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Optimization of reaction conditions for synthesis of [^{18}F]FMISO using stable [^{19}F]F$^-$

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ABSTRACT: The increasing number of fluorinated pharmaceuticals in pharmaceutical chemistry and fluorine radiopharmaceuticals in radiochemistry highlights the importance of optimizing their synthesis processes. [^{18}F]Fluoromisonidazole ([^{18}F]FMISO) radiopharmaceutical synthesized using aqueous [^{18}F]F$^-$ and 1-(2'-nitro-1'-imidazolyl)-2-O-tetrahydropyranyl-3-O-toluenesulfonylpropanediol precursor (NITTP), is one such example. This radiolabeled compound is used for imaging tumor hypoxia by positron emission tomography (PET). When working with ionizing radiation, ensuring the operator's safety is crucial. As a result, the synthesis process for [^{18}F]FMISO takes place within automated modules in closed lead-shielded hot cells. This protective measure prohibits the collection of control samples during the synthesis process. Our experiments involved utilizing the stable isotope [^{19}F]F$^-$ instead of [^{18}F]F$^-$ to examine various aspects. These included analyzing the intermediate compound produced after the fluorination reaction, assessing unhydrolyzed/hydrolyzed intermediates, and detecting unexpected or unknown chemical impurities in both the unpurified and final purified products. HPLC analysis was employed to analyze the collected samples. The results obtained from these experiments proved invaluable in addressing the challenge of unwanted chemical impurities during the radiosynthesis of [^{18}F]FMISO. They provided valuable insights that aided in the further development of the synthesis process. Overall, this study demonstrates the significance of utilizing non-radioactive chemistry to optimize radiosynthesis, allowing for the safe and efficient production of [^{18}F]FMISO without the need for radiation exposure.

KEYWORDS: [^{18}F]Fluoromisonidazole; [^{19}F]F$^-$; synthesis; fluorinated intermediate; impurity.

1. INTRODUCTION

Fluorine-18 ([^{18}F]F) is a favorable halogens atom in radiopharmacy due to its physical properties including a small van der Waals radius (1.47 Å), high electronegativity, and ability to form a strong bond with carbon (C−F energy bond of 112 kcal/mol), which in comparison to a carbon-hydrogen bond (C−H, 98 kcal/mol) is more thermally stable and oxidation resistant [1-5]. Fluorine as a positron emitter has proven to be highly suitable for the development of numerous radiopharmaceuticals used in positron emission tomography (PET). Among the radiohalogens, fluorine-18 along with other isotopes like bromide ([^{75}Br and ^{76}Br]) and iodide ([^{122}I and ^{124}I]) have emerged as the most convenient, efficient, widely accepted, and extensively utilized elements for radiolabeling chemistry [2, 6-10]. The nucleophilic [^{18}F]F$^-$ ions are commonly used in the radiosynthesis of fluorine-18 radiopharmaceuticals, offering numerous advantages over fluorine gas [^{18}F]F_2. The radiosynthesis process typically involves high levels of radioisotope activity, often exceeding 100 GBq [4, 11]. As a result, the synthesis must be conducted within closed, lead-shielded hot cells using remote-controlled processes facilitated by synthesis modules or radiosynthesizers, with commercial cassette-based automated radiosynthesis platforms. These modules not only allow operators to develop and optimize their synthesis procedures but also provide the option to use commercially available kits or in-house prepared kits [12-15].

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However, the development stages of the final product formulation can be challenging and complex. Therefore, implementing non-radioactive chemistry practice (also known as chemistry cold practice), which involves using stable (cold) isotopes such as [^{19}F]Fluoride instead of radioactive [^{18}F]Fluoride, can be beneficial. This practice, described by Daruich de Souza in 2021, encompasses the concepts of basic chemistry, necessary steps, and practical examples to achieve a high degree of success while ensuring operator safety during radioactive reaction investigations [16]. By utilizing non-radioactive chemistry, researchers can gain insights into the optimization of reaction conditions, explore different synthesis platforms, and effectively assess the feasibility and efficiency of radiosynthesis processes. This approach aids in reducing potential risks and streamlining the development of radiopharmaceutical formulations before integrating them into radioactive synthesis platforms.

Before starting with the development of a synthesis reaction condition, the development of a sequence is very important to establish a well-defined synthesis procedure. Finding the optimal reaction condition and adopting a more efficient and flexible radiosynthesis method is the next application where non-radioactive chemistry practice plays an essential role. Multiple inspections during their designing or optimization are required, to allow correct loading and control of the synthesis process: proper moving of reagents from the cassette to the reaction vial (also integrated into the cassette), proper pressurizing, vacuum, heating or cooling and cartridges eluting or washing.

Manufacturing methodologies for fluorine-18 radiopharmaceuticals require short synthesis times with fast and effective purification steps, followed by fast quality control to confirm the quality of the final product according to the appropriate EU Pharmacopeia monograph. For this reason, we were dedicated to achieving the development of a sequence for the radiosynthesis of [^{18}F]Fluoromisonidazole, as well as adjusting the reaction conditions of [^{18}F]FMISO radiosynthesis, by performing cold test runs with stable isotope [^{19}F]F- and the same reagents that are used in the radiosynthesis. The experience in [^{18}F]F- chemistry and the partial bridging of radiochemistry with [^{19}F]F$^-$ chemistry, further facilitated adapting the reaction condition for the radiosynthesis of [^{18}F]FMISO.

