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Article

Synthesis, quality control and dosimetry of the radiopharmaceutical ^{18}F-sodium fluoride produced at the Center for Development of Nuclear Technology - CDTN

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^{18}F-Sodium fluoride (Na^{18}F) is a radiopharmaceutical used for diagnosis in nuclear medicine by positron emission tomography (PET) imaging. Bone scintigraphy is normally performed using ^{99m}Tc-MDP. However, ^{18}F PET scans promise high quality imaging with increased resolution and improved sensitivity and specificity. In order to make available a tool for more specific studies of tumors and non-oncological diseases of bone tissue, the UPPR/CDTN team undertook the production and quality control of Na^{18}F injectable solution with the physical-chemical, microbiological and biological characteristics recommended in the U.S. Pharmacopeia. Na^{18}F radiochemical purity was 96.7 ± 1.3 %, with Rf= 0.026 ± 0.006. The product presented a pH of 5.3 ± 0.6, half life of 109.0 ± 0.8 minutes, endotoxin limit < 5.0 EU.mL^{-1} and no microbial contaminants. The biodistribution of Na^{18}F was similar to that described in the literature, with a clearance of 0.19 mL.min^{-1} and distribution volume of 18.76 mL. The highest bone concentration (5.0 ± 0.5 %ID.g^{-1}) was observed 20 minutes after injection. Na^{18}F produced at the UPPR presented all the quality assurance requirements of the U.S. Pharmacopeia and can be safely used for clinical bone imaging.

Uniterms: Radiopharmaceuticals/biodistribution. Sodium fluoride ^{18}F/production. Sodium fluoride ^{18}F/quality control. Sodium fluoride. ^{18}F/dosimetry. Bone imaging.

O Fluoreto de sódio ^{18}F (Na^{18}F) é um radiofármaco empregado para diagnóstico através da Tomografia por Emissão de Pósitrons (PET). Cintilografias ósseas são normalmente obtidas utilizando-se ^{99m}Tc-MDP. Entretanto, o interesse pelo Na^{18}F é crescente, principalmente devido à obtanção de imagens de elevada resolução. Com o objetivo de tornar disponível uma ferramenta mais específica para estudos de tumores e doenças não-oncológicas do tecido ósseo, o grupo da UPPR/CDTN implementou a produção e o controle de qualidade da solução injetável de Na^{18}F com as características físico-química, microbiológica e biológica preconizadas pela farmacopéia. Sua pureza radioquímica foi de 96,7 ± 1,3 %, com Rf= 0,026 ± 0,006. O produto apresentou pH igual a 5,3 ± 0,6, tempo de meia-vida de 109,0 ± 0,8 minutos, limite de endotoxinas < 5,0 EU.mL^{-1} e ausência de microrganismos. O perfil de biodistribuição em camundongos foi semelhante ao disponível na literatura, com depuração igual a 0,19 mL.min^{-1} e volume de distribuição igual a 18,76 mL. A concentração máxima (5,0 ± 0,5 % DI.g^{-1}) foi observada no osso 20 minutos após a injeção. O Na^{18}F produzido na UPPR do CDTN apresentou os parâmetros de qualidade definidos na farmacopéia americana e pode ser usado com segurança para uso clínico em cintilografia óssea.

Unitermos: Radiofármacos/biodistribuição. Fluoreto de sódio. ^{18}F/produção. Fluoreto de sódio. ^{18}F/controle de qualidade. Fluoreto de sódio. ^{18}F/dosimetria. Cintilografia óssea.

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INTRODUCTION

^{18}F-Sodium fluoride injection (Na^{18}F), a positron-emitting radiopharmaceutical containing no carrier-added (NCA), is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. This radiopharmaceutical became widely used for bone scintigraphy after its introduction by Blau *et al.* (1962) in the early 1960s and was approved for clinical use by the U.S. Food and Drug Administration in 1972. The use of ^{99m}Tc-MDP has been brought into question given the advantages of PET imaging and the limited global supply of technetium-99m (^{99m}Tc). Moreover, bone uptake of Na^{18}F is 2-fold greater than that of ^{99m}Tc-MDP and ^{18}F-fluoride PET is more accurate than planar imaging or SPECT for localizing and characterizing bone lesions (Blau *et al.*, 1962).

