RADIOPHARMACEUTICAL CHEMISTRY AT PNPI SYNCHROCYCLOTRON

$\boxed{\text{V.M.Zaitsev}}$, E.G.Alekseev, V.S.Guselnikov, T.V.Koneva

Introduction

Launching of the PNPI synchrocyclotron in 1970 has coincided with the beginning of a new stage in the development of radiopharmaceutical chemistry. In the previous period the development of radiopharmacy was called forth by the construction of nuclear reactors shortly after the World War II and by the organization of the radionuclide production at them. A number of radionuclides (^{75}Se, ^{131}I, ^{203}Hg and etc.) and radiopharmaceuticals prepared on their basis have found a wide application in medicine.

The appearance at the end of 60s of accelerators of charged particles suitable for the radionuclide production has become a new impulse in the development of radiopharmaceutical chemistry. It was caused by significant advantages which the cyclotron-produced radionuclides had. An absence of corpuscular radiation and short half-lives allowed to lower the radiation dose, both to the organ under investigation and to the whole patient's body. This led to the appearance of new radiopharmaceuticals, creation of which on the basis of the reactor-produced radionuclides was impossible because of considerations of the extreme radiation dose to the patient. Besides, the energy of γ-rays of the cyclotron-produced radionuclides was optimal for the registration with the used apparatus, that allowed to obtain better diagnostic information.

The PNPI synchrocyclotron was built for performing fundamental studies in physics of elementary particles and nuclear physics. It has the proton energy of 1 GeV and the beam intensity of 1 μA. And though the accelerator with such parameters is not very much suitable for the radionuclide production, at that period it was the only accelerator of charged particles in the North-Western region, which could be used for these purposes. That is why organization of investigations in the area of radiopharmaceutical chemistry was highly topical. It appeared that not only the development of methods of production and control of radiopharmaceuticals was of practical importance but also their output by small batches for the realization of experimental and clinical tests and for the consequent clinical use.

Production of ^{123}I radionuclide

When analyzing a possibility of production of radionuclides for nuclear medicine at the available for these purposes accelerator of charged particles, it is necessary to take into account its specific features. Such features of the PNPI synchrocyclotron are a rather high energy of the accelerated protons and a relatively small intensity of the extracted proton beam. At the proton energy of 1 GeV the spallation reactions proceeding in the target lead to formation of a complex mixture of radioisotopes of both the element of interest and elements with a smaller atomic number. It hampers the production of radionuclides with the radionuclide purity necessary for medicine. And a small intensity of the proton beam makes necessary to use massive targets (hundreds grams) for the irradiation, fast radiochemical processing of which being a difficult problem. These circumstances limit extremely the list of radionuclides which could be produced at the PNPI synchrocyclotron for the medical purposes.

One of such radionuclides, the production of which is possible at the PNPI synchrocyclotron, is ^{123}I. The matter is that ^{123}I can be produced through the disintegration of its precursor ^{123}Xe ($T_{1/2} = 2.1$ h). Such a method of production of ^{123}I allows us to avoid the radiochemical processing of the irradiated target, since the xenon radioisotopes can be extracted effectively from the target by a helium stream during the irradiation and transported to large distances to the place of collection and processing.

The other important circumstance, having defined the choice, was the fact that ^{123}I is the most suitable for the purposes of radionuclide diagnostics "*in vivo*" – because of its specific nuclear-physical characteristics among numerous radioisotopes of iodine. ^{123}I has $T_{1/2} = 13.3$ h and disintegrates by the electron capture with the emission of γ-radiation with the energy of 159 keV. Such an energy of γ-quanta is optimal for passing through the biological tissue and enables to obtain pictures of ^{123}I distribution in the organism with a high space resolution. Besides, in comparison with the other isotope of iodine ^{131}I widely used for similar purposes, the radiation dose is reduced tens times at the administration of ^{123}I.

