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JUSTIFICATION OF CHOICE OF THE METHODOLOGY FOR STANDARDIZATION OF COMMON CHICORY HERB (*CICHORIUM INTYBUS* L.)

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One of the promising objects of study in the direction of developing new medicinal herbal remedies is common chicory. The aerial part of this plant can be harvested both from wild plants and used as a secondary raw material in case of industrial root cultivation. As a result of the conducted studies, it was found that the content of the sum of phenolic compounds in the raw materials of wild plants ranges from 2.02±0.01 to 6.25±0.29%, in cultivated plant varieties – from 3.04±0.14 to 4.04±0.17%. The dominant compound in all samples of raw materials is Chicoric acid. In the raw materials of cultivated plants, unlike wild plants, there are no oxycoumarins. The study of the effect of extracts obtained from cultivated and wild plants on the humoral component of immunity showed their comparable activity, which indicates the absence of the contribution of oxycoumarins to this effect. In this regard, for the standardization of raw materials of the wild and cultivated plants, a method of quantification of the sum of phenolic compounds in terms of chicory acid can be used.

Keywords: common chicory (*Cichorium intybus* L.), herb, phenolic compounds, chicoric acid

According to the strategy of development of the pharmaceutical industry of the Russian Federation, one of the priorities is studies aimed at finding new active compounds and creating effective medicines based on them. Among the natural sources of such substances, plants occupy a special place. Biologically active substances (BAS) formed during their secondary metabolism have a greater affinity for the human body compared to synthetic compounds, while BAS have a minimal toxic effect with pronounced pharmacological activity. In this regard, the search for new compounds of plant origin, that are promising for the creation of medicines based on them is of interest to researchers in the field of pharmaceutical development.

Modern requirements for the quality of medicines make it necessary to use a scientifically based approach to the creation of herbal medicinal products, including an assessment of the experience of folk and scientific medicine, combined with the establishment of the structure of active ingredients, the determination of the mechanisms of their pharmacological action and possible side effects. The basic stages of this approach include studies of the chemical composition of new types of medicinal plants, the establishment of the main groups of active substances, the development of methods for their qualitative and quantitative assessment, as well as the definition of criteria and standards that allow assessing the quality of medicinal plant raw material.

Among the representatives of the domestic flora, a promising object of study is common chicory (*Cichorium intybus* L.) – an herbaceous plant of the Asteraceae family *(Asteraceae)*. Genus *Cichorium* includes 6 species *(C. endivia, C. glabratum, C. glandulosum, C. intybus, C. pumilum,*

C. spinosum) [1], among which C. intybus is the most common on the territory of the Russian Federation. This plant grows as a wild one from the White Sea coast in the north to the Black Sea coast in the south and from the Baltic Sea in the west to the Pacific coast in the east of Russia [2].

Cultivated varieties of common chicory are grown to obtain roots, which after roasting are used for the production of "chicoric coffee".

The aerial and underground parts of common chicory are widely used in folk medicine in China and Mongolia as an immunomodulatory, choleretic, hepatoprotective, hypoglycemic agent, as well as are objects of scientific studies in foreign countries [3–6]. This plant (herb and roots) is described in the Pharmacopoeia of the People's Republic of China. Chicory herb extract is included in the complex preparation "Liv. 52" (India).

The aerial part of this plant can serve as the most promising medicinal plant raw material. The wild chicory herb is convenient for harvesting during the long flowering phase (June-August), in the case of a cultivated plant it serves as a secondary raw material on plantations for harvesting roots for the food industry.

According to the literature, the pharmacological activity of extracts of the common chicory aerial part is provided by a complex of phenolic BAS, represented by hydroxycinnamic acids, oxycoumarins and flavonoids [3,5,7].

In this regard, the **purpose** of our work is to study the accumulation of phenolic compounds in the aerial part of wild and cultivated plants to justify the choice of a methodology for standardization of this type of plant raw materials.

MATERIALS AND METHODS

The objects of the study were the dried aerial part (herb) of wild chicory, harvested during the mass flowering phase in the Moscow, Ryazan, Lipetsk, Samara, Tula, Arkhangelsk regions and the Krasnodar Territory in 2016–2020, as well as the aerial part (root rosette) of plants harvested during the end of the vegetation phase of cultivated plants of the first year of life on experimental plots of the Botanical Garden of VILAR: varieties – Spicak, (Czech Republic), Tid Wog (France), Alexandrite (France) in 2020.

Quantification of the sum of phenolic compounds in the aerial part of common chicory was carried out by direct spectrophotometry using a UV-1800 spectrophotometer (Shimadzu, Japan) according to a previously developed and validated method (the relative error of a single determination is 4.72%). Optical density was determined at the absorption maximum at a wavelength of 330±2 nm. The content of the sum of phenolic compounds was calculated in terms of chicory acid and absolutely dry raw materials, using specific absorbance of 782 [8].

The quantification of the main phenolic compounds was carried out by HPLC-UV method using a high-performance liquid chromatograph Prominence-I LC-2030C 3D (Shimadzu) with a diode-matrix detector. The separation was carried out using XTerra ® RP18 3.5 µm 2.1×150 mm Column (temperature control at 30°C). Elution was carried out at a flow rate of 0.3 ml/min. As a mobile phase, solvent systems of 0.2% formic acid solution (A) and acetonitrile (B) were used in a gradient elution mode: (0–20 min. – 10% B, 20–30 min. – 25% B, 30–40 min. – 40% B, 40–44 min. – 60% B, 44–48 min. – 80% B, 48–60 min. – 10% B). Detection was performed at a wavelength of 330 nm. Each determination was carried out in three repetitions.

Chicory acid, chlorogenic acid, esculetin and chicoryin, previously isolated from the aboveground part of wild chicory and identified by NMR spectroscopy, were used as Reference Standards (purity of at least 98%).

Extracts from the wild and cultivated raw materials were obtained by extraction with 70% ethyl alcohol, concentration, purification from

lipophilic compounds and drying to humidity of no more than 5%.

The study of immunomodulatory activity to identify the factors of the humoral components of immunity was carried out using male mice of the F1 line (CBA×C57Bl/6) weighing 18–20 g. The effect of the extracts was studied using normal animals, as well as animals in a state of immune suppression caused by the cytostatic azathioprine, which was administered to animals at a dose of 50 mg/kg orally once a day for 5 days.

Extracts of common chicory were administered to 1.0 and 1.1 experimental groups of mice on the background of azathioprine and to 3.0 and 3.1 experimental groups of intact mice at a dose of 30 mg/kg orally once a day for 14 days. The experimental therapeutic dose of dry chicory extract, equal to 30 mg/kg, was determined experimentally in preliminary tests on 30 mice. Immunal (Lec Pharma, Slovenia) was used as a reference substance. Immunal was administered to the 2nd experimental group of mice on the background of azathioprine and to the 4th experimental group of intact mice at an isoeffective dose of 5 ml/kg orally once a day for 14 days. The intact and control groups of animals received purified water according to a similar scheme. The studies were conducted on the 20th day of the experiment.

The effect of chicory extract on the state of humoral immunity was assessed by the number of antibody-forming cells (AFC) determined by the method of local hemolysis according to A.J. Cunningham (1965) [9]. The obtained results were processed by the statistical method using the t-Student criterion.

RESULTS AND DISCUSSION

As a result of a previously conducted phytochemical study by HPLC–MS/MS method, it was found that the aerial part of wild chicory growing in the territory of the Russian Federation contains a phenolic complex of BAS, represented by oxycoumarins (esculetin and chicoryin); derivatives of hydroxycoric acid (esters of caffeic, ferulic, coumaric acids with organic acids such tartaric and quinic ones in various combinations) and flavonoids (quercetin and kaempferol glycosides). In this case, the dominant compounds are esculetin and its glycoside – chicoryin, as well as the chicory and chlorogenic acids.

Taking into account that the aerial part of a wild plant is represented by stems with leaves and flowers, we studied the accumulation of the sum of phenolic compounds and dominant compounds in various parts of the herb on the example of a sample of raw materials harvested in the Moscow region in 2020 (Table 1).

As a result, it was shown that the largest number of phenolic compounds (7.19±0.33%) accumulates in the stem leaves, while the dominant compound of this part of the plant is chicoric acid (0.401±0.012%). The flowers also have significant content of phenolic compounds (3.74±0.17%), among the dominant compounds there is a relatively high amount of coumarins such as esculetin (0.030±0.001%) and chicoryin (0.251±0.008%), which is typical for plants of the Asteraceae family

The results of the analysis of samples of raw materials harvested in various regions of the Russian Federation showed that the content of the sum of phenolic compounds ranges from 2.02±0.01 to 6.25±0.29% (Table 2).

In turn, when cultivating common chicory for the food industry, the roots are harvested at the end of the first year of the plant's vegetation, so the aboveground part is represented by the leaves of the root rosette. The results of the analysis of phenolic compounds of raw materials of three varieties are specified in Table 3.

The resulted data indicate that chicoric acid is also predominant among the main metabolites of raw materials of the cultivated plants. Oxycoumarins (esculetin and chicoryin) are absent in this raw material, which confirms their accumulation

Table 1

THE CONTENT OF BIOLOGICALLY ACTIVE SUBSTANCES IN VARIOUS PARTS OF COMMON CHICORY

Part of a plant	The sum of phenolic compounds in terms of chicoric acid, %	Chicoric acid, %	Chlorogenic acid, %	Esculetin, %	Chicoryin, %
Flowers	3.74±0.17	0.111±0.003	0.052±0.002	0.030±0.001	0.251±0.008
Pediculate leaves	7.19±0.33	0.401±0.012	0.108±0.001	0.000±0.00	0.022±0.001
Flowered stems	2.25±0.10	0.083±0.002	0.030±0.001	0.012±0.001	0.053±0.002
Stems	1.00±0.05	0.030±0.001	0.010±0.001	0.000±0.000	0.000±0.000
Herb	2.02±0.09	0.121±0.004	0.032±0.001	0.001±0.001	0.061±0.002

Table 2

THE CONTENT OF THE SUM OF PHENOLIC COMPOUNDS IN SAMPLES OF WILD CHICORY HERB FROM VARIOUS HABITATS

Habitat	Year of raw material harvesting	The sum of phenolic compounds in terms of chicoric acid, %
Moscow region, Shatursky district, Krivandino village	2016	3.63±0.18
Tula region, Kryukovo village	2016	3.50±0.18
Republic of Bashkortostan, Ufa district	2017	4.97±0.25
Republic of Bashkortostan, Tuymazinsky district	2017	4.41±0.22
Arkhangelsk region, Kargopolsky district	2017	2.73±0.14
Lipetsk region, Galichya Gora, Chechery village	2017	2.38±0.12
Moscow region, Serpukhov city district, Volkovo village	2017	2.08±0.10
Samara region, Sergievsky district, Antonovka village	2017	4.57±0.23
Kursk region	2017	4.28±0.21
Kursk region	2018	6.25±0.29
Ryazan region, Rybnovsky district, Ramenki village	2018	2.06±0.10
Krasnodar Territory, Ust-Labinsky district, Voronezhskaya Cossack village	2019	3.98±0.19
Moscow region, Serpukhov city district, Volkovo village	2020	2.02±0.01
Krasnodar Territory, Dinskoy district, Vasyurinskaya Cossack village	2020	3.86±0.18

Table 3

THE CONTENT OF PHENOLIC COMPOUNDS IN THE ABOVEGROUND PART OF CULTIVATED COMMON CHICORY

Variety	The sum of phenolic compounds in terms of chicoric acid, %	Chicoric acid, %	Chlorogenic acid, %	Esculetin, %	Chicoryin, %
Spicak	4.04±0.17	0.250±0.008	0.040±0.001	0.00±0.00	0.00±0.00
Tid Wog	3.54±0.16	0.211±0.006	0.051±0.001	0.00±0.00	0.00±0.00
Alexandrite	3.04±0.14	0.182±0.005	0.020±0.001	0.00±0.00	0.00±0.00

in the flowers during the second year of the plant's life. The use of secondary raw materials for industrial root cultivation involves obtaining the aerial part from plants of the first year of life, when there are no flowers.

A further study of extracts obtained from the aerial part of wild (with content of phenolic compounds of 8.30±0.40%) and cultivated common chicory (with content of the sum of phenolic compounds of 10.42±0.48%) showed comparable data on the effect on the factors of humoral immunity in *in vivo* experiments. Both extracts restored the parameters of the humoral immune response under the conditions of azathioprine immunosuppression. When the studied medicines were administered against the background of immunosuppression, significant increase in the number of AFCs was observed both in absolute values and when calculated for 106 splenocytes, while there was no effect of extracts on the parameters of humoral immunity in animals without immunosuppression.

Table 4

THE EFFECT OF DRY CHICORY EXTRACT ON ANTIBODY FORMATION

Groups of animals	Absolute number of AFCs per spleen	Number of AFCs per 106 splenocytes
Intact, n=10	46199±2203	272±22
Control (azathioprine), n=10	29328±2368*	163±10*
Experimental 1.0 (azathioprine + wild chicory extract), n=10	42022±3629**	252±12**
Experimental 1.1 (azathioprine + cultivated chicory extract), n=10	53517±2671**	235±15**
Experimental 2 (azathioprine + Immunal), n=10	41059±2763**	212±13**
Experimental 3.0 (wild chicory extract), n=10	40655±3821	244±18
Experimental 3.1 (cultivated chicory extract), n=10	45321±3719	198±12
Experimental 4 Immunal), n=10	39842±2546	237±21

Notes. The differences are reliable compared to the data:

** – in the intact group, ** – in the control group with p≤0,05; n – number of animals in the group*

The effect of the extract of cultivated chicory slightly exceeded the effect of a similar extract of a wild plant, which is probably due to higher content of phenolic compounds.

The resulted data suggest that coumarins do not affect the immunomodulatory activity of extracts of the aerial part of common chicory.

Thus, to standardize the aerial part of wild and cultivated chicory, a method of determination of the sum of phenolic compounds in terms of chicoric acid can be used as one of its dominant metabolites, which makes the main contribution to the immunomodulatory effect of extracts of its aerial part.

CONCLUSIONS

1. The study of the distribution of phenolic compounds in the aerial part of wild chicory has shown that the greatest amount of them accumulates in the stem leaves and flowers. In this case, the dominant metabolite is chicoric acid. Taking into account the volume of biomass, it is advisable to harvest the entire aerial part – herb as a raw material. The content of the sum of phenolic compounds in terms of chicory acid in samples of herb harvested in various regions of the Russian Federation ranges from 2.02±0.01 to 6.25±0.29%. The aerial part of cultivated varieties contains more phenolic compounds than the herb of wild plants, while chicoric acid is also the dominant compound, and there are no oxycoumarins.

2. Presumably, it is the derivatives of hydroxycoric acid and chicoric acid as the main component of this group of BAS that make the main contribution to the immunomodulatory effect of the aerial part of a wild and cultivated plant. This circumstance allows us to use the method of quantification of the sum of phenolic compounds in terms of chicoric acid to assess the quality of this raw material according to the parameter "Quantification". According to the results of the analysis of raw material samples from various harvesting sites and cultivated varieties, the standard content for this parameter can be set at the level of at least 2%.

The studies were carried out as part of the implementation of the plan of research work of the VILAR on the subject No. FNSC-2019-0010 "Search for active fractions of natural compounds, development of methods for their production from plant raw materials, standardization methods and creation of modern dosage forms based on them"

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DEVELOPMENT AND VALIDATION OF METHODS FOR QUANTITATIVE DETERMINATION OF SUM OF FLAVONOIDS IN LIQUID AND DRY EXTRACTS OF HERBAL COMPOSITION

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The aim of the study was to develop a method for quantifying the sum of flavonoids as the main therapeutically active compounds in experimental liquid and dry extracts of a unique plant composition, including the herb of motherwort, St. John's wort, lemon balm and thyme, as well as validation of the created methods. The sum of flavonoids was determined by differential spectrophotometry at a wavelength of 410 nm. The method is based on the flavonoid complex formation reaction with trivalent aluminum chloride, resulting in a bathochromic shift of the absorption band from 330–350 nm to 390–410 nm, which allows quantitative detection of the desired compounds in solution by the difference in the analytical signal of the same solutions without the addition of aluminum salts. A solution of a reference standard (RS) of rutin in 70% ethyl alcohol was used as a standard. Validation of the created methods was carried out according to the requirements of the State Pharmacopoeia of the Russian Federation of the XIV edition, OFS.1.1.0012.15 "Validation of analytical methods".

As a result, methods have been developed for the quantitative determination of the sum of flavonoids in terms of rutin in liquid and dry extracts of a unique plant composition. The created methods were validated, during which the criteria for their acceptability were established, namely: specificity, linearity, correctness, convergence and reproducibility, which were recognized as positive. The data obtained during validation make it possible to consider the developed methods suitable for reliable quantitative determination of the sum of flavonoids

in the studied dry and liquid extracts for their further standardization and quality control.

Key words: quantitative determination of phenolic compounds, flavonoids, standardization, validation, differential UV spectrophotometry

Today, nervous disorders and neuroses caused by the accelerated pace of life, stress and lack of adequate rest are one of the most common reasons for patients to refer to both general practitioners and neurologists. The sedatives prescribed at the same time, reducing the reaction to external stimuli, help to reduce excitement, relieve anxiety, facilitate the sleep onset, eliminate phobias, preventing the onset of severe somatic complications that can be caused by neuroses. It is generally recognized that herbal preparations act milder than synthetic ones, which is due to the inclusion of related components made of medicinal plant raw materials in their composition [1–5]. Sedatives of plant origin are mainly represented by products based on valerian, motherwort, common peony, peppermint.

We have developed a unique combination of plant components, which includes crushed raw materials of motherwort, St. John's wort, lemon balm and thyme in a ratio of 4:2.5:2.5:1, respectively [6–9]. These plants were harvested in the North Caucasus branch of VILAR and by shade drying. A comparative pharmacological study of the effect on the nervous and cardiovascular system of the developed plant composition in comparison with herbal medicines "Phyto Novo-Sedom" and "Novo-Passit" established a more pronounced sedative and hypotensive effect for the studied combination of plant components [7].

The liquid and dry extracts obtained from this harvest can become completely new domestic sedatives having no analogues in the composition. An undoubted advantage is growing in the wild or cultivating the medicinal plants used in the harvest on the territory of the Russian Federation, which eliminates dependence on foreign suppliers.

Due to the fact that the increased requirements for the standardization of medicinal herbal preparations lead to the need for quantitative assessment of the content of active ingredients (and for the raw materials from which the production of extracts is provided, these are flavonoids) [10], it seems appropriate to assess their quality by the main active ingredients – flavonoids [11–13].

Purpose of the study was to develop a method for quantifying the sum of flavonoids in liquid and dry extracts of a new plant composition, as well as its validation.

MATERIALS AND METHODS

The study used equipment that had passed metrological certification and had the appropriate certificates and acts (Table 1).

The objects of the study were liquid and dry extracts of a plant composition, for the analysis of which the following reagents were used:

- purified water (pharmacopoeial monograph "Purified water. FS.2.2.0020.18", State Pharmacopoeia of the Russian Federation, XIV edition, volume III);

Table 1

EQUIPMENT AND INSTRUMENTATION

Name of measuring instrument	Model
Analytical balances Vibra Shinko Denshi, класс 2	HRT-220CE
Analytical balances AND, Class 2	ER-182A
Spectrophotometer Shimadzu	UV-1800
Spectrophotometer Cary	100 Scan Varian

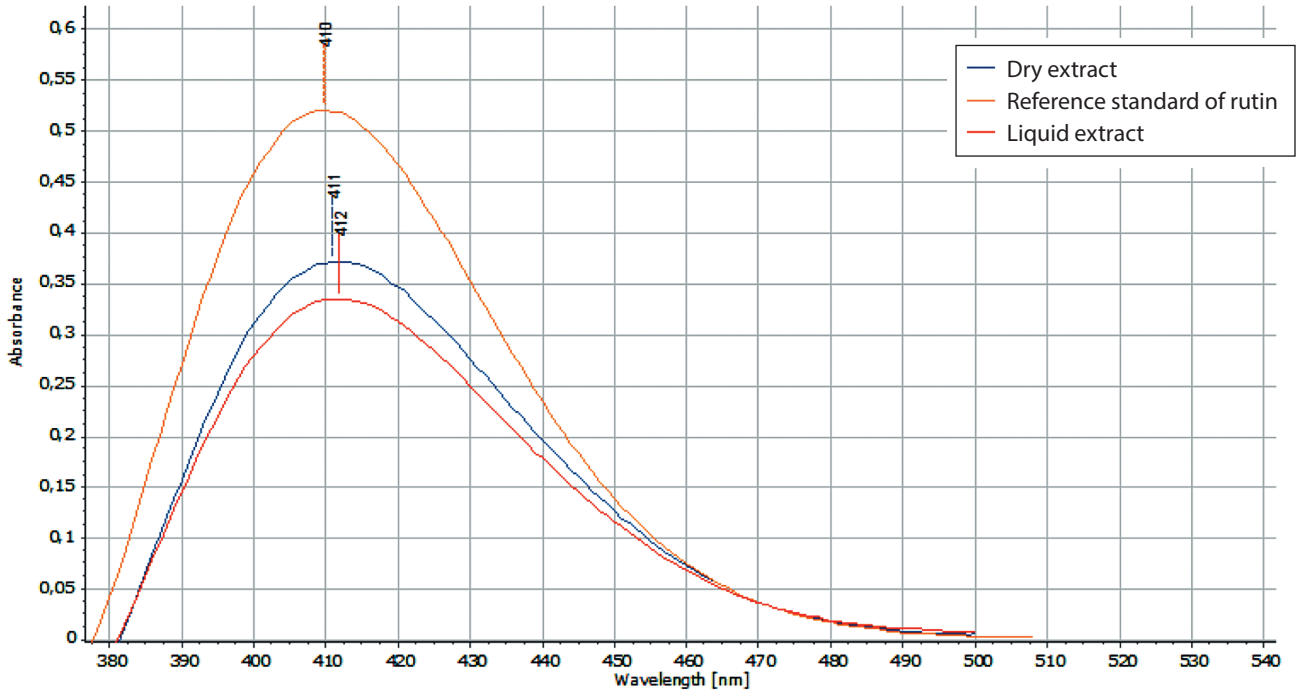

FIG. 1. *Differential UV spectra of the studied liquid and dry extracts and the rutin standard with $AlCl_3$*

- ethyl alcohol (GOST R 5962–2013);
- aluminum chloride (Panreac, cat. number: 7784-13-6);
- acetic acid (GOST 61–75; ST SEV 5375–85).

