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A method of obtaining a kit for the Technetium-99m Generator based on copper (I) salt 2-methoxyisobutyl-isonitrile tetrafluoroborate (MIBI) with divalent tin, for the preparation of a diagnostic agent

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ABSTRACT: A technology has been developed for producing a kit of 2-methoxyisobutyl isonitrile tetrafluoroborate with divalent tin (MIBI-Sn(II)) for the Technetium-99m Generator, which guarantees consistently high quality characteristics with sterility and pyrogen-free final product in the form of a lyophilisate. The influence of the concentration of the reducing agent Sn^{2+} complexing agent of 2-methoxyisobutyl isonitrile tetrafluoroborate (MIBI) was studied the efficiency of formation of the MIBI^{99m}Tc complex in solutions is in the range of 0.01-0.12 mg/ml and 0.4-1.2 mg/ml, respectively, and the pH of the medium is 5.0-6.0. The formation efficiency of the stable MIBI^{99m}Tc complex was established to be more than 99.0% in kits containing: Sn2+ 0.06 mg/ml and MIBI 0.8 mg/ml and solution pH 5.5 after 20 minutes of boiling in a water bath of incubation after adding to the kit radioactive 99mTcO4^{-}. The stability of the kit MIBI-Sn(II) stored for 12 months was determined by obtaining the radiopharmaceutical MIBI^{99m}Tc. Also, a draft regulatory and technical documentation for quality control has been developed.

KEYWORDS: radiopharmaceutical; substance; radionuclide; technetium-99m.

I. INTRODUCTION

The wide prevalence of coronary heart disease (CHD), which tends to increase among people of working age, the emergence and increase in the frequency of atypical, including painless forms of CHD, necessitate the use of new, if possible, atraumatic methods for diagnosing this disease.
Currently, radionuclide methods for studying the cardiovascular system are increasingly used in clinical practice. In addition to measuring central hemodynamics, it became possible to assess the contractility of individual cardiac chambers and segments, visualize foci of acute infarction and myocardial ischemia.
Currently, the main choice among radionuclides around the world for the synthesis of diagnostic radiopharmaceuticals (RPs) is focused on the radionuclide ^{99m}Tc, which is explained by its optimal nuclear physical properties. One of the radiopharmaceuticals based on the ^{99m}Tc radionuclide is labeled copper (I) salt 2-methoxyisobutyl-isonitrile tetrafluoroborate (MIBI^{99m}Tc).
This complex compound in the form of a lyophilisate, after labeling with technetium-99m radionuclide, is used in medicine for diagnostic purposes, used to assess myocardial perfusion in various pathological processes that lead to disruption of its blood supply (coronary atherosclerosis, acute myocardial infarction, post-infarction and post-myocardial cardiosclerosis, ischemic heart disease), as well as for imaging malignant neoplasms of the lungs and breast.

There is a known method for the synthesis of a complex compound based on the ligand of copper salt 2-methoxyisobutyl-isonitrile tetrafluoroborate (MIBI) with divalent tin (Sn^{2+}), used to obtain a lyophilisate for the Technetium-99m Generator, performed by various approaches[1-10].

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This work is devoted to the research and development of a sequential cold kit of MIBI-Sn(II) for the Technetium-99m Generator for the preparation of diagnostic agents, guaranteeing the receipt of consistently high quality characteristics while ensuring the sterility and pyrogen-freeness of the final product in the form of a solution that entails additional sterilization after the production of a lyophilisate from it. . In addition, study the effectiveness of the label kit and the kinetics of the educational complex (MIBI^{99m}Tc), and the stability of the kit during storage.

