Production of the PET bone agent ^{18}F-fluoride ion, simultaneously with ^{18}F-FDG by a single run of the medical cyclotron with minimal radiation exposure- A novel technique

Rajeev Kumar[1] MSc Nucl Med, Rajendra G Sonkawade[2] PhD, Madhavi Tripathi[1] MD, Punit Sharma[1] MD, Priyanka Gupta[1] MSc, Praveen Kumar[1] MSc, Anil K Pandey[1] PhD, Chandrasekhar Bal[1] MD, Nishikant Avinash Damle[1] MD, Gurupad Bandopadhayaya[1] PhD

1. Department of Nuclear Medicine and Medical Cyclotron Facility, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India
2. Inter University Accelerator Centre, Aruna Asaf Ali Marg, New Delhi-110 057, India

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Correspondence address:
Rajeev Kumar MSc, Department of Nuclear Medicine and Medical Cyclotron Facility, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110029, India
Tel: +9126546739
E-mail:
rajeevraj.aiims@gmail.com
rajeevraj_aiims@yahoo.com

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Abstract

Our aim was to establish an easy and convenient procedure for the preparation of fluorine-18-sodium fluoride (^{18}F-NaF) for bone positron emission tomography (PET) during routine ^{18}F-FDG production using the Explora FDG4 radiochemistry module (EFRM) by single run of Cyclotron with negligible radiation exposure. *We compared three techniques* for ^{18}F-NaF production during routine PET radiochemistry at our setup. In one method we used synthesis module and in other two methods we did not. In the first and third method, F-18 was directly extracted from the V-vial and in the second method, ^{18}F-NaF was extracted by post processing from the EFRM. In the first method, F-18 was extracted directly from V-vial manually by opening the V-vial cap. In the second method, Explora FDG-4 Module was used. First, F-18 was transferred from the V-vial. Then, after post processing in EFRM, pure F-18 was obtained in the product vial. In the third method, pure F-18 was obtained in the product vial with the help of a mechanical robotic arm. The above were followed by routine quality control of ^{18}F-NaF produced by each method. *Results of quality control* of the ^{18}F-NaF obtained by all three methods satisfied all parameters prescribed by the United States Pharmacopeia (USP) and the British Pharmacopeia (BP) including biological, physical and chemical specifications. The radiochemical purity was 98.5±1.5% with Rf 0.006. The level of Kryptofix-222 (K222) in ^{18}F-NaF was within the prescribed limit. Mean pH of ^{18}F-NaF was 6.0±1.5. The exposure rate around the hot cell was negligible. *In conclusion*, from the results it was obvious that by our method number three ^{18}F-NaF was directly obtained from the V-vial using mechanical robotic arms. This method was the most appropriate with minimized radiation exposure to the handling Radiochemist and was also saving time as compared to the other two methods.

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Introduction

Fluorine-18-sodium fluoride (^{18}F-NaF) was introduced as a bone scintigraphy agent in 1962 by Blau et al [1]. It was approved for clinical use by the United State Food and Drug Administration in 1972 [2]. The introduction of technetium-99m (^{99m}Tc) bisphosphonates led replaced ^{18}F-NaF, because the latter did not have ideal imaging properties for the then usually available gamma cameras. Although ^{99m}Tc-bisphosphonates are still the most widely used agents for bone scintigraphy, their use has been questioned due to the limited global supply of ^{99m}Tc. In addition, the introduction of positron emission tomography/computed tomography (PET/CT) technology with a higher sensitivity and resolution than planar imaging and with the additional advantage of CT coregistration has renewed the interest in performing bone imaging with ^{18}F-NaF [3].

