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RADIATION CHEMISTRY

Autoradiolysis of Radiopharmaceutical 2-[^{18}F]Fluorodeoxyglucose with Activity Concentrations of 4–5.5 GBq/mL

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Abstract—The kinetics of the autoradiolytic decomposition of the radiopharmaceutical 2-[^{18}F]fluorodeoxyglucose ([^{18}F]FDG) with initial activity concentrations of 4.02–5.45 GBq/mL in physiological saline solution has been studied. It has been shown that an increase in the initial activity concentration or a decrease in the concentration of ethanol (chemical impurity) leads to a greater buildup of radiolytic [^{18}F]fluoride and a decline in the radiochemical purity of the drug. During storage of the radiopharmaceutical, a decrease in the concentration of ethanol and the formation of acetaldehyde, a product of its radiation-induced transformations, have been detected, the aldehyde concentration correlating with the relative activity of [^{18}F]fluoride. It has been found that after storage of [^{18}F]FDG with the same initial activity concentration in sealed 15-mL vials for 8 hours, the relative activity of [^{18}F]fluoride is significantly higher in 8-mL than in 1.5-mL solutions. This difference may be due to both an increase in the dose absorbed by the drug and the inhibitory effect of oxygen on the autoradiolytic dehalogenation process. An [^{18}F]fluoride removal procedure for purifying [^{18}F]FDG is described, which ensures the preservation of aseptic and pyrogen-free injectable drugs under the conditions of an operating positron emission tomography center.

Keywords: autoradiolysis, [^{18}F]FDG, positron emission tomography, radiopharmaceutical

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INTRODUCTION

The degradation of radioactive pharmaceutical drugs under the influence of radiation of their own radionuclide (autoradiolysis) leads to the loss of the pharmacologically active component and the formation of undesirable radiochemical impurities that increase the dose burden on patients and worsen the specificity and selectivity of diagnostic studies using radiolabeled compounds [1, 2]. Owing to autoradiolytic degradation, the availability of nuclear medicine methods for the population is hampered by a short shelf life of radiopharmaceuticals and the necessity of fast delivery of radionuclide-labeled products [3].

One of the most popular radiopharmaceutical at present is 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), an analogue of the most important carbohydrate for humans, containing the radioactive isotope fluorine-18 instead of the hydroxyl group at the C2 atom. Due to the favorable nuclear physical properties of the radionuclide and in vivo metabolism of radiopharmaceutical, [^{18}F]FDG is widely used for the diagnosis of cancer, cardiac, and neurological diseases using positron emission tomography (PET) [4]. To consistently meet the diagnostic needs of medical community, both local [^{18}F]FDG manufacturers and large centers that deliver products daily for 1–6 h using air and road transport are simultaneously operating in the United States, Western Europe, and recently in Russia. The increase in the duration of transportation and the release of drugs with high activity concentrations [5] caused by economic factors significantly aggravate the problem of autoradiolytic degradation of [^{18}F]FDG. For example, the unstabilized drug with an initial activity concentration on the order of 19–22 GBq/mL has a shelf life of less than 1 h [6], which excludes the possibility of its diagnostic use. This suggests that a detailed study of the features of autoradiolytic degradation of [^{18}F]FDG and a scientifically based search for inhibitors of this process are necessary.

In our previous study [7], we examined in detail radiation-induced transformations of [^{18}F]FDG with an initial activity concentration on the order of 1–2 GBq/mL. In this paper, we consider the changes in chemical and radiochemical purity in an air-saturated physiological solution of [^{18}F]FDG with initial activity concentrations of 4.02–5.45 GBq/mL, as well as the change in the relative activity of [^{18}F]fluoride in this solution. Such activity concentrations are most often used in multidose vials for charging automatic injectors used to prepare individual [^{18}F]FDG doses for patients in modern PET centers.

