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Development of Dietary Supplement Capsules "Nigelit" using Mathematical Methods

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Development of Dietary Supplement Capsules "Nigelit" using Mathematical Methods

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Abstract- The research featured the development of formulae and technology of obtaining biologically active additives for functional foods with potential anti-inflammatory activity using a substance containing zinc (microelement) and plant raw material as source of natural biologically active substances. The relevance of the study is comes from the need for more effective use of natural biologically active compounds, the need to expand the range of domestic dietary supplements, in particular, those recommended for the prevention of disorders of the prostate activity and erectile dysfunction, with natural ingredients and import substitution. On the basis of scientific data and the results of the conducted research, substance containing zinc and a promising plant raw material containing biologically active substances were selected; their safety and potential properties were assessed. The optimal ratio and dosage of active ingredients in the composition has been scientifically substantiated. The technological properties of the mixtures of active ingredients that determine the choice of technology and the quality of the finished product were studied. Researches were carried out to select the optimal composition for the capsules "Nigelit" using a mathematical method of experimental design, the 4 × 4 Latin square. The experimental results were processed using mathematical methods of statistical and variance analysis, involving the Fisher statistic - Fstatistic (also called the F-ratio) and the generalized desirability function. As a result, the composition and technology of dietary supplement - capsules "Nigelit" were developed.

Keywords: biologically active additives, dietary supplement, raw material, mathematical method, experimental design, factor, optimization parameters, capsules, "nigelit", excipients.

I. Introduction

Erectile dysfunction or the inability to achieve or maintain an erection sufficient for satisfying sexual activity, often becomes a real problem for men. According to the WHO information every 10th managed older 21 has the erectile disorder and after the age of 60 years every third man is not able to perform sexual intercourse. About 35% of men aged 40 to 70 years suffering from partial or total inability to achieve erection [1].

To date, effective approaches of pharmacological correction of disorders of sexual function in men have been developed. Depending on the indications for use, these drugs should have separately or in combination neurotropic, vasodilating, anti-inflammatory, antimicrobial, antihypoxic, immunotropic effect [1]. The basis of drug therapy for erectile dysfunction, as a rule, is made up of phosphodiesterase inhibitors: vardenafil, sildenafil, tadalafil [1]. However, all of these drugs are available with a doctor's prescription. At the same time, significant advances in the prevention and treatment of male genital pathology can be achieved with the use of over-the-counter herbal remedies. Compared to synthetic ones, natural components have a milder and more versatile effect due to the variety of components actively affecting the body and, as a rule, rarely cause side effects [1]. Most of the herbal remedies for correcting erectile dysfunction are presented in the form of biologically active additives.

Today the market of dietary supplements for the correction of erectile dysfunction mainly offers complex drugs of a certain functional orientation, most often combining herbal ingredients with a pronounced stimulating effect on sexual function and a general tonic effect [1].

When reviewing the literature, it was found that one of the types of plant raw materials that have a beneficial effect on the function of the prostate is the seeds of Nigella sativa [2], and of the microelement – zinc [3, 4].

Based on the analysis of the pharmaceutical market of the manufactured dosage forms, we have selected hard gelatin capsules as the rational dosage form for the medicinal preparation under development. Capsules represent a prospective solid dosage form with a number of advantages. For instance, they are attractive in appearance, easy to swallow, contain accurate dose, protect encapsulated medications against light, air and moisture since capsule shells provide a high level of airtightness, can quickly swell up, dissolve and get absorbed in the gastrointestinal tract, have high bioavailability [5].

The aim of the research is to develop the composition and technology for obtaining dietary

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supplements with specified characteristics using plant raw materials - seeds of Nigella sativa and a microelement – zinc.

II. Materials and Methods

Seeds of Nigella sativa, zinc sulphate, their mixture, their mixtures with different excipients and capsules on their base were selected as the materials of research. The technological properties of the materials that determine the composition, technology and the quality of the finished product and the capsule disintegration were studied using conventional methods, described in [6, 7, 8]. In order to select the optimal composition for the capsules "Nigelit" a mathematical method of experimental design, the 4 × 4 Latin square was used. The experimental results were processed using mathematical methods of statistical and variance analysis, involving the Fisher statistic (F statistic) and the generalized desirability function [9, 10, 11, 12]. In order to create granules moisture activated dry granulation (MADG) was used [13, 14, 15].

