Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2022-10-1-69-81

APPLICATION OF MULTIVARIATE ANOVA AND GENERALIZED DESIRABILITY TO OPTIMIZE THE COMPOSITION AND TECHNOLOGY OF TABLETS CONTAINING N-BENZYL-N-METHYL-1-PHENYLPYRROLO [1,2-A] PYRAZINE-3-CARBOXAMIDE

S.V. Tishkov, E.V. Blynskaya, K.V. Alekseev, V.K. Alekseev, D.I. Gavrilov

Research Institute of Pharmacology named after V.V. Zakusov
8, Baltiyskaya St., Moscow, Russia, 125315

E-mail: sergey-tishkov@yandex.ru

Received 25 Sep 2021 After peer review 29 Dec 2022 Accepted 11 Feb 2022

The creation of drugs with an anxiolytic activity, which do not have the main side effects characteristic of drugs of this group, is an important and socially significant task. For its implementation, within the framework of the development of an original drug with an anxiolytic activity, the composition and manufacturing of GML-1 tablets (N-benzyl-N-methyl-1-phenylpyrrolo [1,2-a] pyrazine-3-carboxamide) are being developed.

The aim of this article is to study, using a four-factor analysis of variance, the influence of composition factors on the manufacturing properties of GML-1 tablets and the selection of the type, the amount, stage of the disintegrant addition and the type of lubricating excipients used in the technology of wet granulation of GML-1 tablets.

Materials and methods. The materials used are: the substance – GML-1 (N-benzyl-N-methyl-1-phenylpyrrolo [1,2-a] pyrazine-3-carboxamide). Excipients: microcrystalline cellulose 101 (MCC 101); polyvinylpyrrolidone (PVP); crospovidone, croscarmellose sodium (CCS), sodium starch glycolate (SSG); magnesium stearate (MS), sodium stearyl fumarate (SSF). To obtain tablet mixtures, wet granulation and tableting with the study of their main pharmaceutical and technological properties was used.

Results. Model compositions were developed and their pharmaceutical and technological properties were studied. These results have been analyzed, the degree of these factors' influence and their interactions have been determined. In most of the cases considered, the interactions of the factors did not cause a significant change in the optimization criteria. With an increase in the amount of a disintegrant, the disintegration time decreased unevenly, so an increase in the amount of these excipients from 4 to 6 mg had a stronger effect than from 2 to 4 mg. Factor B affected the release degree non-linearly. Factor A influenced all the optimization criteria considered, especially a PS release. The best release and disintegration were observed with crospovidone, which was of a particular importance when processing the test results using a generalized desirability method.

Conclusion. In view of the conflicting variance analysis results, for particular factors, the resulting values were additionally analyzed using the generalized desirability function. The use of this method made it possible to reduce the conflicting variance analysis results to the most optimal composition.

Keywords: GML-1; tablet; analysis of variance; four-factor; influence of factors; interaction of factors; desirability function

Abbreviations: MP – medicinal product; DP – drug product; DF – dosage form; PS – pharmaceutical substance; API – active pharmaceutical ingredient; PVP – polyvinylpyrrolidone; MCC – microcrystalline cellulose; SCC – sodium croscarmellose; SSG – sodium starch glycolate; MS – magnesium stearate; SSF – sodium stearyl fumarate; GPM – General Pharmacopoeia Monograph.

For citation: S.V. Tishkov, E.V. Blynskaya, K.V. Alekseev, V.K. Alekseev, D.I. Gavrilov. Application of multivariate anova and generalized desirability to optimize the composition and technology of tablets containing N-benzyl-N-methyl-1-phenylpyrrolo [1,2-a] pyrazine-3-carboxamide. *Pharmacy & Pharmacology.* 2022;10(1):69-81. **DOI:** 10.19163/2307-9266-2022-10-1-69-81

Для цитирования: С.В. Тишков, Е.В. Блынская, К.В. Алексеев, В.К. Алексеев, Д.И. Гаврилов. Применение многофакторного дисперсионного анализа и обобщённой желательности для оптимизации состава и технологии таблеток, содержащих N-бензил-N-метил-1-фенилпирроло [1,2-а] пиразин-3-карбоксамид. *Фармация и фармакология.* 2022;10(1):69-81. **DOI:** 10.19163/2307-9266-2022-10-1-69-81

RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

ПРИМЕНЕНИЕ МНОГОФАКТОРНОГО ДИСПЕРСИОННОГО АНАЛИЗА И ОБОБЩЁННОЙ ЖЕЛАТЕЛЬНОСТИ ДЛЯ ОПТИМИЗАЦИИ СОСТАВА И ТЕХНОЛОГИИ ТАБЛЕТОК, СОДЕРЖАЩИХ N-БЕНЗИЛ-N-МЕТИЛ-1-ФЕНИЛПИРРОЛО [1,2-А] ПИРАЗИН-3-КАРБОКСАМИД

С.В. Тишков, Е.В. Блынская, К.В. Алексеев, В.К. Алексеев, Д.И. Гаврилов

Федеральное государственное бюджетное научное учреждение
«Научно-исследовательский институт фармакологии имени В.В. Закусова»
125315, Россия, Москва, ул. Балтийская, 8

E-mail: sergey-tishkov@yandex.ru

Получена 25.09.2021 После рецензирования 29.12.2021 Принята к печати 11.02.2022

Создание лекарственных средств (ЛС) с анксиолитической активностью, которые не обладают основными побочными эффектами, характерными для лекарственных препаратов (ЛП) данной группы, является важной и социально значимой задачей. Для её выполнения в рамках разработки оригинального ЛС с анксиолитической активностью проводится разработка состава и технологии таблеток ГМЛ-1 (N-бензил-N-метил-1-фенилпирроло [1,2-а] пиразин-3-карбоксамид).

Цель. Изучение с помощью четырёхфакторного дисперсионного анализа влияния факторов состава на технологические свойства таблеток ГМЛ-1 и подборе типа, количества, стадии добавления дезинтегранта и смазывающего вспомогательного вещества (ВВ).

Материалы и методы. Используемые материалы: субстанция: ГМЛ-1 (N-бензил-N-метил-1-фенилпирроло[1,2-а] пиразин-3-карбоксамид). Вспомогательные вещества: микрокристаллическая целлюлоза 101 (МКЦ), поливинилпирролидон (КВП), кросповидон, натрия кроскармелоза (НКК), натрия крахмала гликолят (НКГ), магния стеарат (МС), натрия стеарил фумарат (НСФ). Применялось получение таблеточных смесей с помощью влажной грануляции и таблетирование с изучением их основных фармацевтико-технологических свойств.

Результаты. Разработаны модельные составы и изучены их фармацевтико-технологические свойства. Данные результаты проанализированы, определена степень влияния факторов и их взаимодействия. Взаимодействия факторов в большинстве рассматриваемых случаев не вызывали существенное изменение критериев оптимизации. Время распадаемости при увеличении количества дезинтегранта сокращалось неравномерно. Так, увеличение количества данных ВВ с 4 до 6 мг оказывало более сильное влияние, чем с 2 до 4 мг. На степень высвобождения фактор В воздействовал нелинейно. Фактор А влиял на все рассматриваемые критерии оптимизации, особенно на высвобождение ФС. Наилучшее высвобождение и распадаемость наблюдались при использовании кросповидона, что имело особенное значение при обработке результатов испытаний методом обобщённой желательности.