2. RESULTS AND DISCUSSION

In this paper, we describe the non-radioactive chemistry practice in setting up the radiosynthesis method for [^{18}F]FMISO. The primary objective was to develop a well-defined sequence for the automatic synthesis of this radiopharmaceutical. The second one was to perform a synthesis with a stable isotope [^{19}F]F$^-$ and through those results to overcome the challenges in the development of [^{18}F]FMISO radiosynthesis.

To achieve a successful sequence for implementation in automated radiosynthesis, several factors need to be taken into consideration. One crucial aspect is the selection of a command and step design strategy that controls each reaction of the synthesis process. This strategy forms a vital part of sequence development. We modified the standard sequence used for [^{18}F]FDG synthesis, without any hardware changes or disposable cassette changes. Figure 1 shows the main page, slightly modified at the schematic design for connection setup.

This module interface offers remote observing (or control at manual mode) of operations and following the predefined automated command related to the sequence selected before (opening/closing of the reagent vials, tube, gas, and vacuum flow, pressure and temperature setpoint panel as well as the pump control). Furthermore, the synthesis process allows graphical monitoring of various parameters such as temperature, pressure, and activity. This allows monitoring and visualization of synthesis progress in real-time.

Visual inspection of IFP, reagents position, tube connection, and cartridges before is very important before starting the sequence. The most important part is the follow-up and verification of the commands in the defined sequence by the operator. Proper flow of fluid along a tube, from the reagent vial to the reaction vial was our challenge during the test for sequence implementation. During the optimization of the synthesis sequence, it was observed that there were instances of leakage or incomplete transfer in most of the runs. To address this issue, a series of non-radioactive tests were conducted to identify the underlying factors contributing to the problem. It was discovered that the problem was not solely dependent on the sequence command but also on the type of vial cap septa material through which the needle enters, as well as the proper crimping of the vial. By changing the septa material to a more suitable option, the issue of leakage or incomplete transfer was successfully resolved.

