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QUALITY-BASED DESIGN AND STABILITY ASSESSMENT OF SODIUM [^{18}F]FLUORIDE RADIOPHARMACEUTICAL FOR PET IMAGING

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This study presents the results of a stability assessment conducted on three production batches of sodium [^{18}F]fluoride radiopharmaceutical intended for intravenous injection. The objective was to evaluate the physicochemical and microbiological stability, establish an appropriate shelf life, and confirm the overall quality of this radiopharmaceutical over a defined period under controlled storage conditions. The stability study was designed to assess the quality of in-house-produced sodium [^{18}F]fluoride, with quality control tests performed at two-hour intervals. All pre-release and post-release tests outlined in the sodium [^{18}F]fluoride specification were conducted, including appearance, identification, pH, chemical, radiochemical, radionuclidic purity, bacterial endotoxins, and sterility. The results of pH, chemical, radiochemical, and radionuclidic purity tests met acceptance criteria at all tested time points across the three batches, demonstrating physicochemical stability. Microbiological stability was confirmed through compliance with bacterial endotoxin and sterility requirements. Overall, the findings confirm that sodium [^{18}F]fluoride remains stable for up to 10 hours after the end of synthesis, ensuring its suitability for clinical use.

Keywords: sodium [^{18}F]fluoride; radiopharmaceutical; stability; quality control; shelf life

ДИЗАЈН ЗА ПРОЦЕНА НА КВАЛИТЕТОТ И СТАБИЛНОСТА НА РАДИОФАРМАЦЕВТИКОТ НАТРИУМ [^{18}F]ФЛУОРИД ЗА ПЕТ-ВИЗУЕЛИЗАЦИЈА

Оваа студија ги претставува резултатите од проценатa на стабилноста спроведена на три производни серии од радиофармацевтикот натриум [^{18}F]флуорид наменет за парентерална, интравенска администрација. Целта беше да се оцени физичко-хемиската и микробиолошката стабилност, да се утврди рокот на употреба и да се потврди квалитетот на [^{18}F]NaF во дефинирани временски период под контролирани услови на чување. Студијата за стабилност беше дизајнирана за да се определи квалитетот на натриум [^{18}F]флуорид произведен во лабораториите на установата, при што тестовите за контрола на квалитетот се спроведуваа во интервали од два часа. Испитувањата за одобрување на серијата за инјектирање и финално одобрување (идентификација, pH вредност, хемиска и радиохемиска чистота, бактериски ендотоксини, стерилност и радионуклидна чистота), дефинирани во спецификацијата за квалитет, беа соодветно спроведени. Резултатите од pH, хемиската, радиохемиската и радионуклидната чистота ги задоволија критериумите за прифаќање во сите испитувани точки за сите три серии, што ја потврди физичко-хемиската стабилност. Микробиолошката стабилност беше потврдена преку усогласеност со барањата за испитување на бактериски ендотоксини и стерилност. Сите добиени резултати потврдија дека растворот на натриум [^{18}F] флуорид за инјектирање останува стабилен 10 часа по

завршување на синтезата, со соодветна стабилност за понатамошна примена во клиничката пракса.

Клучни зборови: натриум [^{18}F]флуорид; радиофармацевтик; стабилност; контрола на квалитет; рок на употреба