With the purpose of choosing the most suitable target for ^{123}Xe production, the cumulative yields of ^{123}Xe and ^{125}Xe (the source of the main long-lived ^{125}I admixture) from caesium, barium and lanthanum were determined. The obtained results are presented in Table 1 and testify that the best target for ^{123}Xe production by spallation reactions at the 1 GeV proton energy is caesium. In this case ^{123}I can be produced with the biggest yield and the least contents of ^{125}I.

Table 1
The cumulative yields of ^{123}Xe and ^{125}Xe, mb

Isotope	Target		
	Cs	Ba	La
^{123}Xe	17 ± 2	15 ± 2	10 ± 1.5
^{125}Xe	19 ± 2	22 ± 3	13 ± 2

The production of ^{123}I (^{123}Xe) was performed at a setup, the scheme of which is shown in Fig. 1. The plan of its disposition at the PNPI accelerator complex is given here also. The setup consists of a target facility, a system for ^{123}Xe transportation by a helium stream, a monitoring system of the gas stream, a system of clearing and a trap for collection of ^{123}Xe (^{123}I). The target facility represents a cylinder of the stainless steel filled with a concentrated caesium chloride water solution.

The method of ^{123}I production developed by the authors consists in the extraction of ^{123}Xe together with other xenon isotopes by a helium stream from the irradiated target, transportation it through a polyethylene hose (of 120 m length) to the radiochemical laboratory for the consequent purification and absorption in the U-shaped trap cooled with the liquid nitrogen. The collection of ^{123}Xe is carried out for 4 hours, then the accumulation of ^{123}I lasts for 2 hours, nondisintegrated xenon radioisotopes are removed and, finally, the disintegration of ^{121}I and other short-lived iodine isotopes occurs for 14–17 hours. The produced ^{123}I has the radionuclide purity better than 98%. Later on, ^{123}I is extracted from the trap and used for the synthesis of various radiopharmaceuticals [1–3].

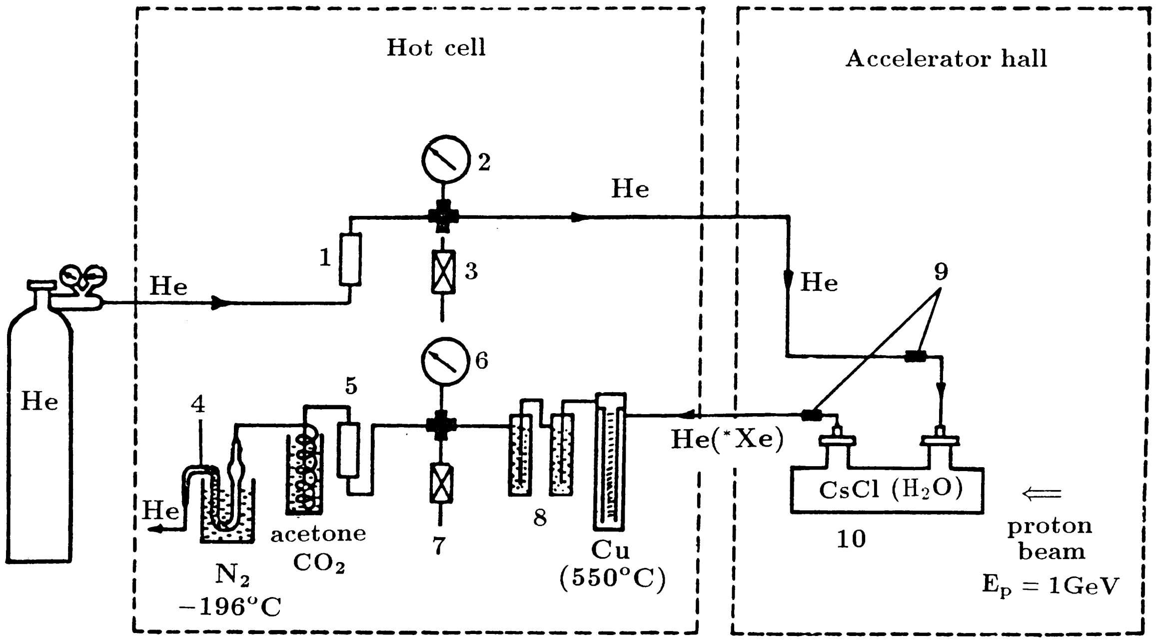


Fig. 1. Scheme of the setup for production of ^{123}Xe (^{123}I) on-line with the synchrocyclotron. 1,5 – rotameters, 2 – entry pressure gauge, 3 – entry safety-valve, 4 – trap for Xe*, 6 – exit pressure gauge, 7 – exit safety-valve, 8 – dryers, 9 – connectors, 10 – target.