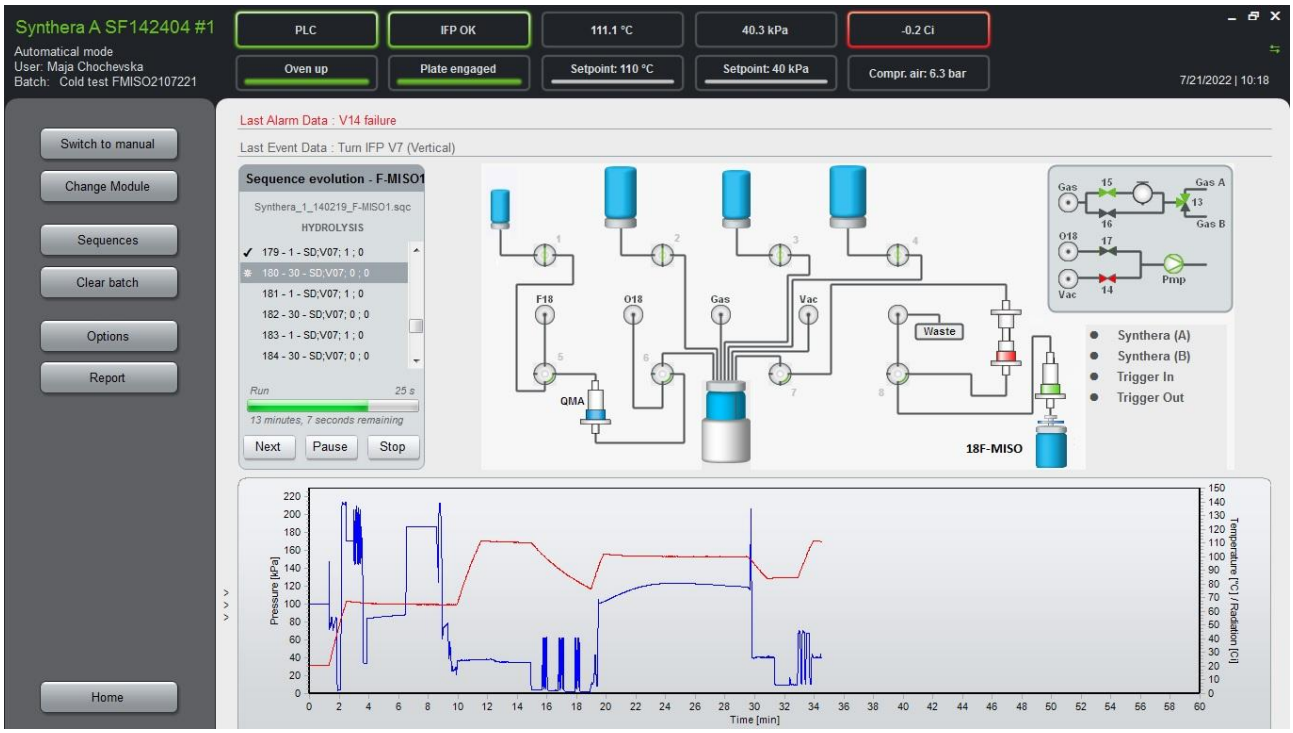

Figure 1. Module main page for control and process following

After optimization of the sequences, a stable isotope [^{19}F]F$^-$ solution was employed as the fluoride source, as an analog to [^{18}F]F$^-$ produced by a cyclotron. The [^{19}F]F$^-$ was adsorbed on anion exchange resin (QMA, see Figure 1) and eluted with elution solvent (the first vial at valve 1, see Figure 1). The eluent based on potassium carbonate, accompanied by a phase transfer catalyst (cryptand) and polar aprotic solvents such as acetonitrile (1:8). The aprotic conditions in S_N2 nucleophilic reactions are very important for the reactivity of fluoride, as a nucleophile. This reaction mechanism is the most prominent reaction in the production of a variety of clinically relevant [^{18}F]F$^-$ radiopharmaceuticals, using common leaving groups such as sulfonic acid esters or halides [2, 17, 18]. Fluoride ions in water as strongly hydrated anion is generally unreactive in nucleophilic substitution reactions. Therefore, evaporation to dryness by heating under reduced pressure is an important step to increase the reactivity of fluoride ions and incorporate with nucleophilic substitution reactions which occur by heating and re-dissolving the dried residue [11, 19, 20]. After adding the precursor NITTP (second vial at valve 2, see Figure 1) to the reaction vial, the [^{19}F]Fluorination was conducted at 130°C for 10 min. Sample 1 was collected in the first minute after transferring the precursor.

The UV chromatogram in Figure 2 from testing this sample with HPLC showed a high presence of the NITTP compound and a few minor peaks compound indicating starting of the fluorination.

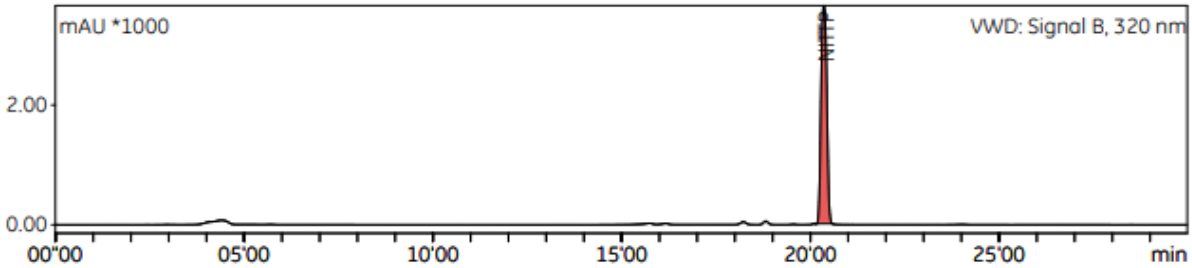

Figure 2. UV chromatogram of sample 1

In this fluorination reaction, electron-rich fluoride ions attack a positively charged electrophile in the precursor NITTP to replace a tosylate-leaving group. In the framework of optimization of fluorination were collected 2 samples, one was Sample 2 – at 5 min after starting of the fluorination (Figure 3 top) and another Sample 3 – at the end of fluorination, after 10 min (Figure 3 bottom).

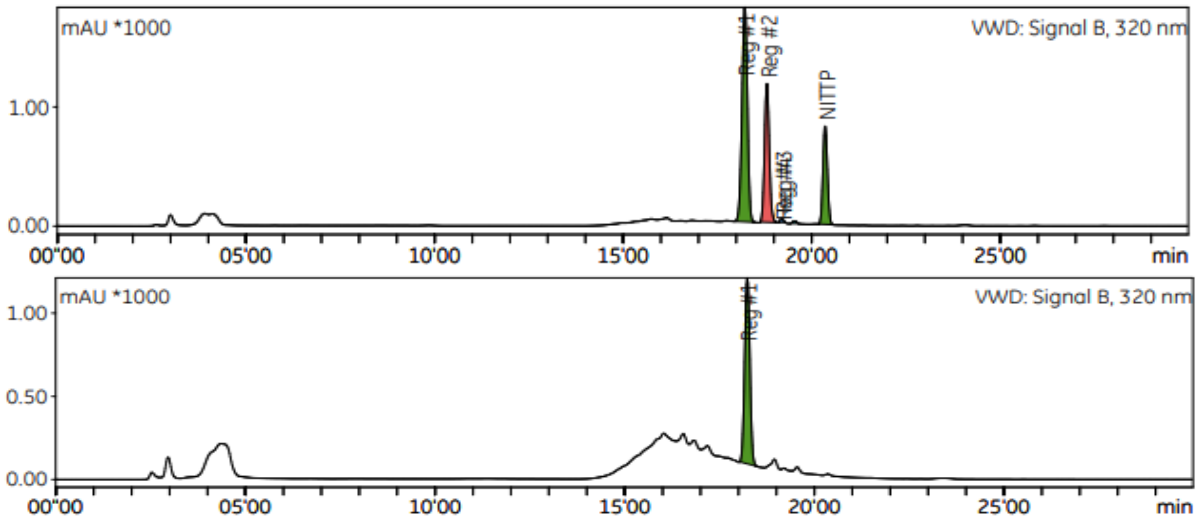

Figure 3. UV chromatogram of sample 2 (top) and sample 3 (bottom)

As shown in Figure 3 (top, sample 2- five min after starting the fluorination), the fluorination was not completed, the NITTP was still present in the reaction mixture. After 10 min fluorination (Figure 3 bottom, sample 3 - at the end of fluorination), are present post-labeled unhydrolyzed fluorinated intermediaries (Reg.1) in the mixture as the major product. These results indicated that the optimal fluorination time at that temperature was 10 min. A shorter fluorination time can lead to a higher amount of unreacted [18F]F-.

Further, the fluorinated intermediate mixture needs to be dried before the next required step, hydrolysis. Drying of the acetonitrile was achieved by heating at 90 °C (180 sec) and repeated azeotropic evaporation with helium gas. Sample collection at the end of drying was done to track if the main byproduct desmethylmisonidazole (DMM) was generated during drying. As illustrated in Figure 4, a high DMM peak was detected. In sample 4, we observed a small peak of [19F]FMISO because, during the collection of the sample, the first portion of hydrolyzing solution (HCl) was added to the reaction vial.