EXPERIMENTAL

The following commercially available chemicals were used without further purification: ethanol, acetonitrile, sodium [^{19}F]fluoride, and 50% NaOH aqueous solution (Sigma-Aldrich); the analytical standards were 2-[^{19}F]fluoro-2-deoxy-D-glucose ([^{19}F]FDG), 2-[^{19}F]fluoro-2-deoxy-D-mannose ([^{19}F]FDM), and 1,2,3,4-tetra-O-acetyl-D-glucose purchased from ABX (Germany). Ultrapure water (Type 1) with a resistivity of at least 15 MΩ was obtained using a Merck Millipore Milli-Q® water purification system.

For investigation of autoradiolytic degradation, the injectable drug 2-[^{18}F]fluorodeoxyglucose for PET diagnostics was used, which was obtained according to a standard technology [8, 9] on IBA Synthera cartridge modules using ABX reagent kits for preparing [^{18}F]FDG.

To study the dynamics of the buildup of free [^{18}F]fluoride and changes in the radiochemical purity of the drug during storage, standard 15-mL vials were filled with 1.5 mL of the radiopharmaceutical each; a volume of 8 mL was used to confirm the specified expiration date. After filling the pharmaceutical, the vials were corked with a butyl rubber stopper, crimped with an aluminum cap, marked, and transferred from the radiation protection chamber in Comecer CF-18 Pb lead-shielded containers.

Complete quality control of the finished pharmaceutical [^{18}F]FDG was carried out after 8 h (certified shelf life) to verify the compliance of the produced radiopharmaceutical with the requirements of the corresponding monograph of the State Pharmacopoeia of the Republic of Belarus, harmonized with the European Pharmacopoeia [10]. The dynamics of the buildup of [^{18}F]fluoride and other radiochemical impurities was monitored by radio-TLC and radio-HPLC immediately after release of the batch and then after 2, 4, 6, and 8 h.

The contents of ethanol, acetaldehyde, and other residual solvents were determined by gas chromatography on an Agilent 6850 with a flame ionization detector according to the procedures given in [11, 12]. The radio-TLC and radio-HPLC analysis procedures are detailed in [7]. During the experiments, a constant temperature regime was maintained in the laboratory at 23 ± 2°C.

To remove [^{18}F]fluoride from [^{18}F]FDG, a Waters Alumina B solid-phase extraction cartridge and a Merck Millipore sterilizing filtration system with a pore size of 0.22 μm were used. The radiopharmaceutical solution was passed at a rate of 5 mL/min through the assembly, after which it was washed with a threefold volume of injection grade water. No [^{18}F]fluoride was detected in the eluate, with its relative activity in the initial of [^{18}F]FDG solution being up to 15%.

All operations with highly radioactive drugs were carried out with strict observance of radiation safety measures by qualified personnel in a specialized radiopharmaceutical laboratory.

RESULTS AND DISCUSSION

During storage of [^{18}F]FDG solutions, the radiochemical purity of the radiopharmaceutical (the proportion of the activity of the main labeled substance in the total activity of the drug) decreases. In this case, the only detected radioactive product of autoradiolysis is [^{18}F]fluoride; other radiochemical impurities have been present in the radiopharmaceutical from the time of production, and their proportion varies within the measurement error [7].

The dynamics of changes in the relative activity of [^{18}F]fluoride during the storage of [^{18}F]FDG is shown in Fig. 1. Note that an increase in the initial activity concentration from 1–2 to 4–5.5 GBq/mL leads to acceleration of radiation-induced dehalogenation of [^{18}F]FDG as shown both by the pharmacopoeial radio-TLC method [10] and by results of radio-HPLC, which has higher accuracy and reproducibility of the data. However, within the range of initial activity concentration under consideration, it can be seen that the [^{18}F]fluoride buildup plots almost coincide for the solutions containing 4.196 and 5.452 GBq/mL at the time of release of the batch. The absorbed dose for the latter radiopharmaceutical solution is 30.0% higher than that for the sample with an initial activity concentration of 4.196 GBq/mL and, therefore, higher [^{18}F]fluoride activities built-up during storage should be expected.