Заключение. Ввиду противоречивых результатов дисперсионного анализа, для частных факторов, получившиеся значения дополнительно проанализированы с помощью обобщённой функции желательности. Использование данного метода позволило привести противоречивые результаты дисперсионного анализа к одному наиболее оптимальному составу.

Ключевые слова: ГМЛ-1; таблетка; дисперсионный анализ; четырёхфакторный; влияние факторов; взаимодействие факторов; функция желательности

Список сокращений: ЛС – лекарственное средство; ЛП – лекарственный препарат; ЛФ – лекарственная форма; ФС – фармацевтическая субстанция; ВВ – вспомогательные вещества; ПВП – поливинилпирролидон; МКЦ – микрокристаллическая целлюлоза; НКК – натрия кроскармелоза; НКГ – натрия крахмала гликолят; МС – магния стеарат, НСФ – натрия стеарил фумарат; ОФС – общая фармакопейная статья.

INTRODUCTION

Currently, the search for new drugs for the treatment of neurotic disorders and other neuropsychiatric diseases is becoming an increasingly urgent task. For example, the global prevalence of anxiety disorders, according to various sources, ranges from 6.0 to 13.6% [1]. In addition, the use of many tranquilizers, in particular the benzodiazepine series, is limited due to the manifestation of a large number of side effects and legal restrictions. Accordingly, one of the most promising areas of psychopharmacology is the creation of drugs based on the structure of mitochondrial translocator protein ligands acting on alternative pharmacological targets without serious side effects and toxicity.

In the Research Institute of Pharmacology named after V.V. Zakusov, an original active pharmaceutical ingredient (API), which is a derivative of pyrrolopyrazine – N-benzyl-N-methyl-1-phenylpyrrolo [1,2-a] pyra-

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-1-69-81

zine-3-carboxamide (GML-1) [2, 3], having an anxiolytic activity, was developed and synthesized (Fig. 1) [2]. API has an anxiolytic activity; pronounced antidepressant, nootropic and neuroprotective effects have also been revealed [4–6], while there are no sedative, muscle relaxant and amnestic effects characteristic of this group of drugs [7]. In addition, as a result of toxicological studies, GML-1 has shown a low acute toxicity when administered intraperitoneally to mice (LD_{50} > 1000 mg/kg) [7]. The data obtained demonstrate a high potential of this API for the creation of the drug.

For GML-1, it is planned to develop a tableted dosage form (DF), based on the carried out preclinical studies and on the characteristics of the proposed pharmacological application [9, 10].

THE AIM of this work is to study, using an analysis of variance, the effect of the type and amount of the disintegrant on the technological properties of GML-1 tablets, as well as the lubricating excipient type and the stage of incorporating the disintegrant into the tablet mass on the technological properties of GML-1 tablets.

In the presented study, using the analysis of variance and desirability function, it is necessary to select the composition and technology of tableted LF GML-1 obtained by wet granulation.

MATERIALS AND METHODS

The used materials

The substance – GML-1 (N-benzyl-N-methyl-1-phenylpyrrolo [1,2-a] pyrazine-3-carboxamide)) (Fig. 1).

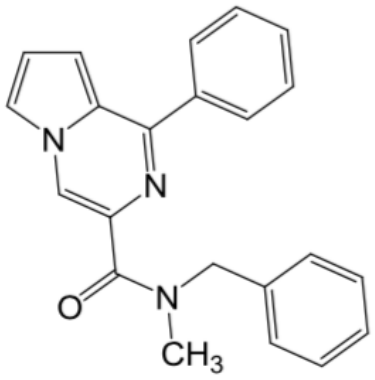

Figure 1 – Structural formula of GML-1

Excipients – microcrystalline cellulose 101 (MCC 101) (Microcel MCC 101, Blanver, Brazil); polyvinylpyrrolidone (PVP, Kollidon 25, BASF, Germany); crospovidone (Polyplasdone XL, BASF), croscarmellose sodium (CCS) (Solutab, Blanver, Brazil), sodium starch glycolate (SSG) (Solutab, Blanver, Brazil); magnesium stearate (MS) (Niticka Pharm. Specialties PVT. LTD.), sodium stearyl fumarate (SSF) (Pruv, JRS Pharma, Gerany).

Equipment and techniques used

To preparation the tablets, a manual hydraulic press PRG-50 was used. A resistance of tablets to crushing (General Pharmacopoeia Monograph (GPM). 1.4.1.0015.15, SP XIV, volume 2)[1] was tested with a resistance analyzer TBF 1000 CopleyScientific® (Great Britain).

The methods for disintegration determining (GPM.1.4.2.0011.15., SP XIV, volume 2)[2] is PTZ-S disintegration tester (Pharma Test, Germany). The test method of "dissolution" for GML-1 tablets, 1 mg, was developed by the analytical group of the Research Institute of Pharmacology named after V.V. Zakusov [11, 12] according to GPM.1.4.2.0014.15 "Dissolution for solid dosage forms"[3]. Herewith, the used device was "Paddle stirrer" type (Erweka, Germany); the dissolution medium was 900 ml of 3% sodium lauryl sulfate solution in water, the dissolution medium temperature was 37 ± 1°C, the stirrer rotation speed was 50 rpm. The samples were taken every 10 minutes. After taking each sample, the medium was replenished. The optical density of the prepared solutions was measured on a spectrophotometer at the wavelength of 256 ± 2 nm in a cuvette with a layer thickness of 10 mm, using a 3% aqueous solution of sodium lauryl sulfate as a reference solution [13].

Statistical analysis

The analysis of variance (ANOVA) is used to determine the degree of influence of factors and their interactions on the technological and physicochemical properties of tablets [14–16]. In the presented work, a cross-balanced full analysis of variance (parametric model) was used to determine the effect of: A – the type of disintegrating excipients; B – the amount of disintegrating excipients in the tablet; C – the type of lubricating excipients; D – the process of introducing a disintegrant into the tablet mass and a combination of these factors (parameters), a resistance of tablets to crushing, disintegration of tablets (c), API release (%).

The S, R and adjusted R-values reflect the correspondence in the mathematical model of the dependence of the random value on the values for the ANOVA model shown in Table 7. The S-value is measured in the units of the response variable and is the standard deviation for the data used. R (R^2) is the coefficient of the determination describing the degree of dependence of the variable explained by the factors of the process under consideration. To compare models with different numbers of variables, the value of the corrected coefficient of determination (adjusted R^2) which cannot be artificially overestimated and takes into account the number of terms in the model, is introduced. [17].

[1] State Pharmacopoeia of the Russian Federation XIV ed. T. I–IV. Available from: http://femb.ru/pharmacopea.php.
[2] Ibid.
[3] Ibid.

