RESEARCH ON THE INFLUENCE OF DIFFERENT TYPES OF ANION-EXCHANGE CARTRIDGES ON THE QUALITY OF [^{18}F]NAF RADIOPHARMACEUTICAL AS PART OF PRODUCTION PROCESS DEVELOPMENT

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Abstract: [^{18}F]Sodium Fluoride radiopharmaceutical is a sterile solution for intravenous administration, intended for skeletal visualization by positron emission tomography (PET). [^{18}F]Sodium Fluoride for bone imaging was introduced in early 1960's, but with the increased availability of PET scanners in the last two decades, this radiopharmaceutical has growing use in clinical practice for the detection of bone metastases. The production process of [^{18}F]NaF includes production of the radioisotope [^{18}F]F$^-$ and purification and formulation of the [^{18}F]NaF radiopharmaceutical. The radioisotope [^{18}F]F$^-$ is produced by a cyclotron via the ^{18}O(p,n)^{18}F nuclear reaction, followed by recovery of [^{18}F]F$^-$ from [^{18}O] proton-irradiated water by adsorption and desorption from anion-exchange resins. The fluoride anions are trapped on the anion-exchange SPE (solid-phase extraction) cartridge, and all other cationic and water-soluble radionuclide impurities present in irradiated enriched water are collected in the waste vial. Next step is desorption of the fluoride anions from the cartridge by elution with saline solution (0.9% NaCl). This study aimed to define the most appropriate type of anion-exchange SPE cartridge which could be used for routine production [^{18}F]Sodium fluoride radiopharmaceutical which meets the quality requirements defined in European pharmacopeia monograph. For that purpose, as part of development of in-house production method, manual productions with four different types of anion-exchange cartridges were performed. The influence of sorbent substrate and counter-ion of the cartridge on the final yield and the quality of the produced radiopharmaceutical was investigated. The study also aimed to define the minimum volume of physiological solution required for the pH parameter to be within limits.
The results have shown that the quality parameters: appearance, chemical purity, radiochemical purity and radionuclide purity were in defined acceptance criteria and did not differ when using different anion-exchange cartridges. The pH analyses have demonstrated that the type of cartridge and counter-ion influence the final pH of [^{18}F]NaF solution. This study confirmed that the three types of anion-exchange resins (QMA-Cl$^-$, QMA-CO_3^{2-} and PS-OH$^-$) could be used for production. In the experiments where QMA-Cl$^-$ was used, the required pH level was obtained even without dilution. The other cartridges could be used in the [^{18}F]NaF production process, but further dilution is necessary in order to obtain the pH value in acceptance criteria. On the basis of this study, the QMA-Cl$^-$ is chosen as a cartridge to be used in the further development of the in-house method for [^{18}F]NaF radiopharmaceutical production.
Keywords: [^{18}F]Sodium fluoride, anion-exchange cartridges, pH, quality

1. INTRODUCTION

Positron emission tomography (PET) is one of the most sensitive and specific non-invasive techniques for imaging molecular pathways in-vivo (Jacobson et al, 2012, Miele et al, 2008 and Visioni, and Kim, 2012). The most common PET radiopharmaceutical used for skeletal imaging and bone metastases detection is [^{18}F]NaF. [^{18}F]NaF radiopharmaceutical has high bone uptake and rapid blood clearance, which results in high sensitivity and specificity in detecting and diagnosing bone diseases (Bastawrous et al, 2014, Langsteger et al, 2016, Ahuja et al, 2020 and Jadvar et al, 2015, Cook and Goh, 2020). [^{18}F]Sodium fluoride injection is a sterile solution for intravenous administration which contains positron-emitting radioisotope fluorine-18 (half-life 109.8 min.) in form of sodium fluoride (Ph.Eur 10, 2020). [^{18}F]NaF, as all other ^{18}F radiopharmaceuticals, is produced in PET centres with a cyclotron installed (IAEA, 2012, Avila-Rodriguez et al, 2022, Wang et al, 2022). The production of [^{18}F]Sodium fluoride starts with the production of [^{18}F]F$^-$ radioisotope and afterwards, is the purification of radioisotope with SPE