As a standard for converting the content of the sum of flavonoids to rutin, a substance – rutin powder (Sigma-Aldrich, CAS-number 207671-50-9) was used, intended for the quantitative analysis of phenolic compounds.

To assess the total content of flavonoids in herbal preparations, differential spectrophotometry is widely used, based on the reaction of complexation of flavonoids with ions of trivalent metals – Al, Zr, Ga, etc. [14,15], which has greater selectivity compared to the direct spectrophotometric method [15,16]. As a result of the complexation reaction with aluminum chloride, a bathochromic shift of the absorption band of flavonoids occurs from 330–350 nm to 390–410 nm [10], which makes it possible to quantitatively detect the desired active ingredients by the optical density of solutions in this spectral region relative to the same solutions without $AlCl_3$.

When a 5% solution of aluminum chloride in 70% ethyl alcohol is added to the solution of the dry extract under study or to the liquid extract, an absorption maximum is observed in the extraction spectrum, which coincides with the maximum absorption of the rutin solution with aluminum chloride (Fig. 1, Table 2). This determined the choice

Table 2

λ_{max} OF SOLUTIONS OF LIQUID AND DRY EXTRACTS OF PLANT COMPOSITION AND RUTIN STANDARD WITH $AlCl_3$

Name of sample to be studied	λ_{max}, X±Δx,% (n=5)
Rutin standard	410±2
Liquid extract	412±1, p>0,05 vs rutin standard*
Dry extract	411±2, p>0,05 vs rutin standard*

** U- Mann-Whitney test*

of a wavelength of 410±2 nm as a characteristic for the quantitative determination of the content of flavonoids in the studied plant extracts.

Pharmacopoeial methods for the quantitative determination of flavonoids in the raw materials of motherwort, thyme and St. John's wort provide for the addition of acetic acid to the reference solution to suppress the dissociation of flavonoids and conducting spectrophotometry 30 minutes after the preparation of solutions [17]. At the same time, the literature describes spectrophotometric methods for determining the total flavonoids without acidification of solutions or with acidification not only of the reference solution, but also of the test sample [18]. We studied the effect of adding the acetic acid to the reference solution (a solution of a liquid extract without $AlCl_3$) on the value of its optical density. It is shown that the acidification of the reference solution does not affect the value of its optical density (Fig. 2a).

The differential optical density of the liquid extract solution relative to the reference solution with and without acidification remains constant for at least two hours (Fig. 2b). The obtained data indicate the possibility of measuring the optical density of the solutions of the studied extracts within two hours after the preparation of the solutions and without acidification of the reference solution.

Method for determining the content of the total flavonoids in terms of rutin in a dry extract of a plant composition

Preparation of a 5% solution of aluminum chloride

5 g of aluminum chloride is placed into a Dewar flask with a ground stopper with a capacity of 200 ml and 100 ml of 70% ethyl alcohol is added and mixed. The shelf life of the solution is one month.

An analytical sample of a dry extract of about 0.1 g (exact weight) is transferred to a measuring flask with a capacity of 25 ml and dissolved in 20 ml of 70% ethyl alcohol; the volume is brought to the mark with 70% ethyl alcohol and mixed (solution A). Into a measuring flask with a capacity of 25 ml, 1 ml of solution A and 5 ml of 5% alcohol solution of aluminum chloride are added and the volume is brought to the mark with 70% ethyl alcohol (solution B). 1 ml of solution A is added into another measuring flask with a capacity of 25 ml, the volume is brought to

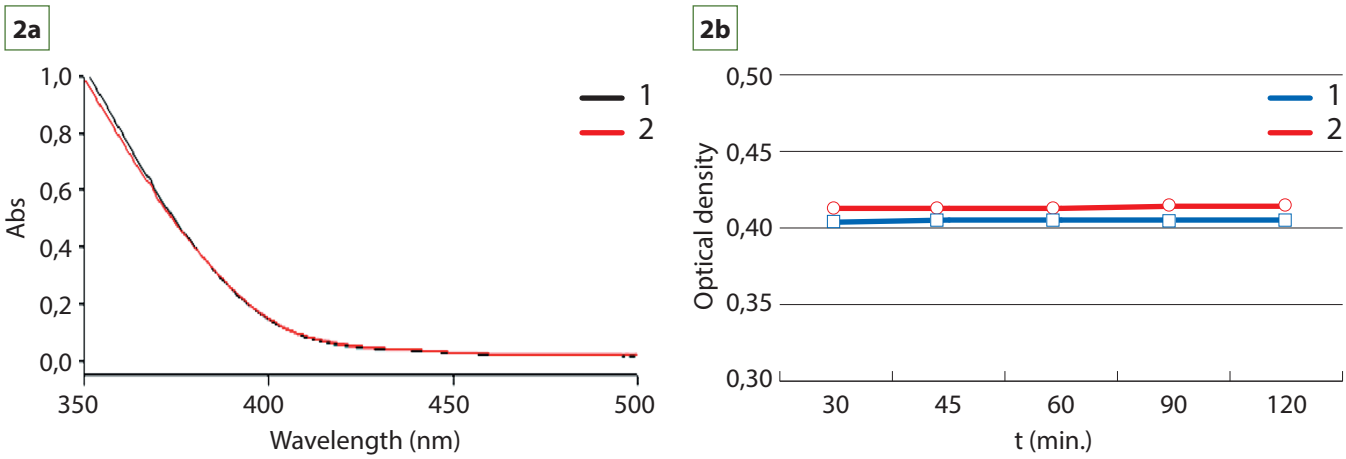

FIG. 2. *The constancy of the optical density in the analytical range of the spectrum of solutions of a liquid extract of a plant composition with and without the addition of $AlCl_3$: a – the optical density of the reference solution – a liquid extract without $AlCl_3$ with the addition of acetic acid (1) and without the addition of acetic acid (2) relative to 70% ethyl alcohol; b – the differential optical density (410 nm) of the liquid extract solution with $AlCl_3$ relative to the reference solution with the addition of acetic acid (1) and without the addition of acetic acid (2)*

the mark with 70% ethyl alcohol (solution C) [12]. The optical density of solution B is measured after 30 minutes using a spectrophotometer in a cuvette with a layer thickness of 10 mm at a wavelength of 410 nm. As a reference solution, solution C is used.

The percentage of the total flavonoids in terms of rutin is calculated by the formula:

$$X = \frac{A \cdot 25 \cdot 100}{m \cdot 1 \cdot A_{1см}^{1\%} \cdot (100 - W)},$$

where A – optical density of the sample solution (solution A) at 410 nm; $A_{1см}^{1\%}$ – the specific absorbance of the rutin standard complex with aluminum chloride at 410 nm, equal to 260; m – weight of the dry extract taken for analysis, g; W – moisture of the dry extract, %.

Method for determining the content of the total flavonoids in terms of rutin in liquid extract of a plant composition

An analytical sample of liquid extract (1 ml) in a measuring flask with capacity of 50 ml is dissolved in 20 ml of 70% ethyl alcohol and the volume is brought to the mark with 70% ethyl alcohol, mixed (solution A). Into a measuring flask with capacity of 25 ml, 2 ml of solution A and 5 ml of 5% aluminum chloride solution are added and the volume is brought to the mark with 70% ethyl alcohol (solution C). In another measuring flask with capacity of 25 ml, 2 ml of solution A is added, the volume is brought to the mark with 70% ethyl alcohol (solution C). The optical density of solution B is measured after 30 minutes using a spectrophotometer in a cuvette with a layer thickness of 10 mm at a wavelength of 410 nm. As a reference solution, the solution C is used [13].

The percentage of the total flavonoids in terms of rutin is calculated by the formula:

$$X = \frac{A \cdot 50 \cdot 25}{V_a \cdot 2 \cdot A_{1см}^{1\%}},$$

where A – optical density of the sample solution (solution A) at 410 nm; $A_{1см}^{1\%}$ – the specific absorbance of the rutin standard complex with aluminum chloride at 410 nm, equal to 260; V_a – volume of the liquid extract taken for analysis, ml.

Statistical processing of the results was carried out in accordance with the requirements of the State Pharmacopoeia of the Russian Federation of the XIV edition [9] using the Statistica 8.0 software package.

Method validation

The qualification of the method (validation) was carried out in accordance with the requirements of the State Pharmacopoeia of the Russian Federation of the XIV edition according to the criteria: specificity, linearity, correctness, convergence and reproducibility [17].

RESULTS AND DISCUSSION

Results of the specificity test

The differential UV spectrum of the sum of flavonoids of dry and liquid extracts in the wavelength range from 350 to 500 nm (Fig. 1) has an absorption maximum at a wavelength of 410±2 nm. The differential spectrum of a solution of a standard sample of rutin has a similar absorption maximum

The differential UV spectrum of the sum of flavonoids of dry and liquid extracts in the wavelength range from 350 to 500 nm (Fig. 1) has an absorption maximum at a wavelength of 410±2 nm. The differential spectrum of a solution of a reference standard of rutin has a similar absorption maximum

The results of testing the method validity according to the criteria: linearity, correctness, convergence and reproducibility are presented in Table 3–7, respectively.

Linearity was determined at 7 concentration levels 40%, 60%, 90%, 110%, 140%, 160%

Table 3

RESULTS OF TESTING THE LINEARITY OF THE METHOD OF THE RUTIN STANDARD

Measuring No.	Content, % of the normalized value (about)	The volume of the aliquot of the standard solution (rutin), ml	Standard concentration (rutin), μg/ml	Analytical response (optical density)
1	40	0.4	6.40	0.135
2	60	0.6	9.60	0.219
3	90	0.9	14.40	0.371
4	110	1.1	17.60	0.5
5	140	1.4	22.40	0.701
6	160	1.6	25.60	0.793
7	190	1.9	30.40	0.908

Table 4

RESULTS OF TESTING THE CORRECTNESS OF THE METHOD FOR DRY EXTRACT

No.	Found, mg/g	Added rutin standard, mg/g	Expected value, mg/g	Obtained value, mg/g	Absolute error, mg/g	Yield, %
1.1	4.57	1.14	5.71	5.77	–0.06	100.98
2.1	4.57	2.29	6.86	7.04	–0.19	102.72
3.1	4.57	3.43	8.00	7.91	0.08	98.95
1.2	4.57	1.14	5.71	5.61	0.10	98.29
2.2	4.57	2.29	6.86	6.60	0.25	96.33
3.2	4.57	3.43	8.00	8.17	–0.17	102.16
1.3	4.57	1.14	5.71	5.61	0.11	98.12
2.3	4.57	2.29	6.86	6.86	–0.01	100.14
3.3	4.57	3.43	8.00	7.92	0.08	99.01
Average value of yield, %				99.6		

Table 5

RESULTS OF TESTING THE CORRECTNESS OF THE METHOD FOR THE LIQUID EXTRACT

No.	Found, mg/g	Added rutin standard, mg/g	Expected value, mg/g	Obtained value, mg/g	Absolute error, mg/g	Yield, %
1.1	88.00	22.00	110.00	108.17	1.83	98.34
2.1	88.00	44.00	132.00	130.77	1.23	99.07
3.1	88.00	66.00	154.00	152.88	1.12	99.28
1.2	88.00	22.00	110.00	106.25	3.75	96.59
2.2	88.00	44.00	132.00	132.21	–0.21	100.16
3.2	88.00	66.00	154.00	153.85	0.15	99.90
1.3	88.00	22.00	110.00	107.45	2.55	97.68
2.3	88.00	44.00	132.00	130.05	1.95	98.52
3.3	88.00	66.00	154.00	156.01	–2.01	101.30
Average value of yield, %				98.98		

Table 6

RESULTS OF TESTING THE CONVERGENCE OF THE METHOD FOR DRY EXTRACT

Test No.	The content of the total flavonoids in terms of rutin in the analyte, %	
	Dry extract	Liquid extract
1	4.71	0.88
2	4.68	0.85
3	4.58	0.90
4	4.81	0.88
5	4.77	0.87
6	4.70	0.87
Average value of content, %	4.71	0.87
S, % (test unit)	0.0794	0.015
CV, %	1.69	1.66
ε, %	1.8	1.7

Table 7

RESULTS OF TESTING THE REPRODUCIBILITY OF THE METHOD FOR DRY AND LIQUID EXTRACTS

	Analyst 1	Analyst 2	Analyst 1	Analyst 2
	Dry extract		Liquid extract	
Sample No.	Day 1	Day 2	Day 1	Day 2
1	4.78	4.90	0.88	0.88
2	4.70	4.68	0.89	0.89
3	4.55	4.76	0.86	0.87
4	4.72	4.61	0.86	0.90
5	4.71	4.74	0.87	0.87
6	4.66	4.76	0.88	0.87
7	4.90	4.83	0.86	0.86
8	4.83	4.82	0.89	0.88
9	4.77	4.79	0.88	0.87
Average content of rutin, %	4.74	4.77	0.87	0.88
S, %	0.1009	0.0852	0.0124	0.0125
CV, %	2.13	1.79	1.42	1.42
D	0.010178	0.007253	0.00015325	0.0001555
Fisher's criterion F (95%, f_1=8, f_2=8) = 3.44	1.40		0.99	

and 190% of the theoretical content of the total flavonoids in terms of rutin (in the range of 6.4–30.4 μg/ml). The correlation coefficient (R2) was 0.9937, which corresponds to the acceptance criterion: the coefficient between a number of the resulted values is not lower than 0.995 (Fig. 3).

The control of the correctness of the method was evaluated on model mixtures with the addition of the rutin standard 25, 50, 75% to its initial concentration in liquid and dry extracts. It was found that the recovery percentage for dry extract is in the range from 96.21% to 102.62% and has an average value of 99.6%, and for liquid extract-in the range from 96.64% to 101.3% and has an average value of 98.98%, which meets the requirements of the acceptance

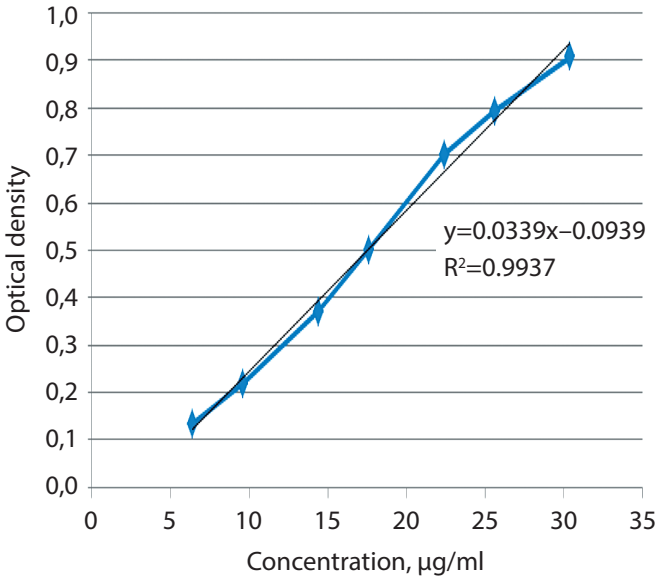

FIG. 3. *Dependence of the optical density of the solution of the rutin complex with $AlCl_3$ on its concentration*

Table 8

THE RESULTS OF THE VALIDATION EVALUATION OF THE METHOD OF SPECTROPHOTOMETRIC DETERMINATION OF THE TOTAL FLAVONOIDS IN TERMS OF RUTIN

Parameter	Validity criteria	Result	
		Dry extract	Liquid extract
Specificity	Coincidence of the spectral characteristics with the rutin standard	Coincidence λ_{max}	Coincidence λ_{max}
Convergence	Coefficient of variation of parallel determinations for 6 measurements CV≤5%	CV≤1.69%	CV≤1.66%
Reproducibility	CV<0% Ttable≥tcalc.	CV1≤2.13% CV2≤1.79% $t_{calc.}$=1.40, (t_{table}=3.44), n=9	CV1≤1.42% CV2≤1.42% $t_{calc.}$=0.99, (t_{table}=3.44), n=9
Linearity	R^2≥0,99	R^2=0.9937; y=0.0339x – 0.0939	
Correctness (accuracy)	Recovery percentage R ϵ [95.0%; 105.0%]	R ϵ [96.21%; 102.62%]	R ϵ [96.64%; 101.30%]

criterion (from 95.0% to 105.0% for vegetable raw materials).

The convergence of the method was determined on one sample of raw materials in 6 repetitions. The coefficient of variation for 6 definitions was 1.69% for dry extract and 1.66% for liquid extract, which satisfies the condition of no more than 5%.

The intra-laboratory reproducibility of the method was determined by two analysts on 9 repetitions of the dry and liquid sample. The obtained values of the coefficient of variation do not exceed 10%, which allows us to consider the intra-laboratory reproducibility of the results acceptable.

The obtained data make it possible to consider the developed methods suitable for reliable quantitative determination of the total flavonoids in terms of rutin in the studied extracts.

CONCLUSIONS

A method of quantitative determination of the total flavonoids in terms of rutin in dry and liquid alcohol extracts of a plant composition has been developed and validated, which includes crushed raw materials of motherwort, St. John's wort, melissa and thyme herbs in a ratio of 4:2.5:2.5:1. The results of statistical processing of the experiments indicate that the error of a single determination of the total flavonoids with a confidence probability of 95% is ±0.99% for a liquid extract and ±1.40% for a dry extract.

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METHODOLOGICAL JUSTIFICATION OF AGE DIFFERENTIATION OF MINOR BUYERS IN THE SALE OF MEDICINES AND OTHER PHARMACY PRODUCTS

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It is known that medicines and biologically active additives (BAA), along with their medicinal properties, can have side effects, contraindications and in some cases be potentially dangerous to the health of children. Currently, in the Russian Federation, the sale of certain goods, the use of which has a potential danger to health, to minors is restricted or prohibited, but such age restrictions are not established for medicines. The current situation contradicts the basic principles of the state policy in the field of children's health protection, as it creates prerequisites for uncontrolled access and use of medicines in childhood. It is established that the share of children's appeals to pharmacy organizations accounts for about 6% of the total number of buyers.

Key words: pharmacy organization, medicines, pharmacy assortment products, minor buyers, pharmaceutical specialists, legal and mental capacity of a minor buyer

The main value of human life is health. According to the Constitution of the Russian Federation, every citizen "has the right to health protection" [1]. The fundamentals of public health protection [2] prescribe the basic principles of preserving and strengthening the health of the population, including the protection and prevention of children's health "as one of the necessary conditions for the physical and mental development of children". It is worth noting that in most countries, including the Russian Federation, a child "is recognized as a person who has not reached the age of eighteen years (majority)" [3–5].

Due to "physical and mental immaturity" [3], the child needs special "care and legal protection"[3], in this regard, parents (legal representatives) must bring up and take care of the health and development of their children «[4], including through the formation of initial knowledge and skills that contribute to the health of the child.

It is necessary to take into account that the maintenance of health in most cases is achieved through a healthy lifestyle, but a significant component of health protection is associated with the use of medicines and other pharmacy products (PP). Based on the definition specified in the federal law [6], medicines should be used "for the prevention, diagnosis, treatment

of the disease, rehabilitation, for the preservation, prevention or termination of pregnancy", however, according to the WHO, "half of all patients receiving pharmacotherapy take medicines incorrectly" [7], which creates prerequisites for a threat to the life and health of people of different ages, including children.

Quite often, violations of the use of medicines lead to unfavorable results, including undesirable reactions from the use of medicines, including serious poisoning requiring intensive therapy and/or caused disability of the child [8]. According to the WHO, up to 20% of fatal medicine poisoning is relating to children [8,9]. The majority of medicine poisoning is accounted for by children of preschool (from 1 to 7 years) and adolescent (from 14 to 17 years) age [9–16]. The analysis showed that in the age group from 14 to 17 years, both accidental poisoning associated with improper use of medicines or episodic use of psychoactive substances in order to search for new sensations, and intentional (suicidal) poisoning are recorded [9,11,13–14,16–17].

It is important to emphasize that in the Russian Federation, the sale of certain goods, the use of which has a potential danger to human health, is restricted or prohibited to minors [18–21], but there are no age restrictions on the purchase of medicinal products, and this creates the possibility of access to potentially dangerous goods for a child of almost any age who is physically able to make purchases independently. It is alarming that children actively use this legal gap, since, according to the results of our research, the share of children's appeals accounts for about 6% of the total number of buyers in pharmacy organizations.

In our opinion, the current situation contradicts the basic principles of the state policy in the field of child health protection, since it creates prerequisites for uncontrolled access and use of medicines in childhood.

The above justifies the need to develop a differentiated approach to the sale of medicinal products and other product groups of the pharmacy assortment by age categories of underage buyers from the point of view of pharmaceutical safety, protecting the health of the child.

The purpose of study is justification and development of approaches to the age differentiation of underage buyers when selling medicinal products and other products of the pharmacy assortment in order to prevent pharmaceutical and pharmacotherapeutic risks in children.

MATERIALS AND METHODS

The sources of information were the current regulatory legal acts regulating the public health protection and the circulation of medicines, including the dispencing (sale) of medicines and other pharmacy products from pharmacy organizations; regulatory legal documents establishing the rights and obligations of minors in the field of health protection; reports of Roszdravnadzor on situations of chemical etiology poisoning in the Russian Federation; collections of statistical materials and official reports of Rosstat on the medical and demographic aspects of the population and individual socio-demographic groups; domestic and foreign scientific publications on the subject of the study, as well as the results of our own research on children's attendance at pharmacy organizations and their purchases.

During the analysis, the methods of logical, statistical analysis, and sociological (survey) were used.

RESULTS AND DISCUSSION

Pharmacy assortment products are a special socially significant group of goods allowed for sale from pharmacy organizations, the list of which is limited to an exhaustive set of product groups approved at the state level. Currently, pharmacy

organizations have the right, along with medicinal products, to purchase and sell "medical products, disinfectants, personal hygiene items and products, dishes for medical purposes, items and products intended for the care of patients, newborns and children under the age of three years, eyeglass optics and care products, mineral waters, products of therapeutic, children's and dietary nutrition, biologically active additives, perfumes and cosmetics, medical and sanitary-educational printed publications, intended to promote a healthy lifestyle" [22].

From the entire list of products, special attention should be paid to medicines as a potential source of danger for children when they are used uncontrolled. The rules of good pharmacy practice [23] regulate "providing the population with high-quality, effective and safe" medicines and other pharmacy assortment products. The official source of information about a medicinal product is the instruction for medical use, which is approved during the registration procedure [22]. According to the established requirements, the list of necessary information prescribed in the instructions for the medical use of medicinal products includes an indication of the need to store medicinal products in the places inaccessible to children, which indirectly indicates the need to restrict access of minors to this group of goods [24–25]. However, an analysis of the requirements of other regulatory legal documents [22–23,26–27] regulating the procedure for the sale of medicinal products and other pharmacy assortment products from pharmacy organizations showed that currently there are no age restrictions for the sale of medicinal products and other pharmacy assortment products.