1. INTRODUCTION

Bone scintigraphy and positron emission tomography (PET) are two imaging modalities used for skeletal visualization in nuclear medicine.[1–3] Bone scintigraphy has primarily been performed using technetium-99m methyl diphosphonate ([^{99m}Tc]Tc-MDP). In contrast, PET skeletal imaging is typically conducted with sodium [^{18}F]fluoride ([^{18}F]NaF), a highly sensitive bone-seeking, intravenous, positron-emitting radiopharmaceutical.[4,5] This radiopharmaceutical exhibits high bone uptake and rapid blood clearance, resulting in enhanced sensitivity and specificity for detecting and diagnosing bone diseases.[6] Over the last decade, [^{18}F]NaF has emerged as a noninvasive, quantitative imaging modality capable of visualizing calcification activity in the vasculature.[7] The growing availability of PET combined with computer tomography (PET/CT scanners), and prolonged shortages of ^{99}Mo/^{99m}Tc generators, have lead to increased use of sodium [^{18}F]fluoride radiopharmaceutical.[8,9] The increasing clinical demand for [^{18}F]NaF necessitates its daily large-scale production, emphasizing the importance of determining storage conditions and an appropriate shelf life during which the radiopharmaceutical meets all the quality requirements and remains safe for clinical application.[9] Shelf life determination for radiopharmaceutical products should be based on the results of stability studies.[10] The purpose of stability testing is to provide evidence of how the quality of a drug substance or drug product varies over time under the influence of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or shelf life for the drug product, along with recommended storage conditions.[11]

Radiopharmaceuticals are medicinal products that contain one or more radioactive isotopes for diagnostic or therapeutic purposes.[12] Due to their specific characteristics, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline Q1A(R2): Stability Testing of New Drug Substances and Products is not fully applicable, especially for positron-emitting radiopharmaceuticals. Notably, the stated storage conditions, requiring a minimum of 12 months for long-term and 6 months for accelerated testing, cannot be applied to PET radiopharmaceuticals with short half-lives, such as fluoride-18, which has a half-life of 109.8 minutes.[13] Furthermore, stress testing of radioactive substances is generally not feasible. The stability of a radiopharmaceutical depends on its type and can be influenced by various factors such as storage temperature, amount of radioactivity, radioactive concentration, and the presence or absence of antioxidants or other stabilizing agents.[14–17] When assessing the stability of ready-to-use radiopharmaceuticals, including PET radiopharmaceuticals, it is important to consider both the minimum and maximum amount of radioactivity – or radioactive concentration – present at the time of manufacture.[14,18–20] Certain PET radiopharmaceuticals may be chemically unstable, leading to rapid chemical changes. Radiochemical impurities can arise from decomposition during synthesis and the labeling process, or as a result of variations in temperature, pH, light exposure, or the presence of oxidizing or reducing agents, as well as radiolysis.[21–23] Therefore, a comprehensive evaluation of quality parameters is essential to define appropriate storage conditions and establish shelf life through a well-defined stability protocol.[24,25] The analytical methods used for testing should be stability-sensitive and capable of identifying degradation products and impurities throughout the defined shelf life.[19] A stability study must be conducted on at least three production batches to establish the product's shelf life and storage conditions.

2. MATERIALS AND METHODS

2.1. *Materials*

The materials used for the production and stability testing of [^{18}F]NaF included: enriched water ([^{18}O]H_2O) (NUKEM isotopes, Alzenau, Germany), 0.9 % sodium chloride injection solution (Alkaloid Ad Skopje, North Macedonia), water for injection (Alkaloid Ad Skopje, North Macedonia), quaternary methylammonium (QMA) cartridges (Waters, Milford, MA, USA), sterile 0.22 μm filter (Merck, Burlington, MA, USA), Clio dispensing kit (BTC Medical Europe, Bologna, Italy), sterile Y-connector (B Barun, Milano, Italy), sterile vials (Huayi isotopes, Changshu, China), 10 ml syringe

(BTC Medical Europe, Bologna, Italy), Endosafe®-PTS cartridges (Charles River Laboratories, Wilmington, MA, USA), sodium fluoride standard (Sigma-Aldrich, St. Louis, MO, USA), pH strips (Macherey Nagel, Düren, Germany), sodium hydroxide solution (50–52 %), eluent for ion chromatography (IC) (Sigma-Aldrich, St. Louis, MO, USA), Type 1 water (Direct Q3, Millipore, Burlington, MA, USA), and Limulus amebocyte lysate (LAL) reagent pyrogen-free water (FUJIFILM Wako Chemicals Europe GmbH – Lab Chem).