ISSN 2307-9266 e-ISSN 2413-2241

The factorial design of the experiment consisted of combinations of factors to describe the degree of influence of the composition, was carried out in a randomized order and to reduce the experimental error, the experiment at the center point was repeated five times on different days. The results of the average responses for the experiments are shown in Table 3. The values indicated the reproducibility of the process. A statistical evaluation of the results was performed by the analysis of variance (ANOVA) using a commercially available statistical software package (Minitab 18, PA, USA). Fisher's test was used to compare the variances of variational series, and the degree of confluence of factors was determined by its relative value of Fisher's tabular value. In addition, for the mathematical analysis of the results, the generalized desirability function was used, which makes it possible to determine the most optimal model composition. During the optimization of the composition, it is necessary to combine the partial responses of technological, physicochemical properties in order to obtain a tablet with the desired characteristics. The use of the desirability function allows this process to be carried out in one dimension and makes it possible to determine the most suitable composition for all desirability criteria.

The combination of responses in a generalized desirability function requires the computation of individual desirability functions [18, 19], which can have one-way and two-way constraints. Within the framework of this study, only one-way constraints will be considered, since the optimization parameters used have only upper and, accordingly, lower permissible values. To transform the selected partial optimization parameters into some subjective estimate or partial desirability, it is necessary to use the following equations with a one-way constraint:

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

The conversion of the values of dimensional (natural) indicators (pharmaceutical and technological characteristics) (x) into dimensionless (y) indicators, under the accepted condition of a linear relationship between them, is carried out as follows: $y = a_0 + a_1x_1$ and this expression can be calculated using the following system of equations:

$$\begin{cases} a_0 + k_1a_1 = 1,51 \\ a_0 + k_2a_2 = 0,01 \end{cases}, \quad (2)$$

where: k_1 is the best parameter value, k_2 is the worst parameter value.

The value of Harrington's generalized desirability is calculated by converting particular desirability indicators (D) into a single comprehensive assessment using the formula:

$$D = \sqrt[n]{\prod_{u=1}^{n} d_u}, \quad (3)$$

where: n is the number of used indicators of comparison parameters in this system

When recalculating according to this formula, the weight coefficients of particular indicators are not taken into account. These indicators are combined into a generalized Harrington desirability function (D) by determining the geometric mean of particular desirability (d_u). [20–23].

RESULTS

At the previous stages of the research, the properties of the API GML-1 were studied, the technology of the GML-1 tablets, wet granulation, was selected. This choice is due to the need to ensure the dosage uniformity for 1 mg of API, which has unsatisfactory physicochemical and technological properties. In addition, a filler, a binder and the optimal amounts of these excipients have been selected. The preliminary stages of optimization of the technological process have been carried out [13]. However, due to the unsatisfactory technological properties of GML-1 tablets, especially in terms of such indicators as disintegration and the API release from the tablets, it was decided to additionally introduce disintegrants.

To implement this research plan, at the next stage, the type and amount of disintegrant, as well as the stage of the introduction of disintegrating excipients and the type of lubricating excipient were selected.

To ensure the necessary technological properties, a four-factor fractional experiment was carried out and the following factors were identified as the factors affecting the quality of the tablets:

A – the type of disintegrant: A_1 – crospovidone, A_2 – sodium croscarmellose; A_3 – sodium starch glycolate;

B – the amount of disintegrant in the tablet: B_1 – 2 mg, B_2 – 4 mg, B_3 – 6 mg;

C – the type of lubricating excipient: C_1 – 8%, C_2 – 10%;

D – the process of adding disintegrant: D_1 – into the tablet mixture before moistening, D_2 – half of the amount of disintegrant into the tablet mixture and the rest at the stage of dusting.

The factors are investigated at three or two levels of change. The range of variation of the selected variable factors is shown in Table 1.

The following criteria were chosen as optimization ones: Y_1 – Resistance of tablets to crushing (N); Y_2 – Disintegration of tablets (s); Y_3 – API release (%).

The compositions of the model mixtures and the results of evaluating the indicators of the tablets are presented in Tables 2 and 3.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-1-69-81

Table 1 – Characteristics of variable factors affecting the technological characteristics of GML–1 tablets

Factor levels	Factors			
	A	B	C	D
	Disintegrant type	The amount of disintegrant in a tablet, mg	Type of lubricating excipient	Disintegrant addition process
1	Crospovidone	2	Magnesium stearate	Into tablet mix before moisturizing
2	Sodium crosscarmellose	4	Sodium stearate fumarate	50% before moisturizing and 50% during dusting
3	Sodium starch glycolate	6	–	–

Table 2 – Model compositions of GML–1 tablets, mg

No.	GML–1	MCC 101	PVP	Disintegrants			Lubricating excipients	
				Crospovidone	NCC	SSG	MS	SSF
1	1.0	90.0	6.0	2.0	–	–	1.0	–
2	1.0	90.0	6.0	2.0	–	–	–	1.0
3*	1.0	90.0	6.0	2.0	–	–	1.0	–
4*	1.0	90.0	6.0	2.0	–	–	–	1.0
5	1.0	88.0	6.0	4.0	–	–	1.0	–
6	1.0	88.0	6.0	4.0	–	–	–	1.0
7*	1.0	88.0	6.0	4.0	–	–	1.0	–
8*	1.0	88.0	6.0	4.0	–	–	–	1.0
9	1.0	88.0	6.0	6.0	–	–	1.0	–
10	1.0	88.0	6.0	6.0	–	–	–	1.0
11*	1.0	88.0	6.0	6.0	–	–	1.0	–
12*	1.0	88.0	6.0	6.0	–	–	–	1.0
13	1.0	90.0	6.0	–	2.0	–	1.0	–
14	1.0	90.0	6.0	–	2.0	–	–	1.0
15*	1.0	90.0	6.0	–	2.0	–	1.0	–
16*	1.0	90.0	6.0	–	2.0	–	–	1.0
17	1.0	89.0	6.0	–	4.0	–	1.0	–
18	1.0	88.0	6.0	–	4.0	–	–	1.0
19*	1.0	88.0	6.0	–	4.0	–	1.0	–
20*	1.0	88.0	6.0	–	4.0	–	–	1.0
21	1.0	88.0	6.0	–	6.0	–	1.0	–
22	1.0	88.0	6.0	–	6.0	–	–	1.0
23*	1.0	88.0	6.0	–	6.0	–	1.0	–
24*	1.0	88.0	6.0	–	6.0	–	–	1.0
25	1.0	90.0	6.0	–	–	2.0	1.0	–
26	1.0	90.0	6.0	–	–	2.0	–	1.0
27*	1.0	90.0	6.0	–	–	2.0	1.0	–
28*	1.0	90.0	6.0	–	–	2.0	–	1.0
29	1.0	88.0	6.0	–	–	4.0	1.0	–
30	1.0	88.0	6.0	–	–	4.0	–	1.0
31*	1.0	88.0	6.0	–	–	4.0	1.0	–
32*	1.0	88.0	6.0	–	–	4.0	–	1.0
33	1.0	88.0	6.0	–	–	6.0	1.0	–
34	1.0	88.0	6.0	–	–	6.0	–	1.0
35*	1.0	88.0	6.0	–	–	6.0	1.0	–
36*	1.0	88.0	6.0	–	–	6.0	–	1.0

Note: * – adding disintegrant to the tablet mixture and when dusting the granulate.