Meanwhile, medicinal products should be considered not only as a socially significant product used to meet the needs associated with the protection of human health, but also as a potential source of health hazards. Earlier, we introduced the concepts of pharmacotherapeutic and pharmaceutical risks when using medicinal products and summarized the main predictors of their occurrence due to illiterate use and violation of the rules of storage at home [28]. The analysis of Russian and international studies devoted to the study of violations in the use of medicines, including in the framework of self-treatment, and information from toxicological centers illustrating situations related to medicine poisoning among children [8–15,29–36], allowed us to form and systematize the main threats to child health associated with the free sale of medicines, their uncontrolled use and violations when used at home (Fig. 1).

Analyzing the situation of limiting the ability of children to independently purchase goods in a pharmacy, it is necessary to take into account their rights regulated by the Civil Code of the Russian Federation and other regulatory legal acts.

Any sale of goods from a pharmacy organization for the purpose of personal, family or home use formally refers to a retail purchase and sale agreement and is considered concluded from the time a cash receipt is issued to the buyer [26, 37]. The possibility of its conclusion is specified by the volume of legal capacity and mental capacity of citizens.

The legal capacity of a citizen is "the ability to have civil rights and bear duties (civil legal capacity)", which arises at the time of his birth and ends with death [38]. Every citizen has the right to live and use the most advanced services of the health system, including health promotion, recommendations for immunization, treatment of diseases with the use of medicines [1,3,39]

The real exercise of the rights and obligations depends on the mental capacity, that is, "the ability of a citizen to acquire and exercise civil rights by his/her actions, create civil obligations for himself/herself and fulfill them" and arises in full with the onset of adulthood, that is, from the age of 18 [38].

From the point of view of the mental capacity of minors, depending on their age, they can be

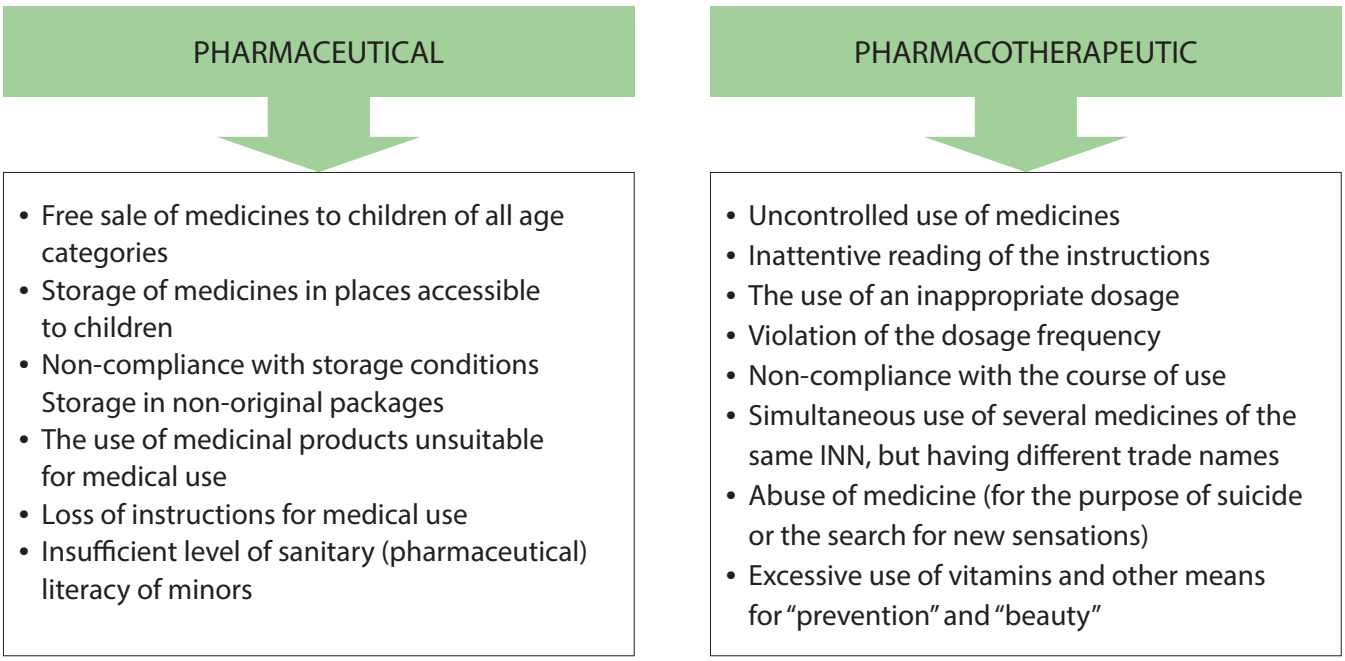

FIG. 1. *Pharmacotherapeutic and pharmaceutical risks when the medicines are used by underage patients*

divided into three groups: a legally incapable child – children from the birth to the age of 6; a minor child with partial mental capacity – children from 6 to 14 years of age; a minor with partial or full mental capacity – children from 14 to 18 years of age [38].

In this regard, we can draw conclusions:

- all transactions of minors under the age of 6 years due to the small age of the child and the inability to understand their actions and responsibility for them can only be carried out on their behalf by parents (legal representatives)
- starting from the age of 6, children acquire partial mental capacity;
- children aged from 6 to 14 years have the right to independently make small household transactions.
- from the age of 16, emancipation is provided, that is, the declaration that the citizen has full capacity to act in two cases: a minor works under an employment contract or marries for a valid reason [38,40].

It is worth noting that the term "small household transaction" does not have a legal definition, it is used in civil legislation to establish the scope of rights of children from 6 to 18 years old [38], the signs of which, according to existing practice, are: the use of cash (belonged to parents or their own); the price corresponds to the age and socio-psychological level of the child; goods for the purpose of satisfying the household, personal needs of an individual [41].

Thus, the sale of medicines and other pharmacy assortment products for children under 6 years of age is impossible due to the incapacity of the individual. At the same time, in order to solve the issue of the sale of medicines and other pharmacy assortment products to children at the age from 6 to 18 years, attention should be paid to the psychological (age) aspects of the personality and other rights of a minor that arise at the certain age of the personality. Thus, in the period from 6 to 10 years, civic qualities begin to be developed and psychological neoplasms begin to be formed, but relationships with the social environment are mediated by relationships with adults. The Family Code of the Russian Federation [4] provides for the right of a 10-year-old child "to express his/her opinion when solving any issue affecting

his/her interests in the family". From this period (10–11 years), according to the age periodization (according to Vygotsky), children enter puberty age, and the main role of mental development at this age belongs to the establishing system of relationships with others.

At the age of 14, every citizen is required to have a passport of the Russian Federation [42], and, according to the Labor Code of the Russian Federation, from this age there is an opportunity to get a job in his/her spare time, to perform easy work that does not harm his/her health, but the consent of the parent and the tutorship and guardianship authority is required [43].

From the point of view of purchasing goods, unlike young children (up to 6 years old), a minor from the age of 14 can [38] independently, disposing of his/her earnings, scholarship allowance and other incomes, make small household transactions without the consent of his/her parents, as well as make other transactions with the written consent of his/her parents (legal representatives).

The Federal Law "On the basics of protecting the health of citizens" provides that when visiting a medical organization, "a necessary condition for medical intervention is the informed consent" [2]. The consent is given by one of the parents (legal representative) for persons under the age of 15. Minors over the age of 15 have the right to independently visit a medical organization and give informed voluntary consent to medical intervention or to refuse it [2].

Minors who have reached the age of 16 can become fully capable [38], work under an employment contract [38,43], marry if there are valid reasons (pregnancy, birth of a child) and independently exercise their parental rights [4].

Thus, from the standpoint of legal capacity, different age gradations of minors are distinguished depending on the goals, since when a child grows up, the minor citizen's mental maturity increases which explains the expansion of his/her rights and obligations.

It should be noted that at present, regulatory legal acts do not regulate at what age children have the right to acquire medicines and other pharmacy assortment products. Accordingly, there are no restrictions for pharmacy organizations selling medicines and other pharmacy assortment products to children of different ages.

The above allows us to find the need to create recommendations for dispensing (selling) the medicines and other pharmacy assortment products to minor visitors, based on the age differentiation of minor citizens from the standpoint of observing their rights and preventing possible risks associated with the use of medicines and other pharmacy assortment products.

Based on the analysis and integration of the studied data, we have developed a conceptual scheme "Recommendations on age differentiation during the dispensing (sale) of medicines and other pharmacy products from a pharmacy organization to minor visitors" from the point of view of minimizing the risks of using the medicines and other pharmacy products, taking into account the legal capacity and mental capacity of a minor citizen, including in the field of protection and promotion of health.

As can be seen from Fig. 2, in our opinion, the sale of medicines and other pharmacy products for children under 10 years when they apply to a pharmacy organization independently is not recommended.

In our opinion, pharmacy organizations can dispense (sell) to the citizens who have reached the age of 10 the separate groups of pharmacy products (medical devices, personal hygiene items and products, mineral waters, clinical, child and dietary food products, items and products intended for child care, sanitary and educational printed publications intended for the promotion of healthy lifestyle). To children aged 10 years and above the pharmacy can also dispense (sell) over-the-counter medicines for external use in case of easily recognizable states, which include abrasions and minor skin injuries, such

FROM 10 YEARS	FROM 14 YEARS	FROM 15 YEARS	FROM 16 YEARS with full mental capacity
• Over-the-counter medications for external use *(for easily recognizable states)*			
• Medical products • Personal hygiene items and products • Products for child, dietary and clinical nutrition • Mineral waters • Items and products intended for the care of children and the sick persons • Sanitary and educational printed publications intended for the promotion of healthy lifestyle			
	• All medicines for over-the-counter dispensing *(if there is a written permission from the parents/legal representatives)*		
	• Perfumes and cosmetics		
		• Medications prescribed by a doctor to a minor visitor (by prescription) • All medicines for over-the-counter dispensing *(for easily recognizable states)* • All medicines *(if there is a written permission from the parents/legal representatives)*	
		• Biologically active additives	
			• All medicines • All pharmacy products

FIG. 2. *Recommendations on age differentiation during the dispensing (sale) of medicines and other pharmacy products to underage visitors from a pharmacy organization*

as wounds, black-and-blue spots, bruises [44–45], with the exception of medicines for internal use, biologically active additives and other medicines for external use.

Perfumes and cosmetics, as well as over-the-counter medicines can be dispensed (sold) to children from the age of 14, in addition to the above product groups, but with the written consent (note) from the parent (legal representative) indicating contact information.

Medicines including those on prescription issued directly to the minor citizen who applied are allowed to be dispensed to the citizens from the age of 15, due to the legal possibility of an independent visit to a medical worker and the independent giving of informed consent to medical care and prescribing treatment, including pharmacotherapy. In addition, with an independent request, it is permissible to dispense drugs in the status of biologically active additives (BAA) to the buyers from the age of 15 [44–45].

We consider it possible to dispense over-the-counter medicines to minors from the age of 15 with easily recognizable symptoms [44–45] such as mild cold-related diseases (sore throat, runny nose, slight fever, etc.), mild to moderate pain, allergic rhinitis, urticaria, heartburn, flatulence, abdominal cramps and discomfort, vitamin deficiency- and mineral deficiency conditions, as well as medicines on prescription with the consent of parents (legal representatives) for them

or other relatives, if there is a written consent and a prescription (for prescription medicines).

The entire assortment list of medicines and other pharmacy products can be dispensed (sold) to minor visitors who have received full legal capacity in compliance with the rules of administration and dispensing of medicines.

It is worth emphasizing that when a minor visitor applies to a pharmacy organization for the purpose of purchasing the pharmacy products, including medicines a pharmaceutical specialist must identify the age of the child by an oral survey (up to 14 years old) or specify the age according to identity documents [46–48].

When selling pharmacy products to minors, it is necessary to take into account the age restrictions specified in the instructions for the medical use of the medicine, as well as the compliance of the purchased product with the age-specific needs of the buyer (with an independent request). In addition, it should be remembered that the information and pharmaceutical counseling of underage visitors should be carried out in accordance with the requirements of the legislation, taking into account their physiological and socio-psychological (age-specific) characteristics. At the same time, the pharmaceutical specialist shall make sure that the information regarding the safety of using the purchased medicines or other pharmacy products is correctly understood by the teenager.

CONCLUSIONS

The proposed recommendations on the age differentiation of underage buyers when selling them goods from pharmacy organizations, aimed at preventing pharmaceutical and pharmacotherapeutic risks among the underage population, will contribute to the protection of children's health by forming a health promotion behavior in their independent handling of medicines and other pharmacy products, which is fully consistent with state and international tasks in the field of the minors health protection and preventive health care.

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THE PRECLINICAL STUDIES OF THE SAFETY OF *RHAPONTICUM UNIFLORUM* ROOTS DRY EXTRACT

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In experiments on white rats of the Wistar line, the chronic toxicity and possible local irritant and mutagenic effect of dry extract prepared from Rhaponticum uniflorum L DC rhizomes were investigated. The effect of dry R. uniflorum extract on the morphofunctional state of internal organs was evaluated after three-month administration (per os) at doses of 100 and 500 mg/kg. The possible local irritant and mutagenic effect of the test agent was determined with its single administration at doses of 100 and 1000 mg/kg. It was found that long-term administration of dry R. uniflorum extract does not have a negative effect on the morphofunctional state of the central nervous, cardiovascular and urinary systems, organs of the gastrointestinal tract, the state of metabolism, peripheral blood parameters and hemostasis systems of laboratory animals. The test agent does not cause local irritant and mutagenic action.

Keywords: *Rhaponticum uniflorum* L. DC, *Fornicium uniflorum* (L.) Zuev., rhizome and root extract, chronic toxicity, local irritant effect, mutagenicity

Rhaponticum uniflorum L. DC. (synonym *Fornicium uniflorum* (L.) Zuev.) is a perennial plant that grows on the territory of Eastern Siberia and the Far East [1]. The underground part of the plant contains triterpenes (ursolic acid), sterols, flavonoids (apigenin, luteolin, quercetin, etc.), amino acids (alanine, arginine, glycine, etc.) and other biologically active substances [2–4]. The content of ecdysteroids in terms of ecdysterone in the underground part is 1.19–1.3% [5]. Previously, in animal studies, it was found that the dry extract prepared from R. uniflorum rhizomes with roots, has a pronounced stress-protective effect in immobilization and emotional stress and increases the body's resistance to intense physical exertion and to oxygen-deficient conditions of various origins [6]. This extract increases the research activity, reduces the level of emotionality and anxiety in conditions of non-punishable behavior [7], as well as has an immunomodulatory effect, increasing the activity of the main parts of the immune system in an immunosuppressive state [8].

The purpose of the study: determination of chronic toxicity, as well as possible local irritant and mutagenic effects of dry extract prepared from *R. uniflorum* rhizomes with roots.

MATERIALS AND METHODS

The studies were performed on white *Wistar* rats of both females and males with an initial weight of 160–180 g. The animals were kept in accordance with the "Rules of Good Laboratory Practice" (GLP) and the Order of the Ministry of Health of the Russian Federation No. 199H of 01.04.2016 "On approval of the Rules of Good Laboratory Practice". The experimental work was carried out in accordance with the Rules adopted in the European Convention for the Protection of Vertebrates (Strasbourg, 1986). The protocol of the study was agreed with the Ethical Committee of the Institute of General and Experimental Biology of RAS SB (No. 4 of 26.01.2017). The experiments were carried out in accordance with the current requirements set out in the Guidelines for Preclinical Studies of Medicines [9].

The object of the study was a dry extract prepared from *R. uniflorum* rhizomes with the roots by sequential extraction with 60% ethyl alcohol and double extraction of crushed plant raw materials with purified water, followed by filtration, evaporation and vacuum drying. A method for preparing a dry extract from *R. uniflorum* rhizomes with the roots has been patented [10]. Standardization of dry extract prepared from *R. uniflorum* rhizomes with the roots is carried out according to the amount of ecdysteroids in terms of ecdysterone, the content of which should be at least 3.0% [11].

The chronic toxicity of *R. uniflorum* dry extract was studied at doses of 100 mg/kg (experimental-therapeutic) and 500 mg/kg. The test agent was administered intragastrically to animals of the experimental groups daily for three months. The control group rats received an equi-volume amount of the water purified according to a similar scheme. The functional state of the central nervous system was assessed using the "open field" method [9], the cardiovascular system was assessed by the value of systolic blood pressure (SM-42115 cardiac recorder, Poland) and bioelectric activity of the myocardium (Axion EK1T-1/3-07 ECG recorder, Russia). The functional state of internal organs and metabolic processes was assessed by the content of total protein, protein fractions, total cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides, urea and creatinine; the activity of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and alkaline phosphatase in blood serum using Sapphir biochemical analyzer (Japan). Hematological blood parameters were determined using Mindray BC-5300 automatic analyzer (China). The study of blood coagulation properties was carried out using standard Sigma reagents (USA) on a Bio bas I coagulometer (Spain). The concentration of potassium and sodium ions was determined in the urine of animals by flame photometry (Flapho-4, Germany); the content of glucose and protein, the creatinine and urea concentrations were determined using a semi-automatic urine analyzer H-500 (Russia). For pathomorphological studies, the internal organs of animals were fixed in a 10% solution of neutral formalin. Histological sections were stained with hematoxylin-eosin, picrofuxin according to van Gieson and cresyl violet according to Nissl.

To identify a possible local irritant effect, phytoextract was administered to animals of the experimental groups once intragastrically at doses of 100 and 1000 mg/kg. 3, 6 and 24 hours after administration of the test agent, the gastric and intestinal mucosa was examined with a magnifying glass. The assessment of possible mutagenic properties of the *R. uniflorum* dry extract was carried out using methods of accounting

for chromosomal aberrations of blast cells of the bone marrow of white male rats. Accounting was carried out 24 hours after a single intragastric administration of the test agent at doses of 100 and 1000 mg/kg. Bone marrow was taken from the femoral bone. The analysis of chromosome aberrations was carried out by the method of viewing of metaphase plates with an ×1000 microscope magnification. From each individual, 100 metaphase plates were examined that met the necessary requirements. Chromosome damage was taken into account according to the recommendations set out in the methodological works [9].

Statistical data processing was carried out using the Statistica software package for Windows 6.0. To assess the differences in samples with a normal distribution, the Student's t-test was used. The differences were considered accurate at the achieved significance level of $p<0.05$.

RESULTS AND DISCUSSION

The results of the studies showed that with the three-month administration of *R. uniflorum* dry extract at doses of 100 and 500 mg/kg, no death of animals and pronounced changes in their general condition (behavior, consumption of the daily volume of feed, secretions, wool, mucous membranes) were observed. The rectal temperature in the rats of the experimental groups did not differ from the temperature value of the control animals. In animals treated with dry *R. uniflorum* extract at a dose of 500 mg/kg, body weight gain for the first two months of follow-up was higher than in animals of the control group.

Testing of animals in the "open field" showed that the overall motor activity and the level of anxiety in the animals of the experimental groups were at the level of the control values. At the same time, the rats treated with *R. uniflorum* extract at doses of 100 and 500 mg/kg showed increase in the number of central squares visited (by 22% and 28%) and rears unsupported (by 25% and 30%, respectively) compared to the data in control animals.

It was found that long-term administration of the dry *R. uniflorum* extract at doses of 100 and 500 mg/kg does not have a negative effect on the respiratory function of white rats: during all the study periods, the respiratory rate in the animals of the experimental groups was within the physiological standard and did not differ from the data in the control group. The studied medicine does not cause changes in the functional status of the cardiovascular system: the blood pressure level of rats, the values of bioelectric activity of the myocardium and the heart rate have no significant differences in comparison with the control animals.

The results of hematological studies have shown that the three-month administration of the test agent does not affect the hemoglobin content and peripheral blood parameters. During the biochemical analysis of the blood of laboratory animals, it was found that the use of dry *R. uniflorum* extract did not have an adverse effect on the functional status of the body: the content of protein, protein fractions, activity of ALT, AST, LDH and alkaline phosphatase did not statistically differ from those in the control group animals. At the same time, against the background of administration of the test agent, there is decrease in total cholesterol, creatinine and urea concentrations in the blood serum. Parameters of the hemostasis system in animals of the experimental groups have no significant differences with those of control animals.

The results of the studies presented in Fig. 1 show that long-term administration of dry *R. uniflorum* extract at doses of 100 and 500 mg/kg has a diuretic effect, increasing diuresis by 24% and 32% compared to the control animal parameters. At the same time, administration of the test agent does not affect the other parameters of the functional status of the kidneys of white rats: there is no glucose, bilirubin in the urine;

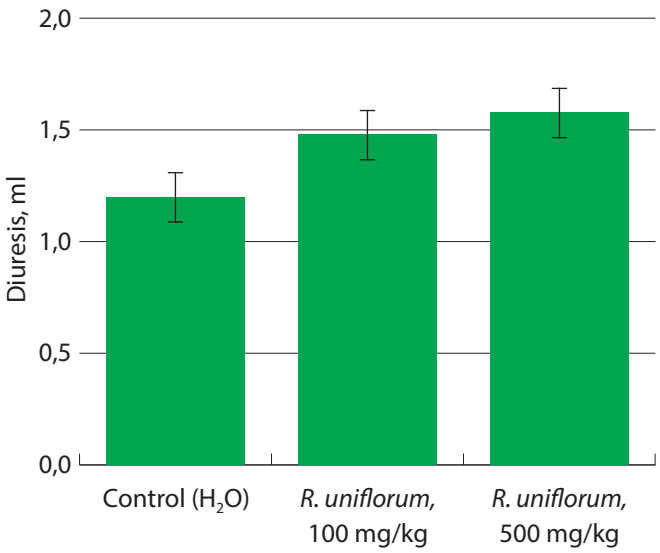

FIG. 1. *The effect of long-term administration of dry extract prepared from rhizomes with roots of R. uniflorum on the diuretic activity of white rats*

concentration of electrolytes, protein and creatinine content are within the physiological standards.

Long-term administration of the test agent does not affect the weight coefficients of internal organs. During the pathomorphological study of internal organs (brain, lungs, kidneys, liver, thymus, red bone marrow, spleen, thyroid gland, adrenal glands, gonads), no pathological changes in their structure were found due to the toxic effect of the test agent.