2.2. *Methods*

2.2.1. *[^{18}F]NaF production*

The radioisotope [^{18}F]F$^-$ was produced via the ^{18}O(p,n)^{18}F nuclear reaction by proton irradiation in a cyclotron of enriched water ([^{18}O]H_2O) contained in a niobium target (GE PETtrace 16.5 MeV). The [^{18}F]F$^-$ radioisotope and irradiated enriched water were transferred through a capillary into the hot cell, where a Clio module had been installed. The Clio module (Comecer S.p.A.) is a volumetric dispenser for radiopharmaceuticals and was used to produce and dispense [^{18}F]NaF radiopharmaceutical using an in-house-developed method.[26] Upon transfer, the [^{18}F]F$^-$ radioisotope was trapped on an anion exchange solid-phase extraction (SPE) cartridge, specifically a quaternary methylammonium (QMA) cartridge. The QMA cartridge was sequentially rinsed with sterile water to eliminate residuals from the irradiated enriched water, followed by helium gas flushing. The final preparation step was the elution of the trapped fluoride-18, which was accomplished using a sterile saline solution. Aseptic dispensing was also carried out continuously within the same batch using the same kit, ensuring an effective and reproducible production process.

2.2.2. *[^{18}F]NaF quality control*

The quality control of [^{18}F]NaF was performed according to the quality requirements specified in the European Pharmacopoeia (EP) monograph,[27] and followed the specifications for batch release that had been previously established by our group.[26]

The produced radioisotope [^{18}F]F$^-$ was identified by calculating the radionuclide's half-life from three radioactivity measurements of the product vial with a dose calibrator (Atomlab 500, Biodex) within 30 min. The half-life was expected to fall within the range of 1.75 – 1.92 hours. The identity of [^{18}F]NaF was also confirmed by examining chromatograms used to determine its radiochemical purity. Typically, the retention time of the main peak in the radiochromatogram obtained with the test solution did not differ by more than 40 seconds from the retention time of the main peak in the reference solution. pH strips ranging from 4.5 to 10.0 (resolution: 0.5 pH units) were used to determine the approximate pH value, and results were expected to fall within the range of 5.5 – 8.0.

T a b l e 1

Specification of sodium [^{18}F]fluoride ([^{18}F]NaF) injection (Ph. Eur 01/2008:2100)[26]

Test		**Method**	**Acceptance criteria**
		Pre-release tests	
Appearance		Visual inspection	Clear, colourless solution
Identification	Half-life determination	Radioactivity measurements	1.75 – 1.92 hours
	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

Chemical and radiochemical purity were evaluated using an ion-exchange high-performance liquid chromatography (HPLC) system (Dionex, ICS 1600 Thermo). This system was equipped with both a radioactivity and a conductivity detector, which were connected in series, along with an anionic suppressor (Dionex ADRS 600). An isocratic method was employed on a Carbopak PA10 column (4 × 250 mm) paired with a guard column (CarboPac PA10, 4 × 50 mm), using a 0.1 M NaOH solution as the mobile phase at a flow rate of 1 ml/min.

Chemical purity was assessed by examining the conductivity detector of the test and reference solutions. The area under the peak of the test should not exceed the area of the corresponding peak in the NaF reference solution at a concentration of 1 mg/ml, which corresponded to a fluoride concentration of 0.452 mg/ml. Radiochemical purity was evaluated by examining the chromatogram obtained with a radioactive detector. Fluoride-18 radioactivity was required to be at least 98.5 % of the total radioactivity.

The rapid, sensitive LAL kinetic chromogenic method was employed to quantify bacterial endotoxins within approximately 15 minutes using the Endosafe PTS, a portable test system licensed by the FDA and produced by Charles River Laboratories. Prior to testing, samples were diluted at a ratio of 1:100 by mixing 10 µl of the sample with 990 µL of LAL reagent pyrogen-free water. A volume of 25 µl of this mixture was added to four wells on the cartridge in the Endosafe PTS. The concentration of bacterial endotoxins was required to be less than 17.5 IU/ml.

