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Development of an automated method for in-house production of sodium ^{18}F-fluoride for injection: process validation as a step toward routine clinical application

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Abstract

Background: Sodium ^{18}F-fluoride for injection can be easily cyclotron-produced and purified, as a simple inorganic salt, by adsorption/desorption onto an anion-exchange cartridge and then dispensed for clinical use. Since the clinical demand for this radiopharmaceutical is constantly increasing, this study aimed to design and develop a simple, fully automated method for the in-house, rapid, and efficient processing and dispensing of injectable solutions of Sodium ^{18}F-fluoride without the need of a synthesis module and disposable kit, but using only the dispensing unit.

Results: A new simple method for the efficient routine production of injectable solutions of [^{18}F]NaF was developed through a straightforward modification of the commercial dispenser Clio (Comecer S.p.A., Italy) and without the need of a synthesis module. The full production, processing and dispensing of [^{18}F]NaF were entirely carried out on the same batch using only the dispensing module. Process validation was carried according to GMP guidelines to ensure consistency of [^{18}F]NaF quality with international standards. The final radiopharmaceutical met all quality criteria specified by Ph. Eur. and chemical, radionuclidic and radiochemical impurities were significantly below the required limits.

Conclusion: A new simple and reliable procedure developed for the preparation and dispensing of injectable [^{18}F]NaF in less than 10 min with a radiochemical yield > 97% (decay corrected) has been successfully developed. Notably, the proposed method also allows the preparation of [^{18}F]NaF using the residual fluorine-18 activity remaining after a [^{18}F]FDG production run, thus making it immediately accessible to patients for further PET imaging investigations.

Keywords: In-house production, [^{18}F]NaF, Cost-effective method, Residual activity, Validation

Background

Sodium ^{18}F-fluoride ([^{18}F]NaF) is a PET radiopharmaceutical used for skeletal imaging. This radiopharmaceutical has high bone uptake and fast clearance that allow improving sensitivity and specificity in bone disease detection and diagnosis (Bastawrous et al. 2014; Jadvar et al. 2015; Langsteger et al. 2016; Broos et al. 2018; Ahuja et al. 2020; Cook and Goh 2020; Zhang-Yin and Panagiotidis 2023). The bone uptake mechanism of [^{18}F]NaF is similar to that of the standard diagnostic radiopharmaceutical for bone imaging [^{99m}Tc]Tc-MDP, but with better pharmacokinetics properties, such as high and rapid bone uptake and very fast blood clearance, which leads to a high bone-to-background ratio (Grant et al. 2008; Czernin et al. 2010; Park et al. 2021). High-quality images of the skeleton can be obtained in less than one hour after intravenous administration of [^{18}F]NaF (Grant et al. 2008; Segall et al. 2010; Araz et al. 2015; Beheshti et al. 2015). Notably, [^{18}F]NaF has been also used for visualization of calcification activity in the vasculature (Moss et al. 2019; Tzolos & Dweck 2020; Kwiecinski et al. 2019; Patil et al. 2023).

Sodium ^{18}F-fluoride as a simple inorganic salt can be effortlessly produced in a few steps using different methods, modules and disposables. Generally, the preparation comprises the following three steps: (i) production of the fluoride ion [^{18}F]F^-, (ii) adsorption onto an anion exchange cartridge (AEC) and (iii) elution with 0.9% NaCl. Chih-Hao K. et al. investigated how the AEC counter ion affects the pH of the final product (Kao et al. 2010). Jae Yong Choi et al. investigated the impact of the type of strong cation exchange (SCX) column on the presence of radionuclide impurities and assembled a module for [^{18}F]NaF preparation (Choi et al. 2016). For the scope of the present work, multiple [^{18}F]NaF productions have been carried out with different modules, namely AllInOne and miniAllInOne (Trasis), and TracerLab® MXFDG and Tracerlab FX-FN (GE Healthcare) (Nandy et al. 2006; Hockley and Scott 2010; Kao et al. 2010; Collet et al. 2015; Choi et al. 2016). Interestingly, in recent years different procedures have been accomplished on different modules to produce [^{18}F]NaF and [^{18}F]FDG starting from the same batch of cyclotron-produced [^{18}F]F^- (Awad et al. 2022; Singh et al. 2023).

