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DEVELOPMENT OF THE COMPOSITION AND TECHNOLOGY OF CAPSULES OF THE MEDICINAL PREPARATION CONTAINING THE DRY EXTRACT “SHARQ TABIBI”

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ABSTRACT

A mathematical method of experimental design, the 4 × 4 Latin square, was used to identify an optimal composition for the capsules. The method allows minimizing the amount of materials used and time spent on research. The experimental results were processed using mathematical methods of statistical and variance analysis, involving the Fisher criterion and the generalized desirability function. Technological properties of the materials and quality indicators of the capsules were determined using conventional methods.

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Key words: mathematical method of experimental design, factor, optimization criteria, capsules of the dry extract “Sharq Tabibi”, excipients, moisture activated dry granulation (MADG).

抽象的

实验设计的数学方法，即 4 × 4 拉丁方，用于**确定胶囊的最佳**组成。 该方法可以最大限度地减少使用的材料量和研究时间。 使用统计和方差分析的数学方法处理实验结果，涉及费舍尔准则和广义合意性函数。 **胶囊材料的工**艺性能和质量指标采用常规方法测定。

关键词：实验设计的数学方法，因素，优化标准，干提取物“Sharq Tabibi”**胶囊**，赋形剂，水分活化干法制粒（MADG）。

INTRODUCTION

At present there is a discernible upward trend in the number of patients suffering from the disorders of the cardiovascular and nervous systems. This is primarily due to the impact on the body of unfavorable social and living conditions, ecological disturbances and other factors, which lead to stress, nervous breakdowns, cardiovascular diseases, and decreased performance. These, in turn, result in an increased demand for medications used in the treatment of neurological and cardiovascular conditions, most of which are currently being supplied to the pharmaceutical market of Uzbekistan from abroad.

Due to favorable geographic and climate conditions, Uzbekistan is one of the richest regions with a high concentration of medicinal plants. Despite this fact, the production of medications based on the local plant raw materials is not well established in Uzbekistan at the moment [1].

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, quickly swell up, dissolve and get absorbed in the gastrointestinal tract, have high bioavailability [2].

With the above taken into consideration, we carried out research on developing formulation and technology of capsules of the dry extract “Sharq Tabibi”, producing the adaptogenic and cardiovascular effect.

MATERIALS AND METHODS

For the development of the new preparation, firstly, a suitable dose of the dry extract “Sharq Tabibi” was calculated, based on the study of its efficacy, action mechanisms and effect on the cardiovascular system. Then the physicochemical and technological properties of the dry extract “Sharq Tabibi” were studied. It was established that the dry extract has a high

level of hygroscopicity, which is characteristic of all dry extracts. Consequently, it turns into a lumpy mass and loses its flowability rather quickly. 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 with highly therapeutic effect, while keeping the probability of side effects to a minimum, it is necessary to incorporate excipients, and to use granulation, which prevents the segregation (stratification) of the mixture [3].

In order to choose the most rational composition and the encapsulation technology of the dry extract "Sharq Tabibi", we took advantage of a mathematical method of experimental design, the method of the 4 × 4 Latin square and performed variance analysis. 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 criteria [4, 5, 6]. In this case, fillers, hygroscopicity-reducing substances, lubricants, and binders were selected as factors affecting optimization criteria (see table 1); while flowability, bulk density, angle of repose of the granules, and disintegration time of capsules were selected as the optimization criteria (see table 2). Technological properties of the materials and the capsule disintegration were studied using conventional methods [7, 8, 9]. Taking the high hygroscopicity of the dry extract "Sharq Tabibi" into account, moisture activated dry granulation (MADG) was used [10, 11]. This method allows for simultaneous mixing and grinding of ingredients, as well as forming of a product with homogeneous dispersion [10]; minimization 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 [12]. 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 [10]. Purified water was used as the moisturizing liquid for granulation.

TABLE 1
FACTORS AFFECTING OPTIMIZATION CRITERIA FOR THE CAPSULES OF THE DRY EXTRACT "SHARQ TABIBI"

Name of the capsules	Factors			
	A - fillers	B - HRS*	C - lubricants	D - binders for MADG
Capsules of the	a_1 - MCC PH-102	b_1 - aerosil	c_1 - magnesium	d_1 - rice starch

dry extract "Sharq Tabibi"			stearate	
	a_2 - lactose monohydrate	b_2 - MCC	c_2 - calcium stearate	d_2 - corn starch
	a_3 - calcium carbonate	b_3 - magnesium oxide	c_3 - stearic acid	d_3 - gelatin
	a_4 - sucrose	b_4 - lactose	c_4 - PEG-400	d_4 - CMC

*HRS - hygroscopicity-reducing substances

TABLE 2
OPTIMIZATION CRITERIA FOR THE CAPSULES OF THE DRY EXTRACT "SHARQ TABIBI"

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 (°)

Various formulations of the dry extract "Sharq Tabibi" and excipients were designed; the technological properties of the mixtures and the disintegration of the capsules prepared according to these formulations were studied (see table 3).