The obtained experimental data can be explained by differences in the concentrations of chemical impurities, primarily ethanol, in the radiopharmaceutical solutions studied. For example, the ethanol content in the [^{18}F]FDG solution with an initial activity concentration of 5.452 GBq/mL was 28.6% higher than in the drug with an activity of 4.196 GBq/mL at the batch release time (Table 1). Thus, the increase in the dose absorbed by the drug was offset by a higher concentration of the scavenger of radical products of water radiolysis.

The active involvement of ethanol in radiation-induced reactions during [^{18}F]FDG storage is also evidenced by the decrease in alcohol concentration that we observed in all the studied radiopharmaceutical batches, this process being most active within the first 2 hours after the batch release time. Moreover, Fig. 2 clearly shows that the chemical impurities formed by the autoradiolysis of [^{18}F]FDG include acetaldehyde, a product of radiation-induced transformations of ethanol in air-saturated solutions [13]. A comparison of the [^{18}F]fluoride buildup profiles (Fig. 1) and the data given in Table 1 reveals that aldehyde concentrations correlate with the percentage of [^{18}F]FDG dehalogenation. At the same storage time, the acetaldehyde

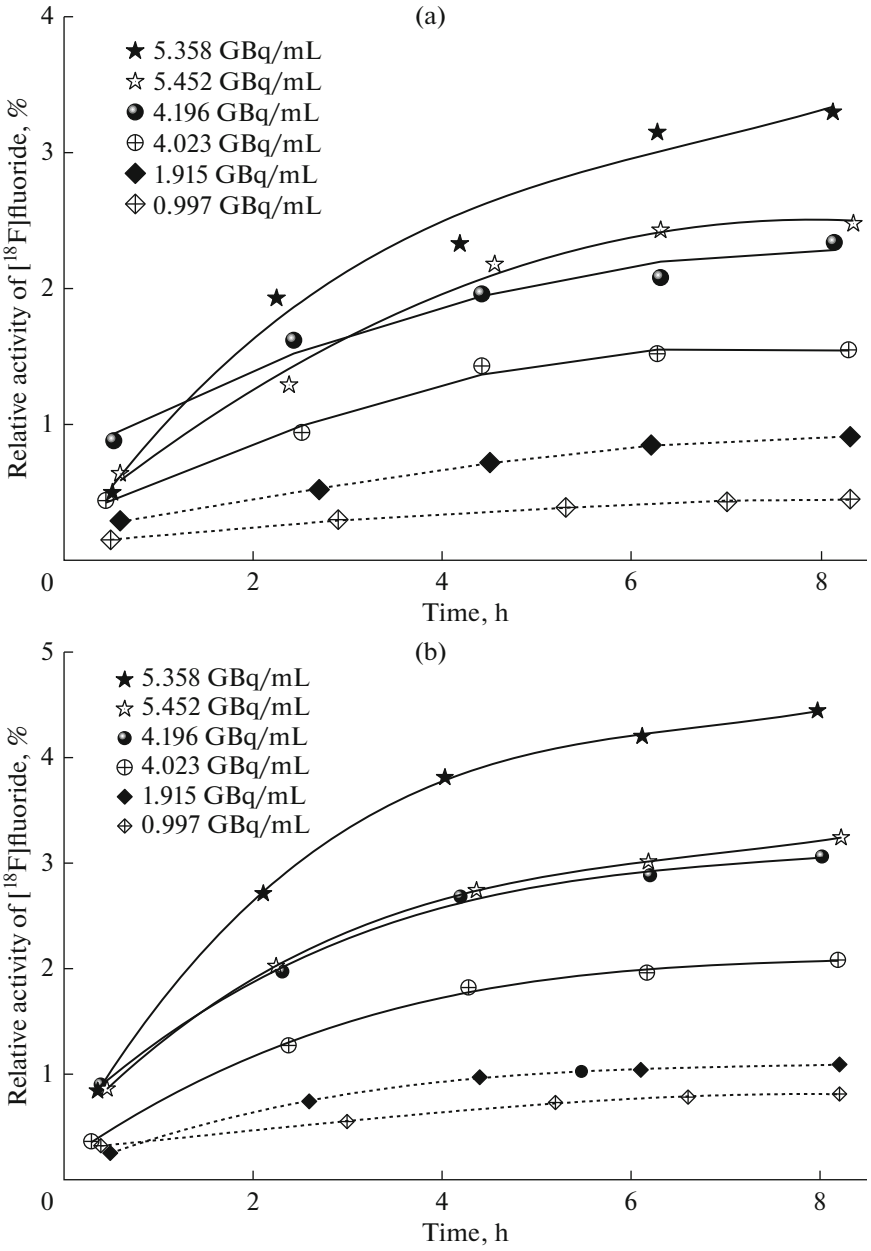


Fig. 1. Change in the relative activity of [18F]fluoride during storage of solutions of the radiopharmaceutical [18F]FDG depending on the initial activity concentration according to (a) radio-TLC and (b) radio-HPLC data.

content was higher in the samples with higher relative activities of [18F]fluoride. It should be noted separately that acetaldehyde is a highly toxic compound and its content in injectable drugs is strictly limited by the pharmacopeia to 50 ppm or 1.14×10^{-3} mol/L. Since we found that the concentration of acetaldehyde was close to the limiting concentration of 9.32×10^{-4} mol/L in one of the samples after 8 h of storage, with a further increase in the initial activity concentration of [18F]FDG, the drug may not stand pharmacopoeial tests not only for radiochemical purity, but also for the amount of chemical impurities.