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

Table 3 – Research results of technological characteristics of tablet mixtures and tablets (average values)

Formulation number	Y_1	Y_2	Y_3
	Resistance to crushing (N)	Disintegration time (s)	API release (%)
1	108.1±0.03	268±0.3	78.8±1.0
2	97.4±0.02	244±0.2	79.3±0.5
3	95.8±0.02	231±0.2	77.6±0.6
4	91.4±0.03	227±0.1	78.9±0.4
5	109.3±0.05	212±0.4	89.1±0.5
6	89.9±0.04	190±0.2	87.8±0.3
7	88.7±0.04	196±0.1	81.7±0.3
8	80.1±0.02	189±0.1	83.6±0.8
9	95.4±0.03	170±0.1	83.1±1.0
10	96.1 ±0.06	165±0.2	85.3±0.5
11	75.9±0.02	157±0.5	80.2±0.4
12	78.7±0.03	159±0.2	85.1±0.2
13	117.3±0.03	249±0.5	84.6±0.3
14	114.6±0.01	243±0.4	83.1±0.2
15	106,2±0.02	239±0.6	80.4±0.1
16	107.9±0.02	238±0.5	79.6±0.4
17	105.9±0.03	351±0.6	71.5±0.2
18	104.4±0.03	349±0.3	71.3±0.3
19	93.1±0.04	230±0.5	72.7±0.4
20	90.0±0.03	224±0.4	72.8±0.5
21	99.8±0.03	210±0.2	77.2±0.2
22	102.5±0.04	213±0.2	79.4±0.3
23	88.9±0.02	201±0.1	77.6±0.6
24	85.5±0.03	200±0.2	78.1±0.5
25	127.7±0.04	378±0.5	81.4±0.3
26	115.6±0.03	367±0.2	80.9±0.2
27	100.5±0.05	360±0.6	76.4±0.3
28	99.7±0.02	355±0.5	73.2±0.6
29	101.9±0.03	351±0.4	71.5±0.3
30	101.1±0.04	349±0.4	71.3±0.3
31	99.4±0.06	233±0.2	70.7±0.5
32	98.9±0.08	232±0.6	70.9±0.6
33	115.2±0.05	212±0.6	69.7±0.4
34	108.1±0.02	224±0.5	69.5±0.4
35	89.4±0.03	215±1.0	68.3±0.3
36	85.5±0.04	214±0.9	67.8±0.4

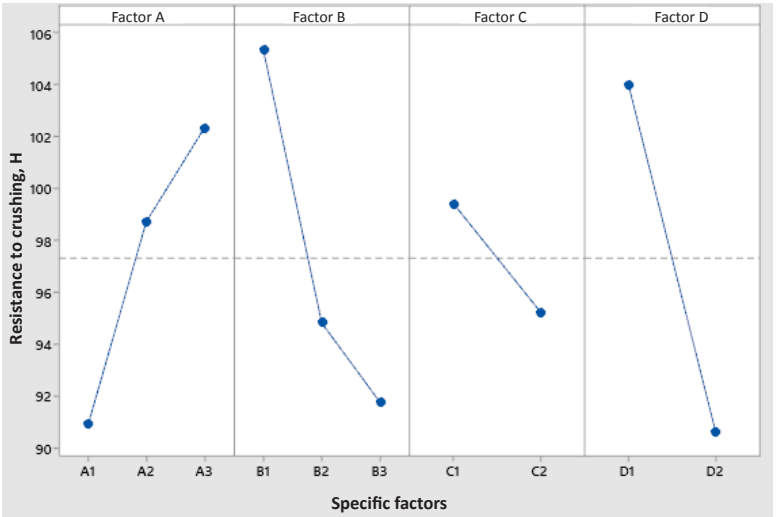

Figure 2 – Graph of the influence of the main factors effects on the average values of tablets GML-1 resistance to crushing

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-1-69-81

Table 4 – Analysis of variance for the resistance to crushing of GML–1 tablets

Source of dispersion	Degrees of freedom, number	Sum of Squares (SS)	Average square (AS)	F_{exp}	$F_{tab.}$
Factor A	2	2465.7	1232.86	81.02	3.14
Factor B	2	3686.2	1843.11	121.12	3.14
Factor C	1	474.0	474.05	31.15	3.99
Factor D	1	4847.4	4847.39	318.55	3.99
Factor A* Factor B	4	128.3	32.07	2.11	2.52
Factor A * Factor C	2	53.2	26.60	1.75	3.14
Factor A * Factor D	2	109.6	54.81	3.60	3.14
Factor B * Factor C	2	106.3	53.13	3.49	3.14
Factor B * Factor D	2	377.7	188.85	12.41	3.14
Factor C * Factor D	1	10.9	10.89	0.72	3.99
Factor A * Factor B * Factor C	4	236.1	59.03	3.88	2.52
Factor A * Factor C * Factor D	2	79.7	39.86	2.62	3.14
Factor A * Factor B * Factor D	4	768.3	192.09	12.62	3.14
Factor B * Factor C * Factor D	2	85.0	42.49	2.79	
Within cells	76	1156.5	15.22	–	–
Total	107	14585.0	–	–	–

Table 5 – Analysis of variance for the disintegration of GML-1 tablets

Source of dispersion	Degrees of freedom, number	Sum of Squares (SS)	Average Square (AS)	F_{exp}.	$F_{tab.}$
Factor A	2	140526	70262.9	183.07	3.14
Factor B	2	159138	79568.8	207.32	3.14
Factor C	1	1836	1836.2	4.78	3.99
Factor D	1	36834	36834.4	95.97	3.99
Factor A* Factor B	4	61568	15392.0	40.10	2.52
Factor A * Factor C	2	604	302.2	0.79	3.14
Factor A * Factor D	2	6426	3212.9	8.37	3.14
Factor B * Factor C	2	175	87.5	0.23	3.14
Factor B * Factor D	2	22852	11425.9	29.77	3.14
Factor C * Factor D	1	11	10.6	0.03	3.99
Factor A * Factor B * Factor C	4	726	181.6	0.47	2.52
Factor A * Factor C * Factor D	2	970	485.0	1.26	3.14
Factor A * Factor B * Factor D	–	–	–	–	–
Factor B * Factor C * Factor D	2	814	407.2	1.06	3.14
Within cells	80	30704	383.8	–	–
Total	107	463184	–	–	–