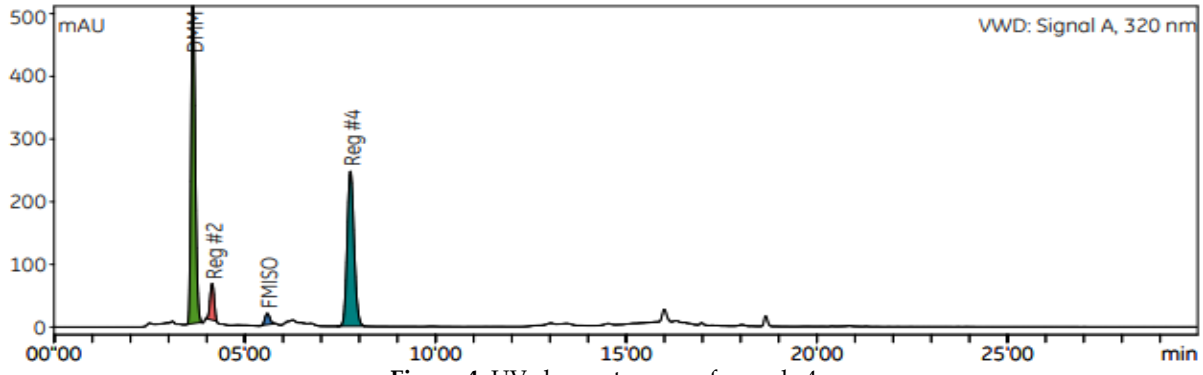

Figure 4. UV chromatogram of sample 4

The DMM and FMISO signal was verified by reference standards. These results open the possibility of conversion of [19F] (or [18F]) - intermediaries to basic molecule desmethylmisonidazole (from fluoromisonidazole precursor), probably due to prolonged heating at higher temperatures. Although the temperature was reduced after fluorination to 85°C to reduce the internal pressure of the reaction vial, the step was spontaneous without an internal cooling system. Therefore, attempts were made to evaluate the generation of DMM with decreasing drying time. To determine the quantity of acetonitrile the final product was analyzed with gas chromatography. In addition, analyzes were made on other final products obtained with different acetonitrile drying times. These data, demonstrate that acetonitrile amounts were lower than 410 ppm (permitted daily exposure to acetonitrile and limited according to the monograph Fluoromisonidazole (18F) injection 01/2014:2459) in the samples performed with acetonitrile evaporation time from 75 sec to 180 sec. This suggests that this step could be performed in less time, for example, an acetonitrile evaporation time of 80 sec would be suitable for this step, taking into consideration achieving a good balance

between acetonitrile content and a low amount of the DMM. It should also be emphasized that during the purification step, the liquid final reaction mixture was washed out in the waste vial as described below, indicating that the acetonitrile was sent to waste.

After this step, 0,1 M hydrochloric acid (third vial at valve 3, see Figure 1) was then transferred into the reaction tube for hydrolysis of fluorinated intermediates and producing the final product [19F]FMISO. Therefore, sample 5 was collected after the hydrolysis reaction, at the end of hydrolysis. UV chromatogram of this mixture is shown in Figure 5.

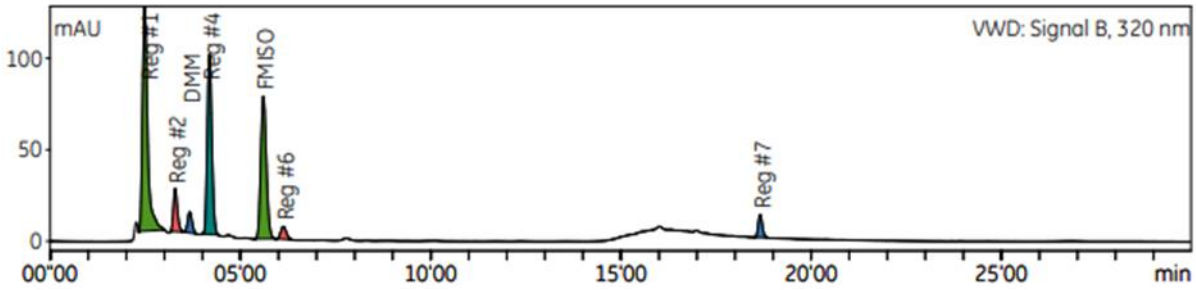

Figure 5. UV chromatogram of sample 5

With chromatogram results we showed the detection region of chemical impurity of the hydrolyzed and unpurified mixture which may be potentially present as 1-chloro-3-(2-nitro-imidazol-1-yl)-propan-2-ol (Chloromisonidazole), 5-hydroxypentanal; 4-methylbenzenesulfonate, 2-nitro-1-phenylpropane-1,3-diol or 2-(5-nitroimidazol-1-yl)ethanol. After this reaction, the main challenge is the effective purification of the final product. The separation of the final product [18F]FMISO from the unwanted side radiochemical and chemical impurities is performed by solid phase extraction (SPE). The presence of radiochemical or chemical impurities in a radiopharmaceutical contributes to an unnecessary radiation burden for the patients or to an undesirable high radioactivity background. Therefore, a purification step is unavoidable. Purification by a solid-phase extraction resulted in a radiochemical pure product that had the same HPLC retention time as a cold fluorinated compound. The purification of [18F]FMISO is characterized by a two-step procedure in which [18F]FMISO has to be separated from the final [18F]FMISO mixture. In the first step, the unpurified mixture (final mixture) was sent to waste through the purification cartridges, where [18F]FMISO was trapped on the RP cartridge but the 18F-intermediaries and chemical by-products were eluted in the waste (sample 6). In the second step, the final elution contents from the last vial (valve 4, see Figure 1) were transferred into the reaction vial and then through the cartridges in order to elute the trapped product. The purpose of sending the reaction mixture to the waste was to remove as much as possible of the more hydrophilic by-product DMM, which was detected in the waste, the chromatogram is shown in Figure 6.