II. METHODS, MATERIALS, REAGENTS AND EQUIPMENT

The following chemical reagents were used in the preparation of the kit MIBI-Sn(II):
-Tetrakis (copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate), purity not less than 98%, CYMIT QUÍMICA S.L.;
- tin dichloride, purity not less than 99%, Sigma Aldrich;
Radiometric measurements of the samples were carried out on a gamma spectrometer with a semiconductor Ge(Li), detector and Aspect software using a spectrometric device SU-03P No. 0037-06. The preparation of experimental batches of the kit MIBI-Sn(II) was carried out in a reaction unit. Solutions of the kit dispensed in vials with a capacity of 10 cm^3, were lyophilized in the sublimation devices Epsilon2-16D. Qualitative and quantitative characteristics of the main substance of copper salt 2-methoxyisobutyl-isonitrile tetrafluoroborate (MIBI) and excipients were determined by the spectrophotometric method on the Genesys 10S UV-Vis spectrophotometer, (Thermo scientific, USA).

III. METHOD OF OBTAINING A KIT BASED ON COPPER SALT 2-METHOXYISOBUTYL-ISONITRILE TETRAFLUOROBORATE (MIBI) AND THE REDUCING AGENT Sn^{2+}

Experimental batches of the kit MIBI-Sn(II) were prepared in a reaction unit (Figure 1), which consists of a container for the cleaning mixture (1), a glass for the synthesis of the kit solution (2) on a magnetic stirrer (3), a tube for supplying argon (4), through which purified argon is supplied from a vessel with a cleaning mixture, a tube for supplying a solution of the kit, equipped with a nozzle with a 0.22 μm membrane filter (5), installed in a conical flask with an outlet connected to a vacuum pump designed to collect a solution of the complex compound (6).

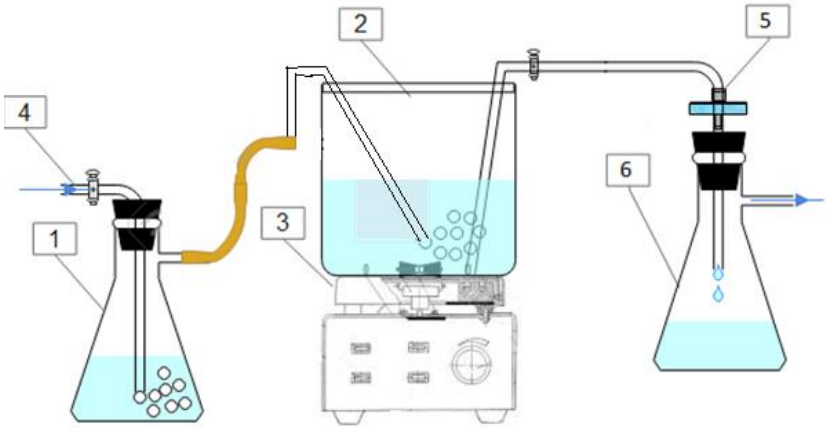

Fig. 1. reaction unit for the synthesis of the kit MIBI-Sn(II).

The synthesis was carried out in a class B clean room, in a laminar flow hood.

The synthesis of the MIBI-Sn(II) radiopharmaceutical kit in the form of a lyophilisate was carried out by adding 100 ml of deoxygenated water for injection to a beaker standing on a magnetic stirrer with a citric acid sample of 0.210 ± 0.001 g. The solution was stirred until the citric acid was completely dissolved for 10 minutes. 0.006 ± 0.0002 g of anhydrous stannous chloride was added to the resulting solution. The solution was stirred for 5 min until the tin was completely dissolved. After dissolving anhydrous tin dichloride, 0.10 ± 0.002 g of copper salt 2-methoxyisobutyl isonitrile tetrafluoroborate was added to the flask and dissolved for 10 minutes. Then 0.128 ± 0.001 g of L-cysteine hydrochloride monohydrate was added to the solution. After dissolving L-cysteine, 1.0 ± 0.01 g of mannitol was added