Considering the relative simplicity of the manufacturing approaches employed for [^{18}F]NaF production, we speculated that it might be possible to develop an even simpler method that could allow the preparation and dispensing of [^{18}F]NaF in a single step, using only the commercial volumetric dispenser Clio (Comecer S.p.A.). Since Clio is a module exclusively dedicated to dispensing PET/SPECT radiopharmaceuticals immediately after preparation, the approach implemented in this study was to remove the synthesis module and other commercial synthesis kits from the standard assembly used for the production of [^{18}F]NaF retaining only the dispenser and its disposable kit. This modification was accomplished by installing a Y-connector and an AEC into the dispensing unit. With this simple modification, it was possible to design a procedure for the preparation and dose dispensing of [^{18}F]NaF as a continuous process. The quality of the final [^{18}F]NaF was found to fully meet the physical, chemical and biological quality standards as reported in the European Pharmacopoeia (Ph. Eur).

Materials and methods

Materials

Enriched water ($H_2{}^{18}O$) was purchased from Nukem isotopes, Alzenau, Germany. Sodium chloride (0.9% w/v of NaCl) injection solution (1000 mL), and water for injection (10 mL) were obtained from Alkaloid AD, Skopje, Republic of North Macedonia. Anion exchange Sep-Pak Accell Plus QMA Plus Light Cartridges (WAT023525, 186,004,051) were purchased from Waters, Milford, MA. Sterile 0.22 μm filters were obtained from Merck, Burlington, MA, and sterile Y-connector from B Braun, Milano, Italy. The kit Clio, sterile vials, and 10 mL syringes were supplied by BTC Medical Europe, Bologna, Italy.

Materials used for quality control of [^{18}F]NaF were: sodium fluoride (NaF) reference standard and sodium hydroxide (NaOH) in H_2O, 50–52%, for IC (Sigma Aldrich, St. Louis, MO), pH strips (Macherey Nagel, Düren, Germany), Endosafe®-PTS (Charles River Laboratories, Wilmington, MA) and Water type 1 (Millipore, Burlington, MA).

Methods

Description of the equipment

Sodium ^{18}F-fluoride was produced on a semi-automated volumetric dispenser for radiopharmaceuticals Clio (Comecer S.p.A, Castelbolognese, Italy). This device operates on the user-friendly software platform Movicon, which simplifies the dispensing process of radiopharmaceuticals and allows manual control. The Clio was installed in a Talia dispensing hot cell (Comecer S.p.A) equipped with a class B pre-chamber and a class A main chamber.

Disposables

The Clio module includes a single-use sterile disposable kit with four three-way valves, tubes for different purposes, and a 0.22 μm filter for final sterilisation installed between valve four and the dispensing needles, ensuring sterile filtration on each dose dispensed. To produce [^{18}F]NaF, the original commercial disposable kit was modified by installing additional disposables as follows.

(a) Y-Connector with two proximal female luer lock connectors, two backcheck valves, and one distal male luer lock.
(b) 0.22 μm filter.
(c) Anion exchange cartridge (AEC) Sep-Pak Accell Plus QMA Plus Light Cartridge.
(d) 5 mL of 0.9% NaCl solution in a sterile vial connected to the Y-connector.

The AEC was first preconditioned with 5 mL of sterile water before being connected to the distal part of the Y-connector, and then to the first valve of the Clio kit, thus bypassing the radiopharmaceutical transfer line. One proximal end of the Y-connector was connected to the cyclotron [^{18}F]F^- delivery line, while the other end was connected to a vial filled with 5 mL of 0.9% NaCl for elution.