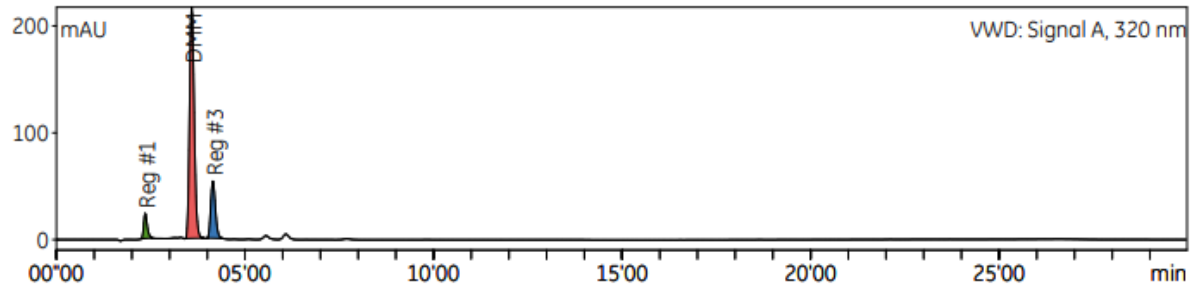

Figure 6. UV chromatogram of sample 6

Substitution reactions with [18F]fluoride are in principle the same as those performed with non-radioactive [19F]Fluoride. When [19F]FMISO synthesis was carried out with the same concentration (4 ppm) of fluoride starting solution in [18F]FMISO synthesis, the fluorination was unsuccessful. In the UV chromatogram, (Figure 7 top) of the final product sample was not observed [19F]FMISO peak. These results indicated the well-known concept for differences between [19F]fluoride and [18F]fluoride chemistry. In [18F]Fluoride chemistry, [18F]F- is

produced in very high levels of radioactivity but in nanomole level and its concentration in reaction mixtures is significantly lower than the precursor concentration. For each precursor molecule, there should be at least one fluorine-19 atom that is part of the reaction mechanism for efficient labeling methods. To find a satisfactory way, the next experiments were performed with a very higher concentration of [19F]fluoride solution (2 mg/ml) at the same reaction condition and reagents. In this condition, the fluorination reaction was successful, from the UV chromatogram shown in Figure 7. bottom.

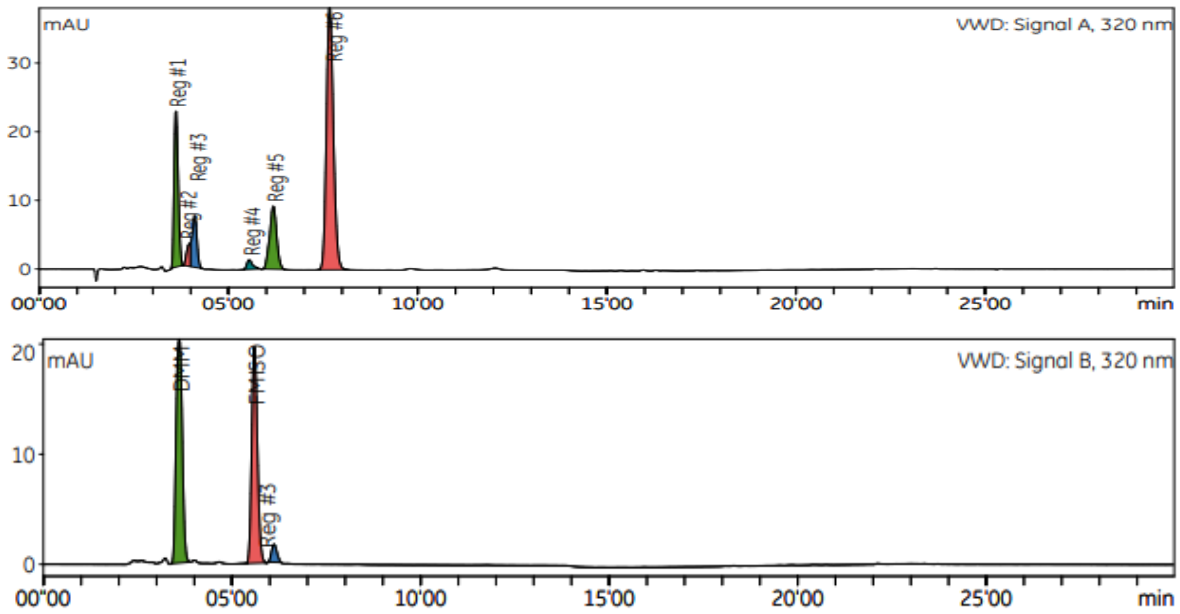

Figure 7. UV chromatograms of the purified [19F]FMISO. (top): synthesis was carried out with the same concentration of [19F]Fluoride as in [18F]Fluoride starting solution, and (bottom): synthesis was carried out with a higher concentration of [19F]Fluoride

The low peak of [19F]FMISO compared with DMM was most likely because of not complete elution of the final product from the RP cartridge. The area of DMM impurities peak was not more than the area of corresponding peaks in the chromatogram obtained with reference solutions (< 0.1 mg/V). The area of each other impurity was not more than the area of the principal peak in the chromatogram obtained with the FMISO reference solution.