TABLE 3
EXPERIMENT DESIGN MATRIX AND RESEARCH RESULTS ON THE EFFECT OF THE EXCIPIENTS ON THE OPTIMIZATION CRITERIA FOR THE CAPSULES OF THE DRY EXTRACT "SHARQ TABIBI"

Experiment number	Factors				Optimization criteria				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	5.2	600	19	42	0.66
2	a_1	b_2	c_2	d_2	4.5	630	20	47	0.58
3	a_1	b_3	c_3	d_3	4.8	610	22	45	0.60
4	a_1	b_4	c_4	d_1	4.7	585	20	45	0.59

5	a_2	b_1	c_1	d_2	5.9	840	15	36	0.83
6	a_2	b_2	c_2	d_1	5.2	810	16	41	0.73
7	a_2	b_3	c_3	d_3	5.6	825	18	38	0.80
8	a_2	b_4	c_4	d_1	5.2	800	17	42	0.71
9	a_3	b_1	c_2	d_3	5.6	760	19	39	0.78
10	a_3	b_2	c_1	d_2	5.0	780	17	42	0.69
11	a_3	b_3	c_3	d_1	5.4	745	21	40	0.75
12	a_3	b_4	c_4	d_4	5.2	710	20	42	0.69
13	a_4	b_1	c_1	d_4	5.4	660	18	40	0.74
14	a_4	b_2	c_2	d_3	4.8	685	19	45	0.63
15	a_4	b_3	c_3	d_2	5.0	705	21	42	0.65
16	a_4	b_4	c_4	d_1	5.0	670	20	44	0.65

RESULTS AND DISCUSSION

The effect evaluation for each factor was performed by variance analysis (table 4) [6, 13], which upon studying the effect of excipients on the optimization criteria showed that:

- the type of fillers has a significant effect on the flowability, bulk density, angle of repose of the granular material as well as the disintegration of capsules;
- the type of hygroscopicity-reducing substances, lubricants and binders does not have a significant effect on the flowability, bulk density, angle of repose of the granular material as well as the disintegration of capsules;

TABLE 4
VARIANCE ANALYSIS OF THE EXPERIMENTAL DATA FROM THE STUDY OF THE INDICATORS OF THE CAPSULES OF THE DRY EXTRACT "SHARQ TABIBI"*

Optimization criteria	Source of variation	Degrees of freedom (f)	Sum of the squares (SS)	Mean square (MS)	F_{exp}	$F_{0.05\ table}$
Flowability	Factor A	3	1,0419	0,3473	4,18	3,49
	Factor B	3	0,9369	0,3123	3,40	3,49

	Factor C	3	0,337	0,112	0,79	3,49
	Factor D	3	0,032	0,011	0,06	3,49
	Residual	3				
	Total sum	15				
Bulk density	Factor A	3	99780	33260	69,34	3,49
	Factor B	3	2880	960	0,11	3,49
	Factor C	3	2630	877	0,10	3,49
	Factor D	3	5380	1793	0,21	3,49
	Residual	3				
	Total sum	15				
Disintegration	Factor A	3	32,25	10,75	5,49	3,49
	Factor B	3	19,25	6,42	2,11	3,49
	Factor C	3	22,25	7,42	2,66	3,49
	Factor D	3	3,25	1,08	0,25	3,49
	Residual	3				
	Total sum	15				
Angle of repose	Factor A	3	68,75	22,92	4,82	3,49
	Factor B	3	50,75	16,92	2,71	3,49
	Factor C	3	28,25	9,42	1,16	3,49
	Factor D	3	0,8	0,3	0,02	3,49
	Residual	3				
	Total sum	15				

*Variance analysis 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 overall (generalized) evaluation of the optimization criteria - the disintegration of capsules and the technological properties of the model mixtures - was carried out using a desirability function [6, 14]. In order to generalize the values of the optimization criteria

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) [6, 15].