Furthermore, to prevent microbiological and particulate contamination from fluoride-18 produced and transferred directly from the cyclotron, we have installed

an additional 0.22 μm filter between the capillary line and the proximal end of the Y-connector.

Production of [18F]NaF

The modified kit was placed into the Clio module, and the recovery vial was positioned on the syringe holder. Using the Movicon software, the Clio module was set on the vial-fill position, and the valves were switched to direct the radioisotope flow toward the recovery vial. Specifically, valve 1 was set to position 4, while the other three valves were set to position 3. With this setting, the modified kit was ready to receive the produced $[^{18}F]F^-$ radioisotope. The $[^{18}F]F^-$ ion was generated through the $^{18}O(p,n)^{18}F$ nuclear reaction, by proton irradiation of ^{18}O-enriched water contained in a niobium target installed on a GE PETtrace cyclotron, (16.5 MeV). At the end of production (EOP), the $[^{18}F]$fluoride ion was transferred through a capillary from the cyclotron and 0.22 μm filter to the modified Clio kit hosted in the Talia hot cell. The radioisotope was trapped by a quaternary-methyl-ammonium (QMA) anion-exchange solid-phase extraction cartridge, while the residual irradiated enriched water was collected in the recovery vial. This step separated the cationic and water-soluble contaminants in the irradiated enriched water from the final $[^{18}F]$fluoride. An additional washing step with sterile water was added to the procedure to ensure the complete removal of the enriched water from the kit, which was also collected in the recovery vial. A flow of helium was subsequently passed through the kit. After radioisotope purification, the trapped $[^{18}F]$fluoride was eluted from the cartridge using 5 mL of saline. To achieve this, the first valve was switched to position 2, enabling a flow through the bulk vial for the final recovery of $[^{18}F]F^-$. The saline from the vial was then delivered using an inert nitrogen gas at a pressure of 2.3 bar. At the end of production (EOP), the same batch of $[^{18}F]$NaF was dispensed, in a continuous process, using the same kit. After EOP and dilution of the bulk to the target concentration, 1 mL of $[^{18}F]$NaF bulk was transferred to the recovery vial. This step was included to ensure that any residuals left in the kit lines and the final 0.22 μm filter were removed. Following this, the recovery vial was taken out of the holder. Subsequently, vials or syringes were placed on a holder, and the final doses were dispensed according to the dispensing batch. By keeping the entire production process within a single hot cell, the time required to transfer the final product to another hot cell for dispensing is eliminated.

Quality control of sodium 18F-fluoride

The quality control of $[^{18}F]$NaF was performed based on the quality requirements stated in the monograph (Ph. Eur. 01/2008:2010). The quality parameters in the specification were defined as reported in the general monograph on radiopharmaceuticals (Ph. Eur. 10.0, 0125 (07/2016), 2020) and the monograph on Sodium ^{18}F-fluoride published in the European Pharmacopoeia (Ph. Eur. 2100 (01/2008), 2020) (Table 1).

The identification of $[^{18}F]$fluorine was confirmed within 30 min after EOP by three activity measurements performed with a dose calibrator. Similar evidence was obtained by analyzing the chromatograms collected to determine the radiochemical purity. The retention time of the principal peak in the radiochromatogram of the test solution showed a difference $\leq$ 40 s compared to the retention time of the principal peak in the reference solution. The pH value, measured with a pH strip, was 4.5–10.0 (resolution, 0.5 pH units). To

Table 1 Quality Specifications of Sodium ^{18}F-fluoride ([^{18}F]NaF) for injection (Ph. Eur. 01/2008:2100)