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and dissolved until the mannitol was completely dissolved. Then 1.4±0.2 g of sodium citrate trisubstituted was added to the flask with the kit solution. After complete dissolution of all components, ≥3 ml was taken to determine the pH of the solution. The pH of the kit solution should be in the range of 5.5±0.1. The entire process of preparing the kit solution was carried out with stirring in a flow of inert gas. The solution of the kit MIBI-Sn(II) was dispening in 1.0 ml vials. The vials were placed in a sublimator chamber and freeze-dried under vacuum - 0.16 Pa and dried for 24 hours, with a temperature gradient of -50°C, increasing the temperature by 5°C every 2 hours to + 15±2°C. At the end of the lyophilization process, the chamber was disconnected from the vacuum pump and filled with dry inert gas. After lyophilization, the vials were quickly closed with rubber stoppers, aluminum caps.

IV. METHOD OF OBTAINING THE RADIOPHARMACEUTICAL MIBI^{99M}Tc

To obtain radiopharmaceutical MIBI^{99m}Tc, the kit MIBI-Sn(II) in the form of a lyophilisate was dissolved by adding 3.0 ml of sodium pertechnetate solution ($Na^{99m}TcO4$) and incubated at a temperature of 90^0C for 20 minutes. After the incubation process, the resulting of MIBI^{99m}Tc radiopharmaceutical solution was cooled to room temperature and the MIBI^{99m}Tc drug labeling efficiency was tested.

V. METHOD OF DETERMINING THE STABILITY OF THE KIT MIBI-Sn(II)

The method for determining the stability of the kit MIBI-Sn(II) is as follows: to study the stability of the kit MIBI-Sn(II), previously prepared kits with a shelf life of 3, 6, 9 and 12 months were selected. The criterion for the stability of the kit MIBI-Sn(II) is the preservation of its quality, i.e. appearance, quantitative content of basic substances and efficiency of labeling with radionuclide ^{99m}Tc.

VI. METHOD OF DETERMINING THE CONTENT OF COMPONENTS OF THE KIT MIBI-Sn(II)

Determination of copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate

Add 10 ml of water to a 50 ml flask, add 0.2 ml of the kit solution, add 1 ml of 20% potassium-sodium tartrate 4-aqueous solution, 1 ml of 0.1 mol/l Trilon B solution, 5 ml of 0.1% sodium solution diethyldithiocarbamate and 5 ml of chloroform.

The mixture is shaken for 2 minutes and after separation, the aqueous and organic phases are separated. The optical density of the organic phase is measured at the absorption maximum at 435 nm in a cuvette with a layer thickness of 10 mm. Chloroform is used as a reference solution.

The content of copper salt of 2-methoxyisobutyl isonitrile tetrafluoroborate in the vial (G) in milligrams is calculated by the formula:

$$G = (5{,}0*3{,}0*602{,}9)/(0{,}2*13300),$$

where: D- is the optical density of the test solution;

5.0 - volume of the test solution, in milliliters;

3.0 - volume of the MIBI-Sn(II) solution, in milliliters;

602,9- atomic mass of copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate;

0,2 - volume of the MIBI-Sn(II) solution taken for analysis, in milliliters;

13300- is the conventional molar absorption rate.

Determination of divalent tin. 3.5 ml of a 2.5 mol/l aqueous-alcoholic solution of hydrochloric acid is added to a test tube with a capacity of 5 ml, add 0.3 ml of a 0.16% solution of potassium rhenium acid, 0.2 ml of a 20% solution of potassium rhenium, 1 ml of a solution of the set and mix. The optical density of the solution is measured within no more than 10 minutes after its preparation at the absorption maximum at 353 nm in a cuvette with a layer thickness of 10 mm. As a reference solution, use a solution containing all components in the indicated quantities, except for a solution of the substance, instead of which 1 ml of isotonic sodium chloride solution 0.9% for injection is added. The content of divalent tin in the vial (GSn^{2+}) in milligrams is determined by the formula:

$$G_{Sn^{2+}} = (D*5{,}0*3{,}0*118{,}69)/(1{,}0*16800),$$

where: D- is the optical density of the test solution;

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5.0 - volume of the test solution, in milliliters;
3.0 - volume of the MIBI-Sn(II) solution, in milliliters;
118.69- atomic mass of tin;
1.0 - volume of the MIBI-Sn(II) solution taken for analysis, in milliliters;
16800- is the conventional molar absorption rate.