Fluorine-18-sodium fluoride has desirable pharmacokinetic properties of high and rapid bone uptake coupled with very rapid blood clearance, which results in a high bone-to-background ratio within a short time. It provides a better target to non-target ratio and a better count rate as skeletal uptake of ^{18}F-NaF is almost twice that of ^{99m}Tc-bisphosphonates [4]. Images with ^{18}F-NaF PET/CT can be acquired as early as 30min after the injection, good images can be obtained with a dose of only 185MBq and the effective dose nearly equals that of using 925MBq ^{99m}Tc-bisphosphonate, i.e. is 5.3mSv [5]. Fluorine-18-NaF PET is a highly sensitive method for detection of skeletal metastases from lung, breast, prostate, thyroid and head and neck cancers [3-5]. It has superior sensitivity to ^{99m}Tc-bisphosphonates using planar and single photon emission tomography (SPET) protocols [4].

Though it may appear that no processing is required for the synthesis of ^{18}F-NaF after its production in the cyclotron and its transfer to the V-vial, this product has to be made

suitable for intravenous (i.v.) injection, fulfilling pharmacopoeia requirements. Various methods are available for the production of ^{18}F-NaF and most of them require a separate synthesis module. Other researchers also favor the use of a separate radiochemistry module [6-8]. Leading companies in the world like Siemens Ltd, GE Healthcare, Eckert and Ziegler etc supply a radiochemistry module for the production of ^{18}F-NaF for PET bone scan. In an automatic module consumables (like QMA, Kryptofix, K_2CO_3, Acetonitrile, O-16-H_2O and Ag-50 resin) and also space and extra quality control equipments (like Gas Chromatography) would be required which would increase cost. At present, no single method has been described without module.

In order to face this situation, we aimed to establish an easy, effective and safe, from the radiation safety point of view, procedure to procure ^{18}F-NaF without a separate synthesis module, during routine ^{18}F-FDG production, at no added cost.

Materials and methods

This was a prospective study in which we planned to compare three techniques to procure ^{18}F-NaF from the medical cyclotron facility during routine ^{18}F-FDG production using Explora FDG4 radiochemistry module (EFRM).

Production of fluoride ion

The target material stable ^{18}O (enriched water 98%) was irradiated with high energy protons (11MeV) from a medical cyclotron RDS 111(Siemens Ltd, Erlangen, Germany). The yield of ^{18}F- depended on various factors such as enrichment of ^{18}O water, target volume, target current, energy of the beam, variation in argon pressure on the target, bombardment duration, and number of previous bombardments on the target and status of the delivery lines.

The F-18 produced by (p,n) reaction

$_8O^{18} + _{+1}p^1 \rightarrow _9F^{18} + _0n^1$

The duration of bombardment depended upon the day's ^{18}F-FDG requirements. The ^{18}F-fluoride ion produced was transferred to the V-vial (Fig. 1) in the hot cell. It is conventionally called V-vial because its shape in the bottom resembles the letter V. This shape has the advantage of the maximum transfer of activity from the V-vial to EFRM.

Techniques for extracting ^{18}F-NaF

First technique-*Manual extraction of ^{18}F-NaF from the V-vial*

The activity in the V-vial was measured. If the activity in the vial was less than 740MBq, it was opened manually and an appropriate amount of saline was added using a syringe. The V-vial was rotated to dissolve in saline all the spotted activity. All activity present in the V-vial was then extracted by a syringe with Millipore filter,) QMA (SepPaK Light Accell, Plus QMA anion exchange cartridge) and needle assembly. Individual doses were then dispensed behind the L bench (L shaped lead bench).

Second technique - *Extraction of residual ^{18}F-Fluoride with simultaneous synthesis-production of ^{18}F-FDG using synthesis module*

Figure 1. A view of the V-vial.