Sterility testing was caried out at the external microbiology laboratory of the Institute for Public Health of the Republic of North Macedonia, Division of Microbiological Control of Food and Drugs. This testing was performed using the sterility testing method (2.6.1) outlined in the European Pharmacopoeia.[28]

Radionuclidic purity was evaluated by gamma-ray spectrometry (Radek model MKGB-01), and the radionuclidic impurity was not to exceed 0.1 % of the total radioactivity.

2.2.3. *Stability study*

Stability testing of the [^{18}F]NaF injection was performed on three production batches, each formulated at a maximum radioactive concentration of 1000 MBq/ml at the end of synthesis (EOS) time, in accordance with the recommendations of the European Medicines Agency (EMA) Guideline on Radiopharmaceuticals.[13]

According to the European Pharmacopoeia (EP) monograph definition, sodium [^{18}F]fluoride injection was a sterile solution containing fluorine-18 in the form of sodium fluoride. Traditionally, radiolysis was the main cause of instability in radiopharmaceuticals. To reduce this effect, radiostabilizers were added to the formulations, and the most commonly used stabilizer was ethanol.[25] Since sodium fluoride is an inorganic salt without labile chemical bonds or reactive functional groups susceptible to radiolytic degradation, and due to its inherent physicochemical stability, the addition of radiostabilizers was not necessary. Its high chemical stability under both physiological and storage conditions ensured that no degradation of the active substance or solvent was expected during the intended shelf life of the product.

The manufacturing process used for the stability study is was the same as the routine production process, which involved adsorption and desorption onto an anion exchange cartridge, with saline as the elution solution. The production process did not involve a change in pH or temperature, or the use of buffers, stabilizers, or oxidizing agents; therefore, production-related factors influencing stability were not examined further.

The samples were filled into closed sterile borosilicate glass Type A vials with a bromobutyl rubber stopper and an aluminum crimp cap. Borosilicate glass is chemically inert, and interactions between the primary container-closure system and [^{18}F]NaF were considered not relevant. After filling and measuring the doses, the samples were delivered from the hot cell into the shielded lead container.

The use of sterile single-use kits and vials, along with a multidose automatic radiopharmaceutical injector, minimized the risk of microbial contamination, ensuring the final product's sterility throughout its intended shelf life.

In the design of this stability study, apart from the amount of radioactivity and the radioactive concentration, temperature was the only environmental factor considered. Ambient humidity was not evaluated because the samples were filled in a closed vial; hence, moisture did not affect product stability. Additionally, light exposure was excluded as a stability-affecting factor due to the storage of radiopharmaceuticals in a well-closed lead container and the well-known stability of inorganic salt NaF.

The samples were kept in a shielded lead container at a monitored and controlled room

temperature (18 – 22 °C). The product's shelf life could not exceed five radionuclide half-lives; therefore, the stability study was limited to a period of 10 hours.[29]

3. RESULTS AND DISCUSSION

The stability study of sodium [^{18}F]fluoride injection was designed following the ICH guideline Q1A(R2).[11] During the study's design phase, the unique physicochemical characteristics of PET radiopharmaceuticals, such as their short half-life and radioactive nature, were carefully considered. The quality parameters defined in the specification were evaluated at defined intervals throughout the stability study, applying the same acceptance criteria as those used in the release specifications, with validated analytical methods.

The testing frequency was established to adequately investigate the stability profile of the [^{18}F]NaF solution for injection. Tests were conducted every two hours over a total duration of 10 hours. Quality control testing was performed at six time points: end of synthesis (EOS), and two, four, six, eight, and ten hours. At the first point (EOS, 0 hours) and the final point (10 hours), the following parameters were tested: identification, pH, chemical and radiochemical purity, and bacterial endotoxins. Only pH, chemical purity, and radiochemical purity were analyzed at each specified time point.

Radionuclidic purity was evaluated 72 hours later using one sample from each batch. This pe-riod was sufficient for the fluorine-18 radionuclide to decay to a level that permitted the detection and quantification of long-lived radionuclidic impurities.