cartridge to final formulation with saline solution. The radioisotope fluorine-18 in form of anion [^{18}F]F$^-$ is produced with proton irradiation of small volume oxygen-18 enriched water targets. At the end of the bombardment, the irradiated enriched water besides [^{18}F]fluoride ion contains other radioactive as well nonradioactive ions (Kilbourn, Rodnick, and Clark, 2020). According to the European pharmacopoeia monograph, the produced fluoride-18 is purified from target water generally using anion-exchange cartridges or by electrochemical deposition and redissolution (Ph.Eur 10, 2020). The production of radiopharmaceuticals requires special attention due to ionizing radiation, as well as the aseptic conditions that must be satisfied during the process of sterile medical products (EudraLex Annex 3, 2008 and Gillings et al, 2021). Production using single-use cartridges is more convenient to ensure aseptic processing and reduce radiation dose. The [^{18}F]NaF production, either manual or automated, has been reported in several papers using various synthesizers, disposables, and different ion-exchange cartridges (Hockley and Scott, 2010, Mihon et al, 2015, Collet et al, 2015, Choi et al, 2016). Kao, and co-workers developed a manual method for the production of [^{18}F]NaF, and also investigated the influence of various types of anion-exchange cartridges on the pH value (Kao et al, 2010). However, the minimum volume of saline needed for dilution of the final product, to keep the pH value within the limit, was not investigated. In this study, the influence of four anion-exchange cartridges on the yield and quality of the [^{18}F]NaF radiopharmaceutical was investigated, performing manual productions. To completely remove the residues of the target water, before the elution step, a washing step of the cartridge with water for injection was added. The aim of the study was at first to find the most suitable cartridge for further development of an in-house method for the semi-automatic production of [^{18}F]NaF and secondly to define additional dilutions with saline, if that it is necessary for the pH parameter to be within the limits of acceptance.

2. MATERIALS AND METHODS

Materials

The materials used for production of [^{18}F]NaF radiopharmaceutical were: enriched water 18 - [^{18}O]H_20 (NUKEM isotopes, Germany), 0.9% Sodium Chloride injection solution (Alkaloid Ad, Skopje), water for injection (Alkaloid Ad, Skopje), Sep-Pak Accell Plus QMA Plus Light Cartridge (Waters, United States), Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge (Waters, United States), SPE cartridge, CHROMAFIX PS-OH$^-$ (Macherey-Nagel, Germany), $NaHCO_3$ (aqueous) 8,4% w/v / Sodium Hydrogen Carbonate for analysis (5ml in Syringe) (ABX, Germany), kit Clio for dispensing (BTC Medical Europe, Italy), sterile Y connector (B Barun, Germany), sterile vials (Huayi isotopes, China), 10 ml Syringes (BTC Medical Europe, Italy).

The materials used for quality control of [^{18}F]NaF were: Sodium Fluoride standard (Sigma Aldrich, United States), pH strips (Macherey Nagel, Germany), Sodium hydroxide solution 50-52 % for IC (Sigma Aldrich, United States), Water-type 1 (Direct Q3, Millipore, United States).

Methods

[^{18}F]NaF production

The [^{18}F]Sodium fluoride productions were conducted with the following anion-exchange solid-phase extraction cartridges: two Sep-Pak Accell Plus QMA (quaternary methyl ammonium) cartridges filled with silica-based, hydrophilic, strong anion-exchanger, with carbonate and chloride counter-ion. The other cartridge was Chromafix SPE cartridge filled with a strong anion exchanger based on polystyrene-divinylbenzene copolymer (PS/DVB) in OH^- and HCO_3^- form. Prior to production, the QMA-Cl^- and QMA-CO_3^- were activated with 10 mL of water for injection. The PS-OH^- was activated with 10 mL of water for injection. While to obtain the PS-HCO_3^-, the PS-OH^- was preconditioned with 5 mL $NaHCO_3$ (aqueous) 8,4% w/v in syringe followed by rinsing with 10 mL of water for injection. Then the cartridges were dried with 30 mL of air.

The radioisotope [^{18}F]F$^-$ was produced by a PET GeTrace 800 cyclotron (GE Healthcare, United States) via the $^{18}O(p,n)^{18}F$ nuclear reaction in the niobium target. The target was filled with 3 mL of enriched water [^{18}O]H_2O and irradiated with protons, the duration of irradiation and proton beam current depend on required radioactivity. The produced radioisotope was delivered through the delivery line into a sterile vial placed in a hot cell. The produced radioisotope was measured in a dose calibrator. The irradiated enriched water containing [^{18}F]F$^-$ with a syringe was transferred into an anion-exchange SPE cartridge. The fluoride ions were trapped on the anion-exchange cartridge by exchanging the fluoride with the counter-ion (Cl^-,CO_3^{2-}, OH^-, HCO_3^-) and the recovery water was collected into a vial. Subsequently, the cartridge was washed with 3 mL of water for injection. The cartridge with trapped radioisotope was connected with a sterile pyrogen-free vial containing 3 mL of 0.9% sodium chloride. The radioisotope [^{18}F]F$^-$ was eluted with 5 mL of 0.9% sodium chloride. The radioactivity in the final vial containing 8 mL [^{18}F]NaF solution, was measured in a dose calibrator (Capintec, CRC-55TPET). After production, the [^{18}F]NaF solution is diluted to the predefined target concentration (MBq/mL). The volume of saline solution required for dilution increases proportionally with increasing initial radioactivity and yield. Considering the above-mentioned the

