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Optimization of the Synthesis and Purification of 6-[^{18}F]Fluoropiperonal, Synthon for the Preparation of Complex Molecules Used as PET Tracers

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Abstract—An optimized synthesis method for 6-[^{18}F]fluoropiperonal (6-[^{18}F]FP) via nucleophilic substitution of the nitro group in the precursor molecule (nitropiperonal, 6-NP) with [^{18}F]fluoride in the presence of tetrabutylammonium tosylate has been proposed. Using this weakly basic phase transfer catalyst, the amount of initial 6-NP in the reaction was reduced from 4.0 to 0.2 mg with negligible amounts after subsequent treatment of the reaction mixture with a strong base (potassium methoxide). In turn, this made it possible to separate 6-[^{18}F]FP and 6-NP with similar physicochemical properties by a simple and efficient solid-phase extraction technique on disposable cartridges. 6-[^{18}F]FP was fabricated with 99% radiochemical purity and a radiochemical yield of 10%. The content of unreacted 6-NP did not exceed 1 μg/mL, which is comparable to the results of laborious semi-preparative HPLC purification.

Keywords: positron emission tomography, fluorine-18, radiotracers, 6-[^{18}F]fluoropiperonal, solid phase extraction

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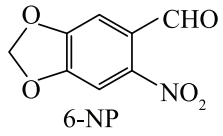
INTRODUCTION

Positron emission tomography (PET) is a rapidly developing nuclear imaging technique, keeping a leading position in modern diagnostics. Fluorine-18 is the most popular ($T_{1/2}$ = 109.7 min) among the short-lived positron-emitting radionuclides. This is caused by both its "ideal" nuclear physical characteristics (97% β^+, $E_{\beta+}$ 0.635 MeV, positron range in tissue 2.4 mm) and a simple and high-performance method for cyclotron production of radionuclide in a water target in the form of [^{18}F]fluoride, used for incorporation of a label into molecules by nucleophilic radiofluorination [1]. In view of the short half-life of fluorine-18, fast techniques for synthesis and purification and automated technologies are used for producing radiopharmaceuticals. The so-called direct incorporation, where fluorine-18 is incorporated directly into a precursor molecule of a similar structure, are the most preferred technique to fabricate the majority of clinically relevant radiopharmaceuticals [1, 2]. However, the conditions of direct radiofluorination reactions (basic conditions, high temperatures, organic solvents) are often unsuitable for introducing a label into complex biologically active molecules or drug analogues that make up a large group of radiopharmaceuticals. In this case, the indirect synthesis techniques are used, where fluorine-18 is introduced into simple reactive compounds with various functional groups (synthons, prosthetic groups) involved in the subsequent building the desired molecule (build-up synthesis) [3]. One of the challenges faced when using synthons is the need to purify them by a labor-intensive and time-consuming method of semi-preparative radio-HPLC, which bring about loss of radioactivity of the target product, increased synthesis time, and difficulties in automation.

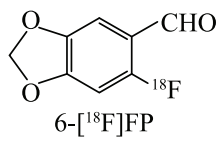
An important synthon is 3,4-methylenedioxy-6-[^{18}F]fluorobenzaldehyde (6-[^{18}F]fluoropiperonal, 6-[^{18}F]FP), utilized in the preparation of 6-L-[^{18}F]FDOPA, a fluorine-18-labeled analogue of L-2,4-dihydroxyphenylalanine (DOPA), which is a well-known PET radiotracer for estimating the density of dopaminergic terminals in Parkinson's disease [4]. The

synthesis of 6-[^{18}F]FP is based on the aromatic nucleophilic substitution of the nitro group in the precursor molecule, 3,4-methylenedioxy-6-nitrobenzaldehyde (6-nitropiperonal, 6-NP) by fluorine-18 [5, 6]. 6-[^{18}F]FP also serves as a synthon in the production of the fluorine-18-labeled derivative of anle138b ([^{18}F]anle138b), a promising radiotracer for imaging alpha-synuclein (α-syn) aggregates [7, 8]. Anle138b (3-(1,3-benzodioxol-5-yl)-5-(3-bromophenyl-1*H*-pyrazole) [9] is a recently developed diphenylpyrazole-based oligomeric modulator selectively binding to α-syn and inhibiting its aggregation processes in Parkinson's disease.