VII. METHOD OF DETERMINING THE RADIOCHEMICAL PURITY OF MIBI^{99m}Tc

The radiochemical purity of MIBI^{99m}Tc was determined by thin layer chromatography. On a plate with a thin layer of silica gel from Merck (No. 5748) measuring 15x100 mm, departing from one of the edges by 15 mm (starting line), applyed the drug an amount 0.002-0.005 ml. After drying the spot applied to the paper, apply chromatography by the ascending method for 20 minutes, using a mixture of acetonitrile and ethyl alcohol in a ratio of 9:1 as a solvent (Figure 2.). In the specified chromatography mode, the Rf of the ^{99m}Tc-methoxyisobutyl isonitrile (MIBI^{99m}Tc) complex is (0.5 ± 0.1), the Rf of sodium pertechnetate, ^{99m}Tc is 1.0. Possible other radiochemical impurities remain on the site of application of the drug with Rf=0. The resulting chromatogram is dried at room temperature and the count rate from the area containing the complex MIBI^{99m}Tc and from the entire chromatogram is measured using a radiometric method. Radiochemical purity in the MIBI^{99m}Tc solution were calculated by the formula:

$$RCP = (\Sigma MIBI^{99m}Tc / \Sigma Ach)*100\%,$$

where, RCP - Radiochemical purity in the MIBI^{99m}Tc solution;
ΣAch. - is the sum of the activity count rate for the entire chromatogram.

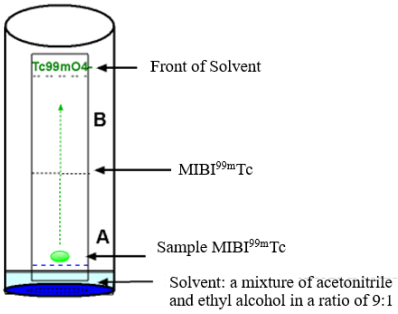

Fig. 2. Glass cylinder chamber for thin layer chromatography

VIII. METHOD OF STUDYING THE BIODISTRIBUTION OF RADIOPHARMACEUTICAL MIBI^{99m}Tc

Studies of the biodistribution of MIBI^{99m}Tc were carried out on male rats weighing 180-250 g. After intravenous administration of the radiopharmaceutical, the animals were killed at intervals of 1 to 120 minutes and the organs of

interest were removed for counting on a scintillation counter. The accumulated activity in each organ was calculated as a percentage of the total administered dose.

IX. RESULTS AND DISCUSSION

When studying the effect of the concentration of MIBI, Sn^{2+} and pH on the efficiency of the formation of the MIBI^{99m}Tc complex in solutions, it varied within 0.4-1.2 mg/ml, 0.01-0.12 mg/ml and 5.0-6.0 respectively. With the minimum amount of Sn^{2+} (0.1 mg/ml) involved in the reduction reaction of $^{99m}TcO_4^-$, complexation of ^{99m}Tc with MIBI content of 0.4 mg/ml and solution pH 5.5, the maximum level of bound ^{99m}Tc was 82.7%. A high level of ^{99m}Tc binding to MIBI 99.2% was observed in kit with a quantitative content: Sn^{2+} 0.06 mg/ml, with MIBI 0.8 mg/ml and solution pH 5.5. The results obtained are shown in table1.

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Table 1. Efficiency of formation of the MIBI^{99m}Tc complex depending on the concentration of MIBI, Sn^{2+} and the pH of the complex solution (in percent), 20 minutes after adding $^{99m}TcO_4^-$ to the kit MIBI-Sn(II).

