SPE method for radiotracer purification rather than the HPLC purification method used on the ELIXYS module, and the final product formulation is slightly different in that the commercial ABX kits use a sodium citrate buffer instead of a sodium phosphate buffer to adjust the final pH. The chemical purity of the final drug product is comparable using these methods, although FASTlab 2 method gave slightly higher cold mass (about twice as high in μg/mL). The inclusion of citrate buffer in the FASTlab 2 method results in a large solvent front peak in the HPLC chromatograms corresponding to citrate, which we have observed in other radiotracers utilizing this buffer [15]. The solvent front peak caused by citrate buffer in HPLC analyses did not affect QC assessment, since it can be separated from other impurity peaks by adjusting HPLC parameters and excluded from the HPLC chromatogram of formulation matrix [15]. Chemical purity release criterion is set as < 100 μg/dose/patient for $_L$-FET and each individual impurity and < 500 μg/dose for the sum of $_L$-FET, residual $_L$-HET and any other unidentified UV-absorbing impurities observed by HPLC exclusive of the formulation matrix. In general, a higher cold mass in [18F]FET can reduce imaging sensitivity, and potentially impact diagnostic accuracy in neuro-oncology by affecting the tracer's uptake and biodistribution in tumors and

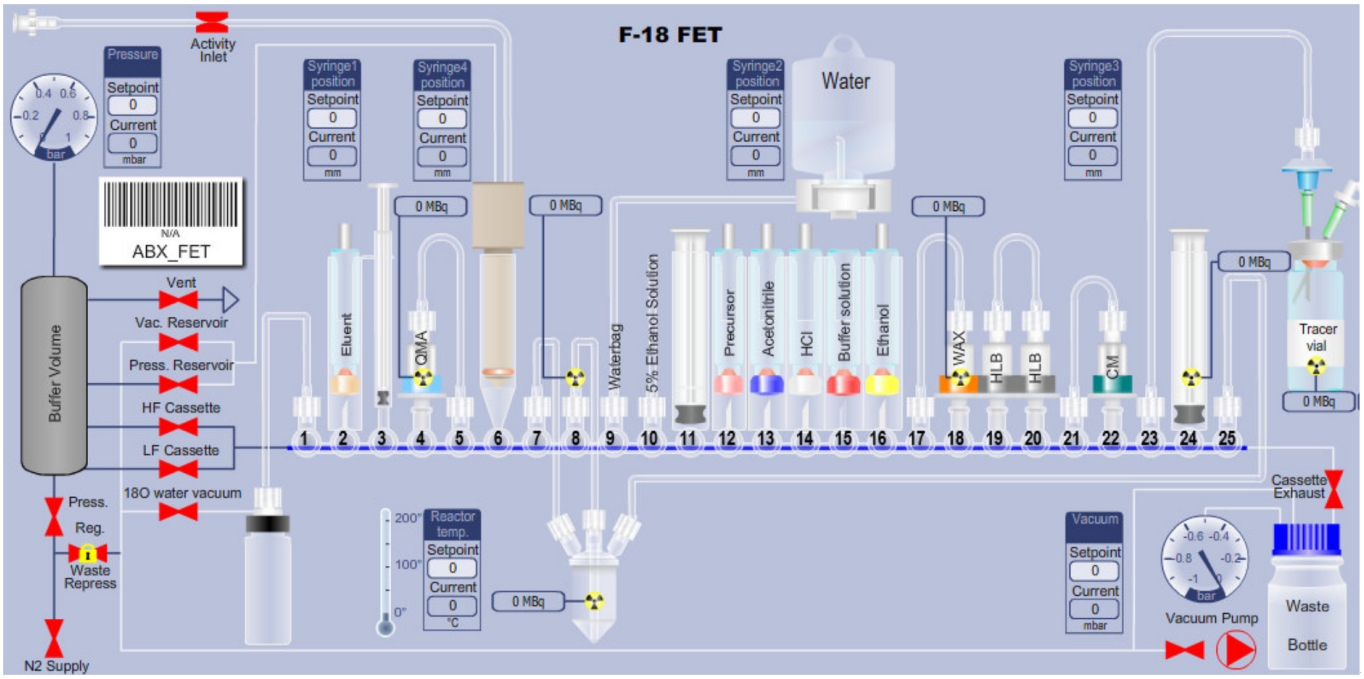


Figure 4. Diagram of GE FASTlab 2 cassette for [18F]FET production. 1: Connect tubing to 18O-water bottle; 2: 1.05 mL TBA·HCO_3 solution; 4: QMA light cartridge; 9: 100 mL water bag; 10: 25 mL 5% ethanol solution; 12: 4 mg precursor TET; 13: 3.3 mL acetonitrile; 14: 1.3 mL 1 M hydrochloric acid; 15: 3.3 mL buffer solution; 16: 4.3 mL ethanol; 18: WAX cartridge; 19: HLB cartridge; 20: HLB cartridge; 22: CM cartridge.