Ethyl alcohol is a component of the alkaline hydrolyzing agent used for the synthesis of [18F]FDG on the IBA Synthera module according to the patented procedure [3], so that it can be introduced into the drug already at the stage of synthesis of the active pharmaceutical substance. In addition, ethanol can get into the radiopharmaceutical because of its active use as an aseptic in the radiopharmaceutical production, in particular, for daily treatment of transfer lines of the active pharmaceutical ingredient, surfaces of radiopharmaceutical synthesis modules, lead-shielded radiochemical hot cells, and other equipment in hot laboratories.

Table 1. Dynamics of changes in the concentration of acetaldehyde and ethanol during storage of the radiopharmaceutical [^{18}F]FDG

Initial activity concentration of [^{18}F]FDG, GBq/mL	Substance	Concentration of substance depending on storage time, mol/L × 10^4				
		0 h	2 h	4 h	6 h	8 h
4.196	Ethanol	150.7	121.7	105.0	109.8	98.5
	Acetaldehyde	–	–	–	–	–
4.023	Ethanol	205.2	151.5	151.1	134.6	132.8
	Acetaldehyde	0	2.05	3.64	3.86	5.23
5.452	Ethanol	193.7	148.3	120.2	117.4	114.3
	Acetaldehyde	0	3.64	4.77	6.14	6.82
5.358	Ethanol	75.4	63.0	57.4	52.0	46.5
	Acetaldehyde	0	6.59	7.05	8.64	9.32

Due to several routes of entry of ethanol, its concentration in the finished radiopharmaceutical of [^{18}F]FDG can vary two- to threefold from batch to batch, thereby directly affecting the intensity of autoradiolytic processes in the radiopharmaceutical and, hence, fluctuations in its radiochemical purity.

In addition to the initial activity concentration of [^{18}F]FDG and the ethanol concentration in the drug, the vial filling volume also affects the rate of radiation-induced dehalogenation. Table 2 shows the relative activity of [^{18}F]fluoride and radiochemical purity of [^{18}F]FDG after 8 h of storage of 1.5 mL and 8 mL of drug solutions in vials. It can be noted that for samples from the same batch of the radiopharmaceutical having identical ethanol concentrations and volumetric activity of the labeled compound at the time of release, an increase in volume from 1.5 to 8 mL leads to an