MIBI mg/ml	**Content of Sn^{2+}, mg/ml**					pH, solution complex
	0,01±0,001	**0,03±0,001**	**0,06±0,001**	**0,09±0,001**	**0,12±0,001**	
0,4±0,02	82,3±0,02	82,7±0,02	86,2±0,02	85,1±0,02	85,9±0,02	5,0
	82,7±0,02	**85,7**±0,02	**88,2**±0,02	**87,1**±0,02	**87,6**±0,02	5,5
	82,9±0,02	82,6±0,02	86,3±0,02	85,2±0,02	85,7±0,02	6,0
0,6±0,02	84,2±0,02	84,8±0,02	88,2±0,02	87,9±0,02	87,3±0,02	5,0
	85,7±0,02	**87,7**±0,02	**92,2**±0,02	**89,1**±0,02	**91,6**±0,02	5,5
	84,5±0,02	84,9±0,02	90,8±0,02	88,2±0,02	88,3±0,02	6,0
0,8±0,02	92,2±0,02	95,8±0,02	97,2±0,02	96,9±0,02	96,3±0,02	5,0
	95,7±0,02	**97,7**±0,02	**99,2**±0,02	**99,1**±0,02	**99,0**±0,02	5,5
	92,8±0,02	96,5±0,02	98,5±0,02	97,2±0,02	97,1±0,02	6,0
1,0±0,02	92,0±0,02	95,1±0,02	97,1±0,02	95,9±0,02	96,3±0,02	5,0
	95,1±0,02	**97,2**±0,02	**99,0**±0,02	**98,9**±0,02	**98,6**±0,02	5,5
	92,8±0,02	95,5±0,02	98,0±0,02	97,2±0,02	96,2±0,02	6,0
1,2±0,02	87,2±0,02	88,8±0,02	94,2±0,02	93,9±0,02	92,3±0,02	5,0
	89,7±0,02	**92,7**±0,02	**96,9**±0,02	**96,1**±0,02	**94,3**±0,02	5,5
	88,0±0,02	89,2±0,02	95,8±0,02	95,2±0,02	88,3±0,02	6,0
	Efficiency of formation of the MIBI^{99m}Tc complex, %					

From the results of table 1, it can be seen that a batch of a substance with a quantitative content of copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate in the range of 0.8-1.0 mg/ml, Sn^{2+} 0.06 mg/ml, and a solution pH of 5.5, forms a fairly stable complex with 99mTc with an efficiency of ≤ 99.0%.

When studying the rate of formation of the MIBI^{99m}Tc complex, the concentration of Sn^{2+} in the reaction mixture was 0.06 mg/ml, MIBI 0.8 mg/ml, and the pH of the solution was 5.5. The results obtained are shown in table 2.

Table 2 - Kinetics of formation of the MIBI^{99m}Tc complex at different time intervals

MIBI, mg/ml	Sn^{2+}, mg/ml	Time, (minutes, hour)						
		5min	10min	15min	20min	1 h	2,5 h	5 h
0,8	**0,06**	**76,7±0,2**	**87,3±0,2**	**96,0±0,2**	**99,2±0,2**	**99,2±0,2**	**98,6±0,2**	**95,1±0,2**
		Efficiency of formation of the *MIBI^{99m}Tc* complex, %						

As can be seen from the results in table 2, at a concentration ratio of copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate to tin of 0.8:0.06 in the reaction mixtures, the MIBI^{99m}Tc complex was formed almost instantly and their amount remained at a high level for 5 hours. A high level of ^{99m}Tc bound to the copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate (99.2±0.2%) was observed after 20 min and remained at this level until almost 1 h. After 1 h, the complex begins to hydrolyze and by 5 h the condition remains 95.1%.