Table 2. Product release specification and validation test results of [18F]FET (n = 3) on the FASTlab 2 module

QC Test	Release Criteria	Run 1	Run 2	Run 3
Visual inspection	Clear, colorless	Clear, colorless	Clear, colorless	Clear, colorless
Radiochemical identity	0.9 < RRT < 1.1	0.99	0.99	1.00
Radiochemical purity (%)	> 95	99.2	99.3	99.7
Chemical purity (μg/dose)	< 500	0.554 μg/mL	0.607 μg/mL	0.551 μg/mL
Molar activity (A_m, GBq/μmol)	≥ 30.7 GBq/μmol at time of injection (TOI)	340#	381#	464#
Residual solvent analysis	Ethanol < 100 mg/mL	28.5	28.6	29.4
	CH_3CN < 0.41 mg/mL	0.223	0.366	0.097
	Acetone < 0.5 mg/mL	ND	ND	ND
Dose pH	4.5-7.5	7.0	7.0	7.0
Residual TBA·HCO_3 (mg/mL)	≤ 0.26	Pass	Pass	Pass
Sterile filter integrity test (psi)	≥ 50	Pass	Pass	Pass
Radionuclidic identity ($t_{1/2}$, min)	105-115	109.1	109.6	109.2
Endotoxin analysis (EU/mL)	≤ 17.5	< 5.0	< 5.0	< 5.0
Sterility testing	No colony growth out to 14 days	Pass	Pass	Pass

#A_m at EOS (end of synthesis); ND: not detectable.

surrounding tissues. In particular, the FASTlab 2 method produces higher cold mass than the ELIXYS method, all 3 runs < 1 μg/mL (**Table 2**), but it is well below the specification total impurities no more than 500 μg/dose. Therefore, the clinical implications of slightly higher cold mass in [18F]FET by the FASTlab 2 method can be ignored. The radiochemical identity, chemical purity and radiochemical purity were confirmed by analytical RP-HPLC, and a representative chromatographic profile for analysis of [18F]FET is shown in **Figure 5**. The enantiomeric purity was analyzed by analytical chiral HPLC, and a representative chromatographic profile is shown in **Figure 6**. The retention time of reference standards $_L$-FET and $_D$-FET were 10.667 and 13.945 min, respectively (**Figure 6A**). The enantiomeric chromatogram of [18F]FET showed only one peak at 11.046 min, which is corresponding with [18F]$_L$-FET (**Figure 6B**). The results showed that enantiomeric purity of [18F]$_L$-FET was > 99%. No changes in chemical, radiochemical and enantiomeric purity were observed in the 5-h stability test, suggesting [18F]FET is stable for at least 5 h following final filtration. An extended stability test for a fluorine-18 radiotracer (18F), like [18F]FDG, is often set at 12 hours to ensure compliance with regulatory standards and clinical practicality [16], because it reflects the effective half-life