The radiopharmaceutical Na^{18}F has the desirable pharmacokinetics 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 frame. After intravenous administration, ^{18}F-fluoride diffuses through the bone capillaries into the bone's extracellular fluid (ECF). From the bone ECF, ^{18}F-fluoride ions exchange with hydroxyl groups in the hydroxyapatite at the surface of bone crystals forming fluoroapatite mainly at sites of bone remodelling with high turnover. Therefore, uptake of ^{18}F-fluoride reflects blood flow and osteoblastic activity (Grant *et al.*, 2008).

^{18}F-fluoride PET is a highly sensitive imaging modality for detection of benign and malignant osseous abnormalities and allows the regional characterization of lesions in metabolic bone diseases. Using hybrid PET/CT systems improves the specificity of ^{18}F-fluoride PET in cancer patients by accurately differentiating between benign and malignant sites of uptake (Grant *et al.*, 2008). The clinical usefulness of ^{18}F-fluoride PET has been demonstrated for monitoring the response to therapy against a wide range of clinical indications such as osteoporosis, Paget's disease, compression fractures, marrow lesion, stress injuries and many other abnormal bone activities (Bridges *et al.*, 2007).

Given the applicability of Na^{18}F for bone imaging has been confirmed, our objective was to obtain a high quality product. The commercial delivery system used for ^{18}F-FDG can also be used for the efficient delivery of other ^{18}F-labeled radiopharmaceuticals, including Na^{18}F. Microbiological, physical-chemical and biological quality control tests were performed, and the Na^{18}F injectable solution met the quality control requirements contained in the United States Pharmacopeia (USP 31). It is now feasible to perform high-quality Na^{18}F bone scans in most nuclear medicine departments, contributing to bone disorder and tumour diagnoses. This radiopharmaceutical is available for clinical use in PET/CT imaging.

All drug manufacture and quality control complied with Current Good Manufacturing Practice regulations described in the regulatory requirements and general guidance published by the Brazilian Regulatory Agency for Medicines (ANVISA).

MATERIALS AND METHODS

Na^{18}F Production

^{18}F-Fluoride was produced on a 16.5 MeV Cyclotron PETtrace® (GE Healthcare) by the ^{18}O (p,n)^{18}F nuclear reaction. The niobium target (with yield of 215 mCi/μA_{Sat}) was filled with 2.2 mL of enriched O^{18} water, which was irradiated with protons for 10 minutes at an intensity of 25 μA. The solution containing ^{18}F$^-$ was transferred into an automatic synthesis module, TracerLab® MX_{FDG} (GE Healthcare), modified and prepared with reagents kit and accessories for Na^{18}F production (Figure1). ^{18}F-fluoride ions were trapped in a SepPak Light Accell, Plus QMA, anion exchange column and were then eluted with NaCl 0.9% solution. Finally, the resulting 15 mL of Na^{18}F was dispensed into sterile, pyrogen-free vials, through a 0.22 μm filter, in an automated dispensing unit (*Theodorico*, Comecer®).

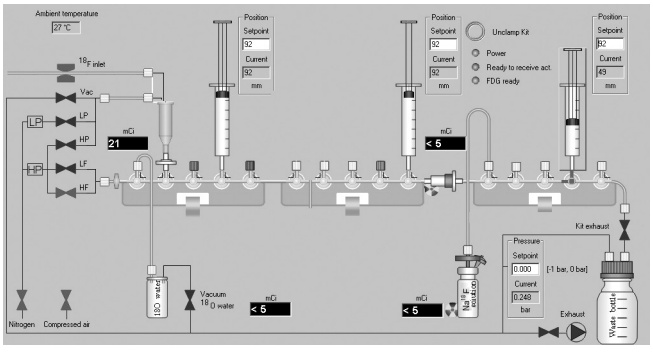

FIGURE 1 - Graphic of general purpose fluorination module.