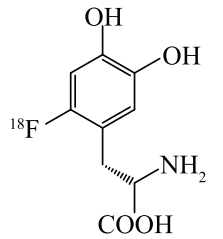
The three-step synthesis of [^{18}F]anle138b described in [8] includes the synthesis of 6-[^{18}F]FP by the



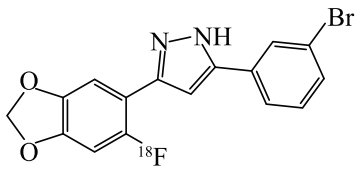
6-NP



6-[^{18}F]FP



6-L-[^{18}F]FDOPA



[^{18}F]anle138b

radiofluorination reaction of 6-NP and subsequent purification through semipreparative radioHPLC, accompanied by losses of radioactive synthon and low radiochemical yield of the target product (1%, corrected for radioactive decay). We believe that the need for a purification step is explained by the presence of the initial 6-NP in the reaction mixture, the presence of which leads to a low yield of the second stage of the synthesis (condensation of 6-[^{18}F]PP with tosylhydrazide [8]). In our recent work on the synthesis of [^{18}F]anle138b [10], we proposed alternative techniques for the synthesis of 6-[^{18}F]FP, the most effective of which is the radiofluorination of iodonium salt—(6-formylbenzo-1,3-dioxol-5-yl)(phenyl)iodonium bromide. The disadvantage of the iodonium salts as precursors in the synthesis of radiopharmaceuticals is the difficulty of synthesis and unavailability from commercial sources. This work is aimed at synthesizing 6-[^{18}F]FP from commercially available 6-NP with replacing the previously proposed method of labor-intensive semipreparative HPLC purification [8] with a much more facile and automated solid-phase extraction (SPE) method on disposable cartridges, which is widely used in automated synthesis of radiopharmaceuticals [11]. The problem of separating nitro- and fluorine derivatives is also of general scientific importance for the radiochemistry of fluorine-18, since the nitro group is one of the most common leaving groups in aromatic radiofluorination reactions.

EXPERIMENTAL

Materials and reagents. All commercially available solvents and reagents listed below: *N,N*-dimethylformamide (DMF) (H_2O content less than 0.005%, Sigma-Aldrich), dimethyl sulfoxide (DMSO) (≥99.9%, anhydrous, Sigma-Aldrich), acetonitrile (MeCN) (H_2O content less than 0.03%, Cryohim LLC), ethanol (HPLC grade, Merck), ethyl acetate (99.8%, PanReac AppliChem), methanol (reagent grade, Vekton JSC), trifluoroacetic acid (TFA) (peptide grade , Iris Biotech GmbH), 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (cryptofix 2.2.2) (≥98%, Sigma–Aldrich), *p*-toluenesulfonate tetrabutylammonium (Bu_4NOTs) (≥98%, Sigma–Aldrich), anhydrous potassium carbonate (99%, Sigma–Aldrich), potassium methoxide (95%, Merck), 6-nitropiperonal (97%, Sigma-Aldrich), were used without additional purification. To prepare fluorine-18, we used water [^{18}O]H_2O enriched with oxygen-18 (≥97%, Global Scientific Technologies CJSC, Sosnovy Bor, Russia); disposable anion exchange cartridges SepPak QMA Light, 130 mg (Waters) were activated by sequential washing with 10 mL of 0.5 M K_2CO_3 and 15 mL H_2O; HLB 3cc solid phase extraction cartridges (Waters) with reversed-phase sorbent were activated by washing with 4 mL EtOH and 10 mL H_2O.

Synthesis of radionuclide fluorine-18. Fluorine-18 was synthesized via the $^{18}O(p,n)^{18}F$ nuclear reaction by irradiating [^{18}O]H_2O with 16.4 MeV protons in a water target of a PETtrace 4 cyclotron (GE Healthcare, Sweden). Irradiated [^{18}O]H_2O containing 1.5–3.0 GBq of [^{18}F]fluoride was delivered by a helium flow to the input of the synthesis module. The radiochemical synthesis of 6-[^{18}F]FP was conducted on a semi-automatic remote-controlled module designed at the Institute of the Human Brain of the Russian Academy of Sciences; fluorination was conducted in a 5 mL reaction vessel (Wheaton vial).