To study the stability of the kit MIBI-Sn(II), previously prepared kit with a shelf life of 3, 6, 9 and 12 months with a content of MIBI and Sn^{2+} 0.8:0.06 mg/ml were selected with radionuclide ^{99m}Tc labeling followed by the formation of the MIBI^{99m}Tc complex and tested quantitative and qualitative characteristics of the complex. The results obtained are shown in table 3.

Table 3. Stability studies of kit MIBI-Sn(II)

The name of indicators	Data on the day of production	Time after production 3 months	Time after production 6 months	Time after production 9 months	Time after production 12 months
Description	white lyophilisate	white lyophilisate	white lyophilisate	white lyophilisate	white lyophilisate
Content Sn^{2+}, mg/ml	0,062±0,001	0,061±0,001	0,06±0,001.	0,059±0,001	0,059±0,001

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Content MIBI, mg/ml	0,81±0,02	0,82±0,02.	0,81±0,02.	0,8±0,02.	0,8±0,02.
Efficiency of complex formation MIBI ^{99m}Tc, in %	99,2±0,2	99,1±0,2	99,0±0,2	98,8±0,2	98,7±0,2

From the given data in table 3. shows that the quality of the kit MIBI-Sn(II) during storage of 12 months differs slightly from the quality of the data on the day of production. Apparently, this is due to the presence of an inert argon gas inside the vial with the substance, which prevents the decomposition of the kit MIBI-Sn(II) and the oxidation of Sn^{2+}, thereby ensuring quality for 12 months and a shelf life of 12 months can be assigned to the kit MIBI-Sn(II).

To quantitatively determine the content of the active substance copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate in solutions of kit MIBI-Sn(II), the spectrophotometric method was used. In the UV absorption spectrum of solutions of the kit MIBI-Sn(II) in the wavelength range from 410 to 470 nm, a maximum is observed at 435 nm (Table 4). When studying the spectral characteristics of solutions of the drug and the excipients included in its composition, it was shown that the excipients do not affect the position of the maxima of the absorption bands of the active kit MIBI-Sn(II), but have a small intrinsic absorption in the studied area (Figure 3).

Table 4.Measurement results solutions of placebo and MIBI-Sn(II)

Wavelength, nm	Optical density of placebo solution	Optical density of solution MIBI(II)Sn
410	0,01	0,169
415	0,011	0,19
420	0,013	0,206
425	0,015	0,213
430	0,013	0,222
435	0,016	0,235
440	0,014	0,221
445	0,01	0,211
450	0,011	0,198
455	0,013	0,191
460	0,015	0,182

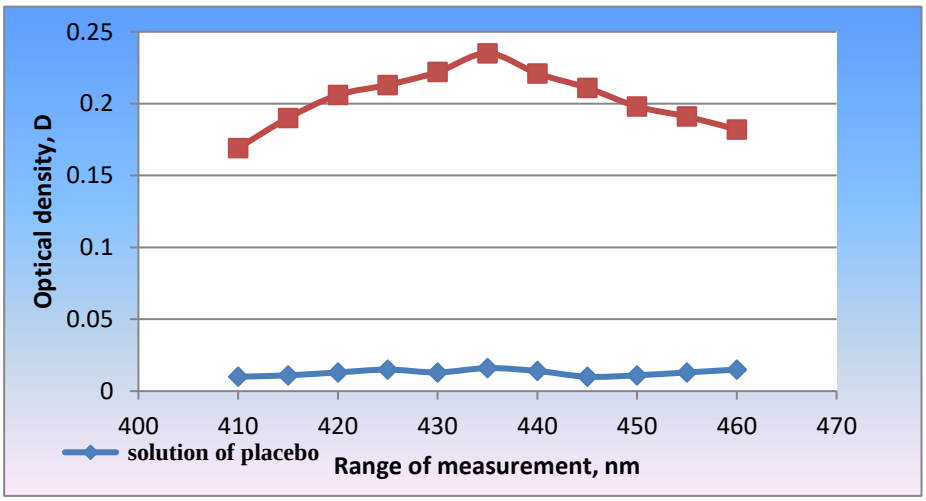

Fig.3. Optical density curve solutions of MIBI-Sn(II) and placebo

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To assess the possibility of using the method, the dependence of the absorption intensity of MIBI-Sn(II) on its concentration in solutions was studied.