Physical-chemical quality control

The pH value of Na^{18}F was measured using pH paper (0-14) which displayed a different colour depending on the pH range of the samples. The results were compared with standard pH buffer and the estimated value was registered.

Radiochemical identity and purity of Na^{18}F were confirmed either by thin layer chromatography (TLC) according to Nandy *et al.* (2007) or using a high-performance liquid chromatography (HPLC) system.

The TLC stationary phase was silica gel and the mobile phase was acetonitrile : water (95:5% v/v). The radioactivity was determined by scanning the TLC SG plate with a suitable collimated radiation detector (*Minigita star beta detector*, Raytest®). The main peak was analyzed to define the retention factor (Rf) value and the radioactivity related to the sample, that must lie between 0.0 - 0.12 and be no less than 95%, respectively.

HPLC analyses were performed on a chromatographic system (Agilent®), connected in serie with a gamma detector (Raytest®). The anion-exchange column (Shimadzu, IC.A1) (size: 46 mm x 10 cm) temperature was kept constant at 25 °C. The flow rate was 1.0 mL.min^{-1}, the sample volume was 20 µL and the solvent system was NaOH 0.1M (pH = 4.0).

Radionuclidic purity was evaluated by gamma-ray spectrometry (Camberra Multichannel Analyzer). Half-life of ^{18}F was calculated after measuring the radioactivity decay of the sample over a 20-minute period in a radioisotope dose calibrator (Capintec CRC®-25R). The equation used is showed below:

$$T_{1/2} = \frac{0.693 \times t}{\ln Ao/A} \quad (1)$$

Where: A_0= initial activity; A = activity measured after 20 minutes; t = time interval (in minutes) between the two measures (t_A-t_{Ao}); $t_{1/2}$ = half-life.

Microbiological quality control

Bacterial endotoxins were quantified by the chromogenic method, using an Endosafe® *Portable Test System* – PTS. This device includes a pumping system, a portable spectrophotometer and internal software to calculate sample data. Na^{18}F samples in duplicate (previously diluted) were applied inside cartridges in parallel with positive control testing. The product was considered apyrogenic when the endotoxins level was no more than 11.6 EU.mL^{-1}

The sterility of the Na^{18}F solution was assayed performing a test by direct inoculation of Na^{18}F solution in tryptic case soy broth and fluid thioglycollate medium. The test was performed in duplicate and a negative control test was also performed. The culture media were incubated at 25 °C and 37 °C, respectively, and verified daily over a fourteen-day period. The product was considered sterile when there was no evidence of microbiological growth.

Physiological quality control

The Na^{18}F physiological quality control was done by biodistribution studies in animals. Female Swiss mice with a body weight of around 25 g purchased from the Animal House Center (CEBIO) of the Biological Sciences Institute (ICB/UFMG). Mice were maintained on a light-dark cycle (12-h light, 12-h dark) at a room temperature of 25 °C and given food and water *ad libitum*. Animal experiments were performed in compliance with the Institute of Laboratory Animal Resources – Commission on Life Sciences – National Research Council, Washington, D.C. and the Brazilian society in science of Laboratory Animals (SBCAL).

Doses of 70 kBq of Na^{18}F were injected by intravenous route into Swiss mice. After different time intervals (2.5 - 60 minutes), the animals were sacrificed. Blood samples were taken, and the thyroid, heart, lungs, liver, spleen, pancreas, kidneys, stomach, intestine, bone, muscle, brain and bladder removed and weighed. Their respective radioactivity was measured in an automatic gamma spectrometer (1480 Wizard 3''– Wallac – Counting efficiency for 0.511MeV: 48%). The biodistribution was evaluated after calculating the percentage uptake of injected dose per gram of organ (% DI.g^{-1}).

Pharmacokinetics parameters were estimated by the Biexp Pharmacokinetics program (Murphy,R., Inaoe tonantzindra, Puebla, México 1991).

