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Optimization of composition and development of technology for capsules of dry extract of Cichorium Intybus l.

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ABSTRACT
To find the optimal combination of active and auxiliary substances, as well as to optimize the technology of capsules of dry extract of chicory, the method of mathematical planning of the experiment was used in order to minimize the consumption of materials and waste of time. At the same time, fillers, glidants, disintegrants and binders were studied as factors affecting optimization criteria, and flowability, bulk density, angle of repose of capsule mass and capsule disintegration were studied as optimization criteria.

Keywords: Cichorium intybus L., dry extract, method, mathematical planning of the experiment, factor, optimization criteria, capsules of dry extract of Cichorium intybus, excipients.

INTRODUCTION
The roots and herbs of *Cichorium intybus L.* have long been used in folk medicine as an aphrodisiac, for the treatment of stomach and duodenal ulcers, belching, heartburn, bloating, slow digestion, nausea and constipation and for improving the metabolism . Therefore, the roots and herbs of *Cichorium intybus L.* are recommended for diabetes and obesity. They also have a choleretic and diuretic effect, effective in hypercholesterolemia and hyperlipidemia [1]. In addition, the roots and herbs of *Cichorium intybus L.* are used as an antimicrobial agent for the treatment of skin diseases - eczema, allergic dermatitis, seborrhea, furunculosis, acne, etc. One species is growing in Uzbekistan - *C. intybus L.*
We conducted studies to optimize the mode of obtaining capsules of dry extract from the roots and the aerial parts of *C. intybus L.*, growing in Uzbekistan. In addition, their numerical characteristics and hypoglycemic activity were studied as well [2].
In order to select a scientifically based composition and technology of capsules of dry extract of

Cichorium intybus L., the method of mathematical planning of the experiment - the Latin square 4x4 was used [3, 4, 5]. Using this method can significantly reduce the experimental error and quantify the effect of various factors on optimization criteria.
The dry extract from the roots and aerial parts of *Cichorium intybus L.* is a polydisperse hygroscopic powder of a dark brown color, with a specific odor and a bitter taste. The residual moisture content is 6.8 ± 0.6%. The powder has unsatisfactory technological characteristics: a small bulk density - 280,0 ± 2,07 kg/m^3, poor flowability - 1.2 ± 0.83 10^{-3} kg/s, high compressibility - 90.0-5.0 N and compaction

coefficient - 3.8-1.2. As can be seen from the results of studies for the packaging of dry extract of *Cichorium intybus L.* in capsules, it is necessary to carry out additional granulation using the appropriate excipients. At the same time, the influence of the following factors, which are presented in Table 1, on the optimization criteria was studied.

Table 1: Factors affecting optimization criteria for capsules of dried extract of Cichorium intybus L.

Capsule name	Factors			
	A – fillers	B – glidants	C – disintegrants	D – binders
Capsules of dry extract of *Cichorium intybus L.*	a_1 – sucrose	b_1 – calcium stearate	c_1 – MCC	d_1 – purified water
	a_2 – dextrin	b_2 – aerosil	c_2 – dried starch	d_2 – 5% starch paste
	a_3 – MCC «Cotton cellulose»	b_3 – talc	c_3 – CMC	d_3 – 96% ethanol
	a_4 – lactose	b_4 – PEO-400	c_4 – Na-KMC	d_4 – 2% MCC

The indicators that served as optimization criteria for capsules of dry extract of *Cichorium intybus L.* are presented in table 2:

Table 2: Optimization criteria for capsules of dry extract of Cichorium intybus L.

Optimization criteria (Y)			
Y_1	Y_2	Y_3	Y_4
Flowability (10^{-3} kg/s)	Bulk density (kg/m^3)	Disintegration (min)	Angle of repose (^{0})

Optimization criteria were determined by the methods described in the literature [6].

The planning matrix of the experiment and the results of studies on optimizing the indicators of capsules of dry extract of *Cichorium intybus L.* are given in Table 3.