When studying the local irritant effect, it was revealed that 3, 6 and 24 hours after administration of the phytoextract, the mucous membrane of all the studied sections of the digestive tube is pale pink, there is no hyperemia, vascular injections, as well as edema, its relief is preserved, the folds have a standard configuration and location. In general, the macroscopic picture of the gastric and intestinal mucosa of animals of the experimental groups corresponds to that of control animals.

The results of the studies presented in Table 1 indicate that a single intragastric administration of phytoextract to male rats at doses of 100 and 1000 mg/kg does not cause increase in the number of damaged cells in the bone marrow of animals of the experimental groups compared with the control.

CONCLUSIONS

1. Dry *R. uniflorum* extract in doses of 100 and 500 mg/kg with prolonged administration does not adversely affect the morphofunctional state of the central nervous, cardiovascular and urinary systems, gastrointestinal tract organs and the state of metabolism, peripheral blood

Table 1

THE EFFECT OF A SINGLE ADMINISTRATION OF DRY EXTRACT PREPARED FROM *R. UNIFLORUM* RHIZOMES WITH ROOTS ON THE NUMBER OF CHROMOSOMAL ABERRATIONS IN THE BONE MARROW CELLS OF WHITE RATS

Parameters	Groups of animals		
	Control	*R. uniflorum*, 100 mg/kg	*R. uniflorum*, 1000 mg/kg
Number of metaphases	800	800	800
Number of aberrations, %	1.0	0.9	0.8
Cells with multiple aberrations, %	0	0	0
Gaps, %	0.4	0.3	0.5
Proportion of damaged cells, %	1.3±0.18	1.4±0.29	1.4±0.32

parameters and hemostasis systems of laboratory animals

2. Three-month administration of *R. uniflorum* extract increases the orientation-research activity of animals and has a moderate diuretic effect

3. Dry *R. uniflorum* extract in doses of 100 and 1000 mg/kg with a single administration does not have a local irritant and mutagenic effect.

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DEVELOPMENT OF ANTIMICROBIAL SPRAY FORMULATION BASED ON A THICK REINDEER LICHEN EXTRACT

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The Article presents the results of the selection of an extractant for preparation of a thick extract from the lichen thallus of the genus Cladonia (reindeer lichen). The stages of developing an antibacterial spray formulation for the oral cavity and throat based on a thick extract are shown. Standardization of the developed spray according to the content of usnic acid was carried out. Preclinical tests have confirmed the antibacterial activity of the medicinal product based on reindeer lichen and its low toxicity.

Keywords: lichen, *Cladonia*, usnic acid, thick extract, spray, medicinal product formulation

Reindeer lichen (lichen of the genus *Cladonia*) has long been known among the northern peoples for its properties. Usnic acid, as it was found by researchers, has antiviral, antibiotic, analgesic, antitubercular and insecticidal activities [1]. In the 1970 s, the V.L. Komarov Botanical Institute of the USSR Academy of Sciences developed and used the medicine "Binan", which is a sodium salt of usnic acid isolated from lichens. The medicine had an antibacterial effect on gram-positive, some gram-negative, acid-resistant bacteria and on certain fungi. "Binan" and other well-known medicines containing usnic acid were alcohol or oil solutions.

Previously, a method for chromatographic determination of usnic acid was developed and conditions for preparation of Reindeer lichen thick extract were selected [2]. The solubility of the thick extract of *Cladonia* thallus in water allows you to create dosage forms based on it in the form of alcohol solutions. In this regard,

a thick Reindeer lichen extract is chosen to create an antibacterial spray for local and external use.

The purpose of this study is to develop a formulation of antimicrobial spray from the layers of the *Cladonia* lichen thallus.

MATERIALS AND METHODS

The lichen thallus of the genus *Cladonia* were harvested in the Republic of Sakha (Yakutia) in August 2020, dried according to the requirements of the State Pharmacopoeia and crushed to the size of particles passing through a sieve of 0.7 mm. To determine the optimal extractant of usnic acid from Reindeer lichen, 10 ml of ethanol with different concentrations were added to weights of 1 g each (exact weight) of raw materials crushed to 0.7 mm, the resulting extracts were settled at room temperature for 1 day. Then the medicinal plant raw material precipitate was separated from the extraction by centrifugation and filtered through a filter paper of the "white tape" type, 0.5 ml of the filtrate was placed in a measuring flask with capacity of 50 ml and brought to the mark with methanol. Chromatography was performed according to the previously developed method [2].

Figures 1 and 2 show chromatograms of the standard usnic acid solution and extraction.

In addition, the extractive power of other organic solvents such as methanol, propanol, isopropanol, butanol, isobutanol, ethyl acetate was studied. In this case, the method, the degree of grinding, the time and the multiplicity of extraction are similar to the corresponding parameters when extracting usnic acid with alcohol solutions.

RESULTS AND DISCUSSION

As a result of the studies on the choice of extractants, Table 1 presents data on the amount of usnic acid in the extracts prepared.

From the data resulted, it can be seen that usnic acid is best extracted from raw materials with 70% ethyl alcohol.

The data resulted in the study of the extractive power of various solvents were used during the development of formulation of a thick extract,

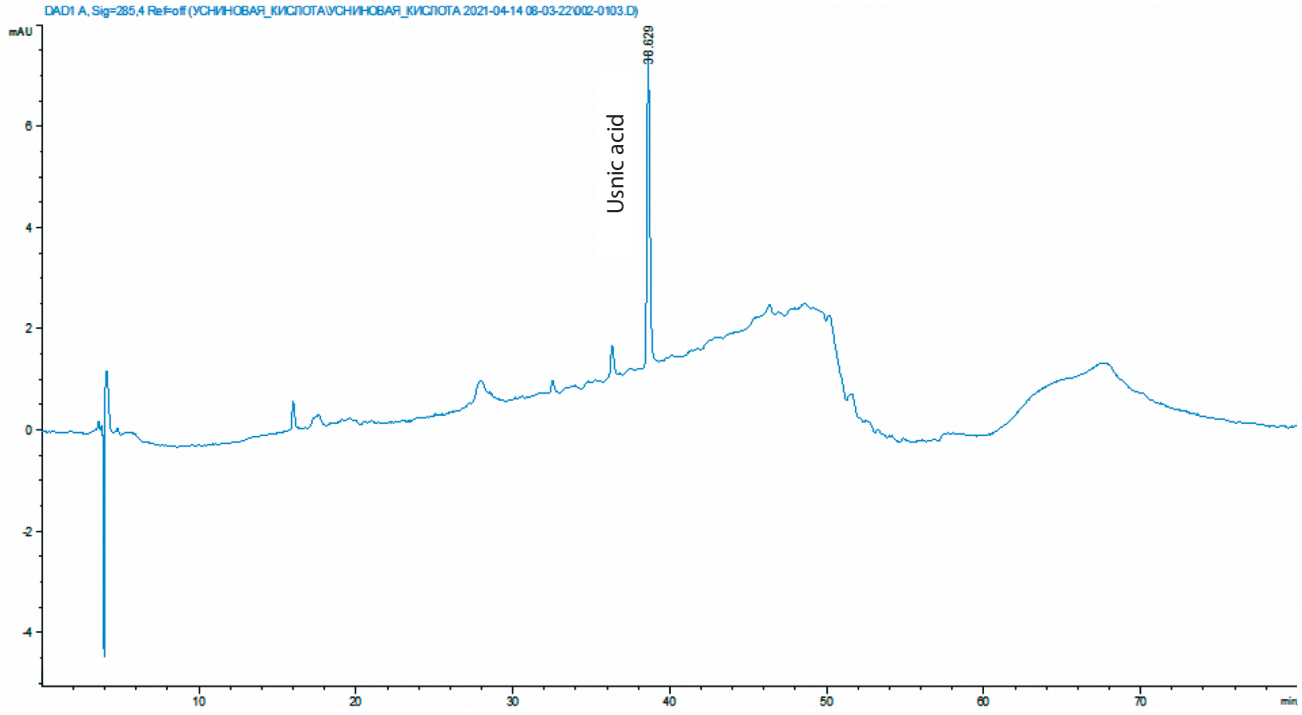

FIG. 1. *Chromatogram of the standard usnic acid solution*

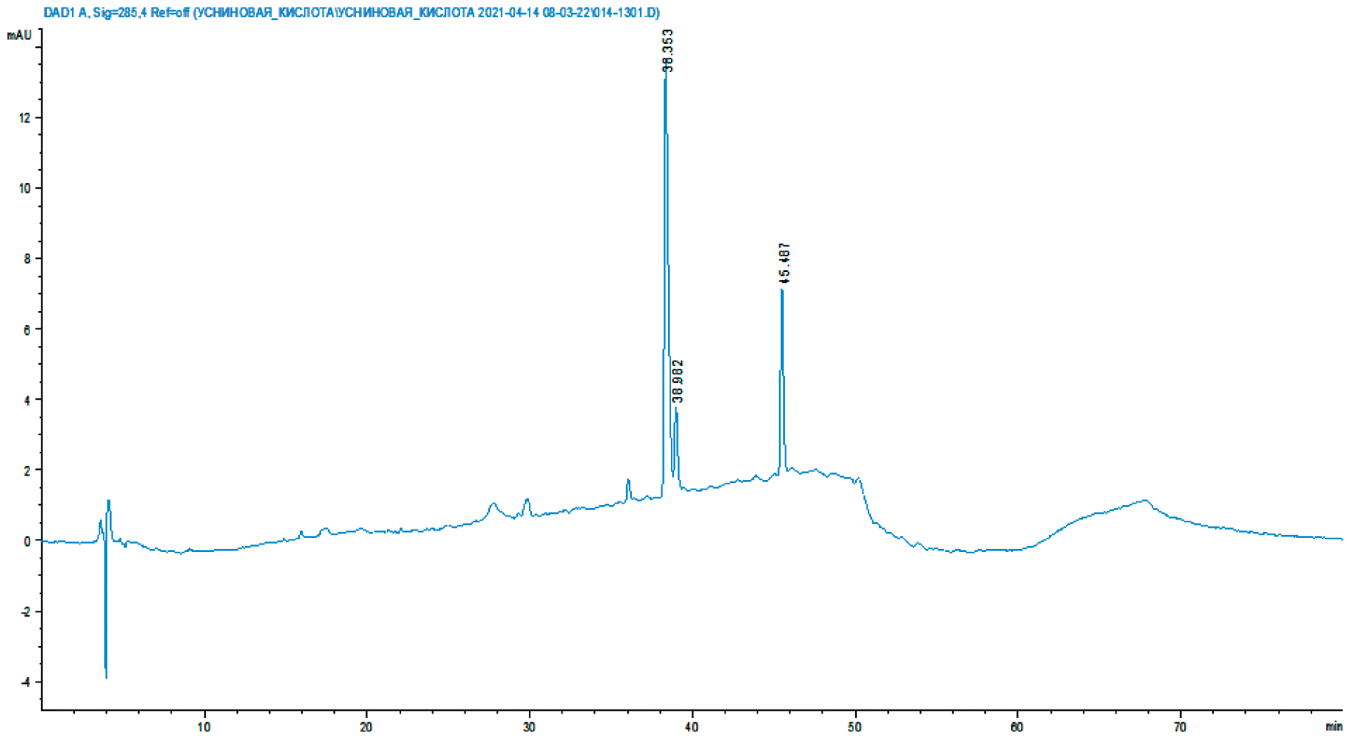

FIG. 2. *Chromatogram of extraction from Cladonia thallus*

Table 1

DEPENDENCE OF THE DEGREE OF EXTRACTION OF USNIC ACID FROM THE *CLADONIA* THALLUS ON THE NATURE AND CONCENTRATION OF THE EXTRACTANT

Extractant	Concentration of the extractant, %	Degree of extraction of usnic acid, %
Ethanol	20	–
	40	–
	60	10.2
	70	25.6
	80	18.2
	96	17.6
1- propanol	100	2.8
Isopropanol	100	3.0
Butanol	100	2.6
Isobutanol	100	2.8
Ethyl acetate	100	2.6
Methanol	100	2.9

on the basis of which the composition of the spray was developed.

The analysis of the compositions of the sprays to be produced showed [3] that most of them are represented by suspensions consisting of a thick extract and a complex solvent. It is more advisable to create a spray according to the type of solution, since the dissolved active substances have a rapid therapeutic effect.

The choice of the dose of the active ingredient in the spray was based on the analysis of data from previous studies. In particular, the reference book "Medicines" by M.D. Mashkovsky describes a 1% water-alcohol solution or 0.5% oil solution (in castor oil), as well as a solution in glycerin or fir balsam with the addition of 2% anesthetic [4].

When developing the composition of the spray based on a thick extract prepared from the *Cladonia* thallus, the solvents, solubilizers, surfactants, taste-making agents, flavorings, antimicrobial preservatives presented in Table 2 were used.

To prepare a solution capable of forming a fine aerosol after passing through the capillary of the spray nozzle, additional solvents

Table 2

EXCIPIENTS IN THE COMPOSITION OF THE SPRAY

Ingredient	Function of the ingredient
Purified water	Solvent
Glycerin	Solvent, plasticizing agents
Isomalt	Taste-making agents
Methyl-4 hydroxybenzoate (Nipagin)	Antimicrobial preservative
Polysorbate -60	Surfactant
PEG-35 hydrogenated castor oil	Solvent, solubilizer
96% ethanol	Solvent, antimicrobial preservative
Mint Essential Oil	Flavoring

Table 3

COMPOSITIONS OF MODEL SPRAY MIXTURES BASED ON A THICK EXTRACT OF *CLADONIA*

Ingredient, g	Composition No.				
	1	2	3	4	5
Thick extract	0.1	0.1	0.1	0.1	0.1
Glycerin	5.0	10.0	15.0	20.0	20.0
Isomalt	1.0	2.0	3.0	4.0	5.0
Methyl-4 hydroxybenzoate (Nipagin)	0.1	0.1	0.1	0.1	0.1
Polysorbate -60	0.5	1.0	1.5	2.0	3.0
PEG-35 hydrogenated castor oil	0.5	1.0	2.0	3.0	4.0
96% ethanol	10.0	10.0	15.0	20.0	25.0
Mint Essential Oil	0.02	0.05	0.1	0.2	0.28
Purified water	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100
Appearance of the composition	Strong opalescence	Strong opalescence	Moderate opalescence	Weak opalescence	Clear solution
Taste of the composition	Bitter	Bitter	Slightly bitter	Sweetish-bitter	Sweet
Spray swath	Jet	Jet	Cloud-jet	Cloud, a round-shaped imprint	Cloud, an oval-shaped imprint, with a dense core
pH	6.30	6.35	6.46	6.50	6.50

and solubilizers were introduced into the spray. The resulting solutions should be clear, stable during storage, not opalescent and should not leave sediment.

The choice of the solvent concentration in the spray composition is presented in Table 3, where model mixtures with various compositions of excipients are shown.

As we can see from the data presented in the Table 2, the model mixture No. 5 had the best characteristics in appearance, taste and spray swath. Mixtures No. 1 and No. 2 formed a highly opalescent solution, which is due to low concentrations of alcohol, glycerin and solubilizer. Opalescence can contribute to the formation of sediment during storage of the solution, since it contains the smallest insoluble particles that can coagulate with each other. These compositions had a bitter taste, since the concentrations of the isomalt and mint essential oil flavorings were insignificant. An increase in the concentrations of solvents and flavorings improved the physical condition of the solution and the organoleptic properties of the composition.

When the substance is sprayed onto the plane, a static imprint of the spray swath is formed, which has an annular shape in most cases. However, when spraying compositions No. 1 and No. 2, the spray in the form of a jet was observed, which is obviously due to low concentrations of excipients, and as a result, the viscosity of the solution is also low and there is strong cohesion between the drops of the solution. When spraying compositions No. 4 and No. 5, a static imprint of the spray swath had three zones: 1 – the zone of the inner dense region formed by large particles, 2 – the useful zone consisting of a mist of finer particles, 3 – the area of the outer zone of particle scattering. With optimal spraying of sample No. 5, the static imprint has the smallest diameter of the dense region, the largest area of the useful zone and the smallest spread in the outer zone.

In in vitro experiments, we evaluated the degree of release of usnic acid from model spray compositions through a cellophane membrane into a phosphate buffer solution of pH 6.8 after 5, 10 and 15 minutes. Dialysis was performed as follows: in a hollow cylinder, the bottom was covered with a cellophane membrane, on which 1 ml of spray was placed. The cylinder was lowered into a glass with a buffer so that the membrane

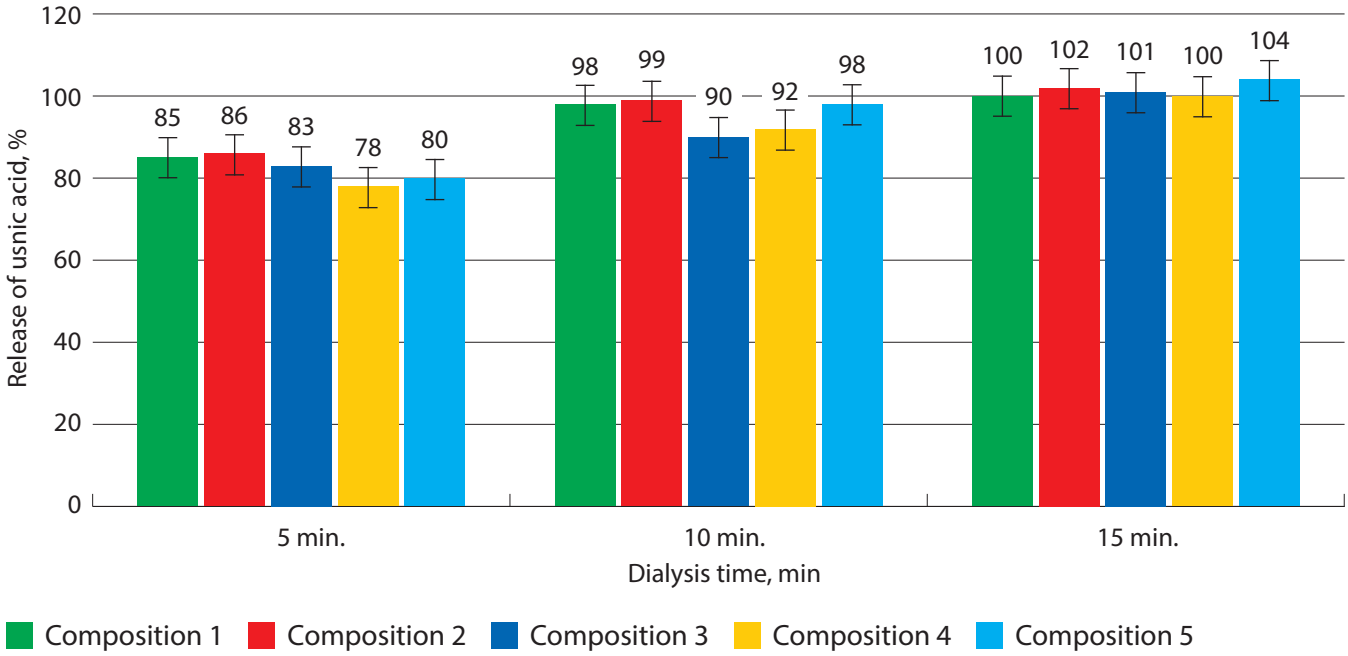

FIG. 3. *Release of usnic acid in in vitro experiments*

touched the surface of the buffer. The results are shown in the diagram (Fig. 3).

As can be seen in the diagram shown in Fig. 3, all model mixtures released approximately the same amount of usnic acid for the certain periods of time, which is explained by the presence of co-solvents and surfactants in their composition. However, compositions No. 1, No. 2 and No. 3 released almost all the active ingredient for 5 minutes of dialysis, while composition No. 5, with good release dynamics, released usninic acid for 15 minutes, which indicates a prolonged effect of this spray composition.

Thus, on the basis of the studies, the composition of an antimicrobial spray for local and external use based on a thick extract prepared from *Cladonia* has been developed. The composition is given in Table. 4. The spray is a yellow transparent liquid with the sweet refreshing taste and the smell of mint.

Table 4

THE COMPOSITION OF THE SPRAY BASED ON THE THICK EXTRACT PREPARED FROM *CLADONIA*

Ingredient	Content in 100 ml of spray, g
Thick extract	1
Glycerin	20
Isomalt	5
Methyl-4 hydroxybenzoate (Nipagin)	0.1
Polysorbate -60	3
PEG-35 hydrogenated castor oil	4
70% ethanol	10
Pepper Mint Essential Oil	0.28
Purified water	Up to 100

The developed spray is standardized according to SP XIV [5]. The conditions were selected and a method for determining usnic acid by HPLC was developed, its content in the spray was 1±0.05%. Based on the data resulted, a draft of regulatory documentation has been prepared.

A preclinical study of the general toxic effect of the spray and antimicrobial activity was carried out. It is shown that the medicine is low-toxic. Experimentally, it was found that the medicine has a pronounced inhibitory activity against Staphylococcus aureus strains.

CONCLUSIONS

A formulation of an antibacterial spray for the oral cavity and throat has been developed. The resulting spray is standardized according to the content of usnic acid. Preclinical tests of the developed spray confirmed antibacterial activity (against Staphylococcus aureus strains) and low toxicity.

The results were obtained within the framework of the State Assignment of the Ministry of Education and Science of the Russian Federation (FSRG-2020-0019)

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ESTIMATION OF THE SIZE AND SHAPE OF GSB-106 GRANULES PRODUCED BY WET GRANULATION USING THE IMAGE ANALYSIS METHOD

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The size, shape and fractional composition of GSB-106 granules produced by wet granulation technology were evaluated using a modern high-speed image analyzer QicPic (Sympatec Inc., Germany).

Keywords: GSB-106, particle diameter, aspect ratio, sphericity, shape factor.

Compressibility and flow character are considered the main parameters of powder materials that define the processing characteristics of tablets produced in the pharmaceutical industry. It is known that the size, shape of particles and their fractional composition (particle size distribution) have a greater influence on the flowability of powders and granules and their redistribution [1,2].

One of the ways to improve the processing characteristics of tablet mixtures is the directional aggregation of particles by granulation process, in particular by wet granulation. However, this method does not exclude the re-evaluation of the produced granules and their properties [3].

Currently, experimental and simulation systems based on digital approaches are widely used, which allow us to measure the physical properties of particles, such as the actual shape and size. One of such methods is the digital analysis of particle images [4].

In this regard, the **purpose** of this study is to evaluate the size, shape and fractional composition of GSB-106 granules produced by wet granulation using the image analysis method [5].