The microbiological properties were evaluated through sterility testing and bacterial endotoxin analysis. In accordance with the European Pharmacopoeia, sterility testing required a 14-day incubation period and employed methods such as membrane filtration and direct seeding. As mentioned earlier, stability testing was conducted at an external laboratory after the decay of radioactivity. Therefore, testing sterility at multiple time points from each batch was unnecessary, as a sample tested after the decay of radioactivity was sufficient to ensure the sterility of the entire batch.

However, bacterial endotoxin testing for microbiological contamination was conducted using a fast, sensitive method based on the kit, so it was performed at three distinct points within each batch.

The results of the tested parameters indicated no evidence of any physical, chemical, or microbiological changes in the [^{18}F]NaF radiopharmaceutical, as presented in Table 2. All of the results from the evaluated batches were within the acceptance criteria defined in the specification.

The stability testing results showed that the pH values of the samples, measured using pH strips, were consistently between 6.5 and 7.0 and remained stable throughout all evaluated time points across the three batches. Using pH strips instead of a pH meter to determine the radiophar-maceutical pH was permitted.[30] This approach reduced radiation exposure since it required a smaller sample volume for testing, fulfilling the ALARA (As Low As Reasonably Achievable) principle.

In terms of identification, the retention times and half-life measurements were used to analyze the samples. The retention times of the samples detected with a radioactive detector were compared to those of a known standard detected via a conductivity detector. The differences in retention time for all tested points across the three batches met the acceptance criteria. The obtained half-life results further verified the radioisotope's identity. The results measured across all samples met the established acceptance criteria, confirming the reliability and consistency of the radiopharmaceutical's decay characteristics.

The radiochemical purity was confirmed by examining the chromatogram obtained from the radioactive detector. The retention time of the single peak on the radiochromatogram corresponded to the reference solution, indicating 100 % radiochemical purity. The overlay chromatograms in Figures 1b, 1d, and 1f display the radiochemical purity of the [^{18}F]NaF samples. The labeled chromatograms from 6 to 1 corresponded to previously specified sampling time points. Chromato-gram No. 6 represented the initial sample (EOS), while chromatogram No. 1 represented the final sample examined after 10 hours. These results indicated that the [^{18}F]NaF final product was free of radiochemical impurities that could affect its use. Radiochemical purity was critical as it correlated with the efficacy and safety of the radiopharmaceutical. The results confirmed that the [^{18}F]NaF radiopharmaceutical was not subject to radiolysis and did not react with the container-closure system during the proposed shelf life.

Additionally, the evaluation of chemical purity confirmed the purity and stability of the produced [^{18}F]NaF throughout the testing period. A potential source of nonradioactive fluoride contamination was the reusable transfer capillary,[31] composed of TEFZEL (ethylene tetrafluoroethylene), which transported fluoride-18 from the cyclotron to the Clio dispensing module. Chromato-

graphic analysis using HPLC coupled to a conductivity detector was used to compare the obtained chromatograms of NaF reference solution with [^{18}F]NaF samples at each testing point. Across all defined time points, the absence of peaks in [^{18}F]NaF chromatograms confirmed its chemical purity, with chemical impurities below the method's detection limit, as illustrated in Figures 1a, 1c, and 1e. Chromatograms labeled 2, 4, 6, 8, 10, and 12 represented [^{18}F]NaF samples collected from EOS to 10 hours, while overlay chromatograms for the NaF reference solution (1 mg/ml) were labeled 1, 3, 5, 7, 9, and 11.

The microbiological testing results met the acceptance criteria. Specifically, bacterial endotoxin evaluation at EOS, 8, and 10 hours demonstrated compliance, with concentrations remaining below 5 IU/ml. Similarly, sterility testing confirmed the absence of microbial growth. These results validated the effectiveness of the previously validated aseptic procedure used in the production process for [^{18}F]NaF. Furthermore, the results demonstrated that the proposed primary packaging – sterile vials – and storage conditions were suitable for maintaining the sterility of the [^{18}F]NaF radiopharmaceutical.