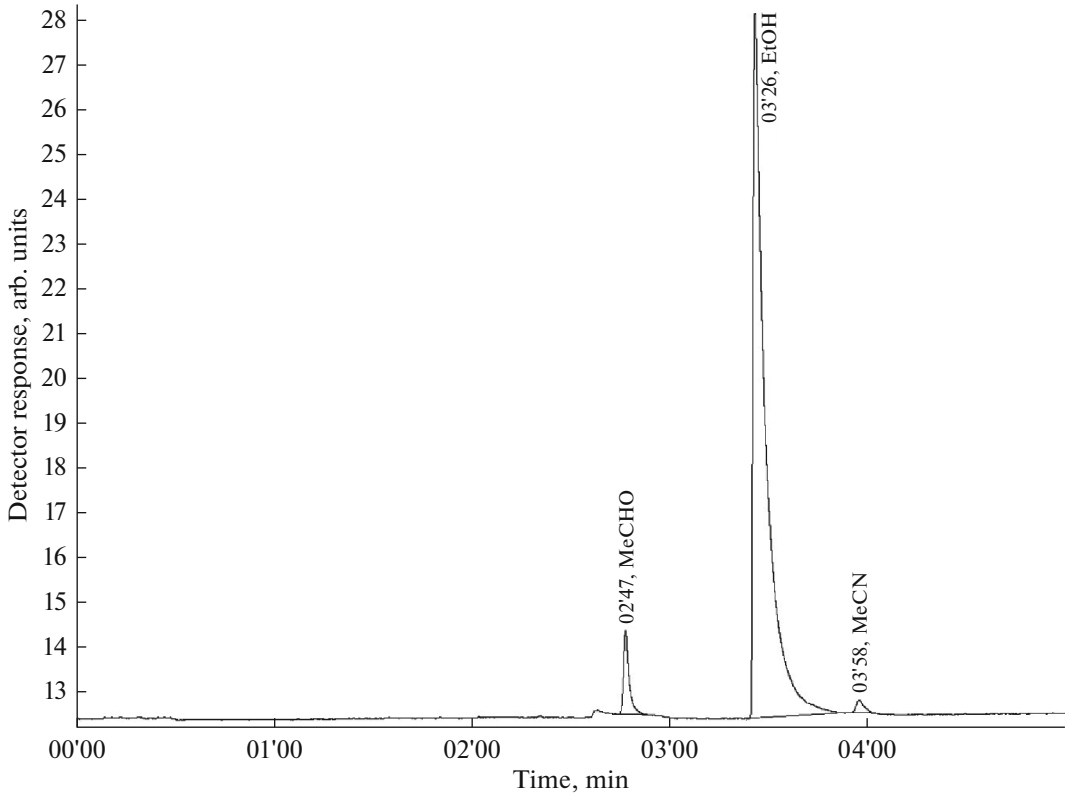


Fig. 2. Chromatogram of residual solvents and volatile compounds in the radiopharmaceutical [^{18}F]FDG with an initial activity concentration of 5.358 GBq/mL after 6 h of storage.

Table 2. The dependence of the fractional activity of [18F]fluoride and radiochemical purity of [18F]FDG after 8 h of storage on the volume of the radiopharmaceutical solution in the vial

Initial activity concentration of [18F]FDG, GBq/mL	Solution volume, mL	Radiopharmaceutical quality indicators			
		according to radio-HPLC data		according to radio-TLC data	
		fractional activity of $[^{18}F]F^-$, %	radio-chemical purity, %	fractional activity of $[^{18}F]F^-$, %	radio-chemical purity, %
4.196	1.5	3.07	96.71	2.34	97.66
	8	4.06	95.75	2.62	97.38
4.023	1.5	2.09	97.77	1.55	98.45
	8	3.56	96.44	2.50	97.50
5.452	1.5	3.25	96.56	2.48	97.52
	8	4.58	95.21	3.35	96.65
5.358	1.5	4.45	95.29	3.30	96.70
	8	6.75	92.90	5.08	94.92