pH value was measured before dilution and after dilutions with different volumes of saline. The first dilution was performed with a volume of 2 mL saline, followed by three subsequent dilutions with 5 mL saline.

[^{18}F]NaF quality control

The quality control of [^{18}F]NaF was carried out according to the European Pharmacopoeia monograph (Ph. Eur 01/2008:2010). The parameters sterility and bacterial endotoxins defined in the Sodium Fluoride ^{18}F injection monograph were not executed due to the manual preparations of [^{18}F]Sodium fluoride without final sterilization.

The quality control test were performed on non-diluted [^{18}F]NaF solution. The parameter approximate pH value was tested after every dilution.

Appearance: The [^{18}F]NaF radiopharmaceutical was visually inspected behind an L- block of lead. The final product must be a clear and colourless solution.

Half-life determination: The [^{18}F]F^{-} half-life was calculated by the measuring the radioactivity three times within 30 minutes using a dose calibrator (Atomlab 500). Half-life acceptance criteria is 1.75-1.92 hours.

Identification: The identity was confirmed by measuring the half-life and comparing the chromatograms obtained in the test for radiochemical purity. The retention time of the main peak in the radiochromatogram obtained with the [^{18}F]NaF solution must be similar to the retention time of the principal peak obtained with the reference solution (differs not more than 40 seconds).

pH: The approximate pH value was determined with a pH strip 4.5-10.0 (resolution 0.5 pH units). The approximate pH must be in the range between 5.5-8.0.

Chemical purity: The chemical purity was assayed by HPLC Dionex ICS 1600 Thermo. Suppressor: Anion (Dionex ADRS 600 max current 500 mA) Column Carbopak PA10 Dionex (4 x 250 mm), CarboPac PA10 Guard Column (4 x 50 mm); detectors: conductivity and gamma (serial connected); mobile phase 0.1M NaOH; flow rate 1 ml/min. The chemical purity was evaluated by comparing the area of the peak in the chromatograms obtained from the reference solution and the sample with the conductivity detector. The area of the peak of the test solution should be not more than the area of corresponding peak obtained with the reference solution (not more than 0.452 mg/mL).

Radiochemical purity: The radiochemical purity was assayed on the same HPLC system by examining the radiochromatogram obtained with [^{18}F]NaF sample. [^{18}F]Fluoride radioactivity should be a minimum 98.5 % of the total radioactivity.

Radionuclidic purity: Radionuclidic purity test was analyzed by gamma-ray spectrometry (gamma spectrometer Radek model MKGB-01) on the decayed sample. The radionuclidic purity should be a minimum 99.9 % of the total radioactivity.

3. RESULTS

The [^{18}F]NaF radiopharmaceutical was manually produced with a yield corrected for decay between 89.41% - 75,72% depending on the used anion-exchange SPE cartridge. The results of the yield, decay corrected (d.c.) and not-decay corrected (n.d.c.) are given in Table No. 1.

Table No. 1 Yield using different anion-exchange cartridges

Sample	Yield (%)	
	d.c.	**n.d.c.**
QMA _Cl.1	85.99	83.84
QMA _Carb.1	88.19	85.99
PS _OH.1	77.40	75.94
PS _Carb.1	75.72	74.30
QMA_Cl.2	85.28	82.62
QMA_Carb.2	87.25	85.07
PS_OH.2	82.51	80.45
PS_Carb.2	81.91	79.86
QMA_Cl.3	87.56	83.77
QMA_Carb.3	89.41	85.00
PS_OH.3	79.40	76.44
PS_Carb.3	77.90	75.00