In the USSR, the production of ^{123}I was realized for the first time at the PNPI synchrocyclotron [4].

Radiopharmaceutical for thyroid diagnosis

Iodine is known to belong to the most important bioelements being the constituent of vital hormones of the thyroid gland. Therefore, when a radioactive isotope of the iodine is injected into an organism, it is absorbed intensively as an organ specific isotope. The most convenient form for the injection is the sodium iodide solution. Registering γ-radiation of an iodine isotope, it is possible to receive a valuable information about the condition of the thyroid gland. It is the reason that the solution of no-carrier-added sodium radioiodide (at first with ^{131}I, then with ^{123}I) is the irreplaceable radiopharmaceutical for the thyroid diagnosis already during several decades.

Using the radionuclide ^{123}I produced at the PNPI synchrocyclotron, we developed a method of obtaining of the radiopharmaceutical sodium [^{123}I]iodide solution. The method consists in absorption of ^{123}Xe in a trap with aluminum oxide, disintegration of ^{123}Xe into ^{123}I and eluation of Na^{123}I by a passage of a NaOH solution with pH = 8.5–9.0 through the trap. The solution is collected in serum vials, sealed hermetically and sterilized at 120°C for one hour.

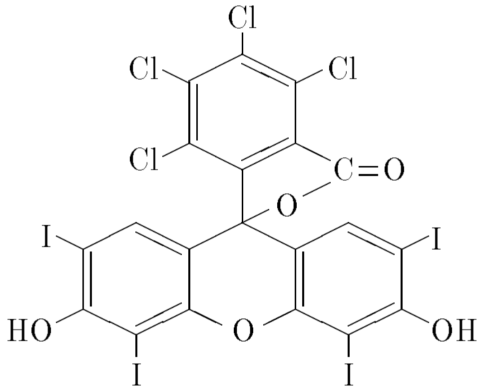
The aluminum oxide L 40/250, which is neutral for the chromatography ("Chemapol", Czechoslovakia), treated preliminary by the NaOH solution with pH = 9, is used as a rule for the trap filling. The use of the aluminum oxide as a sorbent allows not only to capture effectively ^{123}Xe but also to purify the preparation from both the radionuclide (^{119}Te, ^{121}Te) and radiochemical admixtures (oxidized forms of ^{123}I) which are absorbed irreversibly by the aluminum oxide.

The radiopharmaceutical $Na^{123}I$ solution produced this way has $pH = 8.0 - 8.5$ and the radiochemical purity $> 98\%$ [3,4]. After carrying out the experimental-clinical tests at CRIRR [1] and RIO [2], this radiopharmaceutical was allowed by the USSR Ministry of Public Health for a wide clinical application [5,6].

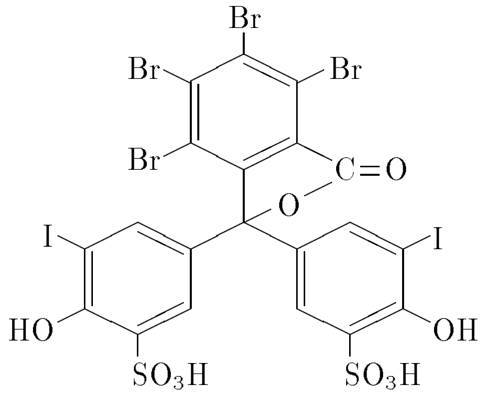
Besides, the $Na^{123}I$ solution can be used as an initial raw material for production of other radiopharmaceuticals (rose bengal, fatty acids etc.). In some cases for the synthesis of iodo-organic radiopharmaceuticals it is more convenient to have $Na^{123}I$ in an organic solvent. In this case ^{123}Xe is absorbed on silica gel and an eluation of $Na^{123}I$ is carried out by an organic solvent (acetone, methanol, ethanol) [7].