MATERIALS AND METHODS

Materials: Pharmaceutical substance (FS) GSB-106 [6], lactose monohydrate (Lactochem

Fine Powder, DFE Pharma, Germany), microcrystalline cellulose (Microcel MC 101, Blanver Farmoquimica Ltda, Brazil), polyvinyl alcohol and polyethylene glycol copolymer (Kollicoat IR, BASF, Germany), purified water (FS.2.2.0020.15), magnesium stearate (EP 01/2008:0229).

The mixture for tableting was made by wet granulation. Wetting was carried out with a 10% aqueous solution of Kollicoat IR, after which the mixture was punched through a sieve with a hole diameter of 2 mm, dried at a temperature of 45°C, then, sieve calibration of the dried granules and powdering were carried out.

Methods: Images, characteristics of the size distribution of GSB-106 granules and their shapes were obtained using a high-speed image analyzer QicPic (Sympatec Inc., Germany) with an air dispersing module Rodos (Sympatec Inc., Germany).

To evaluate the measured data, the particle diameters (the diameter of the circle of equivalent particle projection area and the Feret diameter) were calculated.

EQPC (Equivalent Projection Area of a Circle) is the diameter of a circle that has the same surface area as the particle in actual practice:

$$EQPC = \sqrt{\frac{4 \times P_{EQPC}}{\pi}},$$

where P_{EQPC} – particle perimeter.

The Feret diameter is set by the distance between two parallel tangents to the surface of the particle and is measured for a sufficient number of angles (0 … 180°), from which the maximum F_{MAX}, and minimum F_{MIN}, values are selected (Fig. 1).

If a particle has a non-standard shape, then the diameters have a larger number of values compared to a particle that is close to a spherical shape. F_{MAX}, therefore, can be significantly larger, and F_{MIN} can be significantly less than *EQPC*.

For spherical particles, the particle diameter is equal to both *EQPC*, F_{MAX}, and F_{MIN}. However, for irregularly shaped particles, such an

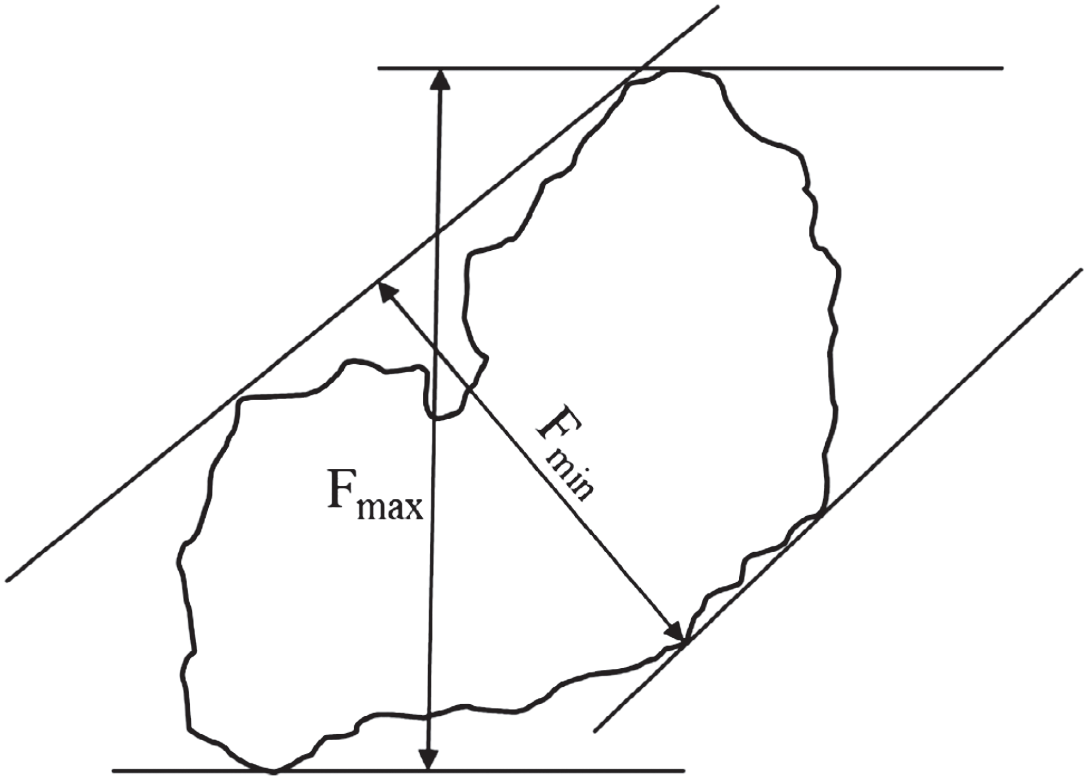

FIG. 1. *Maximum and minimum Feret diameters of granules*

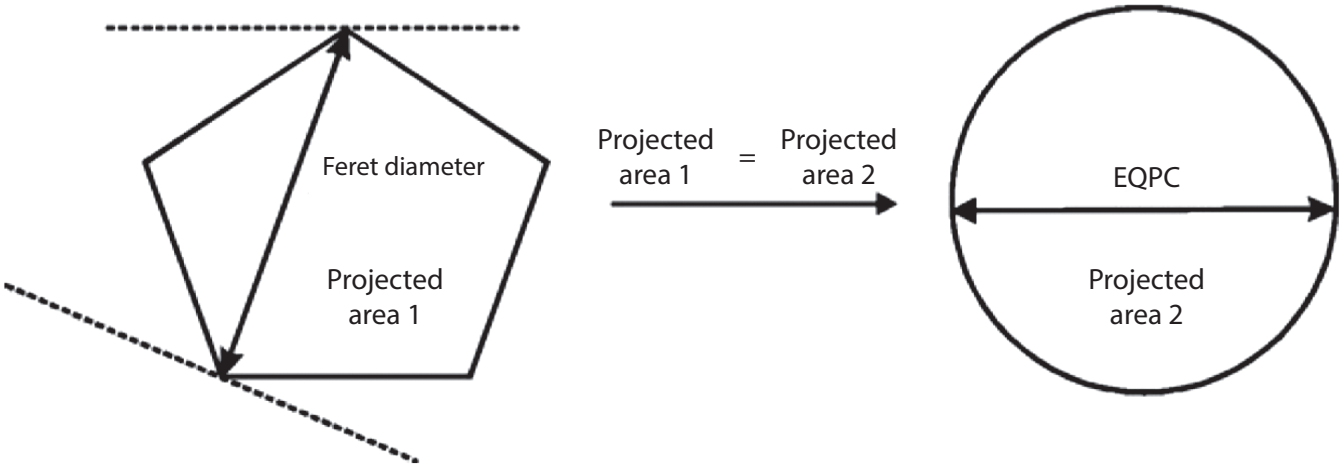

FIG. 2. *Schematic image of the EQPC and the Feret diameter*

equation does not apply and the estimation method will affect the final particle size distribution (Fig. 2) [7].

The shape of the particles was described by the parameters of the shape factor: sphericity and aspect ratio.

Sphericity, S, is calculated by the following way:

$$S = \frac{P_{EQPC}}{P_{realistic}} = \frac{2\sqrt{\pi \times A}}{P_{realistic}},$$

where *A* – particle area, *P* – particle perimeter.

Since the irregular shape of the particle leads to increase in its perimeter, low sphericity values indicate uneven particle boundaries. Thus, the ratio is always based on the perimeter of the *EQPC*, since this is the smallest possible perimeter for this projection area [7,8].

The aspect ratio, AR is defined as the ratio of F_{MIN} to F_{MAX} and represents the information about how elongated the particle is.

The results of *S* and *AR* are represented as values from 0 to 1 [9,10].

RESULTS AND DISCUSSION

The characteristics of the curves of the average integral distribution of GSB-106 granules and their calculation methods are presented in Table 1 and in Fig. 3.

Granules are characterized by a fairly narrow particle size distribution and a low content of fine fraction, but differences in the values of particle diameters and distribution curves indicate the heterogeneity of their shape and size.

The calculated characteristics of the integral distribution of the shape factor are shown in Table 2.

The following Fig. 4 and 5 illustrate the curves of the shape factor depending on the

Table 1

CHARACTERISTICS OF THE SIZE DISTRIBUTION OF GSB-106 GRANULES

Calculation	D_{10}, µm	D_{50}, µm	D_{90}, µm
EQPC	36.91 ± 0.58	86.36 ± 3.56	213.71 ± 75.56
F_{MAX}	45.23 ± 0.59	113.95 ± 4.36	357.32 ± 67.50
F_{MIN}	31.84 ± 0.38	74.52 ± 2.58	255.75 ± 57.21

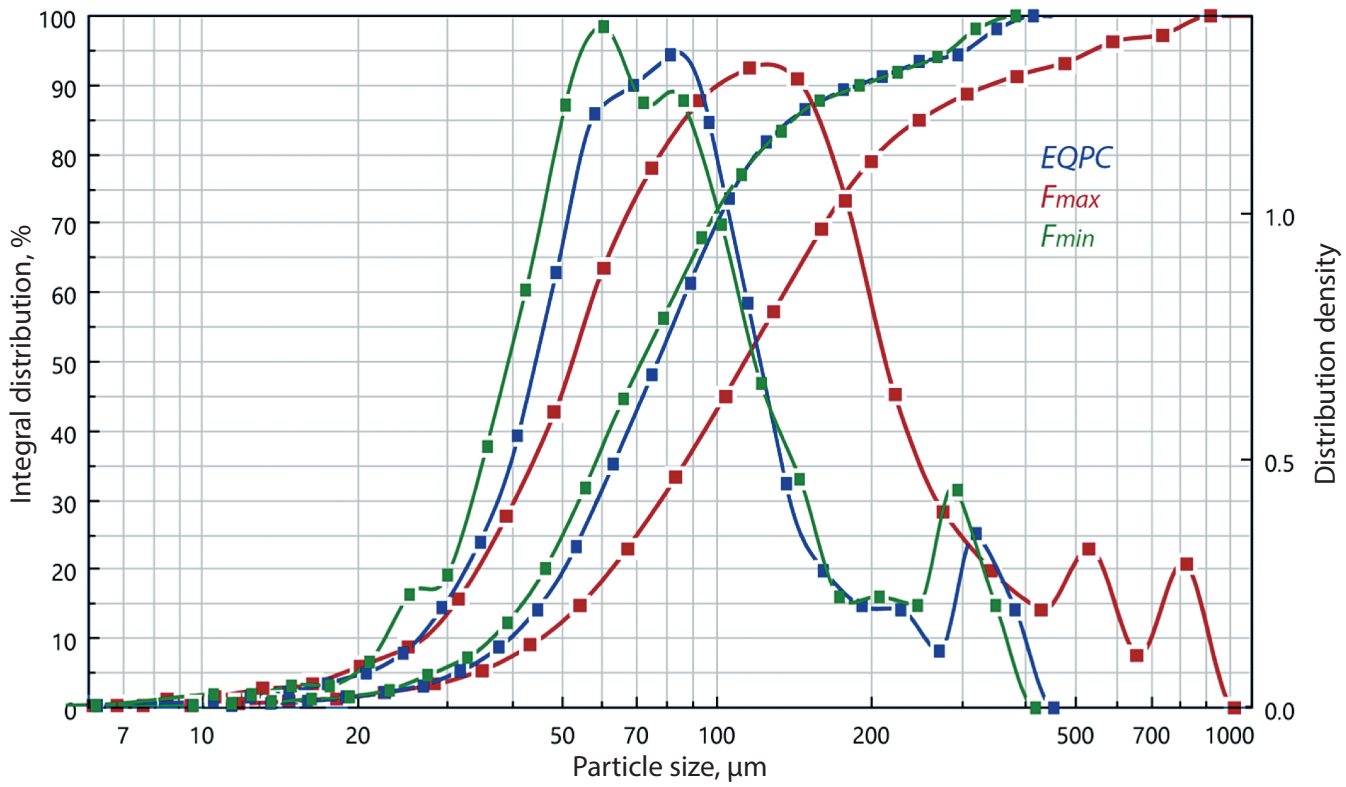

FIG. 3. *Size distribution of GSB-106 granules*

particle size and the curves of the integral distribution.

High values of sphericity (0.79) mean that the surface of the granules does not have significant protrusions and roughness. The wide distribution of the aspect ratio factor (0.70) shows that the tablet mixture contains both elongated and compact granules.

The distribution of particle sizes and shapes was calculated based on the recorded images. Figure 6 shows a sample from the particle gallery.

It is worth noting that the content of the fine fraction is explained by the production process of a tablet mixture, which provides for the stages of calibration and powdering, as a result of which the mixture is re-crushed, as well as small particles are introduced additionally [3].

CONCLUSION

The size, shape and fractional composition of GSB-106 granules produced by wet granulation were evaluated using the image analysis method.

It is established that the granules are characterized by a fairly narrow size distribution. The shape of GSB-106 granules is close to spherical one.

Table 2

CHARACTERISTICS OF THE DISTRIBUTION OF THE SHAPE FACTOR

Shape factor	D_{10}, μm	D_{50}, μm	D_{90}, μm
AR	0.46	0.70	0.87
S	0.66	0.79	0.86

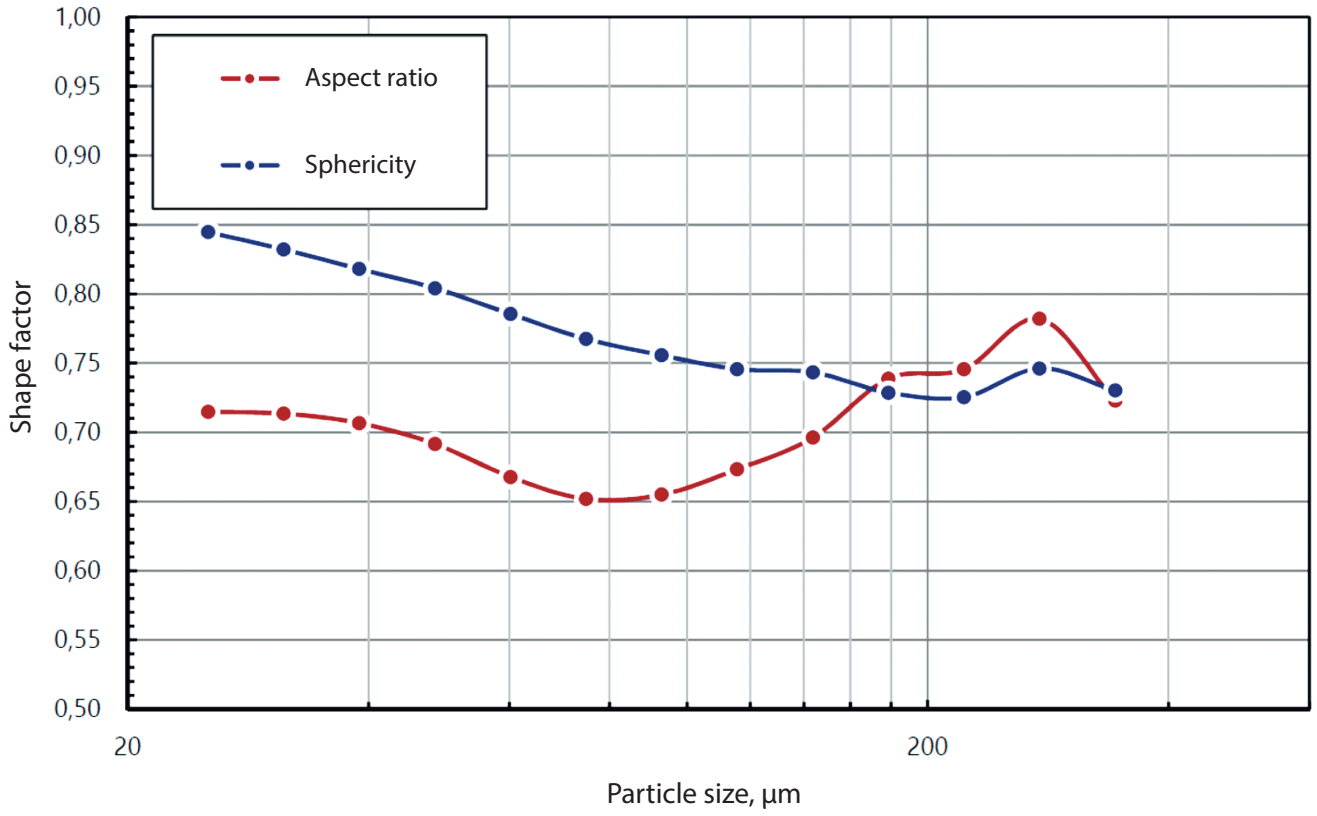

FIG. 4. *The dependence of the shape factor of GSB-106 granules on the size*

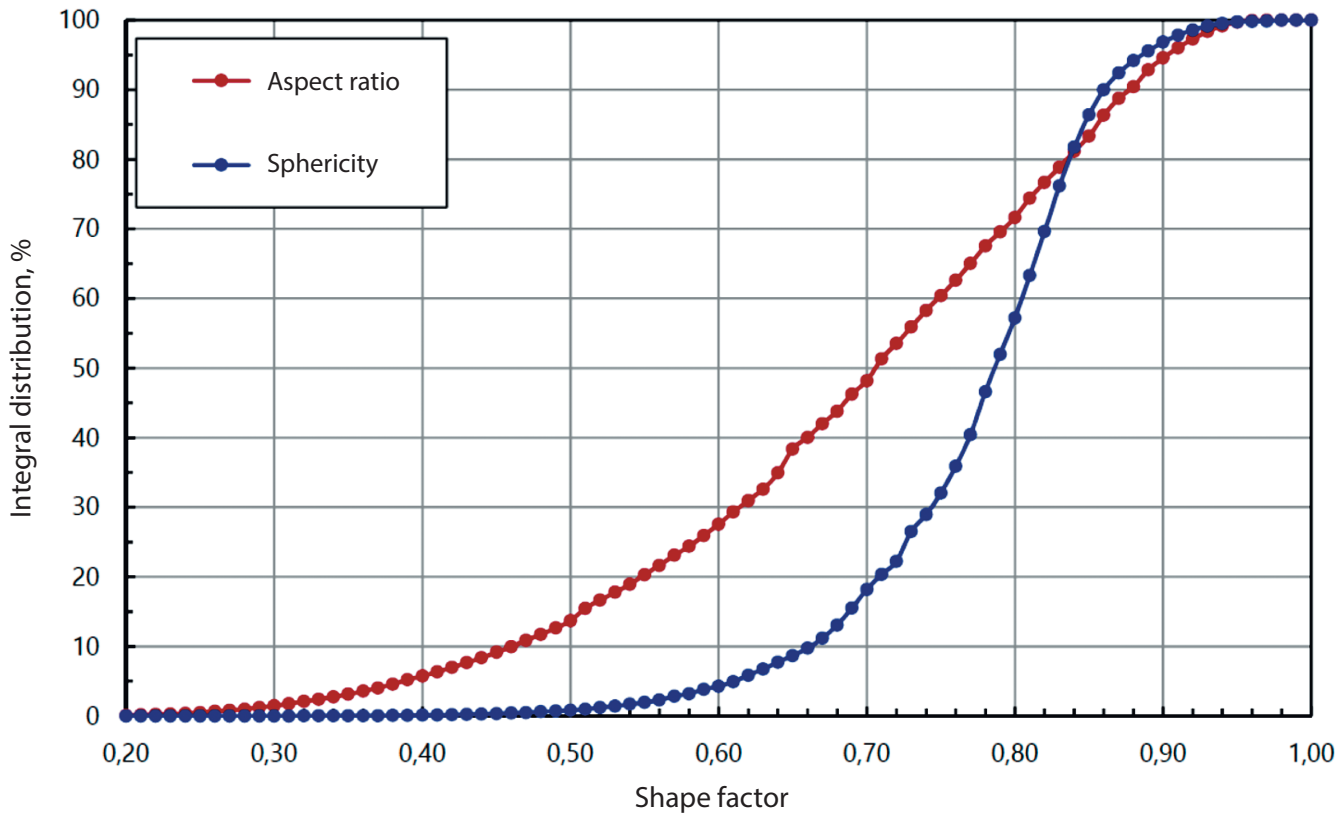

FIG. 5. *Dependence of the GSB-106 granule shape factor on the integral particle distribution*

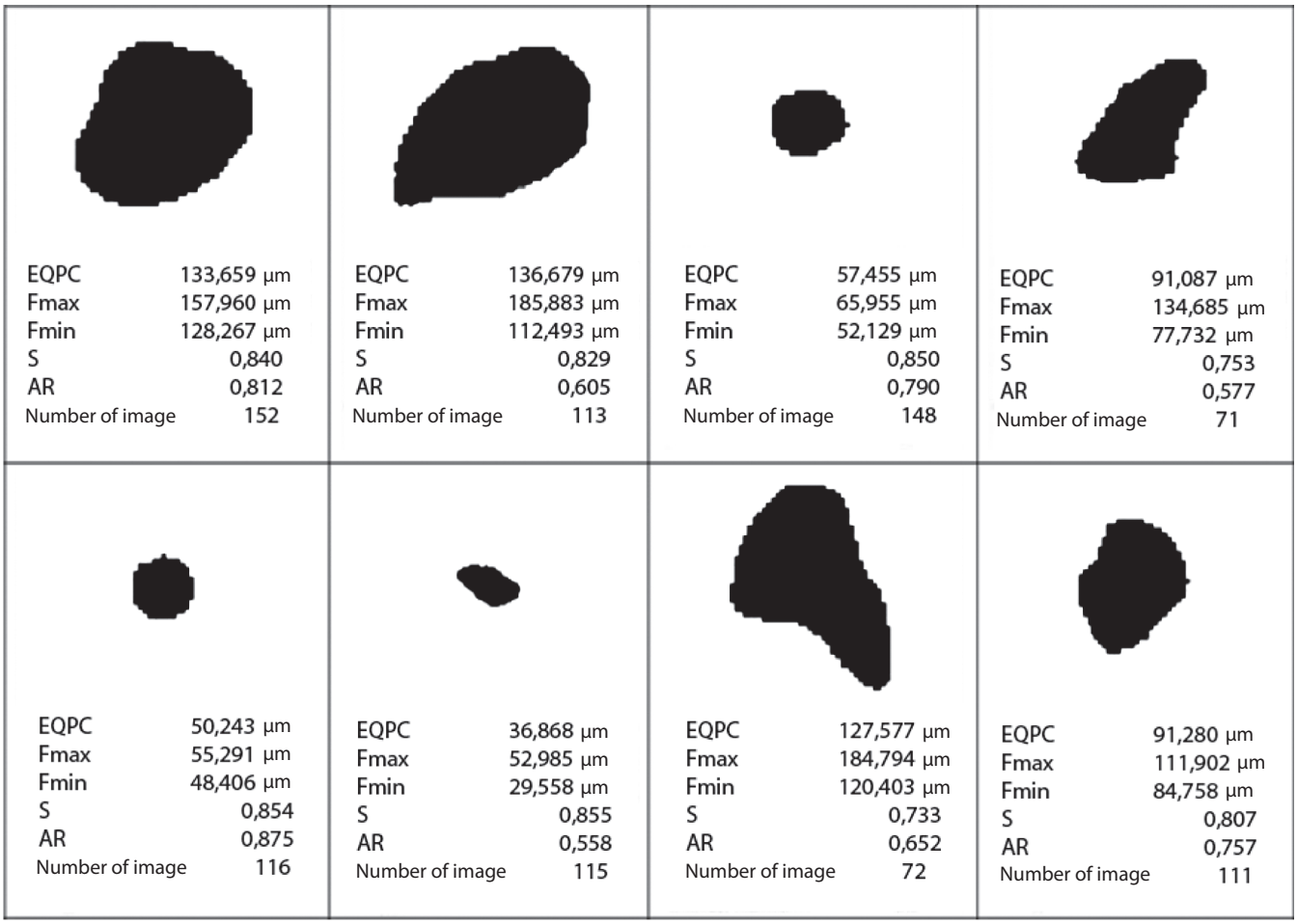

FIG. 6. *GSB-106 granules – sample of 8 out of 45,545 particles*

The analysis of pharmaceutical powders and granules can thus be used to identify the influence of the physical properties of particles on their processing characteristics in order to select excipients of suitable size and shape to increase the uniformity of dosing and reduce the delamination of tablet mixtures.