Further optimization and comparison of results were achieved by performing [18F]FMISO synthesis, where analytical tests can only be carried out in the final product solution. According to the obtained optimization data, the results are consistent with those described above. The [18F]FMISO product was successfully produced with a synthesis time of 35-40 min and good radiochemical yield 53.18 ± 3.44 % d.c. compared with recent published articles. The [18F]FMISO prepared was confirmed by HPLC peak comparison with the commercially available FMISO reference standard. The radio peak of [18F]FMISO was consistent with the standard FMISO peak and radiochemical purity was more than 99%. The areas of FMISO and DMM impurities peaks in final product were not more than the area of corresponding peaks in the chromatogram obtained with reference solutions in Fig.8 (< 0.1 mg/V).

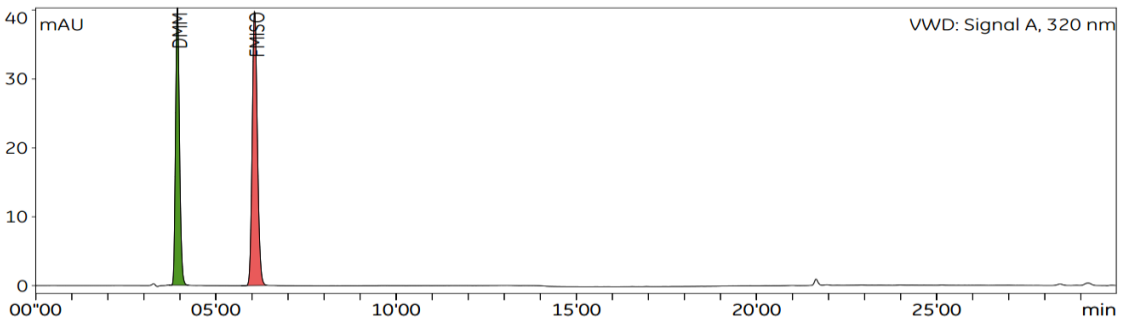

Figure 8. HPLC chromatogram of DMM and FMISO reference solutions (10 μg/mL each)

3. CONCLUSION

Understanding the progress of the reaction and monitoring the formation of by-products and impurities over time is crucial for efficient synthesis. In this study, we focused on the development of the radiosynthesis method using [^{19}F]F$^-$ chemistry practices. This research allowed us to track and collect a sample from each step of the synthesis, unlike radiosynthesis, where such monitoring is impossible. By employing this experimental chemistry approach, we were able to facilitate the development of radiosynthesis. The results obtained from different steps of non-radioactive synthesis can help overcome the challenges, which can impede the reactions or lead to unwanted chemical impurities during radiosynthesis.

This study highlights the importance of experimental chemistry approaches, such as using stable isotopes, in the development of radiosynthesis methods. It offers valuable insights into reaction monitoring and impurity analysis, ultimately leading to advancements in the synthesis of radiopharmaceuticals.

The use of cartridge purification in this process simplifies handling and shortens the total synthesis time, obtaining a product with high purity and high radiochemical yield.

4. MATERIALS AND METHODS

4.1. Reagents and other material

Sodium fluoride was purchased from Sigma Aldrich, Kryptofix®222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo [8.8.8]-hexacosan, and potassium carbonate ≥99.0% ACS were obtained from Sigma-Aldrich (Missouri, United States). Hydrochloric acid solution was prepared by dilution of 36% HCl Suprapur (Merck, Darmstadt Germany). The precursor 1-(2′-nitro-1′-imidazolyl)-2-O-tetra-hydro-pyranyl-3-O-tosyl-propanediol (NITTP), nucleophilic integrated fluidic processor (IFP cassettes), reference standard FMISO and reference standard for byproduct desmethylmisonidazole (DMM) were purchased from ABX (Radeberg Germany). Acetonitrile, 99.9+%, HPLC for gradient analysis, from Thermo Scientific (Geel, Belgium) and ultrapure water (18.2 MΩ·cm) for HPLC was prepared by Direct Q3 Millipore (Merck, Darmstadt, Germany). QMA Carbonate Plus Light Cartridge; Sep-Pak Alumina B; Oasis HLB Plus Light Cartridge, were purchased from Waters (Massachusetts, USA); SCX Cartridge from S Pure (Nordcom One, Singapore).