Table 1. Results of the synthesis of 6-[^{18}F]FP by radiofluorination of 6-NP with various PTCs

System no.	PTC/base	6-NP, mg/μmol	Solvent	*T*, °C/*t*, min	RCC, % (by radio-HPLC)
1	K2.2.2 (25 μmol), K_2CO_3 (12 μmol), MeCN/H_2O 96/4	4/20	DMSO	120/10	69 ± 10 (*n* = 6)
2	K2.2.2 (25 μmol,) K_2CO_3 (12 μmol), MeCN/H_2O 96/4	1/5	DMSO	120/10	3 (*n* = 1)
3	Bu_4NOTs 2.4 μmol/1 mL MeOH	0.2/1	DMSO	120/10	28 ± 3 (*n* = 3)
4	Bu_4NOTs 2.4 μmol/1 mL MeOH	1/5	DMSO	120/10	38 ± 6 (*n* = 3)
5	Bu_4NOTs 2.4 μmol/1 mL MeOH	0.2/1	DMF	140/10	55 ± 4 (*n* = 3)

Synthesis of 6-[^{18}F]FP. [^{18}F]fluoride was recovered from irradiated [^{18}O]H_2O by on-line sorption on a SepPak QMA Light anion exchange cartridge, followed by elution with solutions containing a phase-transfer catalyst and removal of solvents in a nitrogen flow. Eluent composition (method A): 9.0 ± 0.1 mg (25 μmol) of kryptofix 2.2.2 and 2.0 ± 0.1 mg (12 μmol) of K_2CO_3 in 2 mL MeCN/H_2O (96/4 by volume); solvent removal: 120°C, 10 min. Eluent composition (method B): 1 mg Bu_4NOTs (2.4 μmol) in 1 mL MeOH; solvent removal: 90°C, 5 min. A solution of 6-NP (0.2–4 mg, 1–20 μmol) was added to the dry residue containing the activated complex [K/K2.2.2]$^+$[^{18}F]$^-$ (method A) or [^{18}F]Bu_4NF (method B) in 0.6 mL DMSO or DMF, the reaction mixture was heated at 120–140°C for 10 min.

Precursor degradation and separation of 6-[^{18}F]FP. After cooling to 70°C, 20 μL solution of KOMe in methanol (10 mg/mL) in 200 μL of solvent (DMSO/DMF) was added to the reaction mixture. After 1 min, 3 mL of water was added to the mixture and the resulting solution was passed through an activated HLB 3cc cartridge; the cartridge was washed sequentially with 1 mL of 50% ethanol and 1 mL of 60% ethanol, then 6-[^{18}F]FP was eluted with 1 mL of 97% ethanol.

Conditions for analysis by radio-HPLC and radio-TLC techniques. To estimate the radiofluorination efficiency [radiochemical conversion (RCC), Table 1] and identification of 6-[^{18}F]FP, radio-TLC and radio-HPLC techniques were employed. Thin-layer chromatography (TLC) was carried out on Sorbfil-type silica gel plates with a UV indicator (LENCHROM, St. Petersburg); Ethyl acetate was used as the mobile phase. The distribution of radioactivity over the plate was detected using a MiniGITA radio-TLC scanner (Raytest, Germany); The R_f of [^{18}F]fluoride and 6-[^{18}F]FP was 0.13 and 0.56, respectively. For radio-HPLC analysis a Dionex ISC-5000 chromatograph (Dionex, Sunnyvale, CA, USA) was used equipped with a Rheodyne 7125 injector, a UV detector (254 nm), and in series with it a radioactivity detector (Carrol and Ramsey Associates, CA, USA, model 105-S, with a difference in the time of recording peaks by detectors of 0.1 min). Chromatography conditions: X-Bridge C18 column (150 × 4.6 mm), eluent: a mixture of 0.1% trifluoroacetic acid and acetonitrile in gradient mode: 0 min–5% acetonitrile, 0–8 min–5–95% acetonitrile, linear gradient, flow rate 2.0 mL/min. The retention times R_t of 6-[^{18}F]FP and 6-NP were 4.9 ± 0.1 and 4.8 ± 0.1 min, respectively.