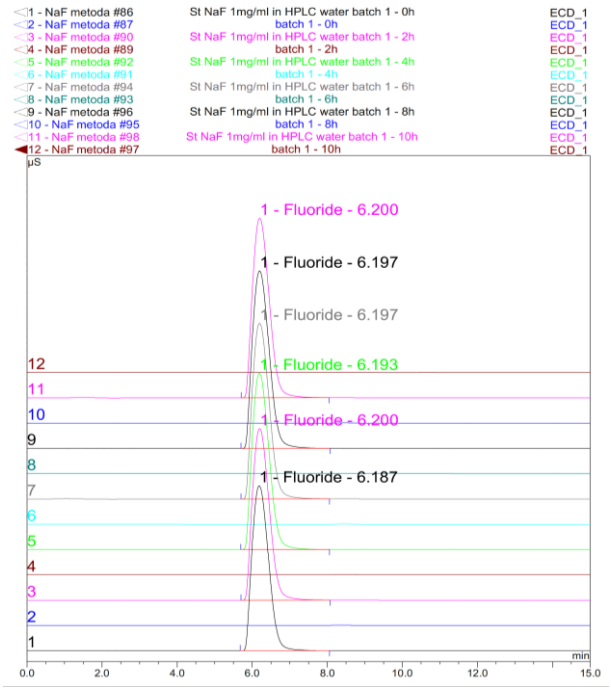
Given its intended use for IV injection, ensuring sterility alongside other essential quality attributes is critical for patient safety. Lastly, radionuclide impurity levels were significantly below the specified limit, reflecting the high radionuclidic purity of the produced radiopharmaceutical.

T a b l e 2

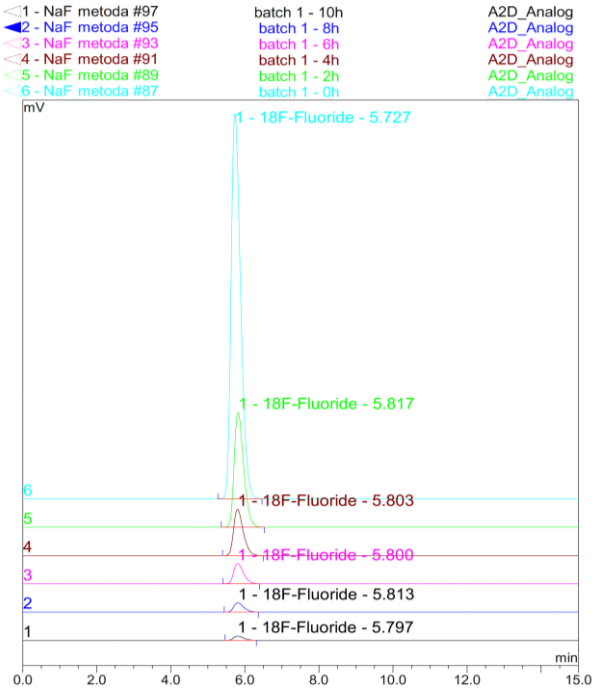
Stability study results of [^{18}F]NaF injection

Batch	Time points	TESTS								
		Appearance	Half-life (h)	Identification Rt*	Approximate pH	Radiochemical purity (%)	Chemical purity (mg/ml)	Bacterial endotoxins (IU/ml)	Sterility	Radionuclidic impurity (%)
Batch 1	EOS	Clear colorless solution	1.82	27.42	6.5–7.0	100	≤ 0.452	< 5.00	Sterile sample	1.2×10^{-05}
	2h		–	22.98	6.5–7.0	100	≤ 0.452	–		
	4h		–	23.40	6.5–7.0	100	≤ 0.452	–		
	6h		–	24.18	6.5–7.0	100	≤ 0.452	–		
	8h		/	26.76	6.5–7.0	100	≤ 0.452	< 5.00		
	10h		1.83	24.36	6.5–7.0	100	≤ 0.452	< 5.00		
Batch 2	EOS	Clear colorless solution	1.84	26.76	6.5–7.0	100	≤ 0.452	< 5.00	Sterile sample	6.6×10^{-05}
	2h		–	24.36	6.5–7.0	100	≤ 0.452	–		
	4h		–	23.82	6.5–7.0	100	≤ 0.452	–		
	6h		–	22.98	6.5–7.0	100	≤ 0.452	–		
	8h		–	23.64	6.5–7.0	100	≤ 0.452	< 5.00		
	10h		1.84	24.24	6.5–7.0	100	≤ 0.452	< 5.00		
Batch 3	EOS	Clear colorless solution	1.81	27.00	6.5–7.0	100	≤ 0.452	< 5.00	Sterile sample	3.9×10^{-05}
	2h		–	23.58	6.5–7.0	100	≤ 0.452	–		
	4h		–	23.22	6.5–7.0	100	≤ 0.452	–		
	6h		–	23.16	6.5–7.0	100	≤ 0.452	–		
	8h		–	23.64	6.5–7.0	100	≤ 0.452	< 5.00		
	10h		1.86	23.40	6.5–7.0	100	≤ 0.452	< 5.00		