III. Results and Discussion

For the development of the dietary supplement, firstly, a suitable dose of the microelement – zinc and plant raw material containing biologically active substances were calculated, based on the study of their safety and potential properties. Then the technological properties of the mixture of active components were studied. It was established that the mixture of active components has unsatisfactory technological properties in particular flow ability. This makes obtaining capsules of an acceptable quality from such a material impossible. In order to eliminate these disadvantages, and to produce good-quality capsules, it is necessary to incorporate excipients, and to use granulation, which prevents the segregation (stratification) of the mixture [16].

In order to choose the most rational composition and the encapsulation technology for the capsules "Nigelit", we took advantage of a mathematical method of experimental design, the method of the 4 × 4 Latin square and performed analysis of variance. The use of this method makes it possible to significantly reduce the experimental error and to quantify the effect of various factors on the optimization parameters [9, 10, 11, 12]. In this case, flowability, bulk density, angle of repose of the granular materials and disintegration time of capsules were selected as the optimization parameters (see table 1); while fillers, antiaderents (anti-sticking agents), disintegrants and glidants were selected as factors affecting optimization parameters (see table 2). Technological properties of the granular materials and the capsule disintegration were studied using conventional methods [6, 7, 8]. In order to create granules moisture activated dry granulation (MADG) was used [13, 14]. This method allows for simultaneous mixing and of ingredients, as well as forming of a product with homogeneous dispersion [13]; minimization grinding of such issues with wet granulation as the need for a significant amount of granulating liquid, the duration and energy intensity of the process of mixing the wet mass, sensitivity of individual components of the mixture to high moisture levels, the necessity of using granule-forming *apparatus* in most cases, the long-lasting stage of drying the granules, accompanied by the unfavorable effect of temperature on active pharmaceutical ingredients, as well as the cumbersome equipment required for the air preparation and air purification processes [15]. The main advantage of this granulation method is that the resulting granules do not need to be dried - this speeds up the technological process, reduces labor and energy costs. Moreover, the resulting granules do not need additional grinding due to the characteristic homogeneous particle-size distribution [13]. Purified water was used as the moisturizing liquid for granulation.

Table 1: Optimization parameters for the capsules "Nigelit"

Optimization parameters (Y)			
Y_1	Y_2	Y_3	Y_4
Flowability (10^{-3} kg/s)	Bulk density (kg/m^3)	Disintegration (min.)	Angle of repose (°)

Table 2: Factors affecting the optimization parameters of capsules "Nigelit"

Name of the capsules	Factors			
	A - fillers	B - antiadherents	C - disintegrants	D - glidants
	a_1 - starch	b_1 - magnesium stearate	c_1 - CMC	d_1 - starch

"Nigelit"	a_2 - Prismalac 60	b_2 – calcium stearate	c_2 - MCC Arbocel A 300	d_2 – aerosil
	a_3 - MCC Arbocel A 300	b_3 - stearic acid	c_3 - UAP	d_3 – talc
	a_4 – dextrin	b_4 – kaolin	c_4-Na-CMC	d_4 – PEG-400

In order to select the optimal composition for capsules "Nigelit" various mixtures of active components and excipients were designed and prepared according to the formulations presented in table 3. Each mixture prepared according to the formulations was granulated using moisture activated dry granulation method. Then the technological properties of thesemixtures and the disintegration of the capsules prepared on their base were studied (see table 3).

Table 3: Experiment design matrix and research results on the effect of the excipients on the optimization parameters for capsules "Nigelit"

(Symmetric fractional factorial experiment, 16 out of 256, 1/16 fraction)

Experiment number	Factors				Optimization parameters				*D*
	A	B	C	D	Y_1, 10^{-3} kg/s	Y_2, kg/m^3	Y_3, min.	Y_4, °	
1	a_1	b_1	c_1	d_1	4,5	387	30	40	0,47
2	a_1	b_2	c_2	d_2	4,3	386	32	43	0,44
3	a_1	b_3	c_3	d_3	5,0	400	33	42	0,48
4	a_1	b_4	c_4	d_4	4,1	385	38	46	0,33
5	a_2	b_1	c_1	d_2	4,1	380	32	41	0,42
6	a_2	b_2	c_2	d_1	4,3	381	28	41	0,47
7	a_2	b_3	c_3	d_3	4,8	392	35	42	0,43
8	a_2	b_4	c_4	d_4	3,9	380	40	46	0,29
9	a_3	b_1	c_2	d_3	5,5	390	20	38	0,69
10	a_3	b_2	c_1	d_2	4,8	377	25	43	0,54
11	a_3	b_3	c_3	d_1	5,1	380	28	44	0,52
12	a_3	b_4	c_4	d_4	4,7	378	30	46	0,46
13	a_4	b_1	c_1	d_4	4,4	388	27	43	0,51
14	a_4	b_2	c_2	d_3	5,2	400	25	40	0,61
15	a_4	b_3	c_3	d_2	4,5	386	30	46	0,45
16	a_4	b_4	c_4	d_1	4,8	390	33	43	0,46