Test		Method	Acceptance criteria
Pre-release tests			
Appearance		Visual inspection	Clear, colourless solution
Identification	Half-life determination	Radioactivity measurements	1.75–1.92 h
	Difference in retention time	HPLC	≤40 s
Approximate pH value		pH strips	5.5–8.0
Chemical purity: fluoride (F^-); max. V = 10 mL		HPLC	≤0.452 mg/mL
Radiochemical purity: [^{18}F]fluoride		HPLC/gamma detector	min 98.5% of the total activity
Post-release tests			
Bacterial endotoxins		Chromogenic LAL method	≤17.5 IU/mL
Sterility		Test for sterility (Ph. Eur.)	Sterile
Radionuclidic purity Fluorine-18		Gamma-ray spectrometry	min 99.9% of the total activity

assess chemical and radiochemical purity, the European Pharmacopeia specifies a High Performance Liquid Chromatography (HPLC) coupled with UV and radioactivity detectors in series and a strong anion-exchange column. We developed an alternative HPLC ion-exchange method, employing a conductivity detector with an anionic suppressor, for routine quality control of [^{18}F]NaF. The conductivity detector is highly sensitive to ions, which improves the overall sensitivity of the developed HPLC method, mainly in evaluating chemical purity. This characterization was carried out on a Dionex ICS 1600 HPLC System (Thermo Fisher Scientific, Waltham, US), equipped with a radio detector and a conductivity detector serially connected and anion exchange Dionex ADRS 600 Suppressor. Dionex IonPac AS10 analytical column connected to a Dionex IonPac AG10 guard column were eluted with 0.1 M NaOH, at a flow rate of 1 mL/min. The run time was 15 min, with fluoride eluting at a retention time of 3.9 min and chloride at 6.7 min. The chemical purity was determined by comparing the chromatograms of the test and reference solutions, using the conductivity detector. The Ph. Eur monograph specifies a fluoride limit of 4.52 mg per maximum recommended dose in mL. Given that the maximum dose is 10 mL, the concentration limit is not more than 0.452 mg/mL. The area under the peak in the chromatogram of the test solution did not exceed that of the corresponding peak in the reference solution when the concentration was 0.452 mg/mL. Radiochemical purity was assessed by analysis of the radiochromatograms recorded with the radioactive detector, and it was found that [^{18}F]fluoride activity was ≥ 98.5% of the total activity. For the determination of bacterial endotoxins, the LAL kinetic chromogenic method was used (Endosafe PTS, Charles River Laboratories). Sterility was tested using the general method published in European Pharmacopeia 10.0 (Sect. 2.6.1: Sterility). A gamma spectrometer (MKGB-01 RADEK, STC RADEK, Saint Petersburg, Russia) was used to evaluate the radionuclidic purity.

Results

The production process was carried out using the modified kit installed on the Clio dispensing module. Initially, the modified kit was checked by carrying out a "non-radioactive" test to verify the connections and determine the pressure required to deliver the

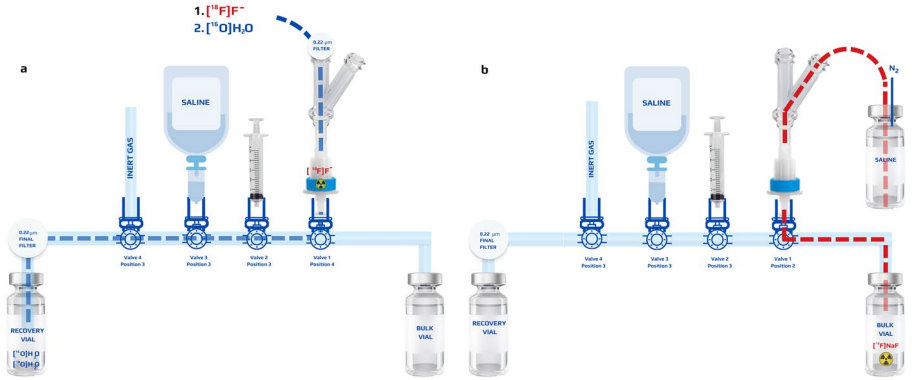

Fig. 1 Schematic representation of the modified Clio kit for the production of [^{18}F]NaF. **a** Schematic drawing of the trapping and washing steps of [^{18}F]fluoride. **b** Schematic drawing of the elution step. Created with Canva.com