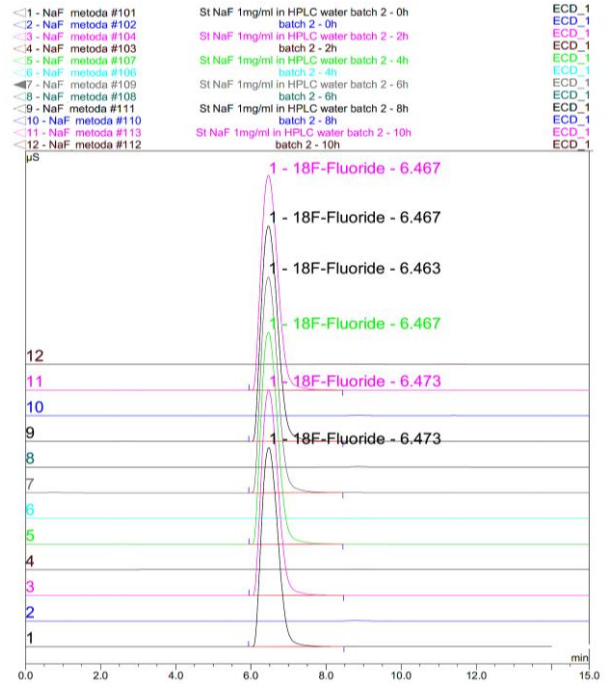
*Difference in retention time in seconds