Radiation dosimetry

The absorbed radiation dose for each mouse organ was calculated applying MIRD formalism (Snyder *et al.*, 1978) to the biodistribution results, according to the relations:

$$\overline{D}_k = \sum_h \tilde{A}_h \, S(r_k \leftarrow r_h) \quad (2)$$

$$S(r_k \leftarrow r_h) = \sum_i \frac{\Delta_i \phi_i (r_k \leftarrow r_h)}{m} \quad (3)$$

Where: $\tilde{A}_h$is the cumulated activity in the target organ; $S(r_k \leftarrow r_h)$ is the mean absorbed dose in the target organ per unit of cumulated activity in the source organ; Δ_i s the mean energy emitted; $\phi_i(r_k \leftarrow r_h)$ is the absorbed energy fraction; m is the target tissue mass.

A value of ϕ = 1 (non-penetrating radiation) was adopted for the ^{18}F positron emission radionuclide. The experimental results of the cumulated activity in the mice organs were extrapolated to humans, assuming a similar concentration ratio among various tissues between mouse and patient. This extrapolation converted mouse %ID.g^{-1} data by adjusting organ mass difference between mouse

and patient (Kirschner *et al.*, 1975 and Shen *et al.*, 2005):

$$[A_0]_{HO} = [A_0]_{MO} \times \frac{M_{HO}}{M_H} \times \frac{m_M}{m_{MO}} \quad (4)$$

Where: $[A_0]_{HO}$ is the activity in the human organ; $[A_0]_{MO}$ is the activity in the mouse organ; M_{HO} is the human organ mass; M_H is the human mass; m_M is the mouse mass; m_{MO} is the mouse organ mass.

This extrapolation was based on the organ masses of mouse used in the experiments and the adult human organ masses of the Cristy-Eckerman phantom (Cristy, Eckerman, 1987).

RESULTS AND DISCUSSION

$Na^{18}F$ production

Enriched water $H_2{}^{18}O$ was successfully irradiated on the Cyclotron. $^{18}F^-$ was produced by the nuclear reaction $^{18}0$ (p,n) ^{18}F, by irradiation with protons for 10 minutes at the intensity of 25 μA. $Na^{18}F$ was produced in high yields of 87.3 ± 6.1%. Samples of the final product were sent to the quality control laboratories in appropriately shielded containers.

Physical-chemical and microbiological quality control

$Na^{18}F$ physical-chemical and microbiological characteristics were evaluated. The analyses described earlier determined its radiochemical identity and purity, radionuclidic identity and purity, pH, bacterial endotoxins and sterility.

The quality requirements used for $Na^{18}F$ were in accordance with those found in the United States Pharmacopeia (USP 31), supplemented with literature data (Nandy *et al.*., 2007) (Table I).

Radiochemical purity of the $Na^{18}F$ solution was assessed by thin-layer chromatography (TLC). The product migration profile was determined by scanning the chromatogram plate with a suitable collimated radiation detector (the radiochromatogram is represented in Figure 2).

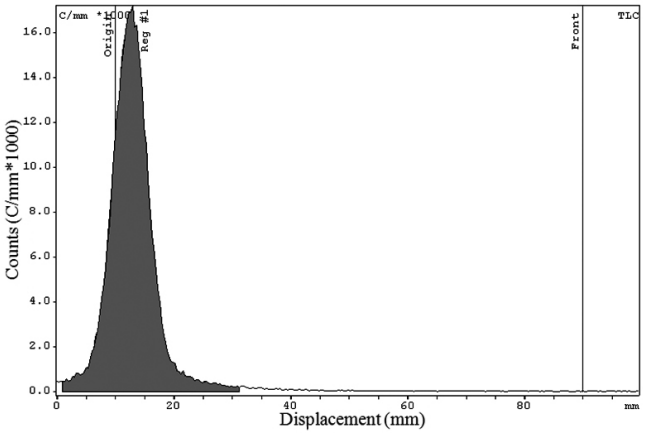

FIGURE 2 - TLC scan of $Na^{18}F$ in 95:5 ACN: H_2O mobile phase: Rf max = 0.05.

