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An Automated Method for Preparation of [¹⁸F]Sodium Fluoride for Injection, USP to Address the Technetium-99m Isotope Shortage

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Abstract

The worldwide shortage of technetium-99m has created an immediate and urgent need for access to [¹⁸F]sodium fluoride for PET imaging of bone metastasis. In order to facilitate global availability of [¹⁸F]sodium fluoride for diagnostic nuclear medicine imaging procedures, a straightforward method for rapid production of [¹⁸F]sodium fluoride for injection, USP, using a modified GE Tracerlab FX-FN is presented.

Keywords

[¹⁸F]sodium fluoride; positron emission tomography; isotope shortage

1. Introduction

Presently, approximately 80% of the world's nuclear medicine diagnostic imaging procedures, including bone imaging, are performed using technetium-99m (for example: Aktoulin, 2001). Technetium-99m is obtained as the decay product from molybdenum-99 ('moly-99'). Despite this enormous demand, only six nuclear reactors around the world supply molybdenum-99 (and the resulting technetium-99m generators) for all of these imaging studies (estimated at 30 million per year globally). At the time of writing, one of these nuclear reactors (Chalk River, Canada) is shutdown for repairs leaving thousands of hospitals in North America without a supply of technetium-99m (Voith, 2009). The result is large numbers of patients being denied essential imaging procedures and a nuclear medicine community in crisis.

Alternatives to technetium-99m scans are clearly in demand and [¹⁸F]sodium fluoride represents an easily accessible positron emission tomography (PET) imaging alternative to technetium-99m bone imaging agents (Schirrmester *et al.*, 1998; Weber *et al.*, 1974). [¹⁸F] Sodium fluoride is approved by the U.S. Food and Drug Administration (FDA) but, presently, the U.S. Centers for Medicare and Medicaid Services (CMS) do not reimburse for PET bone imaging procedures using [¹⁸F]sodium fluoride. However, in an effort to address the worldwide shortage of technetium-99m, CMS is investigating the effectiveness of [¹⁸F]sodium fluoride as an imaging agent for bone metastasis (to monitor the spread of, for example, breast or lung cancer to the bone) and is re-evaluating their non-coverage policy. Consequently, PET centers worldwide have an immediate and urgent need for easy access to [¹⁸F]sodium fluoride suitable for clinical use as demand is expected to increase rapidly in the coming months and years.

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Herein an automated method for the rapid production of [^{18}F]Sodium Fluoride for Injection, USP (USP-32, NF27) using a modified General Electric Medical Systems (GEMS) Tracerlab FX-FN is disclosed. Synthesis time following end-of-bombardment is 10 min.

2. Materials and Methods

2.1 General Considerations

Sodium chloride, 0.9% USP and Sterile Water for Injection, USP were purchased from Hospira. Sterile filters were obtained from Millipore and sterile product vials were purchased from Hollister-Stier. [^{18}O]H₂O was purchased from ABX advanced biochemical compounds. Potassium fluoride, 99.99%, was purchased from Sigma Aldrich. Plus-CM and QMA-light Sep-Pak's were purchased from Waters Corporation. Sep-pak's were flushed with 10 mL of ethanol followed by 10 mL sterile water prior to use. All other reagents and materials were used as received.

2.2 Synthesis Procedure

Fluoride-18 was produced via the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction using a GEMS PETTrace cyclotron. The fluoride-18 as a solution in [^{18}O]H₂O (2 mL) was delivered through an in-line Plus-CM cation exchange cartridge (to remove positively charged recoil nuclei generated alongside fluoride-18 in the cyclotron target) into the dilution flask (pre-charged with 10 mL Sterile Water for Injection, USP) of a Tracerlab FX-FN. The resulting solution was then passed through a QMA-light Sep-Pak to trap the fluoride-18. The QMA-light Sep-Pak was washed with additional Sterile Water for Injection (10 mL) to remove any residual [^{18}O]H₂O and then dried with an argon stream. The fluoride-18 was then eluted from the Sep-Pak with 0.9% sodium chloride, USP (10 mL) into the Tracerlab FX-FN collection vial. This solution was passed through a sterile filter (Millipore Millex-GS) into a sterile dose vial (vented with a Millex-FG sterile filter). The yield of [^{18}F]sodium fluoride was recorded and the product was released for quality control.