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RUSSIAN TESTING CENTERS: ASPECTS OF THE DEVELOPMENT OF QUALITY MANAGEMENT SYSTEMS FOR THE IMPLEMENTATION OF THE PRINCIPLES OF GOOD LABORATORY PRACTICE

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Based on the analysis of the documents, 11 practical steps are proposed for introduction into the activities of testing centers conducting nonclinical trials of medicines in accordance with the requirements of GOST R ISO 9001-2015. Recommendations are provided for the management and those responsible for the implementation of ISO standards in the laboratory. The implementation of a quality management system in accordance with ISO 9000 series standards (GOST R ISO 9000-2015) is the first stage of preparing the testing center for the implementation of the requirements of good laboratory practice. Russian laboratories conducting nonclinical trials at the stage of medicine development can achieve significant success by implementing the requirements of the international standard ISO 9001 in their activities. Based on the ISO 9000 series standards, the main stages for the creation of a quality management system (QMS) in a laboratory conducting preclinical trials are formed.

Keywords: preclinical trials, nonclinical trials, quality system, Good Laboratory Practice, testing center, ISO 9001

The implementation of good laboratory practice (GLP) in international practice into the activities of testing centers (TC) conducting preclinical (nonclinical) trials is required for registration of medicines or marketing approval from the corresponding regulatory authority by conducting safety preclinical tests and clinical trials. The quality and reproducibility of preclinical (nonclinical) trials are the criteria that largely determine the safety and effectiveness of medicines.

Scientific studies in the field of medicine development are becoming more competitive and more complex. This requires developers to constantly improve the quality of their studies, which, in turn, raises questions about the reliability and reproducibility of the data resulted during study, as well as the standardization of methodologies. In addition, globalization and the emergence of new markets require new approaches to the fundamental development of medicines [1].

The implementation of GLP into the activities of Russian laboratories, as well as the confirmation of their compliance with GLP, recognized by international organizations and regulatory authorities, significantly reduces the time and cost of studies [2], and will also allow the use of the results of preclinical trials on the international market.

One of the requirements of GLP is the creation and operation of a quality assurance system. The ISO 9000:2015 standard describes the fundamental concepts and principles of quality management that are universally applicable in the Russian Federation: GOST R ISO 9000-2015 [3]. The ISO 9001 standard – in Russia, it is GOST R ISO 9001-2015 – sets the requirements for the quality management system in organizations [4]. ISO 9001 is widely accepted in the European Union laboratories of various profiles as a quality management standard [5–9]. However, the implementation of ISO cannot guarantee the quality of preclinical trials [10]. The ISO 9001 standard assumes a general approach and is intended for organizations of all sizes and types engaged in various types of activities [11,12]. The requirements of the ISO 9001 standard are a process approach implemented through the PDCA (plan-do-check-act) cycle, providing a logical and scientific management model for continuous quality improvement and a risk-oriented approach [4,13]. The limitation of the application of this standard is that it does not standardize technical requirements, allowing you to set different quality levels for each laboratory, even when the same studies are conducted [5]. Another limitation of the ISO 9001 standard is that there are no performance requirements. By itself, the ISO 9001 standard does not guarantee that the result obtained is an evidence-based result.

In the preclinical trials, increased attention is paid to such aspects as safety pharmacology and toxicological studies that are directly related to the final result and should be conducted in accordance with the GLP principles [14–16]. Many factors are critical for the final result of any preclinical trial [17]. Also, one of the key pillars of ISO i.e. customer satisfaction cannot be fully achieved within the framework of the medicine preclinical trials, since many of the studies conducted by the testing center are "unique, with little predictable results" [18].

The purpose of the study was to study regulatory documents on good laboratory practice and quality systems and to develop the recommendations for implementation of a quality management system in accordance with ISO 9001:2015 standard for implementation of the principles of international GLP standards in Russian laboratories conducting medicine preclinical trials.

MATERIALS AND METHODS

The materials of the study were Russian and international regulations on good laboratory practice and quality management systems. Empirical methods such as analysis and synthesis and logical methods were used in the study.

RESULTS AND DISCUSSION

The legal framework of GLP regulation in Russia. At the moment, the necessary regulatory framework for preclinical trials has been formed in Russia [14]. However, according to the Federal Accreditation Service, as of June 22,

2020, 12 laboratories were accredited for compliance with the OECD GLP requirements, 9 of them – for testing the medicines [19]. The main document regulating the circulation of medicines is the Federal Law "On Circulation of Medicines" dated 12.04.2010 No. 61-FZ. The Rules for the recognition and assessment of compliance of testing laboratories (centers) with the principles of good laboratory practice corresponding to the principles of good laboratory practice of the Organization for Economic Cooperation and Development, approved by the Decree of the RF Government No. 1227 of September 20, 2019 "On the recognition and assessment of compliance of testing laboratories (centers) with the principles of good laboratory practice of the Organization for Economic Cooperation and Development", contain a list of documents regulating the compliance of testing centers with GLP requirements. The Ministry of Health of the Russian Federation has issued a number of resolutions on the implementation of GLP principles for preclinical trials of medicines, and in 2015–2016 the RF Government introduced a series of national standards. Most of these standards are translated ISO documents. Currently, the document regulating the preclinical trials is the order of the Ministry of Health of the Russian Federation No. 199н dated April 1, 2016 "On approval of the Rules of Good Laboratory Practice". This order states that the GLP principles are applicable to all preclinical trials related to the development of medicines. This document contains general provisions related to the national standard GOST 33044–2014 "Principles of Good Laboratory Practice" and other relevant GOSTs that are identical to the OECD GLP.

As the analysis of regulatory documents has shown, the concept of developing a quality system is not specified in the Rules of Good Laboratory Practice. As a basis for the development of a quality system, it is advisable to take the methodology for the development and implementation of a quality system in accordance with ISO 9000 standards. The purpose of the quality system is to prevent errors, identify their sources, improve processes and provide evidence of compliance with requirements. It is convenient to integrate the specific requirements of the GLP with the general requirements of the ISO 9001:2015 standard for the implementation of the QMS, which uses advantages of the more holistic and systematic nature of the latter, while ensuring compliance with the requirements of the GLP.

Implementation of the requirements of GOST R ISO 9001-2015 into the activities of testing centers conducting nonclinical trials of medicines.

Stage 1: Management's adoption of the quality strategy

Since the decision to apply the QMS is a strategic decision for the organization [20,21] the testing center administration shall demonstrate the commitment in the organization to the implementation of the QMS, according to the ISO 9001 standard. To do this, it is necessary to define the testing center policy in the field of quality, set the quality goals at all levels and bring them to the attention of each employee. Examples of goals for the testing center:

1. Obtaining the high-quality results of preclinical trials that meet the regulatory requirements and expectations of sponsors;
2. Focus on both quality standards (ISO 9000 standards) and the international GLP standard.
3. Improving communication and corporate quality culture within the testing center.

Stage 2. Personnel training

It is necessary to conduct information programs on the QMS and the ISO 9001 standard itself to train the testing center personnel in relation of the goals of the quality management system, the advantages it provides, working methods, as well as in relation to the role and responsibilities of each employee within the system. Training

programs should be organized for different categories of employees. The training should cover the basic concepts of the QMS, standards and their overall impact on the strategic goals of the testing center, changed processes and possible consequences of the system for the work culture [22]

Stage 3. Analysis of the initial state

The next step in the implementation process is to compare the existing quality system in the organization, if any, with the requirements of the implemented standard. The standard implies the appointment of one or more responsible persons who will maintain the management policy for the implementation of the QMS. At this stage, it is necessary to take into account the existing QMS. Effective existing standard procedures can be incorporated into a new quality management system. Documents that require changes or improvements shall be identified and listed. When implementing the QMS, the emphasis is on improving the existing processes or reorganizing the processes.

Stage 4. Drawing up a project implementation plan

The project implementation plan or implementation plan provides for the identification and description of the processes required to bring the organization's QMS into full compliance with the standard. The plan should include: high-quality documentation for development, the purpose of the system, the appointment of responsible persons; training, resources, and the expected completion date. The plan should define the responsibilities of different departments, personnel and set the deadlines for completion of activities. Once approved, the plan is reviewed and updated as the implementation process progresses. The result of this stage should be a clearly defined structure of the testing center with separation of powers delegated to departments and employees, as well as the defined and evaluated purposes in relation to the quality [22].

Stage 5. Development of documentation on the quality management system

Documentation is the most common area of non-conformance in organizations wishing to implement a QMS, according to the ISO 9001 standard. The QMS documentation includes [21]: statements on the quality policy and quality objectives; quality guidelines; documented procedures; documents required for the organization to ensure effective planning, operation and control of its processes. These can be: standard operating procedures, forms, quality plans, technical instructions, external documents, records.

Stage 6. Documentary audit

A mandatory requirement of the ISO 9000 standards is the documentation of the organization's quality management system [21,23]. The organization itself can determine the number of necessary and sufficient documents. The main condition is that the document management system should be as easy to operate as possible and allow timely updating of documents [24,25]. The structure of interaction of documents of the quality management system can be hierarchical. It is recommended [21] that documents should be created by personnel directly involved in the performed activity for which documentation is being developed.

Stage 7. Plan implementation

It is good practice to implement a documented QMS as documentation is developed, although this may be more effective in larger testing centers. The QMS can be implemented across the entire testing center simultaneously or in stages.

Stage 8. Internal audit

When the installed QMS has been functioning for several months, it is necessary to conduct

an internal audit – self-control of the enterprise for compliance with the requirements of the ISO 9001:2015 [22]. In the future, scheduled audits are conducted regularly [26]. Internal quality audits are conducted to verify that the established QMS:

- meets the plan and requirements of the ISO 9001:2015;
- effectively implemented and maintained.

It is reasonable to train several employees in auditing. The audit should be carried out by the employees who do not work in the department undergoing the audit.

Stage 9. Review of the management system

After receiving the reports on the results of the internal audit, it is necessary to conduct a management review and take corrective actions. The review should include an assessment of risks and opportunities for improvement and the need for making amendments to the quality management system, including the quality policies and objectives.

Stage 10. External audit

Then an external audit is conducted to assess the organization's readiness and assess the implementation of ISO standards. External audit is carried out with the involvement of a third-party organization, an independent and qualified auditor. Sometimes the certification authorities provide this service.

Stage 11. Certification for compliance with GOST R ISO 9001-2015

After the positive results of the external audit, the application for certification of the testing center according to GOST R ISO 9001-2015 shall be submitted to the certification authority accredited in this area by the Federal Accreditation Service.

Certification for compliance with GOST R ISO 9001-2015 should not be the ultimate goal or a one-time event. In accordance with the ISO principles, the laboratory should constantly strive to improve the effectiveness and suitability of the QMS.

CONCLUSION

1. The necessity for compliance of domestic testing centers which are engaged in preclinical trials is due to the harmonization of Russian regulatory requirements for preclinical trials with the principles of the OECD GLP.

2. Based on the analysis of the requirements of the international standards ISO 9000 and GLP, it is advisable to implement a quality management system in accordance with the ISO 9000 series standards (GOST R ISO 9000-2015, GOST R ISO 9001-2015, GOST R ISO 9004–2019) as a strategic platform for preparing for the confirmation of compliance of the preclinical trials with the principles of good laboratory practice. The testing center conducting the preclinical trials can achieve significant success by implementing the requirements of the ISO 9000 series international standard in its activities, which includes the creation of a QMS specification, for example, a Quality Guideline as a necessary element in the formation of a quality management system.

3. 11 stages for implementation of the QMS into the activities of the testing center have been formulated and proposed.

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PROFESSIONAL COMPETENCIES IN THE SPECIALTY OF PHARMACY PRESENTED IN THE EDUCATIONAL PROGRAMS OF HIGHER EDUCATIONAL INSTITUTIONS

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The introduction of a new educational standard in the specialty 33.05.01 "Pharmacy", which does not specify professional competencies, caused difficulties with the choice of competencies for educational programs of educational institutions. The purpose is to analyze the professional competencies in the specialty of pharmacy (specialist program), presented in the main professional educational programs of higher educational institutions. The analysis showed that more than half of educational institutions use mandatory competencies from the Model Principal Educational Program (MPEP) based on the new educational standard in their educational programs (56.9±8.0%), a sixth of educational institutions use recommended competencies from the MPEP (16.8±6.1%). The third of universities continues education according to the previous educational standard (32.8±2.9%). The most common professional competencies in the educational programs of higher educational institutions are established and presented. The competencies according to the indices of the coincidence of texts and the complexity of perception are analyzed. The positioning of competencies allowed us to clearly demonstrate the results of the analysis.

Keywords: professional competencies in pharmacy, pharmaceutical competencies, educational programs of educational institutions, pharmaceutical education

The active introduction of the competence-based approach into the practice of higher pharmaceutical education in the world dictates the need for the formulation of key professional competencies formed in the process of education [1–5]. According to the new Federal State Educational Standard of higher education in the specialty 33.05.01 "Pharmacy" (specialist's program) (FSES HE 3++) [6], each competence becomes a unit of the curricular program, and the developed system of competencies in the specialty is a kind of final result of professional

education. Therefore, the competitiveness of the future specialist ultimately depends on the clarity and understandability of the interpretations of competencies, their importance, relevance and necessity.

The new educational standard includes universal, general professional and professional competencies. If the first two groups of competencies are declared in the standard, then with respect to the last group, it is specified that these professional competencies can be provided on the basis of the Model Principal Educational Program (MPEP). In 2019, a Draft MPEP was developed by the Federal Educational and Methodological Association in the system of higher Education in the specialty "Pharmacy" (specialist's program) [7]. There are 27 professional competencies presented in the MPEP, 6 of them are mandatory (MPC) and 21 are recommended professional competencies (PC).

Currently, the Draft MPEP is already being used in the system of higher pharmaceutical education in the development of the principal professional educational programs of higher educational institutions. Although many interested parties have contributed to the development of the MPEP, and experienced practical teachers have supported the presented professional competencies, it is not known how many and which higher educational institutions have introduced professional competencies from the MPEP into their educational programs. Recommendations for educational organizations on the formation of educational programs, approved by the National Council for Professional Qualifications under the President of the Russian Federation (Protocol No. 35 of 27.03.2019) played a certain role in the unstable situation of the competencies from the MPEP. So, the question is still not very clear: Does the inclusion of the Draft MPEP into the register of the Ministry of Science and Higher Education of the Russian Federation without approval give to higher educational institutions the right to develop their own versions of educational programs and professional competencies based on the new FSES HE 3++? Or is it possible to use professional competencies from the previous educational standard (FSES HE 3+) before the approval of the MPEP [8]? Such difficulties with the formulation and selection of competencies in the specialty 33.05.01 "Pharmacy" specified the relevance of the analysis of professional competencies presented in the educational programs of higher educational institutions.

Currently, there is no general universal methodology for analyzing professional competencies [9–14].

The purpose of the article is to analyze the professional competencies in the specialty of Pharmacy (specialist's program) presented in the principal professional educational programs of higher educational institutions.

MATERIALS AND METHODS

Currently, 67 higher educational institutions (universities) in Russia are training graduates in the specialty 33.05.01 "Pharmacy". They have 20,546 students, according to the Federal Service for Supervision of Education and Science. Over the past 5 years, there has been a tendency to reduce the number of university students in this specialty (Fig. 1).

The search for the principal professional educational programs in the specialty of "Pharmacy" (specialist's program) was carried out on the websites of universities. Educational programs and professional competencies were found in the public domain at 63 educational institutions (Fig. 2).

The analysis of professional competencies by the coincidence indexes of text was carried out by the Shingles method using the Shingles Expert Pro v1.1 program. The determination of professional competencies for the complexity of text perception (the readability index) was carried

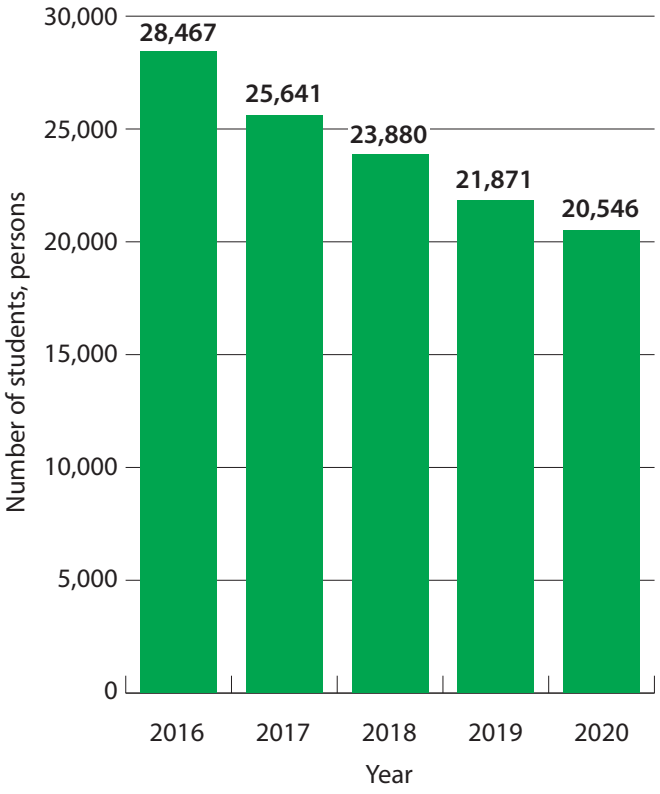

FIG. 1. *The number of students learning in the specialty of Pharmacy (specialist's program) in 2016–2020 in Russia*

out according to the formulas of Coleman-Liau and Gunning adapted for the Russian language (http://ru.readability.io/) [15].

In the analysis of professional competencies, the following variables were used:

- F_{100} – the frequency of occurrence of professional competencies in the educational programs of higher education institutions from the MPEP or FSES HE 3+ with text coincidence indices of 100%
- $F_{50–100}$ – the frequency of occurrence of professional competencies in the educational programs of higher education institutions from the MPEP or FSES HE 3+ with text coincidence indices of 50–100% with Shingle length – 1, and with text coincidence indices more than 0 with Shingle length – 2, 3, 4.
- F_{av} – the average frequency of occurrence of professional competencies in the educational programs of higher education institutions from the MPEP or FSES HE 3+ calculated according to formula:

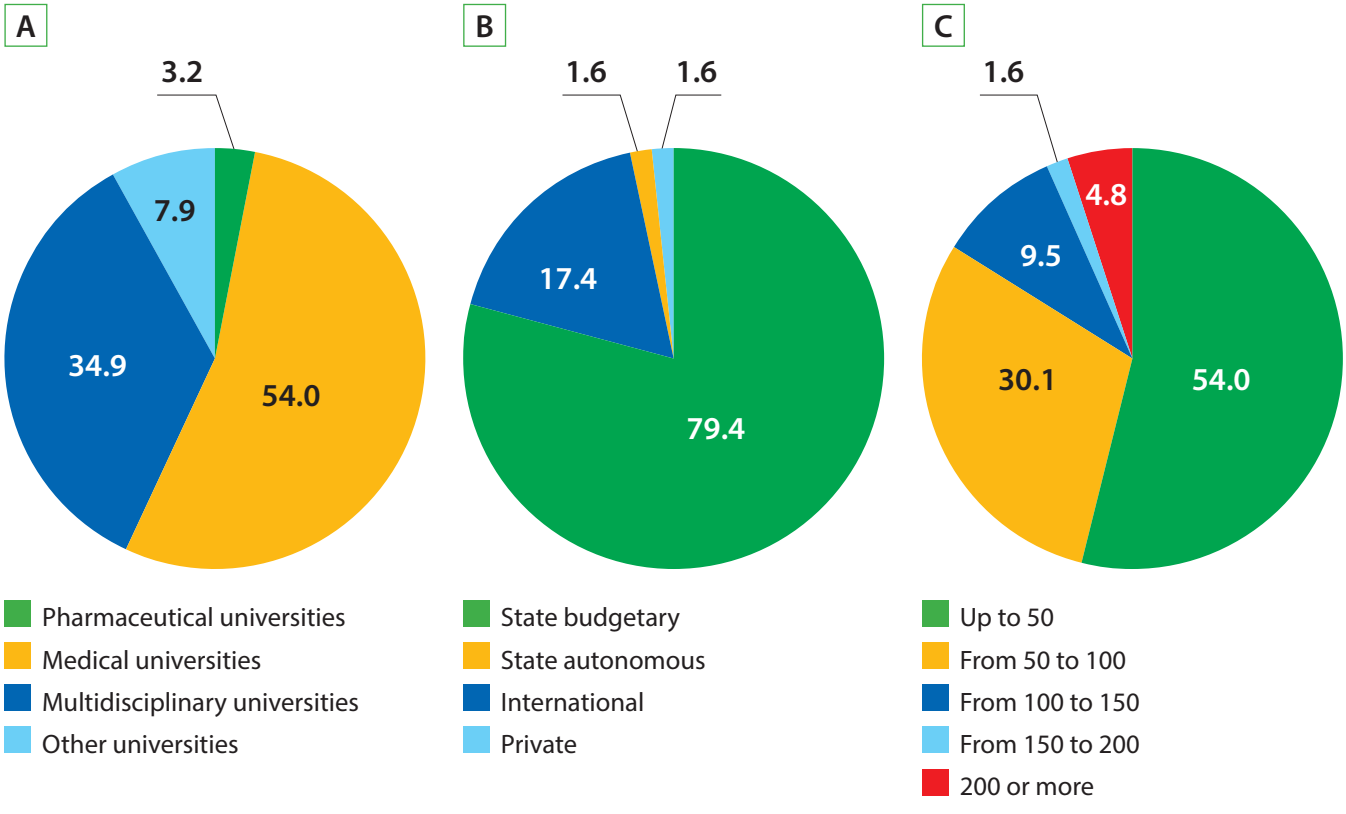

FIG. 2. *Distribution of the studied universities by profile (A), by form of property and financing (B) and by the number of students entered in 2020 (C), %*

$$F_{av} = \Sigma (F_{100} + F_{50-100}) : n,$$

where n – number of mandatory or recommended professional competencies;

- I_S –coincidence index of texts of professional competencies from the MPEP or FSES HE 3+;
- I_E – coincidence index of texts of professional competencies, which are the most common in the educational programs of universities with competencies from the MPEP;
- *CLI* – Coleman – Liau text readability index (Coleman – Liau index), the scale used: 30 and above – high, from 20 to 30 – medium, from 10 to 20 – below medium, from 0 to 10- low.
- *FI* – Gunning text readability index, or Fog index, the scale used: 70 and higher – high, from 60 to 70 – medium, from 30 to 60 – below medium, less than 30 – low.