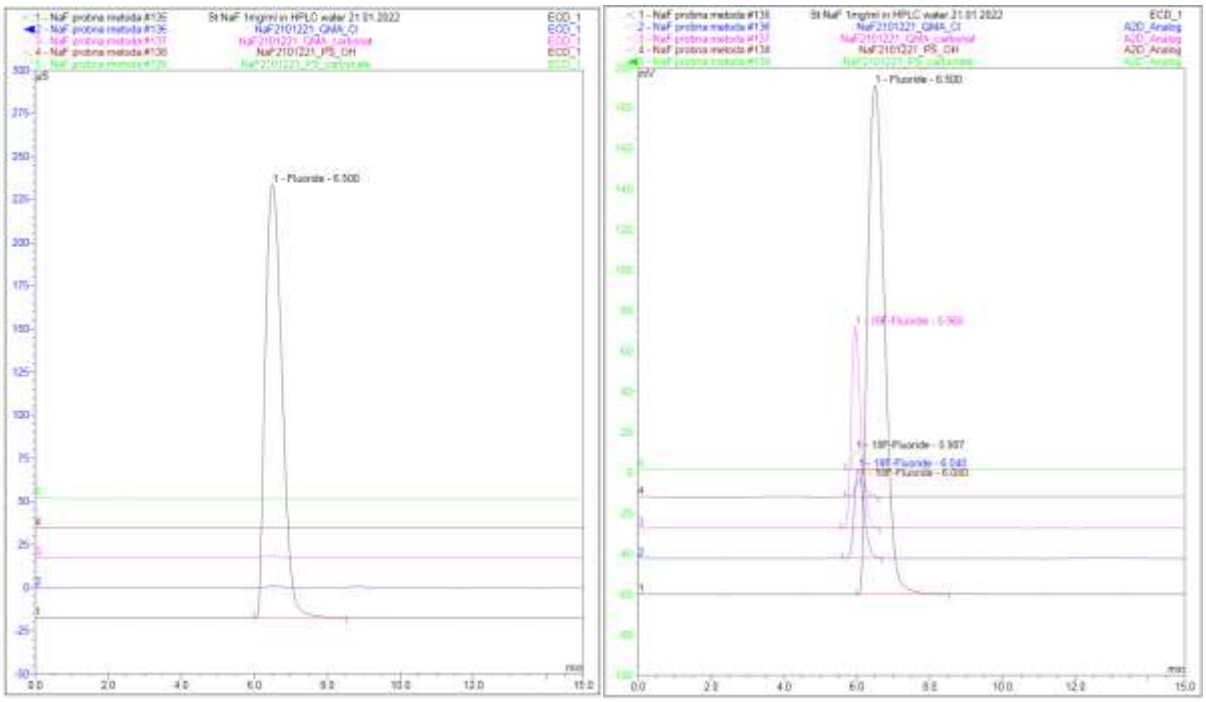
All samples were clear and colourless without particles. The measured approximate pH values are shown in Table No. 2. The measured mean half-life for all samples was 1.83 ± 0.0189 hours. The identification was done by measuring the half-life and comparing the chromatograms obtained from the reference solution (conductivity detector) and test solution (radioactive detector). The retention times could differ not more than 40 seconds, in our tested samples calculated values were below 40 seconds. The chemical purity on analyzed [^{18}F]NaF samples was below 0.425 mg/mL, no peek was detected on the chromatogram obtained from the conductivity detector. The overlay chromatogram from chemical purity is shown in Picture No. 1 a). The only peak represented on the radiochromatogram had a similar retention time, in the comparison with peak from the reference solution on the chromatogram obtained from the conductivity detector (Picture 1 (b)). The peak was identified as [^{18}F]NaF and the radiochemical purity was determined 100%. The radionuclidic purity was 2.16E-05 ± 1.22424E-05.