2.3 Quality Control Procedures

Quality control of [^{18}F]sodium fluoride for injection, USP was carried out according to the U.S. Pharmacopeia [USP-32, NF-27, 2009] as detailed below. Results for 3 repeat batches are reported in Table 1.

Visual Inspection—The [^{18}F]sodium fluoride dose is examined behind a PET L-block and must be clear, colorless and free of particulate matter.

pH—The pH of the [^{18}F]sodium fluoride dose was analyzed by applying a small amount of the dose to colorpHast[®] pH 2.0 – 9.0 non-bleeding pH-indicator strips and determined by visual comparison to the scale provided. Dose pH must be 4.5 – 8.0.

Radiochemical Purity and Radiochemical Identity—Radiochemical purity and identity were analyzed using a Shimadzu VP-Series HPLC equipped with a conductivity detector and a Bioscan FC3300 radioactivity detector. Column: Phenomenex Rezex RHM-monosaccharide (hydrogen form), 300 × 7.8 mm; mobile phase 0.0015 M aqueous sulfuric acid; flow rate = 0.8 mL/min. Potassium fluoride (99.99%) was used as the non-radioactive fluoride-19 reference standard. Radiochemical identity was confirmed and quantified by calculating the relative retention time ($\text{RRT} = [\text{retention time of fluoride-18}]/[\text{retention time of fluoride-19}]$).

Radionuclidic Identity—Radionuclidic identity was confirmed by measuring the half-life of [^{18}F]sodium fluoride and comparing it to the known half-life of fluorine-18 (109.77 min).

Activities were measured using a Capintec CRC®-15R Radioisotope Dose Calibrator and half-life was calculated using equation (1). Calculated half-life must be 105 – 115 min.

$$T_{1/2} = -\ln 2 (\text{Time Difference} / (\ln(\text{ending activity} / \text{starting activity}))) \quad (1)$$

Radionuclidic Purity—Radionuclidic purity is analyzed by gamma-ray spectrometry and doses from our facility are allowed to decay, and then sent out to a CRO (Dade Moeller and Associates, Gaithersburg, MD, USA) to test for the presence of long-lived radioactive contaminants.

Sterile Filter Integrity Test—The sterile filter from the [¹⁸F]sodium fluoride (with needle still attached) was connected to a nitrogen supply *via* a regulator. The needle was submerged in water and the nitrogen pressure was gradually increased. If the pressure was raised above the filter acceptance pressure (50 psi) without seeing a stream of bubbles, the filter was considered intact.

Bacterial Endotoxins—Endotoxin content in doses of [¹⁸F]sodium fluoride was analyzed by a Charles River Laboratories EndoSafe® Portable Testing System and according to the US Pharmacopeia. Doses must contain <175 Endotoxin Units (EU).

Sterility—Culture tubes of fluid thioglycolate media (FTM) and soybean casein digest agar media (SCDM) were inoculated with samples of [¹⁸F]sodium fluoride doses and incubated (along with positive and negative controls) for 14 days. FTM is used to test for anaerobes, aerobes and microaerophiles whilst SCDM is used to test for non-fastidious and fastidious microorganisms. Culture tubes were visually inspected on the 3rd, 8th and 14th days of the test period and compared to the positive and negative standards. Positive standards must show growth (turbidity) on the plates and [¹⁸F]sodium fluoride/negative controls must have no culture growth after 14 days to be indicative of sterility.