Table 2 Results of [^{18}F]NaF process validation

Test		Method	Acceptance criteria	Results		
				1 batch	2 batch	3 batch
Pre-release tests						
Appearance		Visual inspection	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution
Identification	Half-life determination	Radioactivity measurements	1.75–1.92 h	1.80 h	1.84 h	1.82 h
	Difference in retention time	HPLC	≤ 40 s	33.18 s	32.76 s	33.82 s
Approximate pH value		pH strips	5.5–8.0	6.5–7.0	6.5–7.0	6.5–7.0
Chemical purity: fluoride (F^-)		HPLC	≤ 0.452 mg/mL	≤ 0.452 mg/mL	≤ 0.452 mg/mL	≤ 0.452 mg/mL
Radiochemical purity: [^{18}F] fluoride		HPLC/gamma detector	min 98.5% of the total activity	100%	100%	100%
Post-release tests						
Bacterial endotoxins		Chromogenic LAL method	≤ 17.5 IU/mL	< 5 EU/mL	< 5 EU/mL	< 5 EU/mL
Sterility		Test for sterility (Ph. Eur)	Sterile	Sterile	Sterile	Sterile
Radionuclidic purity: radionuclidic impurities		Gamma-ray spectrometry	max 0.01% of the total activity	8.83×10^{-05}%	1.71×10^{-06}%	1.63×10^{-06}%

radioisotope and for the elution of the [^{18}F]fluoride anion. The schematic diagram for [^{18}F]NaF production is shown in Fig. 1a and b. The initial two steps, trapping and washing of [^{18}F]fluoride, are shown in Fig. 1a, while Fig. 1b illustrates the elution step. Following literature methods, several preliminary experiments were manually conducted. Different anion-exchange and cation-exchange cartridges were tested. The process required the use of quaternary-methyl-ammonium (QMA = [$N(Me_4]^+$) anion-exchange solid-phase extraction cartridges with chloride as a counter ion.

Twenty (20) batches were produced with starting activity from 11.1 to 37 GBq. The resulting Sodium ^{18}F-fluoride solutions met the acceptance criteria defined by quality

specifications. The results of the quality assessment obtained in process validation are shown in Table 2.

All product samples were found to have 100% radiochemical purity. In their radiochromatograms only a single peak was observed, its retention time corresponding to that of the reference solution (Fig. 2a). On the other hand, no peaks were observed in the chromatogram recorded with the conductivity detector (Fig. 2b), indicating the absence of significant chemical impurities.

Discussion

Given the growing clinical interest in [^{18}F]NaF its higher production costs compared with [^{99m}Tc]Tc-MDP, the main goal of this study was to develop a simpler, cost-effective, in-house method for producing [^{18}F]NaF solutions for intravenous injection. Due to the radiological risks of working with ionizing radiation, the initial experiments were performed without activity aiming to simulate the entire production process and identify the most appropriate and safe operational conditions. This approach, allowed for the precise determination of the volume of sterile water required for the rinsing step.

Simulation of the washing step after target irradiation and transfer of the [^{18}F] fluoride ion, was carried out using sterile water. The cyclotron target was filled with sterile water (approximately 3 mL) and delivered through the same transfer capillary. Initially, two consecutive transfers of 3 mL of sterile water from the cyclotron target into two separate vials were performed. The dead volume of the modified kit was 2.1 mL. Afterwards, the production with radioactivity was conducted, and the radionuclide purity of irradiated enriched water collected in the recovery vial and vials from the first and second rinses was analyzed. The radionuclide impurity of the recovered water in the vial was 0.000674%, while the purity for the first and second rinses was 00001546% and 0.00000916%, respectively. Both values for the rinsed water were far below the limit specified for radionuclide purity in the European Pharmacopoeia,