The linear nature of the dependence for MIBI-Sn(II) solutions in the concentration range of 0.2–1.4 mg/ml is demonstrated in Figure 4.

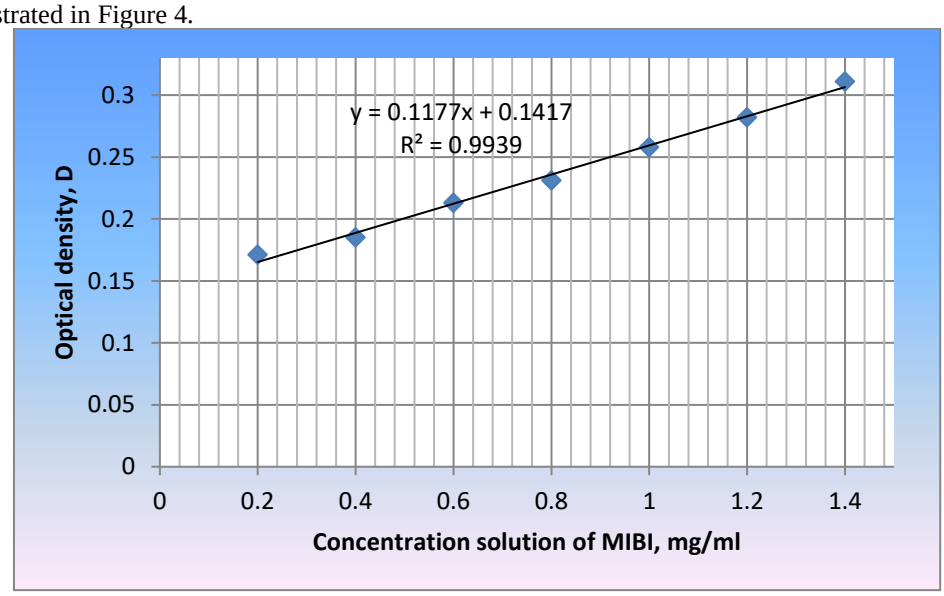

Fig.4. Dependence of the optical density of the solution MIBI-Sn(II) on its concentration

Depending on the concentration of MIBI content from 0.2 to 1.4 mg/ml, there is a linear dependence of the analytical signal (optical density) on the content of the analyte. The accuracy of choosing the regression equation is 99.39%

The radiochemical purity of a radiopharmaceutical is the proportion of total radioactivity in the desired form. The MIBI^{99m}Tc preparation may contain a radiochemical impurity, free pertechnetate ($^{99m}TcO_4^-$). This component is characterized by the Rf value, which is defined as the ratio of the distance traveled by the component from the starting point of application of the compound under study.

Studies of 5 different batches of copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate labeled with technetium-99m using thin layer chromatography showed that the radiochemical purity is not less 99.0 %. The results of thin layer chromatography are presented in Figure 5.