The ^{18}F-Fluoride ion produced by the cyclotron was transferred from target to trap and release column (SepPaK Light Accell, Plus QMA anion exchange cartridge) of first EFRM through the V-vial. Residual ^{18}F-Fluoride in the V-vial was transferred to the second EFRM. As we have two EFRM. At the same time ^{18}F-fluoride ion was also trapped in the trap and release column in both EFRM. ^{18}O-water was collected in a separate collection vial and this was reused as a target material after purification by distillation. Trap and release column removed the silver content coming from the silver target (which was used to produce F-18). Trapped ^{18}F-Fluoride ion was eluted with an eluting agent (mixture of K222, K_2CO_3, water and acetonitrile) and transferred to a sterile empty production vial in the Hot Cell through reaction vessels after filtering through a Millipore (Milex 0.22µm GS) vented filter. Cation exchange resin was used for the removal of K222. Dilution was done with normal saline to form ^{18}F-NaF. Total purification time was about 15min.

Fluorine-18-FDG was synthesized by Nucleophilic substitution reaction in the second EFRM. The basic steps of synthesis of ^{18}F-FDG are similar to the method proposed by Hamacher et al (1986) [9]. This method of production involves following steps: a) Preparation of ^{18}F-fluoride, b) Azeotropic distillation, c) Nucleophilic Radio fluorination, d) Hydrolysis and e) Purification.

Third technique - *Extraction of residual ^{18}F-NaF using mechanical robotic arm*

The V-vial has six opening ports, port one and two are available for incoming activity from the beam lines of the cyclotron. Port three is the opening for venting. This venting port is connected to an air bag. A controller valve which decides the path of ^{18}F-Fluoride activity is placed in venting line. If the valve is straight (parallel to the vent line) ^{18}F-Fluoride activity remains in the V-vial and if in cross position, ^{18}F-Fluoride is transferred from the V-vial. Port four is available for the EFRM and ^{18}F-Fluoride is transferred there for ^{18}F-FDG synthesis. Port five is available for ^{18}F-NaF sterile collection

vial through a sterile filter and QMA. The size of the filter pores is 0.22μm. First ^{18}F-Fluoride is transferred from V-vial for ^{18}F-FDG synthesis, and then the remaining pure ^{18}F-NaF is obtained in a sterile product vial with the help of mechanical robotic arm by generating pressure in the V-vial after rotating the controller valve.

Procedure to obtain F-18 from Hot Cell

We have a mechanical manipulator arm in our Hot Cell. There is a small door for dose transfer in the right side wall of Hot Cell. This door has two lead shieldings. The thicknesses of inner and outer shielding are 10 inch and 5 inch respectively. The inner shielding is immovable and the outer shielding is movable, so that we can take the dose out from the Hot Cell. Both these shieldings are for radiation safety purposes. When the production of F-18 is finished, we divide the single dose with the help of a mechanical robotic arm and kept it inside the inner shielding. Then we open the outer shielding and put inside (between the two shieldings) a single dose transfer Pig vial supplied by Biodex by the help of a mechanical manipulator. Then we put single dose in to the Pig vial and this dose is ready for injection. As for quality control (QC), we can inject it to the patient. In this process the operator will get negligible radiation exposure. The above take place in our Radiopharmacy lab) class C and in our Hot Cell class B with laminar flow environment present.

Quality control

Quality control was done as per to USP and BP guide lines (clarity, pH, radiochemical purity, radionuclide purity by half life).

Character

The product was observed behind a viewing glass in the Hot Cell. The ^{18}F product was clear and colorless.

Radionuclide identity

Radionuclide purity was tested by the dose calibrator and the gamma spectrometry method. Measurement of half life by dose calibrator was carried out by measuring the 10min decay half life of F-18. It lasted for only 10min. By gamma spectroscopy it lasts about 60-70min.

Radiochemical purity

Radiochemical purity was assessed by thin layer chromatography (TLC). A ten centimeters long silica gel thin chromatography paper was used. A small mark was placed on one end and a small drop of ^{18}F-NaF (1μL) was put on TLC strip with a Hamilton syringe. The TLC strip was dried over 5min. Then, this dry strip was put into a TLC developing jar containing developing solution (95:5 acetonitrile: water V/V). Care was taken to make sure that the strip was nearly vertical. When the developing solution reached more than five centimeters on the TLC strip, it was removed and dried. After the TLC paper dried, TLC scanning was started for results.