Radiopharmaceuticals for hepatobiliary system diagnosis

Among labelled iodoorganic compounds tetrachlorotetraiodofluorescein (I) has found a wide application as a radiopharmaceutical. This compound labelled by ^{131}I (which is usually called as "rose bengal") is used for the radionuclide diagnosis of the liver and biliary ducts. In this connection, the production of this radiopharmaceutical with ^{123}I is of practical importance.



(I)



(II)

Usually the radioiodination of the rose bengal is carried out by the isotope exchange reaction with iodine electrophilic species in a solution. In this case, $Na^{123}I$ with a high volumetric activity is required, which is not always available. Therefore, we have considered a possibility of using for this purpose of the heterogeneous isotope exchange reaction, the dynamic version of this reaction between the rose bengal absorbed on a solid carrier and iodine electrophilic species labelled by long-lived ^{125}I being investigated.

The study of influence of various parameters on the yield of the [^{125}I]rose bengal has not only confirmed that the involved radiopharmaceutical could be produced in such a way but has also allowed to select the optimum conditions of carrying out the radioiodination process.

[1] Central Research Institute of Roentgenology and Radiology, the USSR Ministry of Public Health
[2] N.N.Petrov Research Institute of Oncology, the USSR Ministry of Public Health

Fig. 2 shows how the [^{125}I]rose bengal yield depends on these parameters: amount of the rose bengal on the solid carrier (Fig. 2a), the concentration of the oxidant KIO_3 (Fig. 2b) and hydrochloric acid (Fig. 2d), the flow rate of the radioiodination mixture through the column with the radioiodinated compounds on the solid carrier (Fig. 2c). Thus, the developed method makes it possible to produce the [^{123}I] rose bengal with the use of diluted Na^{123}I solutions, the desired product being obtained with larger volumetric activity because it can be eluated from the solid carrier by smaller amount of a solution [8,9].