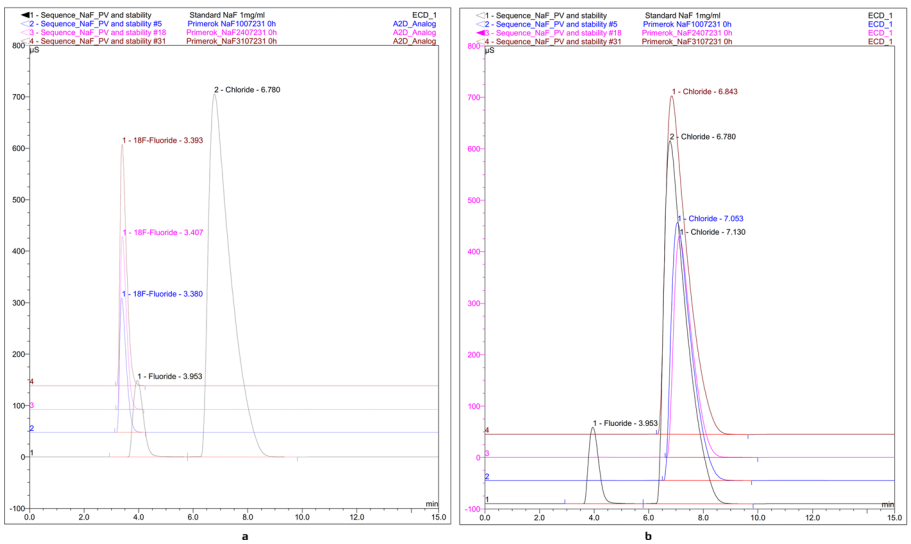

Fig. 2 Chromatograms of three validation batches recorded with a conductivity detector (right) and a radiodetector (left). **a** Radiochemical purity, **b** chemical purity

confirming the washing step effectiveness only with a transfer of 3 mL of sterile water. Additionally, a new inert nitrogen gas line was installed in the hot cell for radioisotope elution and it was connected to the saline vial with a luer lock connection. Elution was done with 5 mL saline under nitrogen pressure. The total production time was 10 min, followed by EOP, transfer of the fluoride radioisotope (2 min), washing (5 min), drying (2 min), and elution (1 min). The [^{18}F]NaF decay-corrected radiochemical yield was ≥ 97%. Furthermore, it was attempted to produce [^{18}F]NaF utilizing the residual [^{18}F]fluoride activity remaining in the target after [^{18}F]FDG synthesis. By rinsing the target with sterile water and subsequently transferring the activity to the Clio module through the modified kit, it was possible to use the recovered activity to produce [^{18}F]NaF for several patients. Approximately 5% of the remaining [^{18}F]F^- activity was washed out and utilized to produce [^{18}F]NaF. Assuming that the dispensing module with a modified kit is used to prepare and dispense [^{18}F]NaF in a Class A environment, conducting a risk assessment is crucial. During the development process, a risk assessment was carried out to identify the most critical factors influencing the production process and analyze and evaluate associated risks. Transferring the produced fluoride-18 from the non-classified controlled area, where the cyclotron is installed, through the direct capillary in a class A hot cell was identified as an operation with a high risk for contamination. The action was taken, and a 0.22 μm filter was installed at the end of the delivery line, specifically between the delivery line and one proximal end of the connector. As a result of this action, the probability of occurrence of the potential contamination was reduced, and the subsequent risk was classified as low as well.

Further, radioactive contamination during the elution step was identified as a high risk operation, with a considerable probability of occurrence. During the development process, the risk mitigation actions were carried out in the direction to reduce the pressure of the inert gas (N_2) for transferring saline: the nitrogen pressure was set to a maximum of 2.3 bar. By reducing the pressure, the probability of contamination was diminished, and the associated risk was afterwards classified as low.

Considering that the activities are performed in a class A environment, a contamination control strategy is of particular importance, and it is essential to reduce the risk of microbiological and particle contamination.