increase in the relative activity of [18F]fluoride by 1–2.3% (by a factor 1.32–1.52) or 0.3–1.8% (by a factor of 1.12–1.54) according to the radio-HPLC or radio-TLC data, respectively. Moreover, for a vial with 8 mL of the [18F]FDG solution with an initial activity concentration of 5.358 GBq/mL, which had a low concentration of ethanol at the end of the synthesis, 7.54×10^{-3} mol/L, the fractional activity of [18F]fluoride according to radio-TLC data exceeds the pharmacopoeia established limit of 5% [10]. Thus, this [18F]FDG sample has an actual shelf life less than 8 h—the period specified in the registration dossier of the radiopharmaceutical. In this case, a vial from the same batch of the radiodrug with a volume of 1.5 mL has no deviations in the [18F]fluoride concentration at the time of expiration.

One of the reasons behind the observed intensification of the autoradiolytic degradation of [18F]FDG with an increase in the volume of filling the solution into vials can be associated with an increase in the dose absorbed by the drug. In 1.5 mL of the radiopharmaceutical, which approximately corresponds to 10% of the vial filling space, a part of positrons and secondary electrons lose their kinetic energy already in the glass. As the degree of filling of the vial increases, this "wall effect" will decrease. However, the average range of the positron emitted by 18F in water is as small as 0.6 mm [14], so it is difficult to explain the observed intensification of [18F]FDG autoradiolysis only by increasing the absorbed dose.

It can be noted that the increase in the relative activity of [18F]fluoride with an increase in the volume of the solution in the vial is the strongest for batches with high initial activity concentrations of [18F]FDG (Table 2), when oxygen is intensively consumed in water-organic systems saturated with air. Therefore, the observed effect of enhancement of [18F]FDG autoradiolysis can be associated with a change in oxygen concentration in the radiopharmaceutical.

Technologically achievable concentrations of [18F]FDG in solutions do not exceed 10^{-6} mol/L; therefore, this organofluorine compound is not able to win competition with oxygen for the hydrated electron. Consequently, in an aerated 0.9% NaCl aqueous physiological solution, the hydrated electron and the hydrogen atom will quantitatively react with oxygen via reactions (4) and (5). The processes of dissociative electron attachment characteristic for chlorinated, brominated, and iodinated organic compounds [15] will be unlikely for the air- saturated [18F]FDG drug.

$$H_2O \rightsquigarrow H_2O^{\bullet\oplus} + e_{aq}^{\ominus} \quad (1)$$

$$H_2O^{\bullet\oplus} + H_2O \rightarrow OH^{\bullet} + H_3O^{\oplus} \quad (2)$$

$$e_{aq}^{\ominus} + H_3O^{\oplus} \rightarrow H^{\bullet} + H_2O \quad (3)$$

$$e_{aq}^{\ominus} + O_2 \rightarrow O_2^{\bullet\ominus} \quad (4)$$

$$H^{\bullet} + O_2 \rightarrow HO_2^{\bullet} \quad (5)$$

$$HO_2^{\bullet} + H_2O \rightleftarrows O_2^{\bullet\ominus} + H_3O^{\oplus} \quad pKa = 4.8. \quad (6)$$

Interacting with chloride ions, $^{\bullet}OH$ radicals will turn into $Cl_2^{\bullet-}$ via reactions (7) and (8):

$$HO^{\bullet} + Cl^{\ominus} \rightarrow HO^{\ominus} + Cl^{\bullet} \quad (7)$$

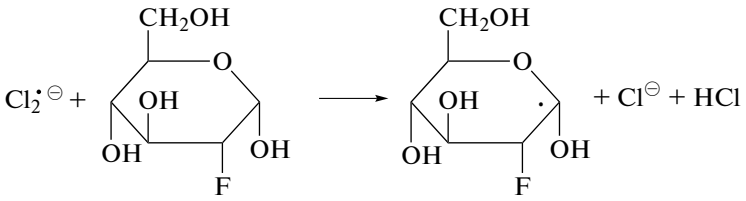
$$Cl^{\bullet} + Cl^{\ominus} \rightarrow Cl_2^{\bullet\ominus} \quad (8)$$

Like $^{\bullet}OH$, the radical anion $Cl_2^{\bullet-}$ exhibits strong oxidizing properties and the radiopharmaceutical will primarily interact with organic substances that occur at higher concentrations, in particular, with ethanol in reaction (9). Only a small part of $Cl_2^{\bullet-}$ will oxidize [18F]FDG, for example, via reaction (10).