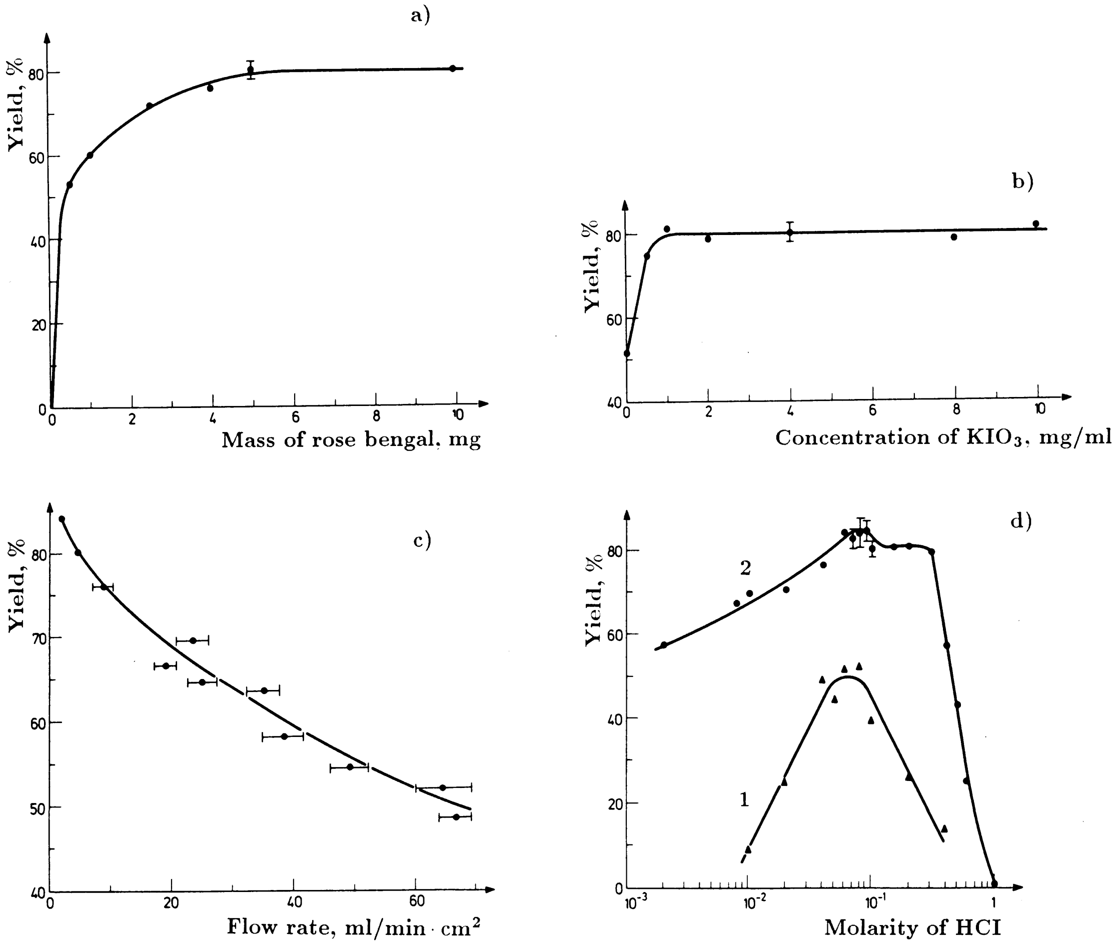


Fig. 2. Dependences of [^{125}]RB yield on: a) the amount of rose bengal absorbed on the solid carrier, b) the KIO_3 concentration, c) the flow rate of the radioiodination solution, d) the HCl concentration (1 – room temperature, 2 – 100°C).

In connection with the ^{123}I production at the PNPI synchrocyclotron through the preliminary extraction of ^{123}Xe, it was of practical interest to combine producing ^{123}I and introducing it in the composition of the rose bengal by the heterogeneous isotope exchange reaction. But as the nature of the solid carrier can influence essentially the chemical form of stabilization of ^{123}I which is formed through the ^{123}Xe disintegration, we determined the [^{123}I] rose bengal yields with the use of various organic and inorganic carriers. The data, presented in Table 2, testify that the involved labelled preparation can be obtained with the yield of 85–86% on a number of inorganic carriers. The proposed method of radioiodination, due to combining the operations of producing ^{123}I and introducing it in the composition of the rose bengal, is convenient in the use and consists in several simple operations: a treatment of the rose bengal on the solid carrier by hydrochoric acid, an absorption of ^{123}Xe with a simultaneous disintegration it in ^{123}I and a radioiodination by passing of the hydrochloric solution of KIO_3. After the eluation of the labelled preparation by an alkaline solution and an additional purification by reprecipitation, the [^{123}I] rose bengal is led to the form necessary for an injection, and it is sterilized. The radiochemical purity of the preparations produced is $> 90\%$ [10].

Table 2
Yields of the [^{123}I] rose bengal for different carriers

Carrier, amount of RB	Yield of [^{123}I]RB
Organic carriers	
2%RB on polychrom–1	77 ± 2
4%RB on polysorb–1	3 ± 1
8%RB on polyethylene powder	24 ± 2
Inorganic carriers	
4%RB on silochrom S–80	85 ± 2
3%RB on silochrom S–120	81 ± 2
2%RB on porochrom–1	71 ± 4
4%RB on celite–545	85 ± 2
2%RB on chezasorb–AW	85 ± 2
2%RB on dinochrom–P	86 ± 2

The radiopharmaceutical [^{123}I]rose bengal produced at the PNPI synchrocyclotron has passed experimental-clinical tests at CRIRR and RIO, and now it is allowed for clinical applications [11,12].