Then the results of studying the optimization parameters (table 3) were subjected to analysis of variance which allows us to test the null hypothesis (all means are equal) against the alternative hypothesis (at least one mean is different) with a specified value of alpha (in our case the value of alpha (α) or the level of significance is equal to0.05 or 5%) and probability (in our case the value of probability (P) is equal to0.95 or 95%). In other words analysis of variance allows us to determine the significance of the studied factors A, B, C, D for the optimized parameters Y_1, Y_2, Y_3, Y_4(table 4) at a given level of significance[11, 17].

It should be mentioned that if the F test statistic (observed) is greater than the F critical value, i.e. $F_{statistic}$>

$F_{critical}$, then the hypothesis of similarity or the null hypothesis H_0 is rejected, and the hypothesis of the difference or the alternative hypothesis H_1 is accepted with a level of significance $\alpha = 0.05$ or 5%. This means that the factor significantly affects the change in the output data - the values of the optimization parameter and the data depend on the factor with a probability of $P = 0.95$ ($P = 1 - \alpha$) or $P = 95\%$ ($P = 100 - \alpha$). If the F test statistic (observed) is less than the F critical value, i.e. $F_{statistic} < F_{critical}$, then the hypothesis of similarity or null hypothesis H_0 is accepted, and the hypothesis of difference or alternative hypothesis H_1 is rejected with a level of significance $\alpha = 0.05$ or 5%. This means that the factor does not significantly affect the output data - the values of the optimization parameter with a probability of $P = 0.95$ ($P = 1 - \alpha$) or $P = 95\%$ ($P = 100 - \alpha$).

Table 4: Analysis of variance of the experimental data from the study of the indicators of the capsules "Nigelit"*

(Four-factor analysis of variance without replication)

Optimization parameters	Source of variance	Degrees of freedom (df)	Sum of squares (SS)	Mean square (MS)	$F_{statistic}$	$F_{critical}$
Y_1–Flowability, 10^{-3} kg/s	Factor A	3	1.26	0.42	3.02	3.49
	Factor B	3	0.45	0.15	0.74	3.49
	Factor C	3	0.73	0.24	1.34	3.49
	Factor D	3	1.66	0.55	5.23	3.49
Y_2-Bulk density, kg/m^3	Factor A	3	268.5	89,5	2.26	3.49
	Factor B	3	78.5	26.17	0.47	3.49
	Factor C	3	156.5	52.17	1.07	3.49
	Factor D	3	467.5	155.83	6.79	3.49
Y_3 – Disintegration, min.	Factor A	3	174.75	58.25	3.41	3.49
	Factor B	3	172.25	57.42	3.32	3.49
	Factor C	3	182.25	60.75	3.69	3.49
	Factor D	3	66.75	22.25	0.85	3.49
Y_4 - Angle of repose,°	Factor A	3	0.5	0.17	0.02	3.49
	Factor B	3	51.5	17.17	5.49	3.49
	Factor C	3	51.5	17.17	5.49	3.49
	Factor D	3	48.5	16.17	4.79	3.49

**Analysis of variance was conducted on the experimental data from table 3, and the statistical indicators in table 4 were calculated, using ANOVA module of the statistics software MiniTab.*

The results of the analysis of variance (table 4) allow us to state the following:

- The selected types of fillers (Factor A) does not have a significant effect on the flowability (Y_1), bulk density (Y_2), angle of repose (Y_4) of the granular materials as well as the disintegration of capsules (Y_3);
- The selected types of antiadherents (Factor B) has a significant effect on the angle of repose (Y_4) of the granular materials and does not have a significant effect on the flow ability (Y_1), bulk density (Y_2) of the granular materials as well as the disintegration of capsules (Y_3);
- The selected types of disintegrants (Factor C) has a significant effect on the disintegration of capsules (Y_3) and the angle of repose (Y_4) of the granular materials and does not have a significant effect on the flow ability (Y_1), bulk density (Y_2);
- The selected types of glidants (Factor D) has a significant effect on the flow ability (Y_1), bulk density (Y_2), angle of repose (Y_4) of the granular materials and does not have a significant effect on the disintegration of capsules (Y_3).