The influence of the type of excipients on the optimization criteria for capsules of dry extract of *Cichorium intybus L.* was evaluated according to Fisher's criteria taking into account the number of degrees of freedom. The significance of factors A, B, C, and D for the optimization criteria for capsules of dry extract of *Cichorium intybus L.* was assessed using the analysis of variance of the experimental results (Table 4). As a result of the analysis, it was found that factor B significantly affects the angle of repose, factor C - on disintegration and angle of repose, factor D - on flowability, bulk density and angle of repose. Selection of the type of excipients for the dry extract of *Cichorium intybus L.* was made according to generalized results of the analysis of the desirability function (D), for all the optimization criteria given (Table 3).

The values of the optimization criteria were subject to analysis of variance (Table 3). 16 experiments were conducted. According to the results of the analysis of the function of desirability and indicators of capsules of dry extract of *Cichorium intybus L.*, excipients can be placed in the following row:

Fillers – $a_3 > a_4 > a_1 > a_2$;
Glidants – $b_1 > b_2 > b_3 > b_4$;
Disintegrants – $c_2 > c_1 = c_3 > c_4$;
Binders – $d_3 > d_1 > d_2 > d_4$.

Table 3: The planning matrix of the experiment and the results of studies on optimizing the indicators of capsules of dry extract of Cichorium intybus L.

Experiment number	Factors				Optimization criteria				D
	A	B	C	D	Y1, 10-3 kg/s	Y2, kg/m3	Y3, min	Y4, 0 degree	
1	a1	b1	c1	d1	4,3	436	25	32	0,58

2	a1	b2	c2	d2	4,1	435	27	35	0,54
3	a1	b3	c3	d3	4,8	450	28	34	0,60
4	a1	b4	c4	d4	3,9	435	33	38	0,43
5	a2	b1	c1	d2	3,9	430	27	33	0,54
6	a2	b2	c2	d1	4,1	430	23	33	0,56
7	a2	b3	c3	d3	4,6	442	30	34	0,52
8	a2	b4	c4	d4	3,7	430	35	38	0,39
9	a3	b1	c2	d3	5,3	470	15	30	0,75
10	a3	b2	c1	d2	4,6	425	20	35	0,61
11	a3	b3	c3	d1	4,9	430	23	36	0,63
12	a3	b4	c4	d4	4,5	430	25	38	0,58
13	a4	b1	c1	d4	4,2	438	22	35	0,58
14	a4	b2	c2	d3	5,0	450	20	32	0,67
15	a4	b3	c3	d2	4,3	435	25	38	0,56
16	a4	b4	c4	d1	4,6	440	28	35	0,57

Table 4: Dispersion analysis (analysis of variance) of experimental data on the study of indicators of capsules of dry extract of Cichorium intybus L.*

Optimization criteria	Source variances	Number of degrees of freedom (f)	Sum of squares (SS)	Medium square (MS)	Fexper	F0,05 table
Flowability	Factor A	3	1,260	0,420	3,02	3,4903
	Factor B	3	0,455	0,152	0,74	3,4903
	Factor C	3	0,735	0,245	1,34	3,4903
	Factor D	3	1,660	0,553	5,23	3,4903
Bulk density	Factor A	3	137	46	0,33	3,4903
	Factor B	3	247	82	0,63	3,4903
	Factor C	3	505	168	1,55	3,4903
	Factor D	3	1191,3	397,1	7,68	3,4903
Disintegration	Factor A	3	174,8	58,3	3,41	3,4903
	Factor B	3	172,3	57,4	3,32	3,4903
	Factor C	3	182,3	60,8	3,69	3,4903
	Factor D	3	66,8	22,3	0,85	3,4903
Angle of repose	Factor A	3	0,50	0,17	0,02	3,4903
	Factor B	3	51,50	17,17	5,49	3,4903
	Factor C	3	51,50	17,17	5,49	3,4903
	Factor D	3	48,50	16,17	4,79	3,4903

According to the experimental data of table 3, analysis of variance was performed using the ANOVA module of the MiniTab statistical program, and the statistical indicators of table 4 were calculated.