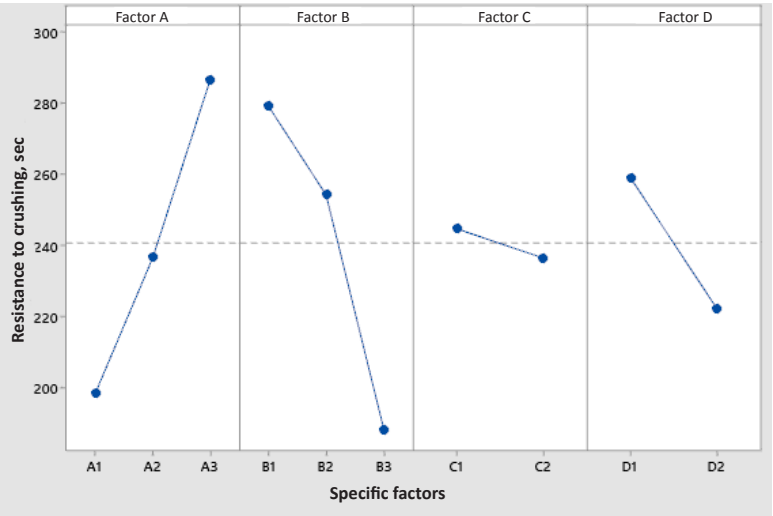

Figure 3 – Graph of the factors influence on the average values of GML-1 tablets disintegration

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

Table 6 – Results analysis of variance of the dissolution test of GML-1 tablets

Source of dispersion	Degrees of freedom, number	Sum of Squares (SS)	Average Square (AS)	$F_{exp.}$	$F_{tab.}$
Factor A	2	1896.08	948.041	131.44	3.14
Factor B	2	263.74	131.872	18.28	3.14
Factor C	1	0.91	0.914	0.13	3.99
Factor D	1	76.71	76.713	10.64	3.99
Factor A* Factor B	4	1145.10	286.275	39.69	2.52
Factor A * Factor C	2	14.10	7.051	0.98	3.14
Factor A * Factor D	2	25.68	12.839	1.78	3.14
Factor B * Factor C	2	21.77	10.886	1.51	3.14
Factor B * Factor D	2	18.95	9.475	1.31	3.14
Factor C * Factor D	1	1.02	1.015	0.14	3.99
Factor A * Factor B * Factor C	4	20.35	5.087	0.71	2.52
Factor A * Factor C * Factor D	–	–	–	–	–
Factor A * Factor B * Factor D	2	20.59	10.294	1.43	3.14
Factor B * Factor C * Factor D	2	1.44	0.720	0.10	3.14
Within cells	80	577.04	7.213	–	–
Total	107	4083.48	–	–	–

Table 7 – Standard deviations and coefficients of variable indicators determination in the model of GML-1tablets

Manufacturing characteristics	S	R^2	R^2 (rate)
Resistance to crushing (N)	3.90089	92.07%	88.84%
Disintegration time (s)	13.3661	97.07%	95.87%
API release (%)	2.49791	88.39%	83.65%

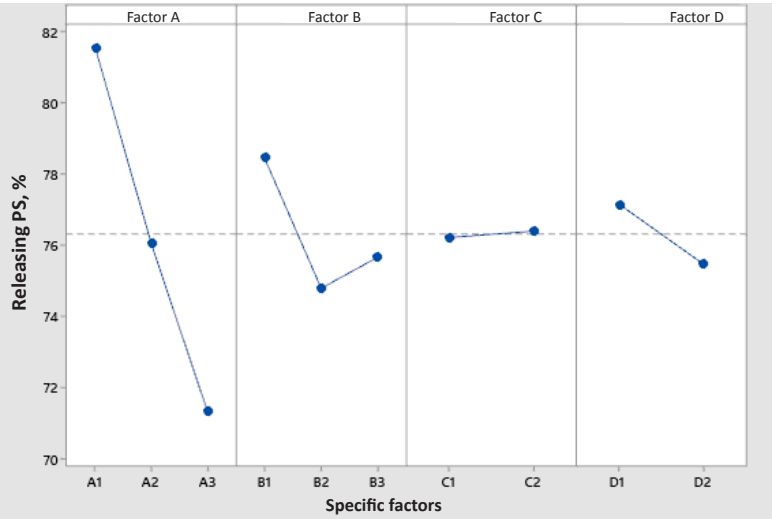

Figure 4 – Graph of the main influence effects of particular factors on the average kinetics values of the GML-1 tablets dissolution

The test results were subjected to the analysis-of-variance method to obtain Fisher's F-test for each term in the model. The experimental values of Fisher's F-test were compared with the tabular value of the F-test, which is described for the significance level α = 0.05, the degrees of freedom for each factor. The shown comparison reveals the degree of influence of each factor on the optimization criteria for model tablets GML-1 (α = 0.05; $F_{exp} > F_{tab.}$), as well as the interactions of factors (Tables 4–8) [24]. The obtained data were additionally compared with the average values of particular factors to explain the obtained regularities.

When processing the analysis of variance results on the resistance to crushing values of GML-1 tablets (Table 4), a significant exceedance of the experimental F-criterion values above the theoretical $F_{80,2,0,95}$ in factors A and B, $F_{80,1,0,95}$, in factors C and D, as well as a relative exceedance in the interaction of factors B and D was observed.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-1-69-81