RESULTS AND DISCUSSION

To participate in nucleophilic fluorination reactions, [^{18}F]fluoride, generated in a highly solvated form in the cyclotron water target, is converted into the form of an activated complex in the presence of phase transfer catalysts (PTCs) [1]. Crown ethers or cryptands in combination with various bases [most often the aminopolyester kryptofix 2.2.2 (4,7,13,16,20,24-hexaoxa-1,10-diazabicyclo[8.8.8] hexacosane, K2.2.2) and potassium carbonate (K2.2.2/K_2CO_3) as well as tetraalkylammonium salts] are used as PTC. The choice of PTC plays a decisive role in the radiofluorination efficiency [1, 12]. The standard

method for separating fluorine-18, used in this work, includes sorption of the radionuclide with an anion exchange resin packaged in commercially available disposable cartridges (Sep-Pak Plus QMA Light, 130 mg), followed by elution of fluorine-18 with a PTC solution and removal of the solvent and water traces by azeotropic drying. Previously, an alkaline eluent containing 12 μmol K_2CO_3 in a MeCN/H_2O mixture (4% H_2O) was utilized in the synthesis of 6-[^{18}F]FP [5, 6] in the presence of kryptofix 2.2.2 (25 μmol). When 7–8 mg of 6-NP was used, the RCC was 53 ± 6% (DMSO, 180°C, 5 min) [5]; the resulting 6-[^{18}F]FP was used in the synthesis of 6-L-[^{18}F]FDOPA without intermediate purification. As already noted [8], the use of 6-[^{18}F]FP in the synthesis of [^{18}F]anle138b requires the removal of unreacted precursor, which in the case of substances with similar physicochemical properties (6-[^{18}F]FP and 6-NP) is quite difficult even using semipreparative HPLC [13], and is also accompanied by large losses of radioactivity of the target product [8]. For separation by SPE, in view of the low sorption capacity of disposable SPE cartridges, it is necessary to reduce the amount of initial 6-NP provided maintaining the radiofluorination efficiency. Table 1 (system 1) demonstrates that using 4 mg (20 μmol) of the precursor and varying the reaction conditions maintain the high radiofluorination efficiency of 6-NP (RCC 69 ± 10%). However, when the 6-NP amount was reduced to 1 mg (5 μmol), this value dropped to 3% (system 2, Table 1), and when fluorination was conducted at 0.2 mg, no product formation was detected.

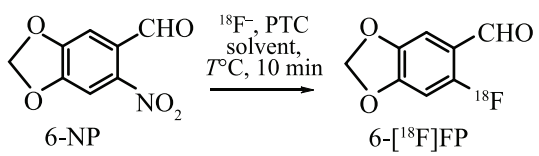
As an alternative to K2.2.2/K_2CO_3, in recent years tetraalkylammonium salts, such as tetraethylammonium bicarbonate (Et_4NHCO_3) [9, 11], are often used, providing less alkaline conditions for radiofluorination and generating a smaller amount of chemical and radiochemical impurities due to the degradation of the precursor under the influence of bases. A number of works from our laboratory demonstrates the effectiveness of using weakly alkaline PTC of this group—tetrabutylammonium *p*-toluenesulfonate (Bu_4NOTs)—in aliphatic radiofluorination reactions [14–16]. The use of an alcohol solution of Bu_4NOTs at the [^{18}F]fluoride elution step makes it possible to eliminate the conventional long-term step of azeotropic drying [1], and most importantly, to reduce the amount of the precursor by 5–10 times [16]. The results of applying this approach to the synthesis of 6-[^{18}F]FP are illustrated in Table 1. To elute [^{18}F]fluoride adsorbed on the QMA anion exchange resin, a solution of Bu_4NOTs in methanol was utilized; elution efficiency exceeded 90%. After removing methanol in a nitrogen flow, a precursor solution was added to the resulting activated [^{18}F]Bu_4NF complex and radiofluorination was carried out at 120–140°C (Scheme 1).

Table 2. Composition of the reaction mixture after reaction with potassium methoxide (70°C, 1 min) according to radio-HPLC data (Figs. 1c, 1d)

Molar ratio KOMe/6-NP	Solvent for KOMe	6-[^{18}F]FP, %	6-NP, %
1/1	DMSO	0–20	5–15
1/1	MeOH	60–65	5–10
2/1	MeOH	50–60	Negligible