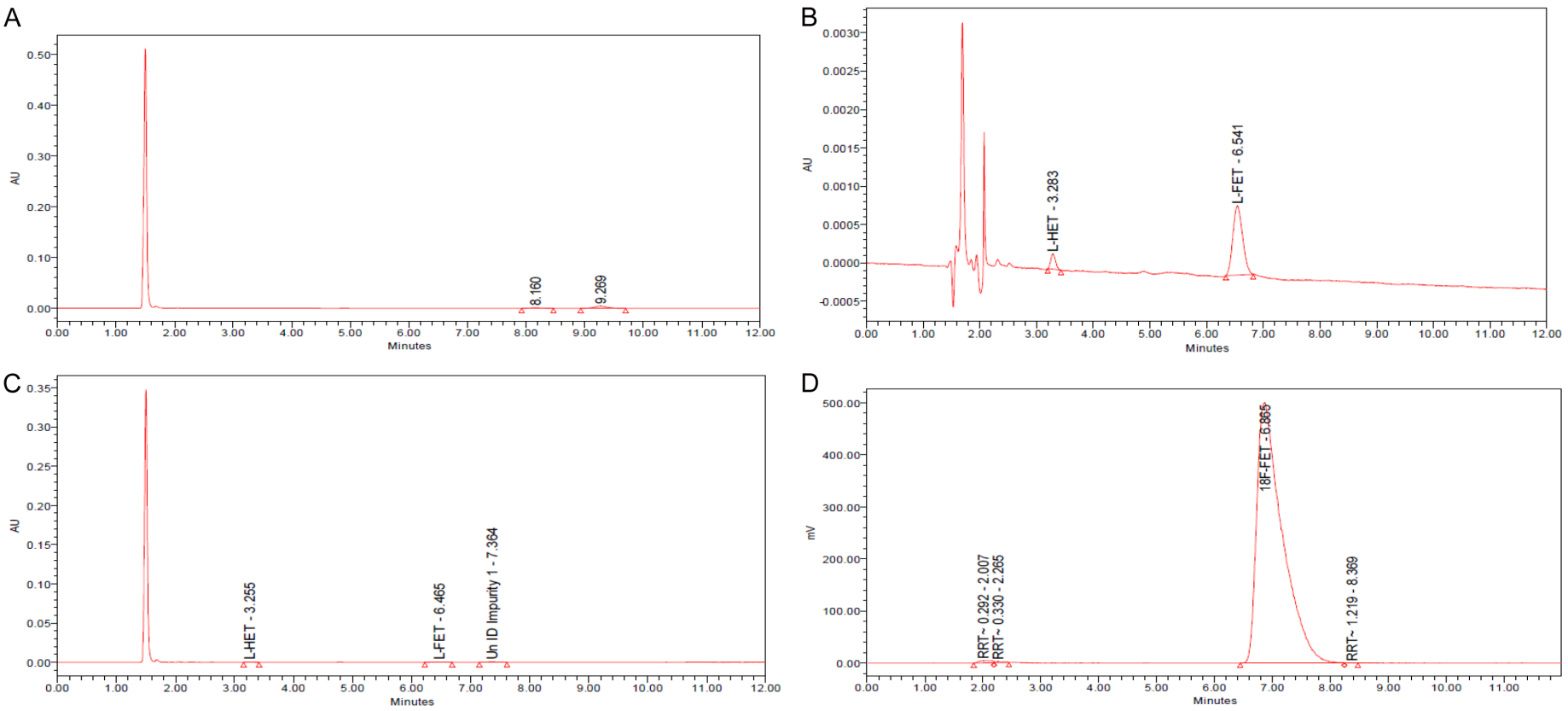


Figure 5. A representative analytical RP-HPLC chromatographic profile for [^{18}F]FET radiochemical identity, chemical and radiochemical purity. A: UV chromatogram of matrix (formulation solution); B: UV chromatogram of FET reference standard; C: UV chromatogram of [^{18}F]FET; D: radioactive chromatogram of [^{18}F]FET.

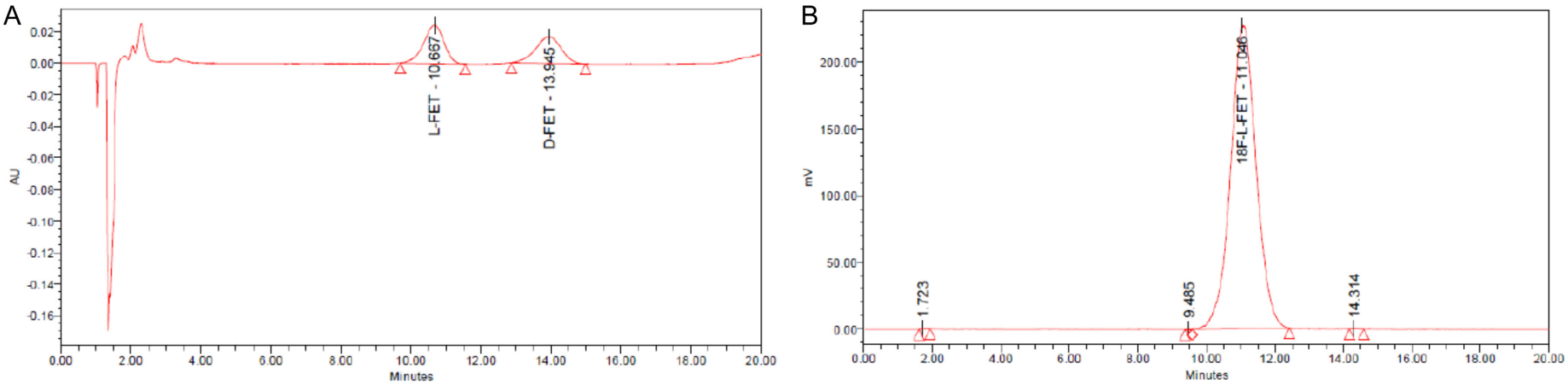


Figure 6. A representative analytical chiral HPLC chromatographic profile for [^{18}F]FET enantiomeric purity. A: UV chromatogram of mixed $_{L}$-FET and $_{D}$-FET reference standards; B: radioactive chromatogram of [^{18}F]$_{L}$-FET.

of ^{18}F, which is approximately 1.83 hours. The exact duration of 5-h stability test for [^{18}F]FET is justified based on its synthesis method, formulation, and intended use in our IND [4], because one batch production of [^{18}F]FET in our radiochemistry facility only supplies 2-5 clinical doses. The color spot test showed the TBA·HCO_3 residue was lower than 0.26 mg/mL in all three batches.

Conclusion

In summary, two facile fully automated radiosyntheses of [^{18}F]FET were achieved using HPLC purification on the Sofie ELIXYS module and by SPE purification on the GE FASTlab 2 module. Since the ELIXYS method has some limitations such as a more labor-intensive setup compared with the commercially available cassette and production sequence, we would recommend the FASTlab 2 method for routine [^{18}F]FET production. In both cases, [^{18}F]FET was produced with high radiochemical yield, reasonable overall synthesis time, high radiochemical purity and A_m, and meets all QC criteria for human brain tumor imaging application on both modules. This demonstrates that both HPLC purification and SPE purification are reasonable approaches for radiotracer production.

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Disclosure of conflict of interest

None.

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