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Experience in production of ^{18}F isotope in the Cyclone-30 for synthesis of fluorinated radiopharmaceuticals

Abstract. This article provides a brief overview of the ^{18}F isotope production using the Cyclone-30 cyclotron and two liquid targets with the volume of 0.5 and 2.0 ml, water enriched with the ^{18}O isotope was used as the target material. The obtained isotope was used for serial production of the [^{18}F]FDG radiopharmaceutical and supply of this medicine to the operating PET centers in Almaty. The isotope was also used for experimental syntheses of [^{18}F]PSMA-1007 and Na[^{18}F]F to assess the possibility of implementation these medicines into the production and medical practice of the Republic of Kazakhstan. The need for the implementation of [^{18}F]PSMA-1007 is associated with the problem of early diagnosis and control of prostate cancer treatment, and Na[^{18}F]F – with the earliest possible detection of bone metastases in malignant tumors of various localization.

This paper provides the average radiochemical yield and the main quality parameters for [^{18}F]FDG, [^{18}F] PSMA-1007 and Na[^{18}F]F.

This scientific and practical work allows us to evaluate the three-year production experience and the possibilities of fluorine production by reaction (p,n) on the cyclotron C-30, and also reflects the prospects of using fluorine in the development of new-generation radiopharmaceuticals for the diagnosis of oncological diseases.

Key words*:* ^{18}F, cyclotron, radiosynthesis, radiochemical yield, radiopharmaceutical, diagnostics, PET, nuclear medicine.

Introduction

Positron emission tomography (PET) is a modern method of nuclear medicine that enables us to obtain *in vivo* information about disturbances of physiological and biochemical processes at the molecular level by determining the concentrations of compounds labeled with positron emitters in biological tissues specified by the researcher [1].

More than 90% of PET procedures in the world are implemented with ^{18}F isotope due to the longest half-life (110 min) among ultra-short-lived radioisotopes as well as the ability to synthesize a fairly wide range of labeled compounds, such as ^{18}F-fluorodeoxyglucose, ^{18}F-PSMA, ^{18}F-tyrosine, ^{18}F-fluorocholine, ^{18}F-fluorothymidine, ^{18}F-fluoromizonidazole, ^{18}F-DOPA, ^{18}F-flumazenyl, ^{18}F-fluoropurine, ^{18}F-fluoroputrescine, ^{18}F-fluoruredine, ^{18}F-fluorocytidine, ^{18}F-flunarizine, etc. [2]. During the last three years, the "Institute of Nuclear Physics" (Almaty) has been performing serial production of Deoxy-2-[^{18}F] Fluoro-D-glucose ([^{18}F]FDG) on the synthesis module Synthera and experimental work on labeling an artificially synthesized protein tropic to prostate-specific membrane antigen (PSMA) with isotope ^{18}F ([^{18}F] PSMA-1007) and preparation of Na[^{18}F]F in the research facility SynthraRNplus.

Electrophilic and nucleophilic fluorination methods are used to introduce ^{18}F into the structure of various molecules [3,4,5]. The first method is associated with production of fluorine by irradiation of neon by the reaction ^{20}Ne(d,α)^{18}F, when the daughter radionuclide is stabilized in the chemical form [^{18}F]F_2 and characterized by the strongest electrophilic properties. The second method is based on preparation of fluorine from oxygen ^{18}O(p,n)^{18}F, which leads to formation of fluoride anion [^{18}F] F^-, which is subsequently used in nucleophilic substitution reactions.

Each of the methods for preparation of compounds with ^{18}F has its advantages and disadvantages. The advantages of the electrophilic method include high rate of the fluorination reaction [6]. The disadvantages of the method include low selectivity of fluorination and the resulting low specific activity of the labeled compound [3]. The advantage of the method for preparation of ^{18}F by nucleophilic

substitution is high selectivity of labeling and production of the preparation with high specific activity; the disadvantages include possible adverse reactions during synthesis, which requires more stringent maintenance of the specified technological parameters of synthesis [7].

Despite the above-mentioned disadvantages of the nucleophilic method, most modern PET centers use the nucleophilic method to prepare ^{18}F compounds, including the radiopharmaceutical production site at the "Institute of Nuclear Physics" in Almaty.

This paper describes the experience of ^{18}F isotope production and production of fluorinated radiopharmaceuticals, obtained in the INP over the past 3 years.