Table 8 – Values of particular and generalized desirability parameters

Sequential number	Y_1	Y_2	Y_3	d_1	d_2	d_3	D
1	108.1±0.03	268±0.3	78.8±1.0	0.677	0.625	0.634	0.645
2	97.4±0.02	244±0.2	79.3±0.5	0.588	0.671	0.644	0.633
3	95.8±0.02	231±0.2	77.6±0.6	0.573	0.694	0.609	0.623
4	91.4±0.03	227±0.1	78.9±0.4	0.532	0.701	0.636	0.619
5	**109.3±0.05**	**212±0.4**	**89.1±0.5**	**0.686**	**0.726**	**0.802**	**0.736**
6	89.9±0.04	190±0.2	87.8±0.3	0.517	0.759	0.785	0.675
7	88.7±0.04	196±0.1	81.7±0.3	0.505	0.750	0.689	0.639
8	80.1±0.02	189±0.1	83.6±0.8	0.416	0.760	0.722	0.611
9	95.4±0.03	170±0.1	83.1±1.0	0.570	0.786	0.714	0.684
10	96.1 ±0.06	165±0.2	85.3±0.5	0.576	0.792	0.749	0.699
11	75.9±0.02	157±0.5	80.2±0.4	0.372	0.802	0.661	0.582
12	78.7±0.03	159±0.2	85.1±0.2	0.401	0.799	0.746	0.621
13	117.3±0.03	249±0.5	84.6±0.3	0.742	0.662	0.738	0.713
14	114.6±0.01	243±0.4	83.1±0.2	0.724	0.673	0.714	0.703
15	106.2±0.02	239±0.6	80.4±0.1	0.663	0.680	0.665	0.669
16	107.9±0.02	238±0.5	79.6±0.4	0.676	0.682	0.650	0.669
17	105.9±0.03	351±0.6	71.5±0.2	0.660	0.439	0.466	0.513
18	104.4±0.03	349±0.3	71.3±0.3	0.648	0.443	0.461	0.510
19	93.1±0.04	230±0.5	72.7±0.4	0.548	0.696	0.496	0.574
20	90.0±0.03	224±0.4	72.8±0.5	0.518	0.706	0.498	0.567
21	99.8±0.03	210±0.2	77.2±0.2	0.609	0.729	0.600	0.643
22	102.5±0.04	213±0.2	79.4±0.3	0.632	0.724	0.646	0.666
23	88.9±0.02	201±0.1	77.6±0.6	0.507	0.742	0.609	0.612
24	85.5±0.03	200±0.2	78.1±0.5	0.472	0.744	0.619	0.602
25	127.7±0.04	378±0.5	81.4±0.3	0.802	0.372	0.684	0.588
26	115.6±0.03	367±0.2	80.9±0.2	0.731	0.399	0.675	0.582
27	100.5±0.05	360±0.6	76.4±0.3	0.615	0.416	0.583	0.530
28	99.7±0.02	355±0.5	73.2±0.6	0.608	0.429	0.508	0.510
29	101.9±0.03	351±0.4	71.5±0.3	0.627	0.439	0.466	0.504
30	101.1±0.04	349±0.4	71.3±0.3	0.620	0.443	0.461	0.503
31	99.4±0.06	233±0.2	70.7±0.5	0.606	0.691	0.446	0.571
32	98.9±0.08	232±0.6	70.9±0.6	0.601	0.692	0.451	0.573
33	115.2±0.05	212±0.6	69.7±0.4	0.728	0.726	0.421	0.606
34	108.1±0.02	224±0.5	69.5±0.4	0.677	0.706	0.415	0.584
35	89.4±0.03	215±1.0	68.3±0.3	0.512	0.721	0.385	0.522
36	85.5±0.04	214±0.9	67.8±0.4	0.472	0.722	0.372	0.502

Table 9 – GML-1 tablets composition, 1 mg, according to the results of research and the mathematical analysis methods

Composition	Quantity, g
GML-1	0.001
MCC 101	0.088
Kollidon 25	0.006
Crospovidone	0.004
Magnesium stearate	0.001
Tablet weight	0.100

Accordingly, all factors of the presented analysis of variance and the interaction of factors B and D influenced the resistance to crushing of the GML-1 tablets.

The stage of adding disintegrant to the tablet mass had the greatest influence on the resistance to crushing index. Fig. 2 can explain this phenomenon by a decrease in the binding capacity for the tablet mass during the compression when the disintegrant is between the granules. The second largest impact was the amount of disintegrant, as well as its type, which is explained by a change in the processes of brittle and plastic deformation with changes in A and B factors. The least effect was exerted by the type of a lubricating excipient, due to its low amount in the tablet mass. Among the interactions of the factors, the interaction between the amount and the stage of adding a disintegrant stands out, since these factors are indirectly interrelated, but their influence is relatively insignificant. The distribution of the average

values of the resistance to crushing of the GML-1 tablets by particular factors is shown in Fig. 2.

The graphs in Fig. 2 make it possible for us to conclude that the lowest resistance of tablets to crushing is when the disintegrant crospovidone is used, and the highest resistance is for the compositions with sodium starch glycolate. There was also an uneven decrease in resistance with an increase in the amount of a disintegrant, as well as a lower resistance takes place for formulations containing sodium stearate fumarate and a disintegrant in the granule dust.

Factors A and B, as well as factor D, had a significant effect on the disintegration rate, as it was expected. The most significant effect was produced by the amount of a disintegrant, and the next was the type of disintegrant and the process of introducing this disintegrant into the tablet mass.

These effects can be explained by the functional purpose of this group of substances. The disintegration time was also affected by interactions between the type, amount and process of adding disintegrant at the stage of dusting, since the total amount of disintegrant affects the amount of disintegrant inside the granules and in the dusting, respectively, exacerbating the influence of this factor. Factor C had the least effect on the disintegration time due to relatively low amounts of lubricating excipients in GML-1 tablets.

Perhaps, partially due to the decrease in the tablet resistance, formulations with crospovidone (Fig. 3) showed shorter disintegration times, and formulations with sodium starch glycolate – longer. As expected, with an increase in the amount of a disintegrant, the disintegration time decreased (Fig. 3), the difference between the compositions with 4 and 6 mg of a disintegrant is much greater than the difference between 2 and 4 mg. The separation of the disintegrant and its addition at different stages of the technological process, on average, can reduce the disintegration time by 40 s. Despite a small effect of the type of lubricating excipients, the inclusion of stearate fumarate in the composition of sodium makes it possible to reduce the disintegration time due to the hydrophilic groups in the composition of the excipients.

The study of the factors determining the degree of the GML-1 release in the dissolution test showed (Table 6) that a type of disintegrant affects the optimization parameter much stronger than other factors due to the different nature of the polymers, which, in addition to the disintegrating effect, may have a solubilizing effect. The effect on the GML-1 release manifested by the interaction of the type and amount of desitegrants, is twice as weak. The next factors influencing the GML-1 release, are exerted by factor B (the amount of disintegrant) and factor D (the process of introducing a disintegrant into the composition of the tablet).

The influence of particular factors on the resistance of GML-1 tablets to crushing is reflected in the graphs of average release values (Fig. 4) from which it can be concluded that the API release from GML-1 tablets is the best when crospovidone is used. The worst results were observed with the use of sodium starch glycolate, with the quantitative content of disintegrant 4 mg and the addition of half of the disintegrant at the stage of dusting.

Table 7 shows the values of the determination coefficients adjusted coefficients of determination, which illustrate the relationship between the factors considered in this model and the parameters responses of the analysis of variance optimization [23].

Based on the coefficients of determination for the mathematical model shown in Table 9, a conclusion can be made about the applicability of the presented model and a high degree of connectivity of the considered factors with the optimization criteria. This conclusion is based on the high values of the determination (R^2) coefficient from 88.39 to 97.07% and the adjusted coefficient of determination (rate R^2) from 83.65 to 95.87% for all considered manufacturing characteristics. The lowest R^2 values among other indicators were observed in the analysis of the API release, since the demonstrated indicator was influenced, to a greater extent, by random factors that were not included in this ANOVA model, e.g., the conditions of the dissolution test, the influence of other excipients, etc.

Due to the multidirectionality of the influence of particular factors of variance analysis and the varying degree of these factors' influence, the generalized desirability method was used to select one of the most rational model composition. To determine the value of the generalized desirability in accordance with paragraph 2.2.5. "Materials and Methods" were transformed into dimensionless quantities considered in Table 2, response values (Table 3): resistance of tablets to crushing (N), disintegration (s), the API release (%), The obtained response values (Y) according to these parameters were converted into partial desirability (d), the values of which were distributed on the desirability curve (Fig. 5) from 0 to 1, where 1 is the best value of the parameter, and 0 manifests absolutely unsatisfactory results. Then the particular desirability was transformed into a generalized one (D) by finding the geometric mean. The values of the optimization parameters, as well as the calculated partial and generalized desirability, are shown in Table 8.