The overall (generalized) evaluation of the optimization parameters - the disintegration of capsules and the technological properties of the granular materials (model mixtures)- was carried out using a desirability function [11, 18]. In order to generalize the values of the optimization parameters that have different units of measurement, we used the well-known and widely accepted Harrington's desirability function, first introduced by him in solving quality control problems of mass production. The Harrington's scale establishes a correspondence between linguistic evaluations of desirability of the values of the indicator *x* and the numerical intervals *d(x)* (table 5) [11, 19].

Table 5: Numerical intervals of the Harrington's scale

Linguistic evaluation	Intervals of the desirability function values *d(x)*
Very good	1.00 - 0.80
Good	0.80 - 0.63
Satisfactory	0.63 - 0.37
Bad	0.37 - 0.20
Very bad	0.20 - 0.00

In order to construct the desirability function scale of the optimization parameters for the capsules "Nigelit"(Fig. 1), the method of quantitative analysis was used with the range of desirability values between 0 and 1 (Table 5). The value $d = 1$ corresponds to the best value of the optimization parameters, while $d = 0$ - to their worst value of ones. The intermediate values of the desirability function reflect specific levels of the product quality: very bad (0.00 - 0.20), bad (0.20 - 0.37), satisfactory (0.37 - 0.63), good (0.63 - 0.80) and very good (0.80 - 1.00). Conversion of the natural values (Y) into individual desirability values (*d*) with a one-sided limit $Y \leq Y_{max}$ or $Y \geq Y_{min}$ was performed using the following equation:

$$d = \exp\left[-\exp(Y')\right] \quad (1)$$

where $Y' = b_0 + b_1$. The coefficients b_0 and b_1 were calculated by assigning the corresponding desirability values d for two of the property values, preferably selected within the range $0.2 < d < 0.8$. The desirability curve (Fig. 1) were plotted in the (Y', d) coordinates based on the equation of the desirability function. At the same time, Y_{max} or Y_{min} on the dimensional scales corresponded to 0 (zero) on the dimensionless scale Y'. The desirability scale (Fig. 1) was used to convert the response values (Y_1, Y_2, Y_3, Y_4) into the dimensionless desirability function (d_1, d_2, d_3, d_4), i.e. to find individual desirability values for the measured values of the optimization parameters Y_i.

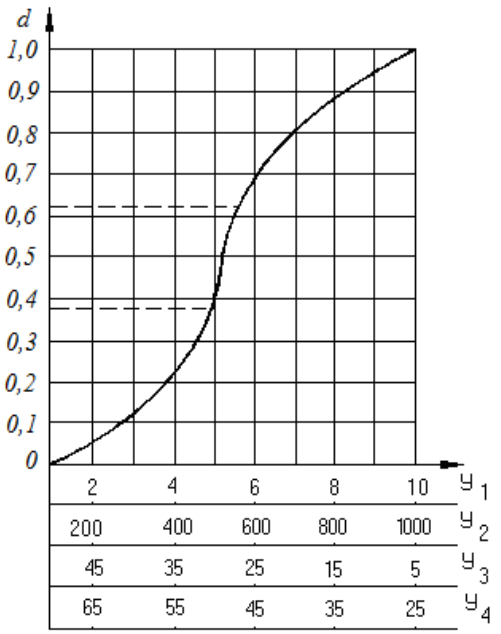

Fig. 1: The Desirability Function Scale of the Optimization Parameters for the Capsules "Nigelit"

Then the overall (generalized) desirability function values were calculated using the formula (2)as the geometric mean of individual desirability values found. It should be noted, this is a more successful approach towards optimization of the parameters for finished products (in our case capsules):

$$D = \sqrt[4]{d_1 d_2 d_3 d_4} \quad (2)$$

where *D* is overall (generalized) desirability function value; d_1, d_2, d_3, d_4 - individual desirability function values.

The values of the overall (generalized) desirability function (*D*) for the capsules "Nigelit" are presented in table 3.