To summarize (generalize) the values of optimization criteria having different units of measurement, the desirability function of Harrington, which he first applied in problems of controlling the quality of mass production is the most well-known and often used. The Harrington scale establishes a correspondence between linguistic assessments of the desirability of the values of the indicator *x* and the numerical intervals *d* (*x*) (Table 5).

With this scaling, the values of the desirability function *d (x)* vary in the range from 0 to 1, and the value $d_i \approx 0$ corresponds to the absolutely unacceptable value of *i*-quality of indicator, and $d_i \approx 1$ to the ideal value.

Table 5: Numerical intervals of Harrington scale

Linguistic evaluation	Intervals of 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 practice often they are limited to three gradations of the Harrington scale, corresponding to the linguistic categories of "bad", "satisfactory", "good" In this case, the area corresponding to the level of "satisfactory" expands from 0.37 to 0.69, and the areas of "bad" and "good" are characterized by the intervals (0.00-0.37) and (0.69-1.00) respectively [7].

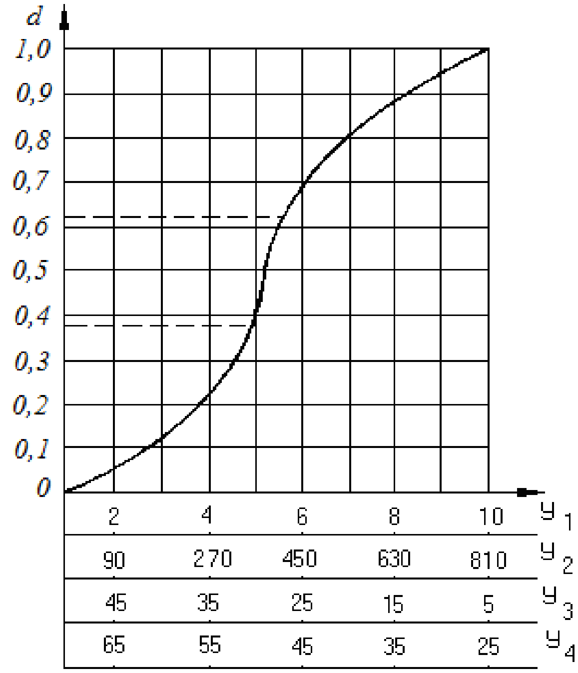

Fig.1: Scale of the desirability function of optimization criteria for capsules of dry extract of Cichorium intybus L.

According to the results of the method of mathematical planning of the experiment and using the function of desirability, the optimal composition of capsules of dry extract of *Cichorium intybus L.* was established. To optimize the indicators of capsules of dry extract of *Cichorium intybus L.*, a more successful way is the generalized desirability function, which is defined as the geometric mean of individual properties:

$$D=\sqrt[4]{d_1 d_2 d_3 d_4} \qquad (1)$$

To construct the scale of the desirability function of the optimization criteria for capsules of dried extract of Cichorium intybus L., the method of quantitative estimates was used with an interval of desirability values from 0 to 1 (Fig. 1.). A value of D = 1 corresponds to the best value of indicators (properties), and D = 0 corresponds to an absolutely bad value of indicators (properties). The intermediate values of the desirability function reflect certain levels of 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). The conversion of natural values (Y) to particular desirability (d) with a one-sided limiting limit Y = <Ymax or Y> = Y min is carried out according to the equation:

$$d = \exp\left[-\exp(Y')\right], \quad (2)$$

where, $y'=b_0+b_{1y}$. The coefficients b_0 and b_1 are calculated by setting for the two property values the corresponding desirability values d, preferably in the range 0.2 <d <0.8. In the coordinates d, Y' according to the equation of the desirability function, a desirability curve is constructed (Fig. 1.). In this case, Y_{max} and Y_{min} of the dimensional scales must correspond to 0 (zero) on the dimensionless scale Y'. On the scale of desirability particular desirability for the measured values of the optimization parameters Y_i are found.

Using the graphical desirability function (Fig. 1.), we converted the response values (Y_1, Y_2, Y_3, Y_4) into a dimensionless desirability function (d_1, d_2, d_3, d_4). The values of the generalized desirability function of capsules of dry extract of *Cichorium intybus L.*, calculated by the formula (1), are presented in table. 3 (D values).