Analyzing the data obtained and the of the particular and generalized desirability functions, the authors conclude that there are no absolutely unsatisfactory model compositions with D values less than 0.2 among the considered ones.

Model composition No. 5 has the value of the generalized desirability function (0.736) closest to 1 and, accordingly, is suitable for the totality of the studied parameters. In addition, the presented composition has the highest values of the API GML-1 release, which is a key optimization parameter under the conditions of a

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-1-69-81

sparingly soluble substance. Based on the obtained results of the generalized desirability and analysis of variance, the following composition of model GML-1 tablets, 1 mg, was selected (Table 9).

DISCUSSION

As a result of the analysis of variance, a conclusion was made about the absence of one factor that most intensively affects all manufacturing characteristics. However, due to the low content of lubricating excipients in the tablets, their appearance had the least effect on the studied manufacturing characteristics, or in the case of the API release, it did not have a statistically significant result. The resistance of tablets to crushing largely determines the process of adding a disintegrant to the GML-1 tablet mass. The duration of disintegration is largely determined by the amount of a disintegrant, and the degree of the API release by the type of disintegrant. Among the particular factors of the dispersion analysis, crospovidone should be distinguished, which most intensively reduces the resistance of tablets to crushing, disintegration time and increases the degree of the API release. At the same time, the amount of disintegrant had a non-linear effect on the degree of release, for example, 4 mg slowed down the API release, and with 2 mg, the release was the most intensive. Besides, the addition of half of the disintegrant during the dusting step decreased the resistance of tablets to crushing, disintegration time, and the API release rate. In most cases, the interaction of factors did not have a statistically significant effect; however, there was a mutual influence of B and D factors on the resistance of tablets to crushing and on disintegration. The interaction of factors A and B had a statistically significant effect on the process of the API release. The use of the analysis of variance in this development did not allow us to identify the most optimal composition, however, a statistically significant relationship was established between the results obtained and the variable factors. In addition, the available data on the predominant influence of factors and the peculiarities of their interaction with pharmaceutical and manufacturing characteristics allows us to draw long-term conclusions for further developments. The selection of the most optimal factor is most conveniently carried out by other methods, for example, using the function of the generalized desirability based on the expert assessments of researchers. In this method, each model composition, regardless of the optimization factors, is considered separately and the combination of its pharmaceutical and technological characteristics determines its position on the desirability curve.

CONCLUSION

The methods of mathematical planning used in this work have shown their effectiveness in optimizing the composition and manufacturing process of adding a disintegrant to the composition of model tablets. The analysis of variance made it possible to identify the factors affecting the resistance of tablets to crushing, disintegration and the API release from GML-1 tablets. It is shown that the main number of interactions of factors did not cause a significant change in the considered optimization criteria. In addition, the consideration of the influence of each factor led to conflicting results and did not allow us to identify the most optimal composition.

The use of the generalized desirability method made it possible to reduce the conflicting results of the analysis of variance to one, the most optimal composition. As a result of using the methods of mathematical analysis, composition No. 5 was selected: it has the most optimal composition and technology for preparing GML-1 tablets and meets all manufacturing requirements.

FUNDING

This study did not receive any financial support from outside organizations.

CONFLICT OF INTEREST

The autors declare no conflict of interest/

AUTHORS CONTRIBUTION

Sergey V. Tishkov – obtaining the research material. writing the text of the manuscript; Evgeniya V. Blynskaya – development of the research design. generalization of the research material; Konstantin V. Alekseev – development of the research design. analysis of the data obtained; Viktor K. Alekseev – the review of publications on the topic. the material analysis; Dmitry I. Gavrilov – review of publications on the topic, analysis of the material, conducting an experiment.

REFERENCES

1. Korabelnikova EA. Sovremennyj podhod k diagnostike i terapii trevozhnyh rasstrojstv [Modern approach to the diagnosis and therapy of anxiety disorders]. Therapy. 2018; 7(8): 63–8. DOI: 10.18565/therapy.2018.7-8.63-68. Russian
2. Seredenin SB, Mokrov GV, Gudasheva TA, Deeva OA, Yarkov SA, Yarkova MA, Zherdev VP, Alekseev KV, Durnev AD, Neznamov GG. 1-Aril-pirollo[1,2-a] pirazin-3-karboksamidy s nejrotropnoj aktivnost'yu [1-Aryl-pyrollo [1,2-a] pyrazine-3-carboxamides with neurotropic activity]. Patent No.2572076 (2014). Priority date: 03/26/2014. Russian
3. Seredenin SB, Yarkova MA, Povarnina PYu, Mokrov GV, Gu-

dasheva TA. Ligandy translokatornogo belka TSPO, obladayushchie antidepressivnoj i nootropnoj aktivnost'yu [TSPO translocator protein ligands with antidepressant and nootropic activity]. Patent No. RU 2699568 C2 (2019). Priority date: 12/21/2015. Russian