Based on the generalized evaluation of the optimization parameters - the disintegration of capsules and the technological properties of the granular materials (model mixtures), carried out using a desirability function, the excipients can be arranged in the order of preference as follows:

- The type of fillers (Factor A) – $a_3 > a_4 > a_1 > a_2$;
- The type of antiadherents (Factor B) – $b_1 > b_2 > b_3 > b_4$;
- The type of disintegrants (Factor C) – $c_2 > c_1 > c_3 > c_4$;
- The type of glidants (Factor D) – $d_3 > d_1 > d_2 > d_4$.

The optimal composition for capsules "Nigelit" was formulated based on the results of the mathematical method of experimental design and using a desirability function.

The most optimal combination of levels of factors - composition of the excipients that ensure the required indicators for the capsules "Nigelit" (table 3, composition No. 9) was selected based on the values of the overall (generalized) desirability function (*D*) of the optimization parameters. The excipients included in this composition are listed in table 6.

Table 6: The Most Optimal Composition of the Excipients that Ensure the Required Indicators for the Capsules "Nigelit"

Name of the capsules	No. of the optimal composition	Excipients included in the optimal composition
"Nigelit"	composition No. 9 in table 3	MCC Arbocel A 300 (filler – a_3) Magnesium stearate(antiadherent– b_1) MCC Arbocel A 300 (disintegrant– c_2) talc(glidant – d_3)

Based on the results of the mathematical method of experimental design, we recommend the following formulation and technology:

Formulation:

Nigella sativa seeds ground	-350mg
Zinc sulphate	-20 (equal to 7.3 mgof zinc)
MCC Arbocel A 300	-22mg
Talc	-4mg
Magnesium stearate	-4 mg
Average net weight of capsule	-00 mg

Technological process: A moisturizing liquid (water) is sprayed into the dry mixture during the mixing process of seeds ground of Nigella sativa and zinc sulphate with "granule-forming" excipient- MCC Arbocel A 300(filler)in order to form agglomerates - granules. The "drying" of granules is accomplished by adding a "drying" excipient –the rest amount of MCC Arbocel A 300 (disintegrant) into the mixer, during the continuous mixing process. Since the final moisture content of the product obtained by this granulation method usually does not exceed the final moisture content of the granules obtained by traditional wet granulation, we did not perform additional thermal drying of the granules. In the final stage, talc (glidant) and magnesium stearate (antiadherent) are added to the granules. The resulted compact granules have good technological properties which are presented in table 7.

Table 7: Results of the study of the technological properties of the granules for the capsules "NIGELIT"

No.	Studied indicators	Unit of measurement	Obtained results
1	Appearance		Dark brown granules with a strong, agreeable aromatic odor and a spicy, pungent taste
2	Particle-size distribution: +2500 -2500+1000 -1000+ 500 - 500+ 250 - 250	μm, %	 1.5 23.0 47.5 20.8 7.2
3	Bulk density untapped	kg/m^3	390
4	Bulk density tapped	kg/m^3	455
5	Flowability	10^{-3} kg/s	5.5
6	Angle of repose	°	38
7	Residual moisture	%, 70 °C	4.2

As evidenced by the data in Table 7, in contrast to the mixture of active components, the granular material prepared according to the selected composition and technology has satisfactory technological properties.

Taking into account the amount of granular material to be encapsulated, it's density, empty capsule volume capacity and the requirements for uniformity of the capsule contents the capsule size 00E was chosen to encapsulate the calculated dosage. [17, 20]. The process of filling the capsules with the granular material was performed using the capsule-filling machine MF 30.

IV. Conclusion

Thus, based on the results of study of technological properties of the the mixture of active componentsand the granular material prepared according to the selected composition and technology and using the mathematical method of the experimental design, the 4 × 4 Latin square, an optimal composition was formulated and the rational encapsulation technology for the capsules "Nigelit" with an average net weight of capsule (weight of core material) 400 mg was developed.