Materials and methods

All chemicals, reagents and solvents, required for the synthesis of [^{18}F]FDG, [^{18}F]PSMA-1007 and Na[^{18}F]F, were purchased from ABXGmbH (Germany). In addition, the synthesis kits, disposable synthesis cassettes and reference compounds, used for quality control, were purchased from ABXGmbH. The purchased disposable synthesis cassettes and reagent kits were used as received, with no adjustment of the factory parameters. Methods and standard operating procedures were developed and implemented at the site of radiopharmaceutical production at the "Institute of Nuclear Physics" in Almaty. Synthesis was performed on two different modules: SynthraRNplus and Synthera (Fig.1). Reagents for gas chromatography (GC), high-performance liquid chromatography (HPLC) and (thin-layer chromatography) TLC were purchased from Sigma-Aldrich.

The HPLC analysis was performed using the Agilent Infinity 1260 system with ultraviolet (G1314B) and refractometric (G1362A) detectors, as well as a radiochemical detector from LabLogic. The HPLC system is controlled by the Laura software. Before quality control, reference standards of each compound were used to determine the retention time. Gas chromatography (Agilent 7890A, ChemStantion software) was used to determine the number of residual solvents using a DB-WAX column (0.32 mm, length 30 m). Identification of radionuclides was verified by measuring the half-life using a dose calibrator (VDC-404). Radionuclide purity was determined by gamma-spectrometry with a multichannel high purity germanium detector (Canberra Industries). The level of cryptophix was determined by comparing the staining intensity on chromatography paper. The radiochemical purity was determined by TLC (Scan-RAM Radio-TLC Detector LabLogic and Laura software) using silica gel plates F254 (20×100 mm) and a mixture of acetonitrile: water (95:5, v/v) as a stationary and mobile phase, respectively.

^{18}F production

The utilized in INP ^{18}F production technology is based on the nuclear reaction ^{18}O (p, n) ^{18}F. The threshold of the nuclear reaction is 2.6 MeV, the cross section is growing and reaches its maximum 300 mb at 8 MeV, then it slopes down and at 20 MeV is 16 mb [8]. This means that to produce ^{18}F isotope, it is necessary to irradiate the ^{18}O oxygen nuclei with protons of energies not lower than 3 MeV and not higher than 20 MeV.

A *B*

Figure 1 – synthesis modules A- Synthera, B – SynthraRNplus

In addition to the target nuclear reaction, other reactions occur with the formation of side isotopes [9]. All the resulting isotopes are characterized by very short half-lives, about tens of seconds [10]. The most "long-lived" of them is the isotope ^{13}N, the half-life of which is 10 minutes. It is produced in the reaction of $^{16}O(p,a)^{13}N$. The nuclei of the oxygen isotope ^{16}O are inevitably present in the target material, although in small quantities. In addition, at proton energies above 18 MeV, the reaction of ^{13}N production will already take place on ^{18}O nuclei: the nuclear reaction $^{18}O(p,\alpha 2n)^{13}N$. This is a limitation on the maximum energy of the proton beam used for ^{18}F production.

The Cyclone-30 cyclotron manufactured by the Ion Beam Applications SA (IBA, Belgium) is used to produce the accelerated proton beam. The target material is water, 95% enriched with ^{18}O isotope. The target is a niobium capsule filled with water, covered from the beam side with a foil, made of Havar alloy. The cyclotron, the beam transportation line and the target station are a single complex, which is controlled from the cyclotron control panel.

Taking into account that the energy of the proton beam, produced by the C-30 cyclotron, can be varied from 15 to 30 MeV, the 18 MeV operation mode is an optimal one for the production of ^{18}F. It allows obtaining the maximum yield of the target isotope ^{18}F with a minimum production of by-products. The target provides full absorption of the proton beam. The irradiated water is pumped for further synthesis through the capillaries 0.9 mm in diameter into a receiving tank located in a hot cell. This process is performed automatically using high-purity helium gas. The transportation line is pre-purged with helium, and then the liquid is pumped, the line is re-purged.

Two targets manufactured by IBA are successfully operated in the INP for the production of ^{18}F isotope: a small-volume target of 0.5 ml and a large-volume target of 2 ml for irradiation with currents of 25 and 40 μA, respectively.

^{18}F Separation

The first stage of [^{18}F]FDG, [^{18}F]PSMA-1007 and Na[^{18}F]F synthesis is the extraction of ^{18}F isotope from irradiated $H_2{}^{18}O$. Extraction is performed by solid-phase extraction using a cartridge with anion exchange resin QMASep-Pak®, conditioned with 2 ml of ethanol and 2 ml of water. Irradiated $^{18}F^-$ containing water is passed through a pre-conditioned cartridge with anion exchange resin QMASep-Pak®, while the fluoride ion is retained on the resin. Various eluents were used for elution of the $^{18}F^-$ fluoride ion, for example, during the synthesis of [^{18}F]FDG, an aqueous solution of acetonitrile containing potassium carbonate and an average equimolar amount of the interfacial cryptofix catalyst (K222) was used, where potassium cation in the carbonate composition was used as a counterion for $^{18}F^-$. In the synthesis of [^{18}F]PSMA-1007, a 0.075 M solution of tetrabutylammonium bicarbonate ($TBAHCO_3$) was used as an eluent, and in the synthesis of Na[^{18}F]F -0.9% sodium chloride solution was used (Fig. 2).