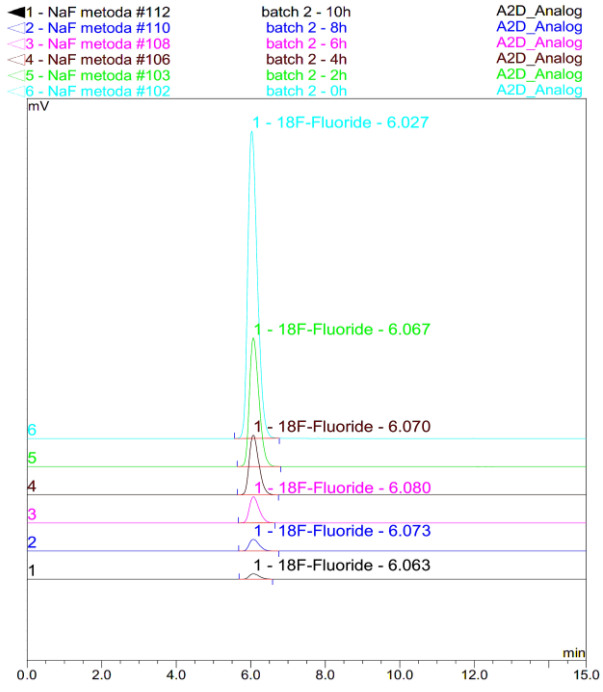
a) Chemical purity of batch 1



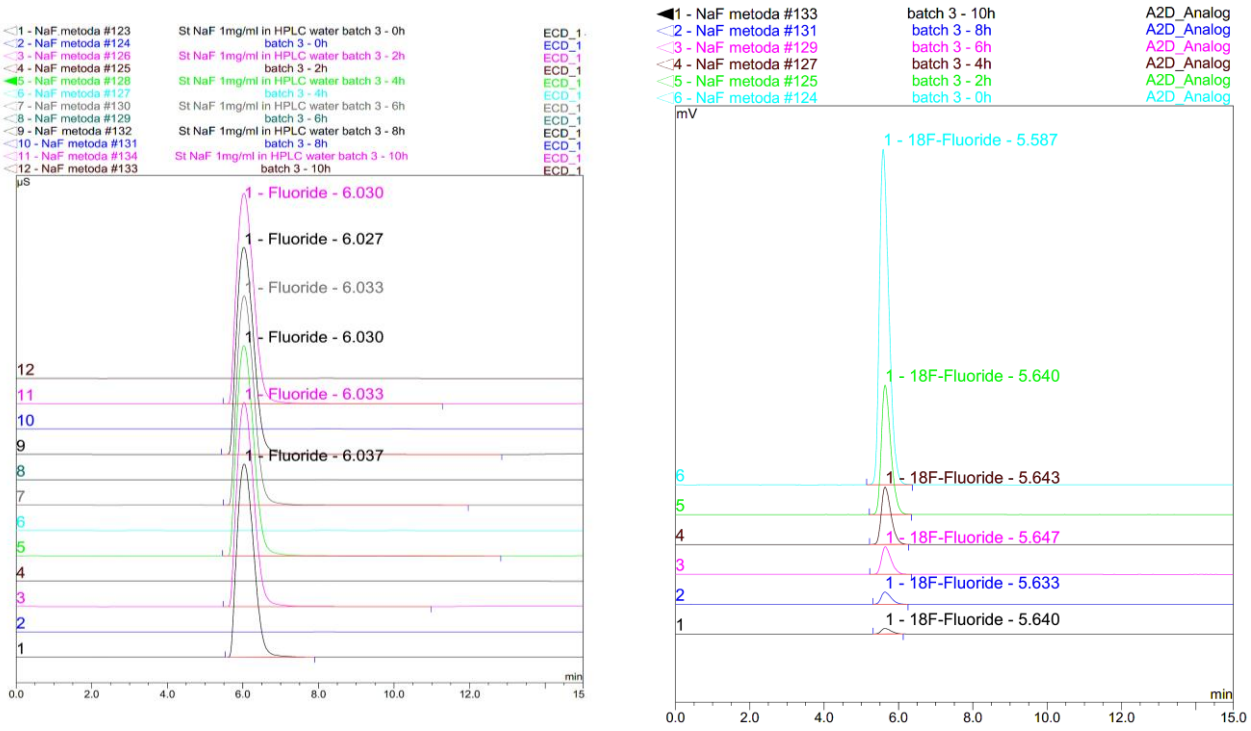
b) Radiochemical purity of batch 1



c) Chemical purity of batch 2



d) Radiochemical purity of batch 2



e) Chemical purity of batch 3

f) Radiochemical purity of batch 3

Fig. 1. Overlay chromatograms acquired using the conductivity detector (ECD_1) and the radiodetector (A2D_Analog)

4. CONCLUSION

The stability evaluation of radiopharmaceutical products is crucial to ensuring their quality, safety, and efficacy throughout their proposed shelf life. The stability profile of [^{18}F]NaF was studied through a carefully designed study based on established guidelines and recommendations, while considering the specific characteristics of radiopharmaceuticals. Our comprehensive stability assessments demonstrated that the quality of sodium [^{18}F]fluoride consistently met the defined acceptance criteria within 10 hours after synthesis.

From the stability data, based on testing of three batches of the sodium [^{18}F]fluoride radiopharmaceutical produced under the same predefined conditions with a maximum radioactive concentration, the shelf life was established at 10 hours when stored at a controlled room temperature of 18 – 22 °C.

These results are critical for ensuring the safe and effective clinical use of [^{18}F]fluoride radiopharmaceutical within the operational constraints of PET radiopharmaceutical logistics.

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