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 criteria for the capsules of the dry extract "Sharq Tabibi", the method of quantitative analysis was used with the range of desirability values between 0 and 1 (Fig. 1). The value d = 1 corresponds to the best value of the indicators (properties), 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 =< Y_{max} or Y >= Y_{min} was performed using the following equation:

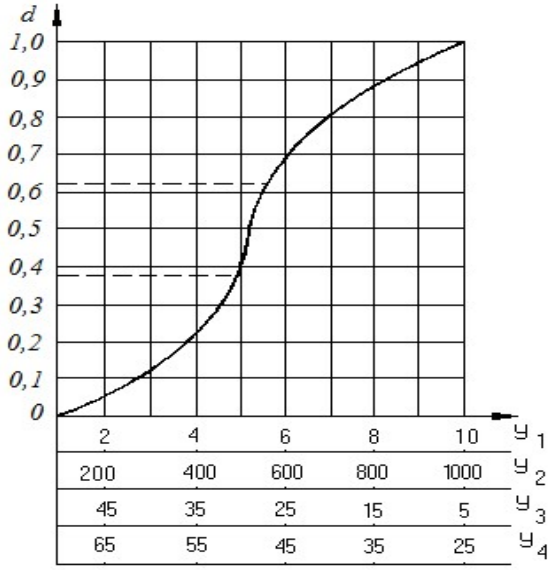
$$d = \exp\left[-\exp(Y')\right], \quad (1)$$

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 CRITERIA FOR THE CAPSULES OF THE

DRY EXTRACT "SHARQ TABIBI"



Based on the generalized evaluation of the capsule quality and the technological properties of the model mixtures, carried out using a desirability function, the excipients can be arranged in the order of preference as follows:

- fillers – $a_2 > a_3 > a_4 > a_1$;
- HRS[1] – $b_1 > b_3 > b_4 > b_2$;
- lubricants – $c_1 > c_3 > c_2 > c_4$;
- binders for MADG[2] – $d_3 > d_1 > d_2 > d_4$.

An optimal composition for capsules of the dry extract "Sharq Tabibi" was formulated based on the results of the mathematical method of experimental design and using a desirability function. The overall (generalized) desirability function, which is calculated using the formula (2) as the geometric mean of individual properties, represents a more successful approach towards optimization of the indicators for the capsules of the dry extract "Sharq Tabibi":

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

The values of the overall (generalized) desirability function for the capsules of the dry extract "Sharq Tabibi" are presented in table 3 (values of D).

The most optimal composition of the excipients that ensure the required indicators for the capsules of the dry extract "Sharq Tabibi" (table 3, composition No. 5) was selected based on the values of the overall (generalized) desirability function (D) of the optimization criteria. 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 OF THE DRY EXTRACT "SHARQ TABIBI"

Name of the capsules	No. of the optimal composition	Excipients included in the optimal composition
Capsules of the dry extract "Sharq Tabibi"	composition No. 5 in table 3	lactose monohydrate (filler – a_2) aerosil (hygroscopicity-reducing substance – b_1) magnesium stearate (lubricant – c_1) corn starch (binder – d_2)

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

Formulation:

Dry extract "Sharq Tabibi"
0.250
Lactose monohydrate
0.090
Corn starch
0.040
Aerosil
0.010
Magnesium stearate
0.010
Average net weight of capsule
0.400 g

Technological process: A moisturizing liquid (water) is sprayed into the dry mixture during the mixing process of the dry extract with "granule-forming" excipients (filler - lactose, dry binder - corn starch) in order to form agglomerates - granules. The "drying" of granules is accomplished by adding a "drying" excipient - aerosil, which has good flowability, ability to absorb and redistribute moisture within the product, 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, a lubricant, magnesium stearate, is 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 OF THE DRY EXTRACT "SHARQ TABIBI"

No.	Studied indicators	Unit of measurement	Obtained results
1.	Appearance		Dark brown granules with a burning sweet taste and specific odor
2.	Particle-size distribution: +2500 -2500+1000 -1000+ 500 - 500+ 250 - 250	μm, %	 4.6 21.4 42.6 19.8 11.6
3.	Bulk density	kg/m^3	840
4.	Flowability	10^{-3} kg/s	5.9

5.	Angle of repose	°	36
6.	Residual moisture	%, 70 °C	5.2

Table 7 data indicates an improvement in the technological properties of the granules in comparison with the mixture of powdery substances.

Taking into account the amount of granular material to be encapsulated, its density, empty capsule volume capacity and the requirements for uniformity of the capsule contents the capsule size 1 was chosen to encapsulate the calculated dosage. [13, 16]. The process of filling the capsules with the granular material was performed using the capsule-filling machine MF 30.

CONCLUSION

Thus, based on the results of study of physicochemical and technological properties of the dry extract - substance “Sharq Tabibi” 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 of the dry extract "Sharq Tabibi" with an average net weight of capsule 0.400 g was developed.

CONFLICT OF INTERESTS AND CONTRIBUTION OF AUTHORS

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article and report on the contribution of each author.

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