Chemical purity

The test of K222 involved spotting ^{18}F-NaF on a TLC-SG plate and then placing the TLC plate directly in an iodine chamber.

Sterility

Sterility was tested by incubating the ^{18}F-NaF with both soybean casein digest medium (SCDM) and fluid thioglycollate medium (FTM) for 14 days at 37°C.

Bacterial endotoxin test (LAL test)

For this test we used Charles River Portable Test System (PTS) reader. The PTS provides quantitative LAL test results in about 15min with a simple, one button operation and can be used for a wide range of applications. Results are displayed on the screen and can be printed or downloaded for reporting and trending. It measures the endotoxin level which is used in this study. The PTS™ (Trade Mark) uses LAL Kinetics chromogenic methodology that measures a color intensity that is directly related to endotoxin concentration in a sample. Each cartridge contains a precise amount of LAL reagent, chromogenic substrate and control standard endotoxin (CSE). The cartridge is manufactured according to rigid quality control procedures promoting test accuracy, consistency and product stability.

Filter membrane integrity test

We passed a stream of air through the millipore filter integrity test device to test the filter integrity. An indicator will show the pressure exerted on the filter membrane by the air stream.

Assessment of the radiation dose

The radiation measurement was performed during daily operation using a calibrated survey meter (RAMGAM 1, Rotem Inc. Israel). The readings were recorded at various time points, before the procedure, during the procedure and after the procedure. The results were recorded and analyzed.

Results

A total of 550 batches of ^{18}F-NaF were synthesized. Each batch was analyzed as regards quality control (Table 1), batch characteristics (Table 2) and radiation exposure levels (Table 3).

Table 1. *Results of quality control for the three methods of ^{18}F-NaF production*

Characteristics	Reference value	Method 1	Method 2	Method 3
Appearance	Transparent, colorless	OK	OK	OK
pH	4.5-8.5	7	7	7
Radiochemical purity	≥ 95%	98%	96%	98%
Radionuclide purity	T1/2=105-115min	110	110	110
Endotoxin test	<175IU/mL	<175IU/mL	<175IU/mL	<175IU/mL
Sterility test	Sterile	Sterile	Sterile	Sterile

Yield

The yield ranged from 0.74-3.7GBq.

Quality control

Quality control checks are mandatory to insure that the procedure fulfills the entire pharmacopeia requirement and the product is ready for injection. First of all we checked visually that every batch was clear and its suspension was free of par-

***Table 2**. Characteristics of three methods of production of ^{18}F-NaF*

Characteristics	Method 1	Method 2	Method 3
No of batches	65	35	450
Yield of ^{18}F-NaF (%)	100	50	95
Time (min)	2	15	7
QC	Pass	Pass	Pass
Radiation exposure	Very high	Negligible	Negligible

***Table 3**. Radiation exposure levels before transfer of F-18 from the medical cyclotron and immediately after transfer of F-18 from the V-vial to the EFRM. These are the average of 10 deferent activity level*

Exposure level before transfer of F-18 from the medical cyclotron (mR/h)			Exposure level on the surface of V-vial after transfer of F-18 from medical cyclotron	
BKG around Hot Cell	BKG inside Hot Cell	BKG on the surface of the V-vial	Activity in the V-vial after transfer to the EFRM	Exposure level in (mR/h)
0	0	1.1	2.44	403
0	0	0.9	3.00	420
0	0	0.02	1.55	362
0.02	0	0.8	1.44	371
0.01	0	0.6	0.92	310
0.01	0	0.02	0.59	291
0.01	0	0.7	0.48	285
0.01	0	1.2	2.26	396
0.01	0	0.8	1.66	383
0	0	0.8	1.48	365
0.01	0	0.694	1.58	358.6