Table No.2 Approximate pH value of [^{18}F]NaF samples

Batch	**Approximate pH-value**				
	Total volume of final sample				
	8 mL	**10 mL**	**15 mL**	**20 mL**	**25 mL**
QMA _Cl.1	6.5 – 7.0	6.5 – 7.0	/	/	/
QMA _Carb.1	7.5 - 8.0	7.5 - 8.0	7.0 - 7.5	6.5 - 7.0	/
PS _OH.1	7.5 – 8.0	7.0 – 7.5	7,0 – 7,5	6,5 – 7,0	6,5 – 7,0
PS _Carb.1	8.5 – 9.0	8.0- 8.5	7.5- 8.0	7.5 – 8.0	7.5 – 8.0
QMA_Cl.2	6.5 – 7.0	6.5 – 7.0	/	/	/
QMA_Carb.2	8.0 - 8.5	7.5 - 8.0	7.0 - 7.5	7.0 - 7.5	/
PS_OH.2	8.0 - 8.5	7.5 - 8.0	7.5 - 8.0	7.0 - 7.5	7.0
PS_Carb.2	8.5 – 9.0	8.5 – 9.0	8.5	8.0- 8.5	8.0- 8.5
QMA_Cl.3	6.5 – 7.0	6.5 – 7.0	/	/	/
QMA_Carb.3	8.0 - 8.5	8.0 - 8.5	7.5 - 8.0	7.0 - 7.5	7.0 - 7.5
PS_OH.3	8.0 - 8.5	7.5 - 8.0	7.5 - 8.0	7.0 - 7.5	7.0 - 7.5
PS_Carb.3	8.5 – 9.0	8.5 – 9.0	8.0 - 8.5	8.0 - 8.5	8.0 - 8.5

Picture No.1 Chromatograms obtained with conductivity detector and radiodetector

a) Chemical purity of [^{18}F]NaF samples b) Radiochemical purity of [^{18}F]NaF samples



(a) (b)

4. DISCUSSIONS

In order to define the most suitable type of anion-exchange cartridge, twelve manual preparations were performed, with the four anion-exchange cartridges in triplicate. Each sample was analyzed for the following quality parameters: appearance, pH-value, identification, chemical purity, radiochemical and radionuclidic purity. The yield corrected for decay was calculated. Regarding the yield the Sep-Pak Accell Plus QMA have shown higher extraction elution capability of the radioisotope [^{18}F]F^-, while the counter-ion did not impact the yield (Table No.1). The parameters appearance, identification, chemical, radiochemical and purity were comparable for exanimated samples regardless of anion-exchange SPE cartridge. No chemical and radiochemical impurities were found in the analyzed samples. On the radiochromatogram one peak from [^{18}F]NaF was detected, and on the chromatograms from the conductivity detector, no peak was observed. Radionuclide impurities in the final sample were effectively removed using anion exchange cartridges (QMA-Cl^-, QMA-CO_3^{2-}, PS-OH^- and PS-HCO_3^-). From the obtained results, it has been proven that the radionuclide purity in the sample is at least four orders of magnitude better than the limit in the European pharmacopoeia.

The pH value was the only parameter that differed when using different cartridges for [^{18}F]NaF production. Samples obtained from the QMA-Cl^-, were found to have approximate pH values of 6.5-7.0 which lies within the acceptance limits. The measured pH value of the samples prepared with the other three types of cartridges was above 8.0, which is not within the acceptance criteria. By further dilution with saline, the pH value could be corrected and be within the defined limit. The dilution with a volume of 7 mL saline (total volume of the final product 15 mL) was sufficient to obtain the pH value of 7.0-7.5. While the pH value of the samples prepared with PS-HCO_3^- was not within the limit even after dilution with a total volume of 17 mL saline (total volume of the final product 25 mL). The other two cartridges (QMA-CO_3^{2-} and PS-OH^-) could be used in the [^{18}F]NaF production process, but further dilution is necessary to obtain the pH value in the acceptance criteria. Based on this study, the QMA-Cl- is chosen as a cartridge to be used in the further development of the in-house method for [^{18}F]NaF radiopharmaceutical production. The measured pH values are in correlation with the results obtained by Kao, and co-workers while regarding the final yield, they obtained higher values compared to our results for all four anion-exchange cartridges. The lower yield was due to remained residual radioactivity in the syringe. With further development of the semi-automatic in-house method for [^{18}F]NaF radiopharmaceutical production, a higher final yield is expected.

5. CONCLUSIONS

This study confirmed that SPE quaternary methyl ammonium cartridges with carbonate and chloride counter-ion and SPE cartridges filled with strong anion exchanger based on polystyrene-divinylbenzene copolymer (PS/DVB) in OH^- form could be used to produce the [^{18}F]NaF radiopharmaceutical. The produced [^{18}F]NaF solution is with high radiochemical yield and quality that meets the acceptance criteria defined in the European pharmacopoeia monograph. From the results obtained, the analyzed quality parameters, except pH, did not differ when using different anion-exchange SPE cartridges. The measured approximate pH value was within the limit without further dilution only for QMA-Cl^-. Consequently, QMA-Cl^- is chosen as a cartridge to be used in the further development of the semiautomatic in-house method for [^{18}F]NaF radiopharmaceutical production.

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