Another radiopharmaceutical for the radionuclide diagnosis of hepatobiliary system is labelled diiodobromsulphalein (II). In comparison with the labelled rose bengal, it is characterized by a faster accumulation in the liver. To search for the optimum conditions of its production, we performed an investigation of the isotope exchange reaction in the system diiodobromsulphalein–radioiodide–HIO_3–HCl using a mathematical model for the process. The obtained mathematical model of the radioiodination process in a canonical form is the equation of an ellipsoid of rotation in which all coefficients for independent variables are less than zero. In such cases, in the optimum region there exists only one extremum point, which is the centre of the ellipsoid. When carrying out the radioiodination reaction in these conditions (the room temperature, the duration of 1 min etc.), the labelled diiodobromsulphalein yield can reach $> 99\%$. Owing to such simplicity and rapidity this method can be used in producing the radiopharmaceutical with ultra short-lived isotope of ^{122}I ($T_{1/2} = 3.6$ min) for the positron emission tomography of the liver.

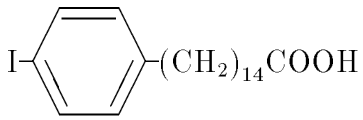
Radiopharmaceuticals for nuclear cardiology

It is known that the power necessities of the heart are satisfied by 90% owing to oxidation of fatty acids. Hence obtaining the information about this biochemical process can play an important role in the early diagnosis and effective treatment of heart diseases. In this respect the nuclear cardiology methods based on the use of fatty acids labelled by ^{123}I and by other radionuclides are unique.

For the use in the nuclear cardiology, a number of iodinated in ω-position carboxylic acids, which are chemical analogs of natural fatty acids, was offered. As such an analog of the natural palmitic acid for the production of a radiopharmaceutical, we have investigated 15–iodopentadecanoic acid labelled by ^{123}I (III). The investigation of kinetic characteristics of the process of its radioiodination in various organic solvents and a comparison of the obtained data with the similar data published in the literature for other processes have shown that the processes of nucleophilic isotope exchange in aprotic solvents (acetone etc.) and in a melt seem to be the most perspective ones [13,14]. The method of the production of the radiopharmaceutical under consideration developed by us is based on these two processes. The method is simple and fast and enables us to produce 15–[^{123}I] iodopentadecanoic acid with the radiochemical purity $> 95\%$ and the required specific activity.

15–I–$(CH_2)_{14}$COOH

(III)



(IV)

Since the solubility of the 15–iodopentadecanoic acid in aqueous solutions is small, for obtaining the injection form, the labelled acid in ethanol was dissolved in 10% albumin. The sterilization of the radiopharmaceutical was carried out by filtering through a 0.22 μm Millipore filter. At present the clinical tests of this preparation are passing at CRIRR.

One of the disadvantages of the aliphatic acids radioiodinated in ω–position is their fast metabolism in the myocardium leading to the deiodination and appearance of a high background radioactivity of radioiodide in the blood, which hampers obtaining the high-performance images of the heart. An alternative concept permitting to avoid the metabolic liberation of radioiodide consists in introducing a phenyl group into an alkyl chain. In this case, an iodine atom is strongly bound chemically to an aromatic ring, and iodobenzoic acid, formed in the result of the metabolism, is eliminated fast by the kidneys without creating background problems. A representative of this radiopharmaceutical group is the 15–(p–iodophenyl)pentadecanoic acid (IV), the method of its production is being developed by us now.

Quality control of radiopharmaceuticals

Among the parameters defining the quality of the produced radiopharmaceuticals, an important role is played by the chemical purity of raw materials, as well as by the radionuclide and radiochemical purity of the finished preparation. The determination of the radionuclide purity by the method of γ-spectroscopy with semiconductor detectors does not present any problem. The measurement of the activity of ^{123}I and ^{121}I is carried out at the moment of the quality control, whereas the measurement of the activity of ^{125}I emitting X-rays is possible only after the full disintegration of ^{123}I. As to the chemical purity of the raw materials and the radiochemical purity of the finished preparations, the development of special analytical methods is necessary for each radiopharmaceutical.