**BKG- 0-0.002mR/hr*

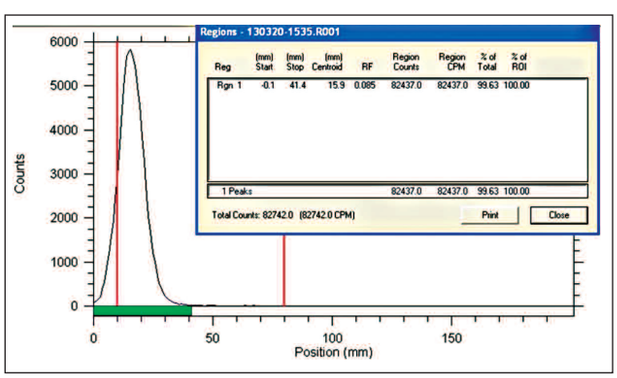

Figure 2. The TLC graph of ^{18}F-NaF showing that more than 99 % is F-18.

ticulate matter. The pH of our F-18 fluoride ion was 6.5±1. This was followed by a half life test. We kept 370MBq of F-18 for 10min. The decay corrected factor for 10min for F-18 is 0.93. So it should be 9.3mCi or 3.44MBq after 10min. We have taken 550 batches for this test and their range of activity was 3.44±0.04MBq. In our study the Rf of ^{18}F-NaF was 0.0 (Fig.3).

Discussion

We compared the three methods for ^{18}F-NaF synthesis-production during routine production of ^{18}F-FDG.

The first method was restricted by the maximum activity of NaF that could be extracted because of direct handling. Thus theoretically, though 100% extraction was possible practically not more than 740MBq were handled. It was however easy, convenient and consumed less time. As radiation exposure level was very high at the surface of V-vial, so the biggest drawback of this method was the radiation exposure to the handling person.

The second method was difficult and consumed more time. The yield was low because a lot of chemicals were used and post processing was required [10].

The third method was easy, convenient, consumed more time than the first method but less time than the second method. The activity that was obtained was more than either the first or the second method. It was also safe from the radiation safety point of view. No separate module was required for the production of ^{18}F-NaF, which could thus be obtained on a daily basis to be used for skeletal PET/CT imaging.

The ^{18}F-NaF was available for injection one hour before the dispatch of ^{18}F-FDG and at this time was convenient for the ^{18}F-NaF PET/CT bone scans without interfering with the ^{18}F-FDG schedule.

Measurement of the half-life with a dose calibrator is a very convenient and reliable method for detecting the presence of ^{18}F. Since the half life of F-18 is very short, we have opted this method because it was completed in 10min.

Due to the short half-life of ^{18}F, not all listed tests can be completed before the release of the ^{18}F product. The British Pharmacopeia allows the ^{18}F to be released before the radionuclidic purity, bacterial endotoxin test, and sterility tests are completed [11]. The TLC results can vary according to different brands of TLC plates and to the operation conditions. It is therefore important to use the same brand of TLC-Silica Gel plate and use freshly prepared mobile phase. The spotting technique also has significant effects on the TLC results. The spot size should be about 1μL. It should be dried and placed above the mobile phase level. Our TLC results tell us that we can use F-18 up to 12-14h after its production. The pH value of an injectable dose should be as close to the physiological pH as possible. The pH value measured using a pH paper is giving only its approximate value. Since the ^{18}F is released and injected into patients before the sterility results are available, there is virtually no assurance of the product sterility. Filter membrane integrity test provide an indirect evident that the product is sterile [12, 13].

Tables 4 and 5 indicate the possibility that a contaminant may be present in the target and the havar foil [14].