The contamination control strategy, aside from personnel gowning, consists of several key practices: cleaning and disinfecting the hot cell, disinfecting raw materials, and daily cleaning and disinfection of the premises. All raw materials used for kit modification were sterile single-use. The raw materials undergo disinfection three times: wiping before being transferred into clean rooms, wiping and UV disinfection in the class C laboratory, and wiping before being put in class B.

It is important to highlight that the cyclotron transfer line is the only component that is not single-use. This line is dedicated only to transferring the fluoride-18. The delivery line is cleaned with sterile water and helium flushing, so no detergent residues or products exist. Cleaning validation was conducted through indirect sampling via rinse samples, which were then microbiologically tested for total germ count and endotoxins. All three analyzed samples were sterile, and the endotoxin results were < 5 EU/mL, confirming that the cleaning procedure was effective.

Physical and microbiological monitoring was applied during the whole [^{18}F]NaF production cycle carried out in the class A Talia main chamber. Airborne particle monitoring was performed during all aseptic processes (preparation and dispensing). The results were consistent with acceptance criteria (the counts for 0.5 m size particles were not higher than 20 particles m^3, and 5 μm size particles were not detected). The microbiological monitoring was accomplished by settling plates in the class A chamber, and fingerprints on the tips of gloves in the class B pre-chamber and class A chamber. Results did not detect any microbial growth, thus confirming the effectiveness of the aseptic procedures applied to [^{18}F]NaF production. At the end of the dispensing step, the bubble point test (B.P.T.) was conducted as a standard component of the quality control of the whole production process. The B.P.T pressure inside each of the 20 batches was within the acceptance criteria (> 3.1 bar) and in the range of 3.8–4.0 bar.

Validation of aseptic procedures was performed, according to the recommendation in PIC/S PI 007-6 (PIC/S Guide PI 007-6, 2011; Atanasova Lazareva et al. 2022). Similarly, the reproducibility of the newly developed production route was assessed following FDA and EANM guidelines (FDA Guidance for industry 2011; Todde et al. 2017). Three consecutive batches of [^{18}F]NaF were produced on different days under the same predefined conditions. The maximum activity in batches used for process validation was 37 GBq, and the target concentration was 1000 MBq/mL. The results confirmed that the new in-house designed production process of Sodium ^{18}F-fluoride was capable of efficiently producing a final radiopharmaceutical that fulfils all the quality requirements defined in the European Pharmacopoeia monograph (Ph. Eur. 01/2008:2100).

Conclusions

The new automated, in-house method for [^{18}F]NaF injection production has been successfully designed and implemented. The method is practical and easy to adopt in any radiopharmacy production laboratory equipped with a dispensing hot cell that hosts the dispensing module. It employs single-use disposables, ensuring aseptic conditions for producing sterile injectable solutions with high reproducibility. The slight modification to the dispensing kit enabled the preparation and dispensing of [^{18}F]NaF with a radiochemical yield of ≥ 97%, meeting the quality requirements specified in the European Pharmacopoeia monograph. Notably, the new in-house method also allows for the cost-effective production of [^{18}F]NaF by recycling the residual activity left in irradiated enriched water after the daily routine production of [^{18}F]FDG.

Abbreviations

AEC	Anion exchange cartridge
B.P.T.	Bubble point test
EOP	End of production
FDA	Food and drug administration
[^{18}F]F$^-$	[^{18}F]fluoride
[^{18}F]NaF	Sodium ^{18}F-fluoride
GMP	Good manufacturing practice
HPLC	High-performance liquid chromatography
QMA	Quaternary-methyl-ammonium
Ph. Eur	European pharmacopoeia
[^{99m}Tc]Tc-MDP	Technetium 99 m-methyl diphosphonate

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Author contributions
MAL, EJ, AU: study conception and design. MAL, MCh, KK, FJ, and MV: performed the experiments. MAL, FJ, MV, PA, EJ: Interpretation of results. MAL and EJ: Wrote the first manuscript and accepted the editing from all authors. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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