The main peak on the radiochromatogram obtained using HPLC for the $Na^{18}F$ test solution had approximately the same retention time (about 2 minutes) as the peak for ^{18}F described in literature data (Olberg *et al.*, 2008). More than 99% of the radioactivity was related to ^{18}F peak (Figure 3).

The final product, analyzed by gamma spectrometry, presented high radionuclidic purity. The spectrum obtained (Figure 4) shows one main peak at 0.511 MeV, an usual energy level for a positron annihilation product.

Energy

The results of the tests performed on the PTS were

TABLE I - Results obtained after testing $Na^{18}F$ microbiological, physical-chemical and biological properties ([1] USP 31; [2] Nandy *et al.*, 2007)

Tests	Quality Requirements (USP 31 and Nandy *et al.*, 2007)	Results
pH[1]	Between 4.5 and 8.0	5.3 ± 0.6
Radiochemical Identity[2]	$0.00 < R_f \geq 0.12$	0.026 ± 0.006
Radiochemical Purity[1]	≥ 95.0 %	96.7 ± 1.3%
Radionuclidic Identity[1]	Between 105 and 115 minutes.	109.0 ± 0.8 minutes
Radionuclidic Purity[1]	Main peak = 0.511 MeV	Main peak = 0.511 MeV
Bacterial endotoxins[1]	≤ 11.6 $EU.mL^{-1}$	< 5.0 $EU.mL^{-1}$
Sterility[1]	Sterile	Sterile

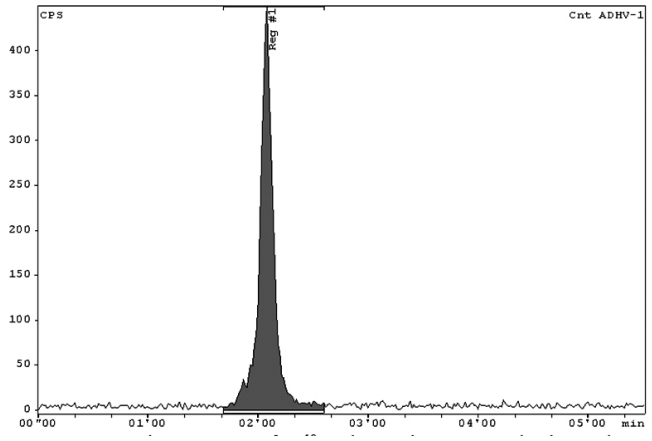

FIGURE 3 - HPLC chromatogram of $Na^{18}F$ solution showing its radiochemical purity, using NaOH 0.1M as mobile phase.

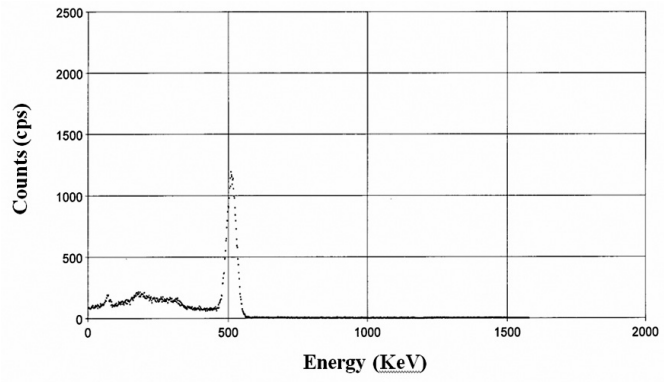

FIGURE 4 - Gamma spectrum obtained with a suitable detector to determine $Na^{18}F$ radionuclidic purity. Main peak can be observed at 0.511 MeV.

in compliance with the requirements established by the USP 31, showing that the samples contained less than 5.0 $EU.mL^{-1}$.

All the samples assayed for sterility were observed for 14 days and none showed evidence of microbiological growth. Therefore, the $Na^{18}F$ solutions were considered sterile.