As can be seen from the data in Table 1, in the presence of Bu_4NOTs, high RCC values were achieved using 1 μmol of precursor (system 5, Table 1), however, in this case, the separation of 6-NP and 6-[^{18}F]FP on a disposable SPE cartridge is very difficult to carry out, since even under gradient HPLC conditions (Figs. 1a, 1b), the retention times of these compounds are practically the same. A report [8] on the synthesis of [^{18}F]anle138b for their separation by SPE proposes to convert 6-nitropiperonal to 6-aminopiperonal by reaction with powdered iron in a concentrated HCl solution in ethanol (100°C, 10 min). However, after purification on a reversed-phase cartridge, the radiochemical yield of 6-[^{18}F]FP was found to be negligible, and, in addition, the proposed method is almost impossible to automate. Another approach to this problem is the use of alkali metal methoxides, which react selectively with the precursor generating products that are significantly more polar than the fluorine-containing analogue, thereby enabling the separation of these compounds. This approach was applied in the automated synthesis

Scheme 1. Synthesis of 6-[^{18}F]FP by nucleophilic radiofluorination of 6-NP.



6-NP 6-[^{18}F]FP

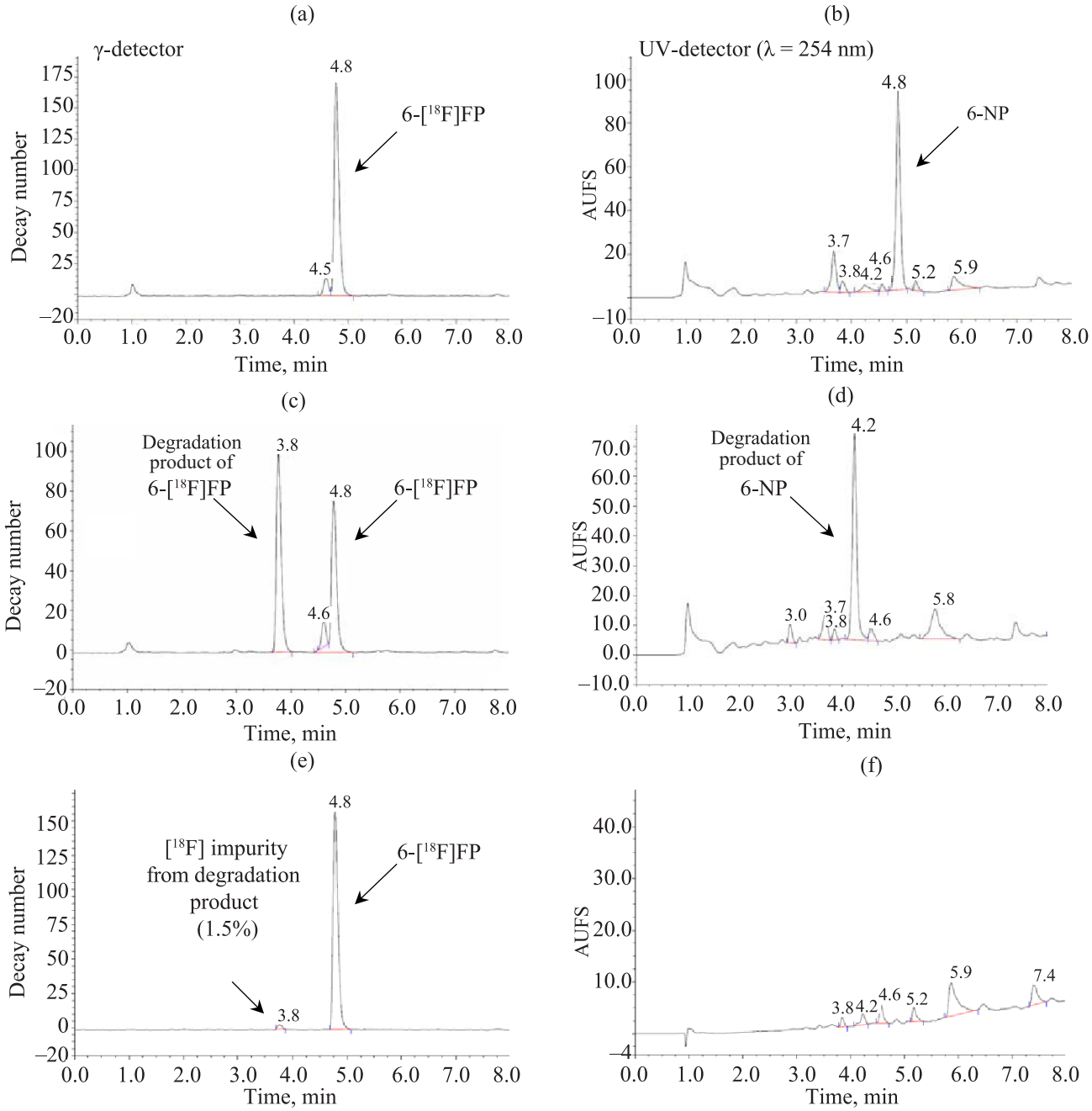


Fig. 1. HPLC analysis data: (a, b) reaction mixture after radiofluorination; (c, d) reaction mixture after reaction with potassium methoxide; (e, f) 6-[^{18}F]FP after SPE purification. (a, c, e) γ-Detector; (b, d, e) UV, 254 nm.

of [^{18}F]flutamethamol [17], a radiotracer for imaging amyloid aggregates in patients with Alzheimer's disease [18]. After radiofluorination of the nitro precursor, sodium methoxide was added to the reaction mixture, both the resulting degradation product and the fluorine-18 labeled radioligand were separated by SPE using a combination of disposable cartridges. Another example (but using potassium methoxide to degrade the precursor) is the disposable cartridge separation of nitromazenil and [^{18}F]flumazenil [19], a radioligand for estimating central benzodiazepine receptor density in epilepsy [20]. According to [20], we also used potassium methoxide (Table 2); the selection of conditions was carried out under the control of radio-HPLC (Fig. 1). It

was shown that at a twofold molar excess of KOMe/6-NP (Table 2, bottom line), virtually no nitro precursor remains in the reaction mixture, as evidenced by the disappearance of the corresponding peak on HPLC and the appearance of a derivative peak with a retention time very different from the fluorine derivative (Figs. 1b, 1d). This made it possible to proceed to the development of conditions for the purification of 6-[^{18}F]FP by SPE. Unfortunately, under these conditions (Table 2, bottom line), partial degradation of the target 6-[^{18}F]FP was also observed with the formation of an unidentified labeled product (Fig. 1c), which complicated the purification step.