4.2. Synthesis process

The synthesis sequence was initially developed based on our experience with radiosynthesis and according to the literature procedure for [^{18}F]FMISO production by Blom [21]. IBA Synthera V2 (Louvain la Neuve, Belgium) was used as a synthesis module using one-pot (single reaction vessel) synthesis and cascade reaction (multi-step strategies) synthesis sequences. To perform an [^{19}F]FMISO synthesis, we used a sodium fluoride starting solution ([^{19}F]Fluoride ions). Sodium fluoride solution was prepared in water with the same concentration as the initial fluoride solution in the radiosynthesis (taking into consideration 500 mCi incoming activity) as well as a higher concentration (500 x concentrated). For [^{18}F]FMISO radiosynthesis, [^{18}F]fluoride was obtained as a solution in [^{18}O]H_2O from a cyclotron. The first step of the synthesis was trapping of fluoride ions on an anion-exchange cartridge. Trapped anions were eluted into the reaction vial using a 1 ml elution solution of acetonitrile/water (8:1) containing 4.2 mg K_2CO_3 and 22 mg Kryptofix®222. Azeotropic distillation under inert gas He at 110 °C was performed in the next 5 min. After drying, the fluorination is the main reaction, during 10 min at 120 °C via the S_N2 substitution mechanism. NITTP precursors dissolved in 2 mL anhydrous acetonitrile and dried fluoride/K2.2.2/K2CO3 mixture were present at the start of fluorination. Afterward, the reaction mixture was cooled and evaporated before hydrolysis. During optimization [^{18}F]FMISO synthesis was carried out by applying acetonitrile drying time from 30 sec to 180 sec to survey the level of acetonitrile and DMM. The hydrolysis was carried out with 0,1 M HCl solution, and the hydrolyzed mixture was passed through the strong cation exchange (SCX) SPE cartridge and reverse phase (RP) purification cartridges to waste. The final product should be retained on reverse phase cartridges, cationic impurity on the SCX cartridge or partially washed out in the waste, and the polar impurities need to be washed out in the waste vial. The last step was the elution of the final product, 10 ml of 5 % ethanol in water was sent through the SCX, RP, and Alumina cartridge into the product vial. In Fig. 9 is represented schematic diagram of synthesis process, where the required time is shown for all steps.

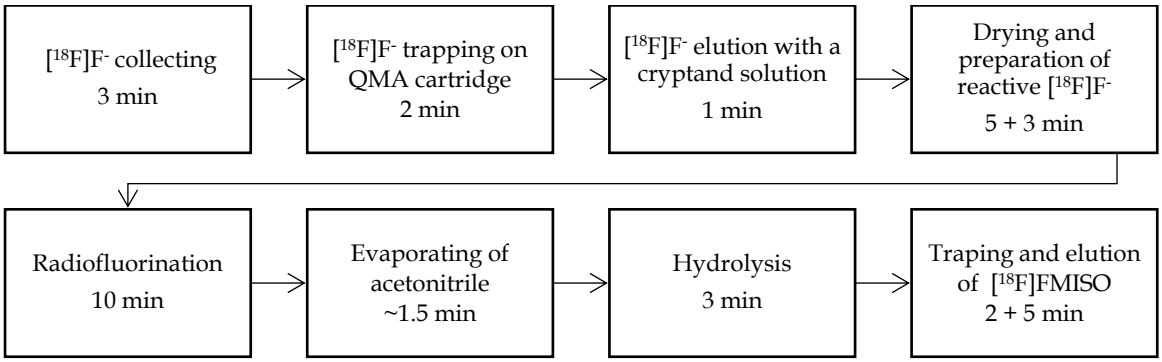

Figure 9. Schematic representation of synthesis process

Several runs test were performed to optimize the automation process and a total of five [19F]FMISO runs were carried out to help us in adopting radiosynthesis conditions for the production of [18F]FMISO. For a better understanding of the synthesis process, and monitoring the chemical intermediates, the synthesis of [19F]MISO, without radioactivity was performed. The samples from the reaction vial during the automated runs were taken and analysed. Figure 10 shows all samples included in the study, collected at the next point: 1 - before fluorination, after transferring the precursor (at first min), 2 - five min after starting the fluorination, 3 - at the end of fluorination (after 10 min, post labeled unhydrolyzed intermediate reaction mixture), 4 – after drying of the acetonitrile (before hydrolysis), 5 - at the end of hydrolysis (hydrolyzed and unpurified mixture), 6 - final purified product solution and 7 -waste wash out elution sample.

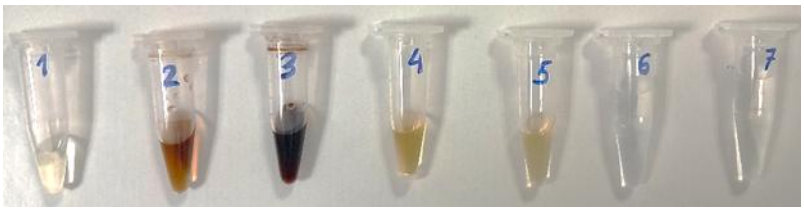

Figure 10. Samples included in the study

4.3. Quality control tests

Quality control is an essential part of radiopharmaceutical production to ensure the safety of the final product and should always be performed prior to patient administration. The tests are focused on identification tests, radiochemical concentration, microbiological tests, pyrogen, chemical purity tests, and radioactive tests for radiochemical and radionuclide purity. This study examined chemical impurities in the samples, using a HPLC chromatography system (Agilent, Santa Clara, USA). Quaternary pump, a 20 µL injection loop, variable wavelength detector, and radio-detector (Gabi Raytest Isotopen Messgerate GmbH, Germany) were used with end-capped polar embedded XTerra Shield RP18 Column, 125Å, 5 µm, 4.6 mm x 250 mm (Waters, United States) and a mixture of water and acetonitrile as mobile phase.

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Author contributions: Concept – M.C., E.J.; Design – M.C.; Supervision – M.C., A.U.; Resources – A.U.; Materials – A.U.; Data Collection and/or Processing – M.C.; Analysis and/or Interpretation – M.C.; Literature Search – M.C., F.J.; Writing – M.C.; Critical Reviews – M.A.L, K.K, M.V, T.T, E.J., B.A., A.U.
Conflict of interest statement: The authors declared no conflict of interest.