Taking into account the desirability function of optimization criteria for capsules of *Cichorium intybus L.* dry extract, the most optimal composition of excipients that provide the necessary indicators for capsules of *Cichorium intybus L.* dry extract was selected (Table 3, composition No. 9). Excipients included in this composition are presented in table. 6.

Table 6: The most optimal composition of excipients that provide the necessary indicators for capsules of dry extract of Cichorium intybus L.

Capsule name	Nmber of optimal composition	Excipients included in the optimal composition
Capsules of Cichorium intybus L. dry extract	composition number 9 according to the table 3	MCC «Cotton cellulose» (filler - a3) Calcium stearate (glidant - b1) Dried starch (disintegrant - c2) Ethanol 96% (binder - d3)

Table 7: The results of studying the technological properties of a mixture of substances and capsule mass of capsules of Cichorium intybus L. dry extract

№	The studied indicators	Unit of measurement	Results	
			Dry extract	Capsule mass
1.	Appearance		Polydisperse hygroscopic powder of dark brown color, with a specific odor and bitter taste	Granules of brown color with white spots, with a specific odor and bitter taste
2.	Particle size: +2500 -2500 +1000 -1000 +500 -500… +250 -250 +150 -150 +125 -125	μm,%	 2,3 2,2 22,9 13,4 12,6 35,4 11,2	 - 0,03 24,14 25,40 38,35 10,80 1,28
3.	Pycnometric density	kg/m^3	1169,0±1,75	12450±2,63
4.	Bulk density	kg/m^3	280,0±2,07	470,0±2,07
5.	Relative density	%	23,95±2,34	32,50±2,14
6.	Porosity	%	76,05±2,05	67,50±2,05
7.	Flowability	10^{-3} kg/s	1,2±0,83	5,25±1,34
8.	Angle of repose	degree	68,5±1,2	28,5±1,22
9.	Compressibility	H	90,0±5,0	50,0±5,0
10.	Compaction factor (Compaction coefficient)		3,8±1,2	2,16±1,32
11.	Residual humidity	%, 70 ^{0}C	6,8±0,6	3,0±2,15

According to the results of the mathematical method of planning the experiment, we recommended the following composition and technology:

Composition:
Dry extract of Cichorium intybus L. 0.300 g
MCC «Cotton cellulose» 0.135 g
Dried starch (with a moisture content of 3%) 0.060 g
Calcium Stearate 0.005 g
Ethyl alcohol 96% up to optimum humidity
The average weight of 1 capsule 0.500 g

Technological process. Cichorium intybus L. dry extract was crushed and sieved through a sieve with a hole diameter of 150 μm, then thoroughly mixed with

previously crushed and sifted through a sieve a uxiliary substances - MCC "Cotton Cellulose" and dried starch (with a residual moisture content of 3%), then wet granulation was performed with 96% ethyl alcohol. The mass obtained was sieved through a sieve with a hole diameter of 2500 μm and dried at a temperature of 40-50^{0}C in an HS 62 A oven. Then the mass was passed through a granulator with a hole diameter of 1000 μm and the granules were dusted with calcium stearate previously sieved through a sieve with a hole diameter of 100 μm. Next, the technological characteristics of the granules ready to be filled into capsules were studied. Then the mass was filled in a capsule-filling machine MF 30 into capsules No. 1 [2, 6].

The results of studying the technological properties of the capsule mass are presented in table. 7.

The data of table 7 indicate an improvement in the technological properties of tablet mass in comparison with the substance.

CONCLUSION

Thus, the physic-chemical and technological properties of the substance - dry extract of *Cichorium intybus L.* have been studied. Based on the method of mathematical planning of the experiment, a scientifically based composition was selected and a rational technology for capsules of dry extract of *Cichorium intybus L.* with an average weight of 0.500 g was developed. The technological properties of mass obtained meets the requirements for filling into capsules, and the disintegration of capsules corresponds to the requirements of normative-technical documentation [2, 6].

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