Biological quality control

The biological quality control of $Na^{18}F$ was carried out through biodistribution studies in Swiss female mice. 70 kBq of $Na^{18}F$ were injected in mice via the intravenous route and, after different time intervals (2.5 - 60 minutes), the animals were sacrificed and radiopharmaceutical distribution in the organs was calculated as percentage uptake of injected dose per gram of organ (%ID.g^{1}).

The biodistribution profile is shown in Figure 5 and the results indicated that the blood concentration of the radiopharmaceutical was quickly reduced in the first hour post injection (4.50 ± 0.35 % ID.mL^{-1}) (Figure 6a). ^{18}F-Sodium fluoride presented biexponential blood clearance with half-life of 5.1 minutes in the fast distribution phase and 87 minutes in the slow elimination phase. The $Na^{18}F$ clearance was 0.19 $mL.min^{-1}$ and the distribution volume was 18.76 mL.

The $Na^{18}F$ kinetics in the main vital organs followed blood kinetics, and the radiopharmaceutical was rapidly cleared out. The only exception was bone kinetics, where the $Na^{18}F$ concentration increased during the time period, reaching a peak (5.0 ± 0.5 % ID.g^{-1}) 20 minutes after the injection (Figure 6b).

Radiation dosimetry

Dosimetric studies aimed to evaluate the safety of the ^{18}F-Sodium fluoride produced in the UPPR/CDTN for bone scintigraphy. The results (Table II) demonstrated that the highest absorbed doses in the mice were in bladder (11.5 mGy.70 KBq^{-1}) and bone (7.1 mGy.70 KBq^{-1}). Absorbed doses for the other organs were significantly lower, ranging from 1.3 - 4.0 mGy.70 KBq^{-1}. The radiation doses extrapolated to patients indicated that radiation doses in bone and bladder were 13.6 and 21.9 mGy.370 MBq^{-1},

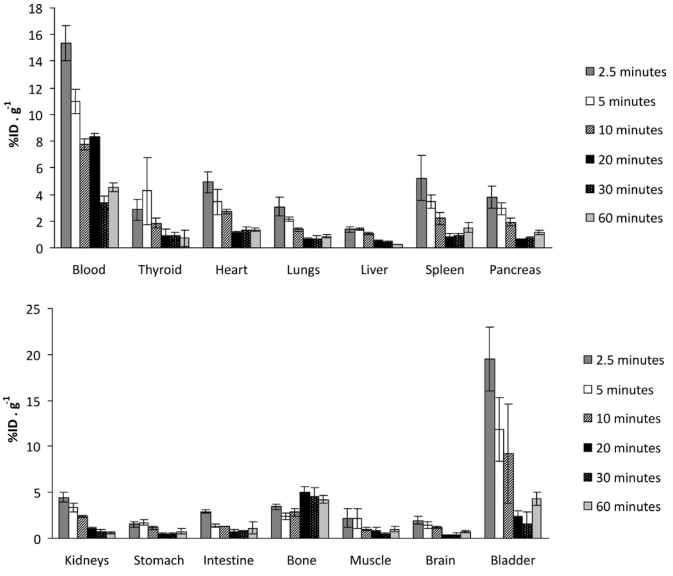

FIGURE 5 - $Na^{18}F$ biodistribution profile in Swiss female mice. 70 kBq of $Na^{18}F$ were injected into mice (*i.v*). After different time intervals, the animals were sacrificed, blood samples were taken, and thyroid, heart, lungs, liver, spleen, pancreas, kidneys, stomach, intestine, bone, muscle, brain and bladder were removed. Organ radioactivity was measured in an automatic gamma spectrometer and data were expressed as the percentage of total injected dose by tissue weight (% ID.g^{-1}).