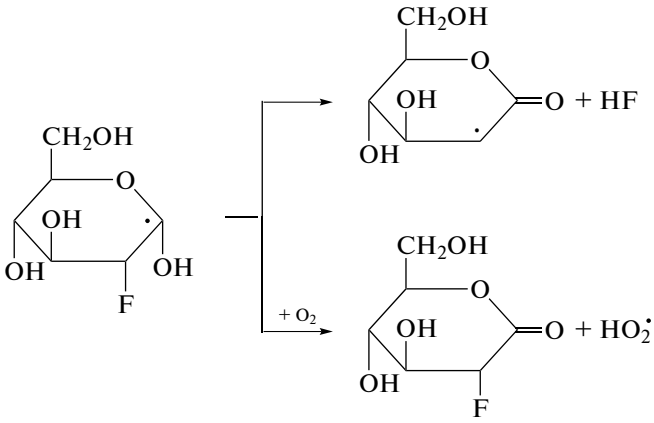
With regard to the molecular structure of [^{18}F]FDG, the most likely mechanism for the elimination of [^{18}F]fluoride is the double β-fragmentation of α-hydroxyl-containing carbon-centered radicals (α-HCR), for example, according to reaction (11). Similar processes are dominant in the dehalogenation of chloro- and bromohydrins [16], dehydration of monosaccharides [17], and cleavage of the O-glycosidic bond in glycosides and disaccharides [18–20].

In [18, 21], it was shown that, due to the oxidation of α-HCR, oxygen effectively inhibits free radical reactions of elimination of functional fragments from glycosides of various structures. It can be assumed that oxygen in our case will also inhibit the autoradiolytic dehalogenation of [^{18}F]FDG in aerated aqueous solutions by oxidation of α-HCR, for example, according to reaction (12).

$$Cl_2^{\bullet\ominus} + CH_3CH_2OH \longrightarrow CH_3\dot{C}HOH + Cl^{\ominus} + HCl \quad (9)$$



(10)



(11)

(12)

Using simple calculations, it can be shown that the concentration of dissolved oxygen in the [^{18}F]FDG drug will rapidly decrease because of radiation-induced processes. At an average energy of 0.25 MeV/positron emitted during the decay of fluorine-18 [14], 1.35×10^{15} eV mL^{-1}s^{-1} will be released in an [^{18}F]FDG solution with an activity concentration of 5.4 GBq/mL. Oxygen will be consumed in reactions (4) and (5) with the reducing radical products of water radiolysis, as well as in the interaction with carbon-centered radicals of organic compounds in reactions (12) and (13). Next, the $HO_2^{\bullet}$ and $O_2^{\bullet-}$ species will disproportionate to give hydrogen peroxide in reactions (14) and (15).

$$O_2 + CH_3\dot{C}HOH \rightarrow CH_3CHO + HO_2^{\bullet} \quad (13)$$

$$HO_2^{\bullet} + HO_2^{\bullet} \rightarrow O_2 + H_2O_2 \quad (14)$$

$$HO_2^{\bullet} + O_2^{\bullet\ominus} \rightarrow O_2 + HO_2^{\ominus}. \quad (15)$$