3. Discussion

In order to fully automate the synthesis of [¹⁸F]sodium fluoride, USP in our laboratory, simple modifications were made to a GEMS Tracerlab FX-FN (Figure 1). The delivery line from the cyclotron, originally just pushed through a septum into the target vial, was fitted with plastic luer lock fittings and transferred to the dilution flask. Luer lock fittings enable easy switching between delivery of fluoride to the target vial for a routine synthesis (e.g. [¹⁸F]FLT), and delivery to the dilution flask for preparation of [¹⁸F]sodium fluoride. These fittings also allow easy incorporation of a Plus-CM cation exchange cartridge into the target delivery line.

With this modification in-place, the cradle used in a typical synthesis for holding a C-18 reformulation Sep-Pak can be used to house the QMA-light Sep-Pak in this [¹⁸F]sodium fluoride synthetic protocol.

To set-up the Tracerlab FX-FN for synthesis, the dilution flask was charged with Sterile Water for Injection, USP (10 mL) to facilitate transfer of the fluoride-18 through the QMA-light Sep-Pak. The extra water was added to the dilution flask as it was suspected that 2 mL of target water might be a problematically small volume to handle. Vial 7 was charged with 0.9 % Sodium Chloride for Injection, USP (10 mL) and Vial 9 with Sterile Water for Injection, USP (10 mL). A QMA-light Sep-Pak, pre-conditioned by flushing with ethanol (10 mL) followed by Sterile Water for Injection, USP (10 mL), was placed in the cradle between V15 and V17

and a sterile product vial with appropriate sterile filters was attached to the product delivery line.

Fluoride-18 was delivered to the dilution flask. Following completion of the cyclotron delivery, the solution of fluoride-18 was transferred (Ar pressure) through the QMA-light Sep-Pak, trapping the fluoride-18 and passing the water to waste. V17 was then switched from the dilution flask to the reagent vials and the QMA-light Sep-Pak was washed with an additional 10 mL of Sterile Water for Injection, USP (from Vial 9) to remove residual [^{18}O]H $_2$ O. V15 was then switched from 'waste' to 'collect' and the fluoride-18 was eluted into the Tracerlab collection vial using 0.9% Sodium Chloride (10 mL from Vial 7) with concomitant generation of [^{18}F]sodium fluoride (Nandy *et al.*, 2007). The 10 mL dose was then passed through a sterile Millipore Millex-GS filter into a sterile dose vial and released for quality control testing. Typical yields of [^{18}F]sodium fluoride were >90% (non-decay corrected).

Quality control was carried out per the U. S. Pharmacopeia monograph for [^{18}F]sodium fluoride [USP-32, NF-27] as described in Section 2.3 above. After successfully meeting all release criteria, doses were released to physicians for clinical use.

4. Conclusions

In conclusion, a simple method for the rapid preparation of [^{18}F]Sodium Fluoride for Injection, USP has been developed. This method is employed in our laboratory using a modified GEMS Tracerlab FX-FN synthesis module and the total synthesis time following end-of-bombardment is 10 min. The method is not exclusively for use with the Tracerlab and can be easily adapted for use with any automated or manual fluorine-18 synthesis equipment.

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Figure 1.
Reconfigured Tracerlab FX-FN for $[^{18}\text{F}]$ Sodium Fluoride Production

Table 1Quality control data for [^{18}F]Sodium Fluoride, USP

QC Test [US-32, NF-27]	Release Criteria	Run 1	Run 2	Run 3
Appearance	Clear, colorless, free of particulates	Pass	Pass	Pass
pH	4.5 – 8.0	5.0	5.0	5.0
Radiochemical Purity	> 95% by HPLC	98.9%	99.4%	99.4%
Radiochemical Identity	RRT ^a = 0.9 – 1.1	1.0	1.0	1.0
Radionuclidic Identity	T _{1/2} = 105 – 115 min	105	114	107
Radionuclidic Purity	>99.9%	>99.9%	>99.9%	>99.9%
Filter Integrity Test	>50 psi	>50 psi	>50 psi	>50 psi
Bacterial Endotoxins	<17.5 EU ^b /mL	<2.00 EU/mL	<2.00 EU/mL	<2.00 EU/mL
Sterility	Sterile	Sterile	Sterile	Sterile

^aRRT = Relative retention time;^bEU = Endotoxin units.