The positioning was carried out by a quantitative method of comparing the frequency of occurrence of professional competencies from the MPEP in educational programs of universities with text coincidence indices of 100% and with text coincidence indices if a shingle length is 1 – 50–100%, if a shingle length is 2, 3, 4 – more than 0.

The results of the study were expressed either in absolute and relative values, or in metric units, such as the arithmetic mean ± standard deviation (M ± SD).

RESULTS AND DISCUSSION

The analysis of mandatory professional competencies presented in the principal professional educational programs of higher education institutions showed that 33.3–50.8% of the general professional competencies completely coincide with the competencies from the MPEP, 28.6–33.3% fully corresponds to the interrelated competencies from the previous FSES HE 3+ (Table 1, column 3). The number of universities the professional competencies of which coincided by 50–100% according to shingle 1 with the texts of competencies from the MPEP or from the FSES HE 3+ and those with shingles 2, 3, 4 – more than 0, amounted to 0–25,4% and 0–6,3%, respectively (column 4). Consequently, more than half of the studied educational institutions switched to general professional competencies from the MPEP (F_{av} = 56.9 ± 8.0%, column 5), a third of the universities continued to learn students according to the previous educational standard (F_{av} = 32.8 ± 2.9%, column 5). The coincidence indices of the texts of professional competencies from the MPEP and from the FSES HE 3+ were equal to 55.6–66.7% with the shingle length of 1, 5.0–30.8% with the shingle length of 2, 0–10.5% with the shingle length of 3 and 0–7.1% with the shingle length of 4 (column 6).

The most common professional competencies in the educational programs of the studied universities, but not completely coinciding with the mandatory professional competencies (MPC) from the MPEP were: capable of preparing medicines for medical use (I_{E1} = 62.5%, I_{E2} = 20.0%, I_{E3} = 14.3%, I_{E4} = 7.7%, MPC-1, column 7), capable of completing the tasks of professional activity when transferring medicines through pharmaceutical and medical organizations (I_{E1} = 83.3%, I_{E2} = 41.7%, I_{E3} = 28.0%, I_{E4} = 2.0%, MPC-2, column 7), capable of providing information and advisory assistance on the selection and rational use of medicines and other pharmacy products (I_{E1} = 57.1%, I_{E2} = 25.9%, I_{E3} = 13.8%, I_{E4} = 6.9%, MPC-3, column 7), capable of monitoring the medicine quality and safety assurance systems (I_{E1} = 60.0%, I_{E2} = 22.2%, I_{E3} = 11.1%, I_{E4} = 5.9%, MPC-4, column 7), capable of participating in planning and organizing the resource support of the pharmaceutical organization and its structural divisions (I_{E1} = 88.9%, I_{E2} = 76.9%, I_{E3} = 69.2%, I_{E4} = 66.7%, MPC-6, column 7).

Some professional competencies in the educational programs of higher education institutions had interesting additions or exceptions of fragments of competencies from the MPEP. For

Table 1

THE RESULTS OF THE ANALYSIS OF MANDATORY PROFESSIONAL COMPETENCIES PRESENTED IN THE MPEP IN THE SPECIALTY OF PHARMACY (SPECIALIST'S PROGRAM), IN THE FSES HE 3+ AND IN THE PRINCIPAL PROFESSIONAL EDUCATIONAL PROGRAMS OF THE UNIVERSITIES UNDER STUDY

Code	Name of the mandatory professional competence from MPEP	Value						
		F_{100}, %[*1]	F_{50-100}, %[*1]	F_{av}, %[*2]	$I_{s1,2,3,4}$, %[*3]	$I_{E1,2,3,4}$, %[*3,4]	*CLI*[*5]	*FI*[*5]
1	2	3	4	5	6	7	8	9
MPC-1	Capability of production of the medicines and paticipation in the production process of finished pharmaceutical products	33.3/ 33.3	25.4/ 0	56.9± 8.0/ 32.8± 2.9	I_{s1} = 55.6 I_{s2} = 5.0 I_{s3} = 0	I_{E1} = 62.5 I_{E2} = 20.0 I_{E3} = 14.3 I_{E4} = 7.7 (15.9)	30.09/ 33.57	34.83/ 28.89
MPC-2	Capability of completing the tasks of professional activity in dispensing and sale of medicines and other products of the pharmacy range through pharmaceutical and medical organizations	46.0/ 30.2	15.9/ 6.3		I_{s1} = 61.5 I_{s2} = 12.1 I_{s3} = 2.6 I_{s4} = 0	I_{E1} = 83.3 I_{E2} = 41.7 I_{E3} = 28.0 I_{E4} = 2.0 (4.8)	25.67/ 32.93	34.14/ 32.52
MPC-3	Capability of providing the pharmaceutical information and consulting during the dispensing and sale of medicines for medical use and other products of the pharmacy range	49.2/ 33.3	12.7/ 1.6		I_{s1} = 57.1 I_{s2} = 6.3 I_{s3} = 0	I_{E1} = 57.1 I_{E2} = 25.9 I_{E3} = 13.8 I_{E4} = 6.9 (3.2)	26.70/ 34.33	34.24/ 35.40
MPC-4	Capability of participating in monitoring the quality, effectiveness and safety of medicines and medicinal plant raw materials	50.8/ 33.3	11.1/ 0		I_{s1} = 66.7 I_{s2} = 27.8 I_{s3} = 10.5 I_{s4} = 0	I_{E1} = 60.0 I_{E2} = 22.2 I_{E3} = 11.1 I_{E4} = 5.9 (3.2)	29.17/ 37.73	30.08/ 32.52
MPC-5	Capability of performing the clinical laboratory studies of the third category of difficulty, including on the basis of the implementation of new study methods and techniques	41.3/ 28.6	0/0		I_{s1} = 58.3 I_{s2} = 14.3 I_{s3} = 10.3 I_{s4} = 7.1	0	20.61/ 19.27	31.19/ 26.48
MPC-6	Capability of participating in planning and organizing the resources' provision of a pharmaceutical organization	47.6/ 30.2	7.9/0		I_{s1} = 62.5 I_{s2} = 30.8 I_{s3} = 0	I_{E1} = 88.9 I_{E2} = 76.9 I_{E3} = 69.2 I_{E4} = 66.7 (3.2)	32.47/ 44.75	36.16/ 32.50

Here and in Table 2.

[*1] *The frequency of occurrence of competencies from MPEP / from FSES HE 3+.*

[*2] *Average frequency of occurrence of competencies from MPEP / from FSES HE 3+, M±SD.*

[*3] *Sub-indexes 1, 2, 3, 4 – length of a shingle.*

[*4] *In parentheses – the number of universities, %.*

[*5] *The index of readability of the text of competencies from MPEP / from FSES HE 3+*

example, it is capability of preparing the medicines *in the conditions of pharmacy organizations, or pharmaceutical organizations, or pharmacies* (MPC-1),… in the technology of production of medicines (MPC-1), it is capability of completing the tasks of *pharmaceutical* activity… (MPC-2),… during the dispensing and sale of medicines for *medical use* (excluded) and other pharmacy assortment goods (MPC-3),… and other pharmacy assortment goods*, including in emergency situations* (MPC-3), it is capability of participating in the planning and organization of *the activities of a pharmaceutical organization* (MPC-6).

When analyzing the mandatory competencies from the MPEP for the difficulties of text reading, it was found that the competencies of MPC-1 and MPC-6 have a high level of the Coleman – Liau index (*CLI* = 30.09 and *CLI* = 32.47, respectively, column 8), the other competencies are at the average level. The results obtained were confirmed by the data on the readability of the text according to the Fog index. Although all the mandatory competencies according to the Fog index were at a level below the average, the competencies of MPC-1 (*FI* = 34.83, column 9) and MPC-6 (*FI* = 36.16) had maximum values. For comparison, the readability indices of the corresponding professional competencies from the FSES HE 3+ were calculated. It is established that according to the Coleman – Liau index, the competence corresponding to the MPC-5 (*CLI* = 19.27, column 8) has a lower-than-average level, the remaining competencies are at a high level. According to the Fog index, the maximum values were related to the competencies corresponding to MPC-2 (*FI* = 32.52, column 9), MPC-3 (*FI* = 35.40), MPC-4 (*FI* = 32.52) and MPC-6 (*FI* = 32.50).

The analysis of the recommended professional competencies from the MPEP showed that their frequency of occurrence in the principal professional educational programs of universities with complete coincidence of the text is only 4.8–25.4% (Table 2, column 3). When the text coincided by shingle 1 as 50–100% and by shingles 2, 3, 4 – more than 0, the frequency of occurrence was equal to 1.6–6.3% (column 4). Thus, only a sixth of the studied educational institutions switched to the recommended competencies from the MPEP (F_{av} = 16.8 ± 6.1%, column 5). There were only three professional competencies from the FSES HE 3+, which were found in the principal professional educational programs of universities with a complete coincidence of the text and corresponded to the recommended competencies from the MPEP, their frequency of occurrence corresponded to 27.0–31.7% (column 3). The coincidence indices of the recommended competencies from the MPEP and the corresponding competencies from the FSES HE 3+ were equal to: 50.0–77.8% – with the length of shingle 1; 37.5–64.3% – with the length of shingle 2; 28.6–64.3% – with the length of shingle 3 and 16.7–61.5% – with the length of shingle 4.

The professional competencies that have been found several times in the educational programs of the universities under study, which do not fully coincide with the recommended competencies from the MPEP, were: capability of participating in the selection and justification of the optimal production process and its implementation in the industrial production of finished medicinal products for medical use with taking into account of all stages of the production process (I_{E1} = 91.7%, I_{E2} = 66.7%, I_{E3} = 55.6%, I_{E4} = 48.2%, PC-11, column 6), capability of searching, analyzing and publicly presenting the information required for completing the tasks in professional activity (I_{E1} = 54.6%, I_{E2} = 23.5%, I_{E3} = 11.8%, I_{E4} = 6.3%, PC-17), capability of participating in scientific study of medicines (I_{E1} = 85.7%, I_{E2} = 71.4%, I_{E3} = 66.7%, I_{E4} = 60.0%, PC-18), capability of participating in development of methods for chemical and toxicological analysis (I_{E1} = 77.8%, I_{E2} = 46.7%, I_{E3} = 25.0%, I_{E4} = 12.5%, PC-21).

Among the professional competencies presented in the educational programs of universities, there were quite often competencies from the previous FSES HE 3+: capability of application

Table 2

THE RESULTS OF THE ANALYSIS OF RECOMMENDED PROFESSIONAL COMPETENCIES PRESENTED IN THE MPEP IN THE SPECIALTY OF PHARMACY (SPECIALIST'S PROGRAM), IN THE FSES HE 3+ AND IN THE PRINCIPAL PROFESSIONAL EDUCATIONAL PROGRAMS OF THE UNIVERSITIES UNDER STUDY

Code	Name of the recommended professional competence from MPEP	Value			
		F_{100}, %	F_{50-100}, %	F_{av}, %	$I_{E1,2,3,4,}$ %
1	2	3	4	5	6
PC-1	Capability of completing of professional tasks within the framework of pharmaceutical activities in the field of circulation of medicines for veterinary use	15.9/0	0	16.8± 6.1/4.2	0
PC -2	Capability of monitoring the quality of clinical laboratory studies of the third category of difficulty at various stages of chemical and toxicological studies	4.8/0	0		0
PC -3	Capability of testing to assess the environmental situation in the production of medicines	15.9/0	0		0
PC -4	Capability of performing the activities for the validation (qualification) of pharmaceutical production	11.1/0	1.6/0		I_{E1} = 75.0, I_{E2} = 55.6, I_{E3} = 33.3, I_{E4} = 25.0 (1.6)
PC -5	Capability of organizing the procurement of medicinal plant raw materials taking into account the rational use of medicinal plant resources	25.4/31.7	1.6/0		I_{E1} = 87.5, I_{E2} = 83.3, I_{E3} = 83.3, I_{E4} = 81.8 (1.6)
PC -6	Capability of organizing the quality control of clinical laboratory studies of the third category of difficulty	6.3/0	0		0
PC-7	Capability of participating in the organization of the work of the staff of the chemical and toxicological laboratory and managing paperwork	11.1/0	0		0
PC-8	Capability of organizing the supply of medicines and medical products when providing assistance to the population in emergency situations at the stages of medical evacuation	20.6/0	1.6/0		I_{E1} = 83.3, I_{E2} = 56.5, I_{E3} = 46.2, I_{E4} = 38.5 (1.6)
PC-9	Capability of taking the measures to control (supervise) the activities of legal entities and individuals which have a license for pharmaceutical activities, to comply with mandatory requirements	14.3/0	0		0
PC-10	Capability of taking part in the measures to ensure the quality of medicines in industrial production	20.6/0	3.2/0		I_{E1} = 80.0, I_{E2} = 57.1, I_{E3} = 42.9, I_{E4} = 38.5 (1.6)

End of the table 2

Code	Name of the recommended professional competence from MPEP	Value			
		F_{100}, %	F_{50-100}, %	F_{av}, %	$I_{E1,2,3,4}$, %
1	2	3	4	5	6
PC-11	Capability of taking part in the selection, justification of the optimal production process and its implementation in the production of medicines for medical use	19.0/0	6.3/0	16.8± 6.1/4.2	I_{E1} = 91.7, I_{E2} = 66.7, I_{E3} = 55.6, I_{E4} = 48.2 (3.2)
PC-12	Capability of taking part in conducting the studies in the field of evaluating the effectiveness and safety of medicines	14.3/0	0		0
PC-13	Capability of developing the quality control methods	14.3/0	1.6/0		I_{E1} = 66.7, I_{E2} = 75.0, I_{E3} = 60.0, I_{E4} – нет (1.6)
PC-14	Capability of taking part in studies on the medicine composition design	19.0/0	1.6/0		I_{E1} = 70.0, I_{E2} = 23.5, I_{E3} = 11.1, I_{E4} = 5.6 (1.6)
PC-15	Capability of taking part in studies on evaluating the effectiveness of dosage forms	14.3/0	0		0
PC-16	Capability of taking part in studies on optimization of the composition and formulation of medicines, including with the consideration of different age groups of patients	17.5/0	0		0
PC-17	Capability of the analysis and public presentation of scientific data	20.6/28.6	4.8/0		I_{E1} = 54.6, I_{E2} = 23.5, I_{E3} = 11.8, I_{E4} = 6.3 (3.2)
PC-18	Capability of taking part in scientific studies	17.5/27.0	4.8/0		I_{E1} = 85.7, I_{E2} = 71.4, I_{E3} = 66.7, I_{E4} = 60.0 (3.2)
PC-19	Capability of taking part in pharmacogenetic studies to solve the problems of personalized medicine	9.5/0	0		0
PC-20	Capability of taking part in development and study of biological medicines	14.3/0	1.6/0		I_{E1} = 83.3, I_{E2} = 75.0, I_{E3} = 55.6, I_{E4} = 33.3 (1.6)
PC-21	Capability of taking part in studies in the field of developing the methods for the purposes of chemical and toxicological analysis	12.7/0	4.8/0		I_{E1} = 77.8, I_{E2} = 46.7, I_{E3} = 25.0, I_{E4} = 12.5 (3.2)

of the basic principles of management in the pharmaceutical industry, including in pharmaceutical organizations and their structural divisions ($F_{100} + F_{50–100} = 36.5\%$), capability of participating in arrangement of the activities of pharmaceutical organizations ($F_{100} + F_{50–100} = 38.1\%$), capability of participating in the examinations provided for during the state registration of medicines ($F_{100} + F_{50–100} = 34.9\%$), readiness to ensure the storage of medicines ($F_{100} + F_{50–100} = 41.3\%$).

Figure 3 shows the general results of the analysis of professional competencies in the specialty of Pharmacy (specialist's program) presented in the educational programs of universities in the form of a perceptual map. The lower frequency of occurrence of the MPC-5 competence ($F = 41.3$, A) in comparison with other mandatory competencies can be explained by its new interpretation in the MPEP, in particular, with the introduction of the provision "perform clinical laboratory tests of the third difficulty category". This item was missing in the previous FSES HE 3+. Perhaps, this reason also caused the low levels of frequency of occurrence of the recommended competencies in the educational programs of universities: PC-2 ($F = 4.8$, B), PC-6 ($F = 6.3$), PC-7 ($F = 11.1$), PC-19 ($F = 9.5$) and others. New professional competencies, including the learning of students for completion the tasks of research activities and having low frequencies of occurrence in educational

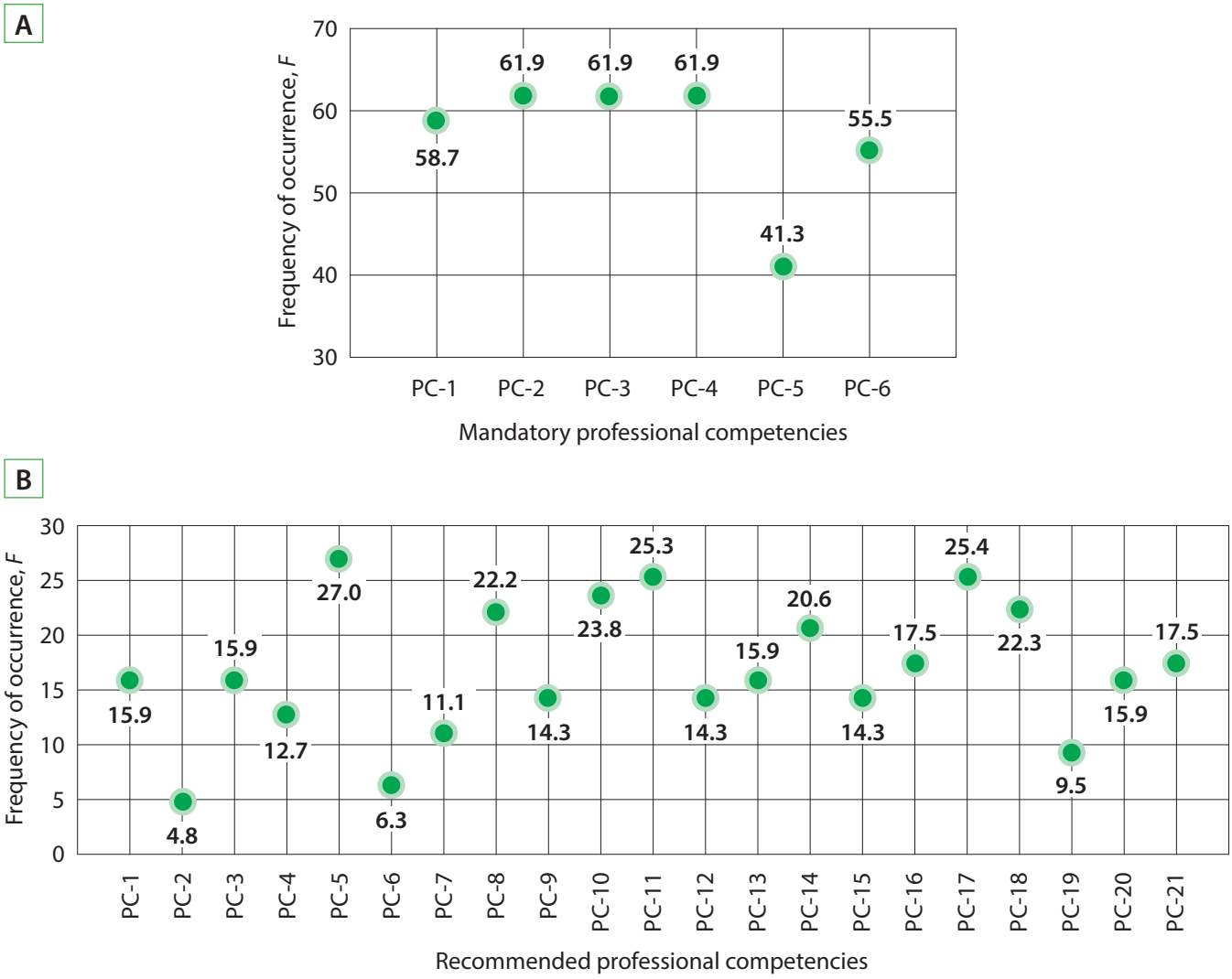

FIG. 3. *Maps of the positioning of mandatory professional competencies (A) and recommended professional competencies (B) from the MPEP in the specialty of Pharmacy (specialist's program), presented in the educational programs of universities ($F = F_{100} + F_{50+100}$)*

programs of universities, for example, PC-12 (F = 14.3), PC-13 (F = 15.9), PC-15 (F = 14.3), PC-20 (F = 15.9), were previously used only when individual students completed degree theses or final qualification works [16].