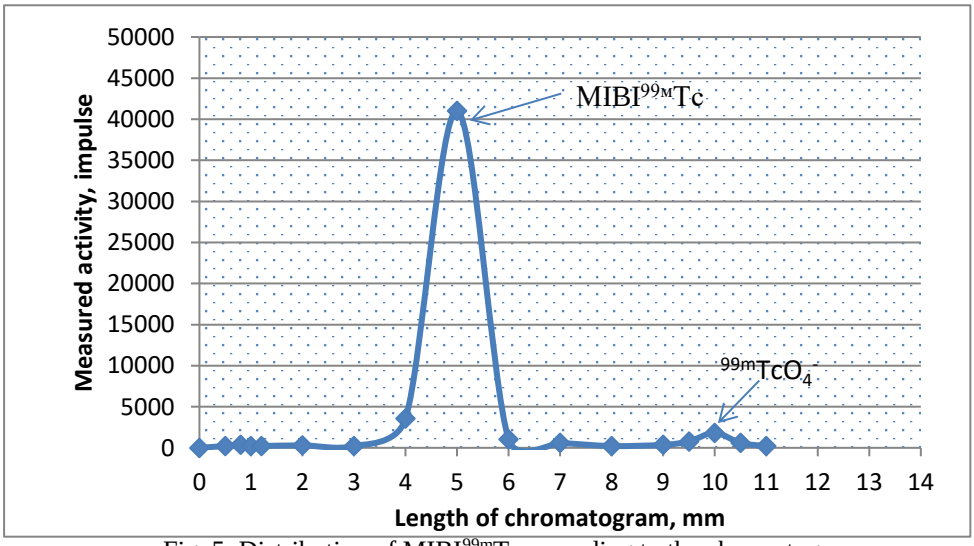

Fig. 5. Distribution of MIBI^{99m}Tc according to the chromatogram
(Solvent: acetonitrile and ethyl alcohol in a volume ratio of 9:1)

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The test results presented in figure 5. prove the specificity of the method for determining the content of the radiochemical impurity pertechnetate ions TcO_4^- in the MIBI^{99m}Tc preparation.

Methods for qualitative and quantitative analysis of radiopharmaceutical kits have been developed. Based on the results obtained, a draft pharmacopoeial monograph of the enterprise (FSP) was prepared.

The results of preclinical tests showed that the drugs MIBI^{99m}Tc did not cause significant changes in peripheral blood, urine and histological changes internal organs at autopsy compared with the control group of animals. The results of these tests showed that the drug MIBI^{99m}Tc accumulating in ischemic areas of the heart muscle, it allows one to detect ischemic myocardial damage with high reliability. Table 5 summarizes the results of studies on the biodistribution of MIBI^{99m}Tc in some organs of rice. The results are presented as a percentage of absorption of the administered dose of total radioactivity to each individual organ or tissue.

Table 5. Concentrations of MIBI^{99m}Tc radioactivity in some organs and tissues after injection for 30 minutes as a % of the administered dose

Organs and tissues	Research time			
	1 minutes	5 minutes	15 minutes	30 minutes
	Content as a percentage of total activity			
Blood	1.43±0.12	0.73±0.06	0.33±0.02	0.22±0.01
Lungs	2.71±0.19	2.62±0.14	2.6±0.06	1.5±0.12
Heart	6.8±0.47	7.0±0.34	8.51±0.47	8.68±0.75
Liver	1.07±0.09	1.07±0.05	1.21±0.05	1.33±0.11
Kidneys	3.29±0.24	4.29±0.41	7.29±0.54	5.04±0.25
Spleen	1.71±0.15	2.31±0.15	1.81±0.11	1.70±0.14

X. CONCLUSION

Thus, in the course of the research work, the optimal ratios of the main substance copper(I) salt of 2-methoxyisobutyl isonitrile tetrafluoroborate and the reducing agent (Sn^{2+}) in the MIBI^{99m}Tc complexation reaction were determined, which amounted to 0.8 mg/ml and 0.06 mg/ml, respectively, created developed technology for obtaining of the kit MIBI-Sn(II). The 5 batches of the MIBI-Sn(II) kit produced have a radiochemical purity of more than 99.0%, the shelf life of the kit MIBI-Sn(II) was determined, which was 12 months, and animal tests showed that the radiopharmaceuticals of MIBI^{99m}Tc accumulates in ischemic areas of the heart muscle, allows you to identify ischemic myocardial damage with high reliability.

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