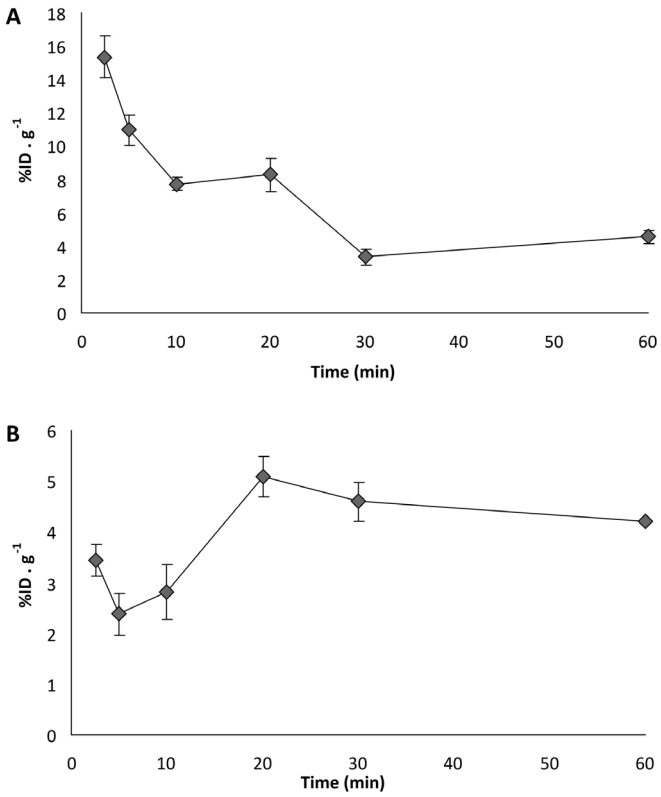

FIGURE 6 - $Na^{18}F$ kinetics in blood (A) and bone (B).

respectively. These results are quite similar to those published by ICPR53 and show that $Na^{18}F$ produced at the UPPR/CDTN can be safely used for clinical bone imaging.

CONCLUSIONS

The automated synthesis of $Na^{18}F$ and its availability was successfully accomplished using the commercial ^{18}FDG synthesizer TracerLab® MX_{FDG}. The final solution presented high quality in accordance with the requirements of the USP 31. The biodistribution of $Na^{18}F$ was similar to that described in the literature and absorbed doses in organs were lower than radioprotection limits.

Considering the clinical importance of ^{18}F-Sodium fluoride and the high resolution PET images provided by it, the UPPR group wish to start $Na^{18}F$ production and make it widely available. This study showed that the product presents good quality and meet the needs of hospitals, clinics, and research facilities. The radiopharmaceutical $Na^{18}F$ was produced according to the regulatory requirements and general guidance of Good Manufacturing Practices, published by the Brazilian Regulatory Agency for Medicines (ANVISA).

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TABLE II - Organ absorbed dose in mice and extrapolated to patients. The results were compared with literature data (ICRP 53). *Values were converted to clinically used doses (370 MBq)

Organ	Absorbed doses in mice (Gy.70 Kbq^{-1})	Extrapolated dose to patients (Gy.370 MBq^{-1})	Patient dose ICRP data*
Thyroid	$2.70x10^{-3}$	$5.14x10^{-3}$	-
Heart	$4.06x10^{-3}$	$7.73\ x10^{-3}$	$1.44\ x10^{-3}$
Lungs	$2.27x10^{-3}$	$4.33\ x10^{-3}$	$1.51\ x10^{-3}$
Liver	$1.32x10^{-3}$	$2.52\ x10^{-3}$	$1.48\ x10^{-3}$
Spleen	$3.49x10^{-3}$	$6.65\ x10^{-3}$	-
Pancreas	$3.08x10^{-3}$	$5.86\ x10^{-3}$	$1.77\ x10^{-3}$
Kidneys	$3.04x10^{-3}$	$5.80\ x10^{-3}$	$7.03\ x10^{-3}$
Stomach	$1.63x10^{-3}$	$3.10\ x10^{-3}$	$1.40\ x10^{-3}$
Intestine	$2.54x10^{-3}$	$4.84\ x10^{-3}$	$2.44\ x10^{-3}$
Bone	$7.14x10^{-3}$	$1.36\ x10^{-2}$	$2.22\ x10^{-2}$
Brain	$1.56x10^{-3}$	$2.98\ x10^{-3}$	$2.01\ x10^{-3}$
Bladder	$1.10x10^{-2}$	$2.19x10^{-2}$	$9.25x10^{-2}$

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