On the whole, despite the enormous advantages of the SPE method (speed, reliability, ease of automation, use of disposable cartridges, etc.), selection of separation conditions that ensure the desired chemical and radiochemical purity of the product is a challenging task. Based on the composition of the mixture to be separated, the most suitable for purification of 6-[^{18}F]FP is the Oasis HLB 3cc reversed-phase cartridge (Waters), which does not have silanol groups, includes both hydrophilic and lipophilic fragments and is suitable for separation under acidic and alkaline conditions (stable in the pH range 0–14). HLB cartridges of various capacities are successfully used at the step of radiopharmaceutical purification in automated synthesis modules [21, 22]. However, when passing the reaction mixture diluted with water, both radioactive products were sorbed onto the HLB cartridge (>99% of the radioactivity was sorbed). To separate 6-[^{18}F]FP, a previously developed fractional elution technique was used in [22], which included sequential washing of the cartridge with 1 mL of aqueous 50% EtOH and 1 mL of aqueous 60% EtOH. Control with radio-HPLC method was used for selecting the optimal concentration and volume of ethanol, ensuring minimal losses of the target labeled product in the eluate fractions. The final elution of the HLB cartridge with ethanol (1 mL, 97%) made it possible to obtain a 6-[^{18}F]FP fraction with a negligible content of 6-NP, ~1 μg/mL (Fig. 1f), which is comparable to the purification efficiency of the conventional semipreparative HPLC method. The radiochemical purity of the resulting 6-[^{18}F]FP exceeded 98% (Fig. 1e). The radiochemical yield corrected for radioactive decay was 10% at a synthesis time of 45 min. The main losses of the radioactive product were due to the formation of radioactive impurities at the 6-NP degradation step by potassium methoxide (40–50%, Fig. 1c).

The possibility of effective separation by SPE of a nitroprecursor (6-NP) and its radiofluorination product (6-[^{18}F]FP) characterized by similar physicochemical properties was demonstrated. This result was due to reducing the amount of the initial 6-NP at the radiofluorination step and subsequent reactions of its degradation with potassium methoxide. The use of relatively mild conditions for this reaction and disposable cartridges at the SPE purification step makes it possible to implement the method into the automated radiopharmaceutical synthesis modules while reducing synthesis time.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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