***Table 4**. Potential radionuclides produced in foils and target bodies*

Target	Particle	Reaction products
^{27}Al	p, d, α	^{22,24}Na
^{nat}Ti	p, d, ^{3}He, α	^{48,49,51}Cr, ^{48}V, ^{43,44m,44g,47,48}Sc
^{nat}Ni	p, d, ^{3}He, α	^{62,63,65}Zn, ^{60,61,64,67}Cu, ^{56,57}Ni, ^{55,56,57,58,60,61}Co, ^{52,54,56}Mn, ^{48}V
^{93}Nb	p, d, α	^{94g,95m,95g,96mg}Tc, ^{90,93m}Mo, ^{89,90,91m,92m,95mg}Nb, ^{86,87,88,89}Zr, ^{86,87m,87,88}Y
^{nat}Ag	p, d, α	^{108g,108m,109mg,110m,111mg,112m}In, ^{107,109}Cd, ^{105,106m,110m}Ag, ^{100,101,103}Pd, ^{99,100,101m,102,105}Rh, ^{97}Ru

Table 5. *Radionuclide impurities produced in havar foils*

Product	$T_{1/2}$*	Reaction	Threshold (MeV)
^{55}Co	17.5 h	^{58}Ni(p,α)	1.36
^{56}Co	77 d	^{56}Fe(p,n)	5.44
^{57}Co	272 d	^{57}Fe(p,n)	1.65
		^{60}Ni(p,α	0.27
		^{58}Ni(p,2p)	8.31
^{58}Co	71 d	^{58}Fe(p,n)	3.14
^{57}Ni	35.6 h	^{58}Ni(p,pn)	12.43
^{51}Cr	27.7 d	^{52}Cr(p,pn)	12.27
^{52}Mn	5.6 d	^{52}Cr(p,n)	5.60
^{95}Tc	20 h	^{95}Mo(p,n)	2.50
^{96}Tc	4.3 d	^{96}Mo(p,n)	3.80
^{181}Re	19.9 h	^{182}W(p,2n)	10.65
^{93m}Mo	6.85 h	^{93}Nb(p,n)	3.60

* $T_{1/2}$ = half-life.

All above mentioned radionuclides are present only in the havar foil and the target body and not in the F-18 solution. The only possibility is the presence of silver, because we are using silver as a target. Silver was removed by a trap and release column. Practically we can also confirm this by using old target, i.e. the target that had been used for more than 40 successive runs, in which case, the color of trap and release column after use becomes grayish.

One more possibility of a contaminant present in the produced F-18 is N-13. This impurity may be present if we use less enriched O-18 water. This possibility is very rare because we use 98 percent O-18 enriched water. The half life of N-13 is much shorter, only 10min. After the production of F-18 from the medical cyclotron it will takes more than one hour to synthesize ^{18}F-FDG and perform its QC. During this time, the total produced N-13 shall decay.

Considering the above, we can say that Na^{18}F produced at AIIMS presented all the quality assurance requirements of the USP and BP and can be safely used for clinical PET bone imaging.

In the literature two different methods have been described for ^{18}F-NaF extraction, one is direct removal and the other is by automated radiochemistry module [6-8]. These methods have however not been directly compared. Martinez et al (2011) [7] described an easy, low-cost, reliable automated method for ^{18}F-NaF preparation using existing equipment for ^{18}F-FDG production and a method by activation of the resin cartridges with ethanol and water, with fluoride ion trapping >95% and pH around 7. Hockley BG et al (2010) [8] described a method using a modified GEMS Tracer lab FX-FN synthesis module with total synthesis time following end-of bombardment of 10min. The automated module has the advantage that no manual intervention is required.

Limitation of the study

The three methods are applicable to the EFRM and Hot Cell using mechanical robotic arm of our radiochemistry lab.

In conclusion, our study describes a simple method whereby ^{18}F-NaF can be obtained without a radiochemistry module and this (method three) using robotic arms is most convenient for every day production of ^{18}F-NaF for skeletal imaging in a PET facility, without interfering with the production of ^{18}F-FDG, in a single run of the Cyclotron with negligible radiation exposure and without the need for the expensive automatic module.

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The authors declare that they have no conflicts of interest.

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