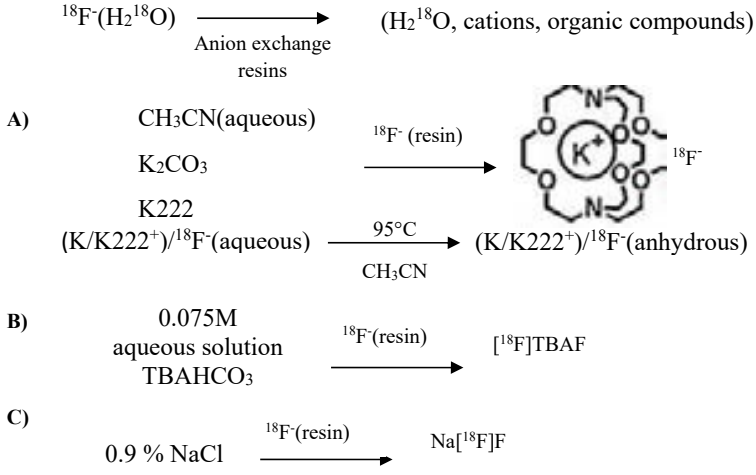

Figure 2 – A) scheme of $^{18}F^-$ extraction from irradiated target for [^{18}F]FDG production, B) scheme of $^{18}F^-$ extraction from irradiated target for [^{18}F]PSMA-1007 production, C) scheme of $^{18}F^-$ extraction from irradiated target for Na[^{18}F]F production

The yield at the stage of $^{18}F^-$ extraction from the irradiated target in case of listed elements is from 87 to 95% of the ^{18}F obtained activity. In case of [^{18}F]FDG and [^{18}F]PSMA-1007 production, for preparation for the next stages of synthesis the eluates are dried in a helium current at a high temperature. In case of Na[^{18}F]F production, the eluate is not dried.

Results and discussion

During serial production of [^{18}F]FDG radiopharmaceutical using the Synthera radiosynthesis module, the following averaged data for 3 years were obtained:

According to the results of 685 cycles of irradiation in the Cyclotron C-30 a target with 2 ml of enriched water with protons of 18 MeV energy and 38±2 μA current and subsequent cycles of [^{18}F]FDG synthesis using the Synthera module, it was shown that activity of ^{18}F in the preparation [^{18}F]FDG was 75±12 GBq at the end of synthesis. The irradiation time was 160±15 min, and the synthesis time was 27±2 min.

The quality parameters of the preparation corresponded to the pharmacopoeia requirements.

The activity of the resulted preparation was sufficient for daily injection up to twenty patients, depending on their weight (target activity is 370MBq/ body weight).

For experimental syntheses of [^{18}F]-PSMA-1007 and Na[^{18}F]F, 6 irradiation cycles were carried out in a target Cyclotron C-30 with 0.5 ml of enriched water with protons of 18 MeV energy and 20±2 μA current. The target was irradiated for 30-60 minutes. The synthesis was carried out at the SynthraRNplus research facility.

[^{18}F]-PSMA 1007

Three experimental syntheses of ^{18}F-PSMA-1007 were carried out. The synthesis time was 45 minutes, the average activity of ^{18}F-PSMA-1007 was 1.6±0.4 GBq, which corresponds to a radiochemical yield of 31± 9%.

Na[^{18}F]F

Three experimental Na[^{18}F]F series were produced using the SynthraRNplus synthesis module. The synthesis time was 15 minutes, the average activity of Na[^{18}F]F was 5±1 GBq, which corresponds to a radiochemical yield of 75±2%.

Conclusion

The process of ^{18}F isotope production using the cyclotron C-30 is stable and provides ^{18}F activity sufficient for both serial production of [^{18}F]FDG and experimental work on the introduction of technologies for the production of new preparations for PET, such as [^{18}F]-PSMA-1007 and Na[^{18}F]F.

The application of the automated synthesis system for mass production is quite reliable since only 5 equipment failures were recorded for 685 production cycles, which is 0.7%.

The synthesis module SynthraRNplus for experimental works is suitable for the production of new radiotracers. The research module was used to produce [^{18}F]-PSMA-1007 and Na[^{18}F] F with a radiochemical yield comparable to that of commercially available cyclotron synthesis modules.

Domestic production of a wide range of radiopharmaceuticals will improve the quality of medical care, reduce the mortality rate and increase the overall survival rate and progression-free survival in patients with various forms of cancer and improve the quality of life of patients.

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