To determine the chemical purity of the raw materials, the high performance liquid chromatography with the spectrophotometric detection was used since this method enables us to detect chemical admixtures on the level of 0.1%. As a rule, the analyses were carried out at columns with silica gel–C_{18} , the mixtures of methanol with water, the acetic acid (15–iodopentadecanoic and 15–(p–iodophenyl)pentadecanoic acids) and the acetonitrile-phosphate buffer solution with addition of an ion-pair agent (rose bengal, diiodobromsulphalein) being used as eluents.

The radiochemical purity of radiopharmaceuticals was determined by the method of the thin-layer chromatography with the radiometric detection. Owing to the simplicity of the instrument design, this method allows to carry out simultaneously several analyses, and thereby ensures obtaining fast and reliable results, which is especially important for operation with short-lived radionuclides. The conditions for separation of the main component and radiochemical admixtures by this method, as well as appropriate values of R_f, were presented in the earlier quoted literature. The optimization of the analysis conditions was performed with the help of a mathematical model of the process [15,16].

Production of ^{77}Br radionuclide

The radionuclide ^{77}Br being of interest for the nuclear medicine can be produced through the preliminary extraction of its precursor ^{77}Kr from the target, similar as ^{123}I. The cumulative yield of this radionuclide in a sequence of Rb–Mo depends weakly on the nuclear composition of the target [17]. Therefore the choice of the target substance is defined mostly by the availability of compounds and their solubility. Taking this into account, for the estimation of possibility of the ^{77}Br radionuclide production, its yield was measured at the PNPI synchrocyclotron for a massive target made of strontium nitrate. The determination of the ^{77}Br yield was carried out at the setup for the ^{123}I production.

Taking into consideration that the ^{77}Br yield amounts to 5 $\text{MBq} \cdot \mu\text{A}^{-1} \cdot \text{h}^{-1}$, and that the maximum intensity of the proton beam is 1 μA, the production of ^{77}Br at the PNPI synchrocyclotron in amounts necessary for the medical use seems to be an extremely expensive task.

Future of the radiopharmaceutical chemistry at HEPD PNPI

The further development of the radiopharmaceutical chemistry at the High Energy Physics Division of PNPI has good perspectives. This development is ensured, first, with the possibility to use the cyclotron MGC–20 available at CRIRR and, second, with the creation of the isochronous cyclotron at PNPI, which will allow to increase the radionuclide production.

The cyclotron MGC–20 has the extracted beam of protons with the energy E_p = 18 MeV and the intensity up to 50 μA. At present, the ^{123}I production up to 500 mCi per run is being established at this accelerator. The direct reaction ^{123}Te(p,n)^{123}I with isolation of ^{123}I by the dry distillation method from melted TeO_2 in an air (oxygen) stream is used. On this base, the production of four radiopharmaceuticals will be organized: of the sodium [^{123}I]iodide, sodium o–[^{123}I]iodohippurate, [^{123}I]rose bengal and 15–[^{123}I]iodopentadecanoic acid.

The isochronous cyclotron with the varied proton energy up to 80 MeV and the extracted beam intensity up to 100 μA, which is under construction now in PNPI, will expand possibilities available for the production of the radionuclides and radiopharmaceuticals on their basis. First of all, it concerns radionuclides, production of which is impossible or unprofitable at the cyclotron MGC–20, such as ^{67}Ga, ^{111}In, ^{201}Tl etc. At present, the methodical studies of different technologies for the production of these radionuclides are being carried out at the PNPI synchrocyclotron. In particular, the use of the extraction technologies with oxygen-containing extractants (butyl acetate etc.) for the isolation of ^{201}Tl from bismuth and lead targets proved to be perspective [18]. For the isolation of ^{111}In from tin targets, the application of extraction by di–2–(ethylhexyl)phosphoric acid from the HF solutions and oxygen-containing solvents (simple and complex ethers) from the HBr and HI solutions is effective. Besides, the production of a number of other perspective radionuclides is possible at this accelerator. Thus, the launching of the isochronous cyclotron will give unique possibilities for the development of the radiopharmaceutical chemistry at HEPD PNPI.