CONCLUSION

1. The analysis of professional competencies in the specialty of Pharmacy (specialist's program), presented in the principal professional educational programs of universities, showed that more than half of Russian universities have switched to mandatory competencies from the MPEP on the basis of the new educational standard (56.9±8.0%), only the sixth of universities use the recommended competencies from the MPEP (16.8±6.1%). The third of universities continues education according to the previous educational standard (32.8±2.9%). The indices of the coincidence of the texts of mandatory professional competencies from the MPEP and the corresponding competencies from the FSES HE 3++ reached the level of 2–4 shingles.

2. The most common professional competencies are established and presented in the educational programs of the universities under study, but they do not completely coincide with the competencies from the MPEP (with a length of shingle 1 – 50–100%, with a length of shingles 2, 3, 4 – more than 0). The revisions of mandatory competencies from the MPEP presented in the educational programs of universities are shown. Professional competencies from the previous educational standard are defined and presented, which are quite often found in the educational programs of educational institutions, but do not coincide with the MPEP.

3. When analyzing the mandatory competencies from the MPEP for the text reading difficulties, it was found that only two competencies (MPC-1 and MPC-6) have a high level of the Coleman – Liau index, the remaining competencies are at the average level. The results obtained were confirmed by the data on the readability of the text according to the Fog index.

4. The positioning of professional competencies in the specialty of Pharmacy (specialist's program), presented in the educational programs of universities, allowed us to clearly demonstrate the results of the analysis. The possible reasons for the low frequency of occurrence of professional competencies from the MPEP in the educational programs of universities are expressed.

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THE ATTITUDE OF THE POPULATION OF THE REPUBLIC OF SAKHA (YAKUTIA) TO HEALTH AND ITS PLACE IN THE SYSTEM OF VITAL SOCIAL VALUES

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An Internet survey of 100 respondents of the Republic of Sakha (Yakutia) was carried out using a specially prepared original questionnaire "Medicines in our life" containing over 80 questions (1st half of 2020). Statistical information was obtained for the following blocks: socio-demographic portrait of respondents, medical portrait, medicine and society, attitude to vital values, attitude to health, personal characteristics of modern patients contributing to the increase in the incidence of diseases of society, attitude to diseases and problems of modern medicalization. The hypothesis of the study about the constant growth of medical and pharmaceutical awareness of the population of certain territories is proved by the example of the Republic of Sakha (Yakutia).

Keywords: medico-sociological study, medical and pharmaceutical literacy/awareness, vital values, modern patients.

Introduction to the issue. Among the universal values, one of the priority qualities for any person is health. Good health provides prosperous youth, main resource of working ability and financial opportunities, professional longevity and quiet old age. According to scientists, the disease can be considered as a condition that prevents the implementation of the technical, physiological, reproductive and social life of an individual. We have formulated a study hypothesis about the constant growth of medical and pharmaceutical awareness of the Russian population [1–6].

It is important to study the attitude of a human and society to the health as a social value and the social conditions in which it is formed

Before a study, according to the methodology, it is necessary to define the terminology of the issue, since there is currently a large amount of scientific literature on public health and healthcare. In this regard, we found it possible to use the basic concepts and definitions specified in the textbook by Lisitsin Yu.P., Ulumbekova G.E. (2015) [7].

At the end of the last century, the concept of a health culture (HC) began to form among scientists and philosophers. As a sociological category, the health culture (HC) is determined by the values and atmosphere in society that ensure such behavior of people which leads to the preservation of health. They believe that the formation of HC requires a creative and critical attitude to the cultural heritage of value aspects. HC should create not only an individual, but also the health of society as an interaction of these individuals [8].

HC is a socio-cultural reality as a specific human component of the environment that provides a level of culture of life [9].

In the scientific publications of the new millennium on health, lifestyle, prevention, health culture and medicine, theoretical studies and practical sociological medical works appear that consider this social problem "health" and "disease" with emphasis on its significance in the system of human values and the individual's personal responsibility for health [5,10,11].

Scientists note that in different countries, ideas about health and illness, the possibilities of medicine, the practice of using medicines and the image of a doctor differ. The American researcher L. Peyer noted in her publications that there is a relationship between cultural factors and medical culture. For example, it is known that treatment standards are associated with a state of health or its disorders, a diagnosis with an implicit etiology; the medical habits of a patient who may be characterized by images of a stoic, a sufferer, an anarchist, a resister or a winner; the image of the figure of a doctor in culture (the image of a father, a wise man, a contemplator, a hero or a warrior); the attitude to the possibilities of medicine (infinitely optimistic, restrainedly rational and skeptically cautious); medicinal practice (highly specialized or general strengthening, massive or cautious, following the nature or going against it); the ideal of health (emphasis on physical or mental health); the image of disease (an external enemy or variation of the natural state) [12]

So in Russia, the word "patient" (the person, who experiences pain, suffers) says that the sick person perceives himself as a sufferer, waiting for understanding or sympathy from the people around him and from the doctor. The European "patient" with the Latin root "pati" (to have patience, to endure) is traditionally perceived in Russia as an external influence, an external enemy, the patients do not associate themselves with their disease.

For a long time, collective attitudes affected the Russian consciousness, less attention was paid to individual health problems and the preventive measures to preserve health were not so widespread. The doctor is perceived as an authoritarian figure in Russian culture, and respect for strong power is traditionally laid down in society [12].

Generally, medical knowledge concentrates on environmental factors, external causes of the disease, which corresponds to the biomedical model of the disease, that is, the model based on the theory of the causative agent (infection, bacterium), epidemiological theory. These are three axioms without pathology, in particular: 1) the disease is a breakdown of the body, anomaly that needs to be corrected; 2) the body is sick, not the mind, so the patient is considered not as a complete person, but as a sick body that needs to be treated; 3) the only specialists in the field of health and disease are doctors (E. Giddens, 2005) [13].

However, at present, as noted above, scientists have come to the conclusion that with the change in theoretical views on medicine, biomedicine is not able to solve the problems of chronic, non-exogenous diseases [13].

Modern biomedical technologies radically expand the processing capabilities of modern scientific medicine, which simultaneously requires solving the problems of medical ethics or medicalization of the entire modern culture.

Medicalization is the expansion of the sphere of medical prevention and the application of medical recommendations in various industries, in social relations and everyday life. This is evidenced by a significant increase in medical services for aesthetic, reproductive or psychological purposes [14,15].

In Russia, the dominant scientific medicine orients the patients to drug treatment, while the experience of alternative medicine is also in demand, which is used by about 26% of patients [16].

Currently, "medicalization" is understood as "penetration into the mass consciousness of the medical language and style of thinking, medical concepts and ideas about the causes, forms of the course and treatment of diseases, increasing dependence on medicine for everyday life and people's activities, fixing medical "labels" for certain human properties or types of behavior" [17].

Preparation for the study. For a medical and sociological study, a special questionnaire "Medicines in our life" was prepared, which includes more than 80 questions grouped into blocks: 1) socio-demographic; 2) medical portrait of the respondent; 3) pharmaceutical portrait of the respondent; 4) medicine and society; 5) commitment to pharmacotherapy; 6) medicines of the future; 7) availability and quality of medicine provision; 8) the place and role of informal medicine in the life of citizens in the Far North and the Arctic

The questionnaire is prepared in the form of an online questionnaire based on Google technology. Survey in the Republic of Sakha (Yakutia) – (RS(Ya)) was provided in January-May, 2020, in this survey 100 Internet users took part, 85 most fully (informative) completed questionnaires were selected for statistical processing. The questionnaire is intellectual property of the scientific school of Professor Dremova N.B., and was modified by the authors to study the problem in the RS(Ya) [3,18].

The purpose of the study is to analyze the attitude of the population of the RS(Ya) to the problem of health, diseases and their prevention. When preparing the questionnaire, the works of Reshetnikov A.V. "Sociology in Medicine" [6] and Gorshkov M.K. and Sherega F.E. were used as the main guidelines [11].

RESULTS OF THE STUDY

Socio-demographic portrait of the respondent – a resident of the RS(Ya). The following characteristics of the socio-demographic portrait were resulted: 1) gender – female 79.8%; 2) age – from 21 to 60 years – 78.8% (capable to work); 3) social status – office-based employees 78.9%; 4) education – higher 83.5%; 5) marital status – 60% married; 6) number of children – 62.4% have 1–3 children; 7) income – 1–3 subsistence levels – 61.2%; 8) place of residence – city 76.5%; 9) specialty: humanities – 22.4%; economists – 8.8%; pharmacists – 16.5%; doctors-9.4%; technical specialties – 11.8% and others.

Conclusion: the respondents have sufficient educational level and life and professional experience to participate in the survey.

Medical portrait of the respondents. This block included the questions of self-assessment of physical, mental, and social health; overall and average health assessment; the presence of seasonal, chronic diseases; reference to a doctor with an exacerbation of chronic diseases; self-assessment of the level of medical knowledge about their diseases. Table 1 shows the results of self-assessment of health types.

As follows from the data in Table 1, regularity has been revealed i.e. the predominance of good and satisfactory self-ratings of all types of health. There is some bias towards good ratings of mental and social health. The remaining ratings are mostly satisfactory.

About a quarter of respondents suffer from seasonal diseases: 24.7% – get sick once a year; 44.7% – 1–2 times a year; 21.2% – 3 times a year; 90.6% get sick in total; 9.4% do not get sick.

82.4% of the survey participants have chronic diseases; 34.1% necessarily visit a doctor in case of chronic diseases; about a tenth (9.4%) does not visit a doctor; the rest, in their opinion, do not have chronic diseases. Respondents with chronic diseases answered the question which systems affected are in them: 1) gastrointestinal system – 30.6%; 2) cardiovascular system – 28.2%; 3) musculoskeletal system – 21.2%; 4) diseases of the ear, throat, nose – 18.8%; 5) respiratory system – 17.6%; 6) genitourinary

Table 1

RESULTS OF SELF-ASSESSMENT OF THE TYPES OF HEALTH OF THE POPULATION OF THE RS(YA) (1st HALF YEAR 2020)

No.	Type of health	self-rating of health, %				
		excellent	good	satisfactory	unsatisfactory	Not sure
1	Physical	2.4	34.1	56.5	2.4	4.6
2	Psychical	11.8	47.1	37.6	1.2	2.3
3	Social	9.4	57.6	31.8	1.2	–
4	In total, health	3.5	30.6	62.4	1.2	2.3
5	In average, health	6.8	42.3	47.1	1.5	2.3

system – 14.1%; 7) endocrine system – 10.6%; 8) eye diseases – 10.6%; 9) other (oncology, nervous, immunology) – 9.5%; 10) dermatological diseases – 3.5%.

The presence of chronic diseases implies that the respondents have a certain level of medical knowledge about their illnesses. The respondents rated their knowledge as follows: a little more than 40% put themselves 4 points (a good level) and 42.4% – 3 points (a satisfactory level). In total it is 82.4%; the remaining 8.2% put 5 points, and 3.6% rated their knowledge with low scores – 1–2 points.

At the next stage, based on the analysis of scientific publications, an information and analytical study of the features of natural and climatic conditions (RS(Ya)) was carried out.

The RS(Ya) is located in the north-eastern part of Eurasia, 40% of the territory is located beyond the Arctic Circle; the climate is sharply continental, negative temperatures persist up to 5 months a year [19]. Residents have to adapt to frequent geomagnetic disturbances, "ultraviolet starvation", sharp fluctuations in atmospheric pressure, low humidity and a constant stressful situation throughout the year.

The influence of natural factors in the Far North contributes to the emergence and development of chronic non-communicable diseases at a young age, accelerating the aging process, reducing life time. Serious diseases (heart attacks, CHD, arterial hypertension) appear in residents about 10 years earlier than in the middle latitudes [20]. A "polar stress syndrome" is formed in the indigenous inhabitants, which is characterized by a persistent increase in the level of stress hormones in the blood and switching energy exchange from carbohydrate to fat, the functioning of the immune system worsens, the adaptive stability of the body decreases [21] and the mental and physical performance also decreases.

As in any society, the population of the Far North and the Arctic has its own behavioral and personal factors such as an unbalanced diet, a shortage of vegetables and fruits; factors of smoking, alcoholism, low physical activity are manifested [22].

Among the incidence, according to the Ministry of Health of the RS(Ya), diseases of the respiratory system, digestive system, circulatory system, genitourinary system, musculoskeletal system are leading in 2019, in total they are about 75% of the overall incidence.

Attitude to vital values. Table 2 presents the results of the analysis of the significance of vital values for the respondents who have been residents of the RS(Ya) in 2020.

Table 2

SIGNIFICANCE OF VITAL VALUES FOR RESPONDENTS IN RS(YA) (2020)

No.	Vital value	Answers	
		Score	R
1	Work	3.88	3
2	Education	4.59	4
3	Family	2.81	1
4	Stability	4.68	5
5	Religion	6.47	8
6	Health	3.11	2
7	Money	4.73	6
8	Friends	5.71	7

Note. R- Rating 1st place – max important, 8th place – min, the most unimportant

As follows from the results of the significance of vital values (Table 2), the average value in scores is related to the family – 2,91–1st place, health – 3,11–2nd place; work – 3,88–3rd place, the last 8th place – 6,47 – religion.

It should be noted that in similar studies provided by Dremova N.B. and co-authors the health and family are also at first and second places of the significances of vital values in the rating.

This trend is recorded in the publications of scientists from other countries. The remaining qualities can take different places in the rating, depending on the segment and the population of respondents studied [2]

Respondents' attitude to health. As shown at the beginning of the article, we have adopted as a standard the WHO definition "Health is a state of complete physical, mental and social well-being and not just the absence of diseases or ailment (physical defects)". The majority – 75.3% of our respondents (three quarters) agree with the WHO definition; a fifth – 21.2% partially agree, in total this is 96.5% and the remaining 3.5% were undecided.

In this regard, at the next stage of the study, the characteristics of a modern patient are studied from the standpoint of medical literacy and awareness. 12 personal characteristics were included into the questionnaire. During statistical processing, positive responses were considered, and the rating level was determined by the direct grading method (1st place – max share, last place – min share).

As follows from the data in Table 3, it can be concluded that modern patients (according to self-assessment) have wide access to medical and pharmaceutical information (60%). These are books, magazines, mass media, television, the Internet, etc.

According to the All-Russian Public Opinion Research Center (VCIOM), 41% of Russians double-check the diagnosis and doctor's appointments [23].

Respondents also identify their own trends of increased medical and pharmaceutical literacy (37.6%), including the emergence of knowledge about their diseases and treatment methods (55.3%).

A fourth of respondents (24.7%) noted that they had negative experience of contacting doctors, which was the trigger of interest in medical and pharmaceutical information.

It is necessary to pay attention to such a characteristic as a critical assessment of the disease treatment prescribed by a consulting physician of respondents – 20% (one fifth).

Summing up the results of the interpretation of the answers received, we can say that the respondents who took part in the sociological survey are people who are interested in their health, who understand the importance of health for their own life, family, relatives, work and their future.

Respondents' opinion on the impact of society's problems on the growth of the population's morbidity. For the analysis, a list of such

Table 3

RATING OF PERSONAL CHARACTERISTICS OF MODERN PATIENTS-RESIDENTS OF THE REPUBLIC OF SAKHA (YAKUTIA) (1st HALF YEAR 2020)

No.	Characteristics	Responses	
		portion, %	R
1	Has wide access to medical and pharmaceutical information	60.0	1
2	Has advanced treatment options	43.5	2
3	Increased medical and pharmaceutical literacy	37.6	3
4	Increased awareness of their diseases and their medicine therapy	35.3	4
5	Negative experience of contacting a doctor	24.7	5
6	Has an increased level of education	23.5	6
7	Interested in the methods and theory of informal medicine	22.4	7
8	Has high suggestibility	21.2	8
9	Critically evaluates the therapy prescribed by the doctor for his diseases	20.0	9
10	Family traditions in the treatment and prevention of certain diseases	16.5	10.0
11	Prefers medicines containing active ingredients from medicinal herbs	15.3	11.0
12	Others	–	–

problems was prepared from 18 scientific publications, systematized by us into 3 groups, in particular: 1) the external environment; 2) consumer behavior; 3) the state of health care (Table 4).

Among the problems there are also those that depend on the state of health care, and are not only financial, but also organizational in nature. Based on the opinion of the population participating in the sociological survey, it can be concluded that there is a multifactorial negative impact of modern problems on the health of the population, which leads to increase in morbidity.

The attitude of the population of the RS(Ya) to diseases. 12 answers expressing the opinion of the attitude to diseases were offered to the respondents. It should be noted that the task caused some difficulties, since the number of positive answers to some questions varied within the range from max 51.8% to min 2.4% (Table 5).

The results of the answers to this question indicate some difficulties in differentiating their opinions in relation to health, since the maximum share is 51.8%, that is, slightly more than half of the respondents preferred the first answer.

The opinion that the disease is an obstacle that must be overcome brings up stoic characteristics, because not always the therapy of

Table 4

SYSTEMATIZATION OF THE PROBLEMS OF SOCIETY THAT CONTRIBUTE TO THE INCREASE IN MORBIDITY, ACCORDING TO THE RESPONDENTS OF THE RS(YA) (1st HALF YEAR, 2020)

Place	External environment	Consumer behavior	State of health care
1	Environmental pollution		
2	Non-environmental friendliness of food		
3		Psychoemotional and social stresses	
4		Prevalence of bad habits and drug addictions	
5		Reduction in the living standards of the general population	
6			Underfunding of healthcare and education in the medical environment
7	Economic instability		
8			Deterioration of the quality of medical care
9	Urbanization		
10			Insufficient State efforts to prevent the spread of dangerous diseases
11	Unemployment		
12	Automation of production		
13	Ageing of population		
14	Increase in population, increase in residential density		
15	Lack of widely available opportunities for physical education and sports		
16		Depersonalisation	
17	Informatization		
18		Increased level of knowledge in health issues	

Table 5

RATING OF THE ATTITUDE OF RESPONDENTS OF RS(YA) TO DISEASES (1st HALF YEAR 2020)

No.	Disease – as	Answers	
		Share,%	R
1	An obstacle that must be overcome	51.8	1
2	An enemy that threatens the integrity of your personality	40.0	2
3	Nothing special, I'm just sick and I want to recover	27.1	3
4	A manifestation of a congenital debility of the body	25.9	4
5	Irrevocable loss or damage	24.7	5
6	Motivation for changing life attitudes	9.4	6
7	The urgent reason for giving up bad habits and the need to follow a healthy lifestyle	8.2	7
8	Punishment for past sins, requiring humility and repentance	5.9	8
9	Others	4.8	9

Note. R – Rating place: 1 – max, 9 – min

the disease is pleasant procedures. It is necessary to take both bitter medicines and perform painful methods of treatment.

About a third (27.1%) of respondents indicated that they are tolerant of diseases and just want to recover. Sentences 4 and 5 were noted, as a rule, by people with chronic diseases or with congenital diseases from childhood, which patients estimate as an irrevocable loss or damage to their life period.

The remaining sentences occupy shares of less than 10%, which, in our opinion, have a positive impact on a person's life. This is the motivation to change life attitudes, the reason for giving up bad habits and the need to follow a healthy lifestyle.

There are also religious answers that consider illness as a punishment for past sins that require humility or repentance (5.9%).

In general, it can be concluded that the majority of respondents consider their illnesses as a signal (motive, argument) for changes in many factors (conditions) of life in order to treat the disease and to provide the preventive health care.

The social medium has formed the statement that society strives to minimize the level of morbidity and mortality, to ensure the availability of high-quality medical care for everyone, to eliminate the consequences of morbidity and disability.

Completing the study of the significancy of diseases for the population, it is necessary to focus on the phenomenon of "medicalization of life", the essence of which is the solution of various life problems that do not require mandatory treatment conditions. In particular, such values have been formed in society and the remedies such as vitamins, herbal medicines,

dietary supplements, homeopathic medicines have been developed to solve the health problems [15].

For example, respondents indicated (in order of direct grading of places) the following problems and values: 1) healthy lifestyle – 71.8%; 2) the cult of healthy diet – 58.8%; 3) the fight against excess weight – 56.5%; 4) sports – 50.6%; 5–6) quitting smoking, alcohol, drugs – 47.1% each; 7) the fight against high cholesterol – 54.1%; 8) self-help (self-treatment) – 32.9% [3].

In the near future, these areas will be included, and some have already been included, into the list of corrections to the strategic policy of developing new medicines by well-known representatives of the pharmaceutical industry.

CONCLUSION

1. The methodology of medical and sociological study of the population's attitude to the problem of health and the analysis of its place in the system of vital social values has been developed. The form of a remote Internet survey was tested using a specially prepared questionnaire among residents of the RS(Ya), for a non-repeated sample (1st half year 2020).

2. In the result of statistical processing of the survey participants' responses, the reliably confirmed information was obtained on a number of questionnaire blocks, which made it possible to identify scientific facts on the problem. The analysis of socio-demographic characteristics showed that respondents with a sufficient educational level and the life and professional experience took part in the survey.

3. During the self-assessment of the types of health, the respondents rated their health in the whole as good and excellent (34.1%) and satisfactory (62.4%). Among the chronic diseases, gastrointestinal (30.6%), cardiovascular (28.2%), musculoskeletal (21.2%), ENT diseases (18.8%) and respiratory diseases (17.6%) predominate. The presence of chronic diseases suggests that the respondents have a certain level of knowledge about their diseases: 83.6% gave themselves 4 and 3 points when assessing such awareness.

4. According to scientific publications, the negative impact of natural and climatic conditions on the health of the population of the RS(Ya) has been identified.

5. Out of the eight vital social values, the respondents gave priority to family, health and work. Among the personal characteristics of modern patients, the following prevail: "wide access to medical and pharmaceutical information" – 60% of positive responses; "they have expanded opportunities for treatment" – 43.5%; "increased medical and pharmaceutical literacy" – 37.6%; "increased awareness of their diseases and medical therapy" – 35.3%

6. According to the respondents, among the problems of society there are a number of factors that negatively affect health, which leads to increase in morbidity. These are problems and health conditions that depend not only on funding, but also on organizational issues.

7. The results of the population opinion on the attitude to diseases are obtained. More than half of the responses can be described as optimistic: "illness is an obstacle that must be overcome" (51.8%) and "illness is an enemy that threatens the integrity of the individual" (40%). These answers show that patients have stoic characteristics for control of the disease and considering the disease as a weighty argument for changing many conditions of their life for the purpose of treatment and prevention of diseases.

8. Thus, based on the results of the interpretation of the answers received, it can be concluded that those who took part in the medical and sociological study are people who are interested in their health, who understand the importance of health for their own life, family, work and their

future. In our opinion, the study allowed us to confirm the hypothesis expressed at the beginning of the article about the constant growth of the health culture of the population in a particular region of Russia on the example of the Republic of Sakha (Yakutia).

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