References Références Referencias

1. Maya Bikbova, Julia Progeria, PhD in Biology. Market of dietary supplements to increase potency: sales leaders and key trends. Remedium. 2016. №10. pp. 25-27, available at: https://cyberleninka.ru/article/n/rynok-bad-dlya-povysheniya-potentsii-osnovnye-trendy-i-lidery-prodazh/viewer
2. Karomatov I.Dj., Kobilova D.S.Nigella sativa new life of an ancient drug (mini review) Electronic scientific journal "Biology and Integration Medicine". 2018. №2 (19). pp. 248 – 261, available at: https://cyberleninka.ru/article/n/chernushka-posevnaya-novaya-zhizn-drevnego-lekarstvennogo-sredstva-mini-obzor/viewer
3. Sayapina Irina Yurievna, Tseluiko Sergey Semyonovich, Cherednichenko Oksana Aleksandrovna Biological role of zinc in the prostate gland (molecular aspects) // Far Eastern Medical Journal. 2015. No. 2. pp. 137-143, available at: https://cyberleninka.ru/article/n/biologicheskaya-rol-tsinka-v-predstatelnoy-zheleze-molekulyarnye-aspekty
4. Iskandarova Sh.F., Djabarov N.A. Minerals are an important part of dietary supplements. Sciencetime. – 2018. № 2 (50). pp. 44-47.available at: https://www.researchgate.net/publication/339302401_Mineraly-vaznaa sostavnaa cast biologiceski aktivnyh dobavok
5. Alekseev K.V., Blynskaya E.V., Suldin A.S., Sizyakov S.A., Alekseeva S.K., Ditkovskaya A.G. Excipients in hard capsule technology. Pharmacy 2009; 5: pp. 31-36.
6. Belousov V.A., Walter M.B. Basics of dosing and tableting of medicinal powders. M.: Medicine 1980; 216 p.
7. Walter M.B., Tyutenkov O.L., Filipin N.A. Step-by-step control in the production of tablets. M.: Medicine 1982; 208 p.
8. N.E. Mamatmusaeva, Sh.O. Khakimzhanova, Kh.L. Ziyaev, A.M. Ermatov. Development of the composition and technology of capsules "Rometin". Pharmaceutical Bulletin of Uzbekistan. - 2020.No. 1, pp. 33-36.
9. Tentsova A.I., Groshovyi T.A., Golovkin V.A. et al., Optimization of pharmaceutical technology by methods of experiment planning, Zaporozhye. - 1981. - pp. 127-132.
10. Markova E.V. Guidelines for the use of Latin plans when planning an experiment with qualitative factors.- Chelyabinsk, 1971.- 135 p.
11. Jalilov U. M., Kambarov Kh.Dj., Fayzullaeva N. S., Bekchanov Kh. K., Karieva E.S. Optimization of composition and development of technology for capsules of dry extract of Cichorium Intybus. International Journal of Pharmaceutical Research | Oct - Dec 2019 | Vol 11 | Issue 4. pp. 619-624, available at: http://www.ijpronline.com/ViewArticle Detail.aspx?ID=11117.
12. Bekchanov K. K., Usubbaev A. M., Usubbaev M. U. The Composition and Technology of Mumifer Tablets Optimized Using Methods of Mathematical Experiment Planning //Pharmaceutical Chemistry Journal. – 2005. – Т. 39. – №. 5. pp. 271-273.
13. Pavlov V.M., Chekhani N.R., Pavlova L.A. Technology of obtaining granulates of dry extracts by the method of moisture-activated granulation using kleptose as an auxiliary substance // Modern problems of science and education. - 2014. - No. 5.; available at: http://www.science-education.ru/ru/article/view?id=14642
14. Sharma DM, Kosalge SB, Lade SN; Review on Moisture activated Dry Granulation Process; PharmaTutor; 2017; 5 (12); 58-67, available at: https://www.researchgate.net/publication/321480420_Review_on_Moisture_Activated_Dry_Granulation_Process
15. Demina N.B., Skatkov S.A., Anurova M.N. Moisture-activated granulation - application prospects. Pharmaceutical technologies and packaging. - 2012. - No. 4.; available at: www.medbusiness.ru ›Images› FTU_4-2012_41-43
16. Yurieva I.N., Vdovina G.P. Development of the composition and technology of powders for the preparation of a suspension for oral administration of a calcium preparation and study of stability. Modern problems of science and education. - 2014;

- No.5., available at: http://www.science-education.ru/119-14586
17. Yuryeva I.N., Vdovina G.P., Koryukina I.P.Development of the composition and technology of capsules of a drug containing calcium // Perm Medical Journal. vol. 33, no. 1, 2016, pp. 71-78. available at: https://cyberleninka.ru/article/n/razrabotka-sostava-i-tehnologii-kapsul-lekarstvennogo-preparata-soderzhaschego-kaltsiy.
18. Koroleva S.V. Practical aspects of using the desirability function in a biomedical experiment. Modern problems of science and education. - 2011. -No. 6.; available at: http://www.science-education.ru/ru/article/view?id=5270.
19. https://studfile.net/preview/5712771/page:2/
20. https://capsuline.com/pages/empty-capsule-size-chart