References

[1] *E.G.Alekseev, V.M.Zaitsev, A.M.Zolotov.* // Radiochem. Radioanal. Lett., 1978. V.36. P.125.

[2] *E.G.Alekseev, A.A.Volkov, V.M.Zaitsev, A.M.Zolotov, E.I.Komarov, V.I.Tikhonov.* // Radiochem. Radioanal. Lett., 1978. V.36. P.133.

[3] *E.G.Alekseev, A.V.Artiushkin, A.A.Volkov, V.S.Guselnikov, V.M.Zaitsev, T.V.Koneva, T.A.Kovrigkina, V.S.Kiaher, I.S.Osipov, G.D.Hudadov, A.V.Iulbarisov, L.A.Iakovleva.* Preprint LNPI–726, Leningrad, 1981. 27p.

[4] *E.G.Alekseev, V.M.Zaitsev, A.M.Zolotov, V.I.Tikhonov.* Avtorskoe Svidetel'stwo No 598301, 1976.

[5] *E.I.Komarov, A.A.Volkov, E.G.Alekseev, V.M.Zaitsev, L.A.Kaschenko, E.A.Lialin, S.N.Koliubaeva, L.G.Undalova.* // Med. radiol., 1978. V.23. P.28.

[6] *A.A.Volkov, A.V. Iulbarisov, V.M.Zaitsev, E.G.Alekseev, A.V.Artiushkin, T.A.Kovrigkina, V.S.Kiaher, I.S.Osipov, G.D.Hudadov, L.A.Iakovleva.* // Med. radiol., 1982. V.27. P.34.

[7] *E.G.Alekseev, V.S.Guselnikov, V.M.Zaitsev.* Avtorskoe Svidetel'stwo No 1709399, 1989.

[8] *E.G.Alekseev, V.M.Zaitsev.* // J. Radioanal. Chem., 1983. V.78. P.53.

[9] *E.G.Alekseev, V.M.Zaitsev.* Avtorskoe Svidetel'stwo No 792878, 1978.

[10] *E.G.Alekseev, V.S.Guselnikov, V.M.Zaitsev.* Avtorskoe Svidetel'stwo No 992516, 1981.

[11] *A.A.Volkov, V.M.Zaitsev, A.A.Kozlov, E.G.Alekseev, V.S.Guselnikov, I.S.Osipov, T.V.Koneva, G.F.Gornaeva, L.A.Iakovleva.* // Med. radiol., 1985. V.30. P.66.

[12] *A.A.Volkov, E.I.Komarov, A.A.Kozlov, S.A.Bikov, A.V.Artiushkin, G.V.Skudrit, L.A.Iakovleva, O.M.Morozova, I.S.Osipov, N.F.Tarasov, V.M.Zaitsev, E.G.Alekseev, V.S.Guselnikov, G.S.Dubrovina.* // Med. radiol., 1989. V.34. P.14.

[13] *V.S. Guselnikov, V.I.Efimovih, V.M.Zaitsev, A.P.Kaschuk, T.V.Koneva, V.E.Popov, S.A.Pavlenko, A.H.Prokofiev, V.A.Serova.* Preprint LNPI–1352, Leningrad, 1987. 16p.

[14] *V.S.Guselnikov, V.M.Zaitsev, T.V.Koneva.* Preprint LNPI–1624, Leningrad, 1990. 14p.

[15] *E.G.Alekseev.* // Chem. Pharm. J., 1988. V.22. P.1136.

[16] *E.G.Alekseev.* // Chem. Pharm. J., 1989. V.23. P.879.

[17] *E.G.Alekseev, V.S.Guselnikov, V.M.Zaitsev, L.A.Ilin, T.V.Koneva.* // Radiochemistry, 1984. V.26. P.667.

[18] *V.S.Guselnikov, V.M.Zaitsev, S.A.Kisel, T.V.Koneva.* // Radiochemistry, 1995. V.37. P.173.