REFERENCES

[1] Müller K, Faeh C, Diederich F. Fluorine in pharmaceuticals: looking beyond intuition. Science. 2007; 317(5846): 1881-6. https://doi.org/10.1126/science.1131943
[2] Cai L, Lu S, Pike VW, Chemistry with [18F]fluoride ion. Eur. J. Org. Chem. 2008; 2008(17):2853–2873. https://doi.org/10.1002/ejoc.200800114

[3] Jacobson O, Chen X. PET designated fluoride-18 production and chemistry. Curr. Top. Med. Chem. 2010; 10: 1048–1059. https://doi.org/10.2174/156802610791384298
[4] Halder R, Ritter T. ^{18}F-Fluorination: Challenge and Opportunity for Organic Chemists, The Journal of Organic Chemistry. 2021; 86 (20): 13873-13884, https://doi.org/10.1021/acs.joc.1c01474
[5] Wang Y, Lin Q, Shi H, Cheng D. Fluorine-18: Radiochemistry and Target-Specific PET Molecular Probes Design. Front Chem. 2022; 10: 884517. https://doi.org/10.3389/fchem.2022.884517
[6] Mason NS, Mathis AC, Radiohalogens for PET Imaging. Springer-Verlag London Ltd 2003; 217–236.
[7] Schirrmacher R., Wängler C., Schirrmacher E. Recent developments and trends in 18F-radiochemistry: syntheses and applications. Mini Rev Org Chem. 2007; 4: 317–329. https://doi.org/10.2174/157019307782411699
[8] Ross TL, Wester HJ. ^{18}F: Labeling chemistry and labeled compounds. Handbook of Nuclear Chemsitry. Springer; New York: 2011; 2021
[9] Littich R, Scott P.J.H. Novel strategies for fluorine-18 radiochemistry. Angew Chem Int Ed. 2012; 51: 1106–1109. https://doi.org/10.1002/anie.201106785
[10] Kumar P, Bacchu V, Irving WL, Semin, The Chemistry and Radiochemistry of Hypoxia-Specific, Radiohalogenated Nitroaromatic Imaging Probes., Nucl Med 2015; 45: 122-135. https://doi.org/10.1053/j.semnuclmed.2014.10.005
[11] Cole EL, Stewart MN, Littich R, Hoareau R, Scott PJ. Radiosyntheses using fluorine-18: the art and science of late stage fluorination. Curr Top Med Chem. 2014; 14(7): 875-900. https://doi.org/10.2174/1568026614666140202205035
[12] Keng PY, Esterby M, van Dam RM. Emerging Technologies for Decentralized Production of PET Tracers. In: Hsieh C-H, editor. Positron Emission Tomography - Current Clinical and Research Aspects. London, UK: InTechOpen; 2012; 10:153–182. https://doi.org/10.5772/31390
[13] Claggett SB., Quinn KM., Lazari M, Moore MD., van Dam RM. Simplified programming and control of automated radiosynthesizers through unit operations. European Journal of Nuclear Medicine and Molecular Imaging (EJNMMI) Research. 2013; 3: 53. https://doi.org/10.1186/2191-219X-3-53
[14] Schopf E, Waldmann CM, Collins J, Drake C, Slavik R, van Dam R.M. Automation of a Positron-emission Tomography (PET) Radiotracer Synthesis Protocol for Clinical Production. J Vis Exp. 2018; 140:58428. https://doi.org/10.3791/58428
[15] Barnes-Seeman D, Beck J. Fluorinated compounds in medicinal chemistry: recent applications, synthetic advances and matched-pair analyses. Curr. Top. Med. Chem. 2014; 14:855–864. https://doi.org/10.2174/1568026614666140202204242
[16] Daruich de Souza C, Joo Kim J, Tae HJ., Start Here When Performing Radiochemical Reactions. IntechOpen. 2022; Chapter 2. https://doi.org/10.5772/intechopen.98766
[17] Kim DW, Jeong HJ, Lim ST, Sohn MH. Recent Trends in the Nucleophilic [(18)F]-radiolabeling Method with No-carrier-added [(18)F]fluoride. Nucl Med Mol Imaging. 2010; 44(1):25-32. https://doi.org/10.1007/s13139-009-0008-1
[18] Rong J, Ahmed H, Steven L. Precision Radiochemistry for Fluorine-18 Labeling of PET Tracers. WILEY-VCH GmbH., Organofluorine Chemistry: Synthesis, Modeling, and Applications. 2021; Chapter 12., 397-425. https://doi.org/10.1002/9783527825158.ch12
[19] Lemaire CF, Aerts JJ, Voccia S, Libert LC, Mercier F, Goblet D, Plenevaux AR, Luxen AJ. Fast Production of Highly Reactive No-Carrier-Added [18F]Fluoride for the Labeling of Radiopharmaceuticals. Angew. Chem. Int. Ed. 2010; 49: 3161–3164. https://doi.org/10.1002/anie.200906341
[20] Sergeev M, Lazari M, Morgia F, Collins J, Javed MR, Sergeeva O, Jones J, Phelps ME, Lee JT, Keng PY, Dam RM. Performing radiosynthesis in microvolumes to maximize molar activity of tracers for positron emission tomography. Commun. Chem. 2018; 1(1): 10. https://doi.org/10.1038/s42004-018-0009-z
[21] Blom E, Koziorowski J. Automated synthesis of [^{18}F]FMISO on IBA Synthera®. Journal of Radioanalytical and Nuclear Chemistry. 2014; 299: 265-270. https://doi.org/10.1007/s10967-013-2753-y