The material balance equation for the radiation-chemical yield of oxygen decomposition takes the following form $G(-O_2) = 0.5\,(G_{HO^{\bullet}} + G_{H^{\bullet}} + G e^{-}_{aq}) =$ 2.975 molecule/100 eV, and the oxygen consumption rate will be 4.02×10^{13} molecule mL^{-1}s^{-1}. At a concentration of oxygen dissolved in water of 2.58×10^{-4} mol/L (25°C), 3856 s or 1.07 h will be sufficient for its complete consumption. The above calculations use a simplified scheme of autoradiolytic transformations and do not take into account a number of other factors; however, they allow quantifying the intensity of consumption of dissolved oxygen. As its concentration in the [^{18}F]FDG drug decreases, oxygen begins to diffuse into the solution from the air contained in the vial. Therefore, the ratio of the volumes of the radiodrug solution and air in the vial directly affects the concentration of dissolved oxygen in the [^{18}F]FDG drug during storage.

Thus, the observed enhancement of autoradiolytic degradation of [^{18}F]FDG with an increase in the vol-

ume of the solution dispensed into vials can be associated with a decrease in the oxygen concentration in the radiopharmaceutical; this decrease results in shifting the ratio of the probabilities of reactions (11) and (12) to the former process—monoradical dehalogenation.

It should be noted that despite all efforts to inhibit autoradiolysis, batches of [^{18}F]FDG are occasionally released, for which the radiochemical purity and relative activity of [^{18}F]fluoride at the time of expiration can exceed the limits established by the Pharmacopoeia. As a rule, this is due to abnormal preparation conditions or problems with the delivery of the radiopharmaceutical. Note that cancellation of scheduled PET/CT examination with [^{18}F]FDG creates significant inconvenience for patients and reputation losses for clinics.

To exclude the radionuclide diagnostics artifacts associated with the presence of [^{18}F]fluoride in [^{18}F]FDG, as well as to reduce the radiation exposure of the red bone marrow in patients, we recommend using the adsorption method for purification of the radiopharmaceutical to remove this radioactive product of autoradiolysis, as given in the Experimental section of the paper. The described procedure can be easily implemented in any PET center and allows [^{18}F]fluoride to be completely removed from [^{18}F]FDG. The loss of the labeled compound and the degree of dilution are acceptable for radionuclide diagnostics. For example, when cleaning 1.27 mL of an [^{18}F]FDG solution with an activity of 380 MBq (equivalent to one diagnostic dose of radiopharmaceutical) containing 57 MBq of impurity [^{18}F]fluoride, 67.2% of the activity of [^{18}F]FDG is detected in the eluate, 20% remain on the cartridge, and the rest is in the syringe and on the filter. The activity concentration of [^{18}F]FDG decreases by a factor of 3.7 in this case. The drug remains sterile and apyrogenic because of the use of a filter with a pore size of 0.22 μm.

CONCLUSIONS

The kinetics of the autoradiolytic degradation of the radiopharmaceutical 2-[^{18}F]fluorodeoxyglucose ([^{18}F]FDG) in an air-saturated physiological solution with initial activity concentrations of 4.02–5.45 GBq/mL has been studied. It has been shown that an increase in the initial activity concentration or a decrease in the concentration of ethanol leads to more intense accumulation of radiolytic [^{18}F]fluoride and a decline in the radiochemical purity of the drug. During storage of the radiopharmaceutical, a decrease in the concentration of ethanol and the formation of acetaldehyde, a product of radiation-induced transformations of ethanol in the presence of oxygen, have been observed, with the aldehyde concentration correlating with the relative activity of [^{18}F]fluoride. It has been found that in the case of storage of [^{18}F]FDG samples with the same initial activity concentration in sealed 15-mL vials, the relative activity of [^{18}F]fluoride and, accordingly, the degree of autoradiolytic decomposition of the starting labeled compound after 8 h are significantly higher in solutions of 8 mL in volume than in 1.5-mL solutions. This difference may be due to both the higher dose absorbed by the drug and the inhibitory effect of oxygen on the process of radiation-induced dehalogenation. To ensure the quality of the radiopharmaceutical, the adsorption method for purifying [^{18}]FDG to remove [^{18}F]fluoride under the conditions of an operating PET center has been proposed, which ensures the preservation of the aseptics and apyrogenicity of the injectable drug.

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