4. Yarkov SA, Mokrov GV, Gudasheva TA, Yarkova MA, Seredenin SB. Pharmacological study of new compounds – regulators of 18 kDa translocator protein. Experimental and Clinical Pharmacology. 2016; 79(1): 7–11. DOI: 10.30906/0869-2092-2016-79-1-7-11. Russian
5. Zhang MR, Kumata K, Maeda J, Yanamoto K, Hatori A, Okada M, Higuchi M, Obayashi S, Suhara T, Suzuki K. 11C-AC-5216: a novel PET ligand for peripheral benzodiazepine receptors in the primate brain. J Nucl Med. 2007 Nov;48(11):1853–61. DOI: 10.2967/jnumed.107.043505.
6. Yarkova MA, Mokrov GV, Gudasheva TA, Seredenin SB. Anksioliticheskoe dejstvie original'nyh proizvodnyh pirrolo [1, 2-a] pirazina, ligandov TSPO, zavisit ot biosinteza nejrosteroidov [Anxiolytic action of the original derivatives of pyrrolo [1, 2-a] pyrazine, TSPO ligands, depends on the biosynthesis of neurosteroids]. Chemical and Pharmaceutical Journal. 2016; 50(8): 3–6. DOI: 10.30906/0023-1134-2016-50-8-3-6. Russian
7. Yarkova MA, Povarnina PYu, Mokrov GV, Gudasheva TA, Seredenin SB. Antidepressivnyj i nootropnyj effekty original'nyh ligandov translokatornogo belka TSPO [Antidepressant and nootropic effects of the original ligands of the TSPO translocator protein]. Experimental and Clinical Pharmacology. 2017; 80 (4): 3–7. DOI: 10.30906/0869-2092-2017-80-4-3-7. Russian
8. Novitsky AA, Bochkov PO, Shevchenko RV, Gribakina OG, Litvin AA, Kolyvanov GB, Kolyvanov GB, Zherdev VP, Mokrov GV, Gudasheva TA, Yarkova MA, Seredenin SB. Farmakokinetika potencial'nogo anksiolitika GML-1 u krys [Pharmacokinetics of the potential anxiolytic GML-1 in rats]. Experimental and Clinical Pharmacology. 2018; 81 (6): 24–28. DOI: 10.30906/0869-2092-2018-81-6-24-28. Russian
9. Yudina DV, Blynskaya EV, Alekseev KV. Razrabotka sostava tabletok GML-1, poluchennyh metodom vlazhnogo granulirovaniya: vybor napolnitelya i svyazuyushchego [Development of the composition of GML-1 tablets obtained by wet granulation: the choice of filler and binder]. Pharmacy. 2018.; 67(3): 35–40. DOI: 10.29296/25419218-2018-03-07. Russian
10. Yarkova MA, Blynskaya EV, Yudina DV, Mokrov GV, Gudasheva TA, Alekseev KV. Razrabotka i ocenka anksioliticheskogo dejstviya tabletirovannoj lekarstvennoj formy GML-1 [Development and evaluation of the anxiolytic action of the tablet dosage form GML-1]. Chemical and pharmaceutical journal. 2019; 53 (4): 39–43. DOI: 10.30906/0023-1134-2019-53-4-39-43. Russian
11. Gaevaya LM, Grushevskaya LN, Sergeeva MS, Dudenkova ME, Avdyunina NI, Pyatin BM. Razrabotka metodiki opredeleniya pokazatelya "Rastvorenie" dlya tabletok novogo soedineniya s anksioliticheskoj aktivnost'yu GML-1 [Development of a method for determining the "Dissolution" index for tablets of a new compound with anxiolytic activity GML-1]. Experimental and Clinical Pharmacology. 2018; 81 (5s): 50–50a. DOI: 10.30906/0869-2092-2018-81-5s-50-50a. Russian
12. Gaevaya LM, Grushevskaya LN, Sergeeva MS, Illarionov AA, Avdyunina NI, Pyatin BM, Bayburtskiy FS, Mokrov GV. Fiziko-himicheskie svojstva i razrabotka metodik analiza substancii novogo original'nogo anksioliticheskogo preparata GML-1 [Physicochemical properties and development of methods for analyzing the substance of the new original anxiolytic drug GML-1]. Chemical and pharmaceutical journal. 2018; 52(9): 43–8. DOI: 10.30906/0023-1134-2018-52-9-43-48. Russian
13. Yudina DV, Blynskaya EV, Alekseev KV, Minaev SV, Marakhova AI. Farmacevticheskaya razrabotka-instrument kontrolya kachestva original'nogo lekarstvennogo sredstva s anksioliticheskim dejstviem [Pharmaceutical development-instrument for quality control of the original drug with anxiolytic action]. Pharmacy. 2018; 67(8): 27–36. DOI: 10.29296/25419218-2018-08-05. Russian
14. Blynskaya EV, Tishkov SV, Alekseev KV, Minaev SV, Alekseev VK. Primenenie dispersionnogo analiza s cel'yu podbora vspomogatel'nyh veshchestv dlya polucheniya liofilizirovannyh tabletok GK-2 [The use of analysis of variance for the selection of excipients for obtaining lyophilized tablets GK-2]. Vestnik VSU. Series Chemistry. Biology. Pharmacy. 2019; (1):117–26. Russian
15. Khoshvaght H, Delnavaz M, Leili M. Optimization of acetaminophen removal from high load synthetic pharmaceutical wastewater by experimental and ANOVA analysis. Journal of Water Process Engineering. 2021; 42:102–7. DOI: 10.1016 / J.JWPE.2021.102107
16. Rashwan SS, Abdelkader B, Abdalmonem A, Abou-Arab TW, Nemitallah MA, Habib MA, Ibrahim AH. Experimental and Statistical ANOVA Analysis on Combustion Stability of $CH_4/O_2/CO_2$ in a Partially Premixed Gas Turbine Combustor." ASME. J. Energy Resour. Technol. 2022; 144(6): 062301. DOI:10.1115/1.4051755.
17. Blynskaya E, Tishkov S, Alekseev K, Povarnina P, Marakhova A, Sachivkina N. Development and optimization of the lyophilized tablets containing a dipeptide mimetic of the Nerve Growth Factor using the desirability function and analysis of variance (ANOVA). International Journal of Pharmaceutical Research. 2020;12: 925–40. DOI: 10.31838/ijpr/2020.SP1.14.
18. Wu J, Jiang Z, Wan L, Song H, Abbass K. Robust Optimization for Precision Product using Taguchi-RSM and Desirability Function. Arabian Journal for Science and Engineering. 2021; 46(3): 2803–14. DOI: 10.1007/s13369-020-05326-4.
19. D'Addona DM., Raykar SJ, Singh D, Kramar D. Multi Objective Optimization of Fused Deposition Modeling Process Parameters with Desirability Function. Procedia CIRP. 2021; (99): 707–10. DOI: 10.1016/j.procir.2021.03.117.
20. Blynskaya EV, Tishkov SV, Alekseyev KV, Minaev SV Creation of loophilisate of GK-2 for preparation of solution for injections with use of polyols. Drug Development & Registration. 2018;(2):26–31. Russian
21. Dadhich M, Prajapati OS, Sharma V. Investigation of boiling heat transfer of titania nanofluid flowing through horizontal tube and optimization of results utilizing the desirability function approach. Powder Technology. 2021; 378: 104–23. DOI: 10.1016/j.powtec.2020.09.077.
22. Castillo DE, Montgomery DC, McCarville DR. Modified Desirability Functions for Multiple Response Optimization. Journal of Quality Technology. 1996;28(3):337–45. DOI: 10.1080/00224065.1996.11979684.
23. Costa NR, Lourenço J, Pereira ZL. Desirability function ap-

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2022-10-1-69-81

proach: a review and performance evaluation in adverse conditions. Chemometrics and Intelligent Laboratory Systems. 2011; 107(2): 234–44. DOI: 10.1016/j.chemolab.2011.04.004.

24. Ganeshpurkar A, Pandey V, Asati S, Maheshwari R, Tekade M, Tekade RK. Experimental Design and Analysis of Variance. Dosage Form Design Parameters. Academic Press; 2018: 281–301. DOI: 10.1016/B978-0-12-814421-3.00008-7.

AUTHORS

Sergey V. Tishkov – Candidate of Sciences (Pharmacy), Senior Researcher of the Laboratory of Finished Dosage Forms, Research Institute of Pharmacology n.a. V.V. Zakusov. ORCID ID: 0000-0002-8321-6952. E-mail: sergey-tishkov@yandex.ru

Evgeniya V. Blynskaya – Doctor of Sciences (Pharmacy), Head of the Laboratory of Finished Dosage Forms, Research Institute of Pharmacology n.a. V.V. Zakusov. ORCID ID: 0000-0002-9494-1332. E-mail: mrsaureussnape@yandex.ru

Konstantin V. Alekseev – Doctor of Sciences (Pharmacy), Professor, Chief Researcher of the Laboratory of Finished Dosage Forms, Research Institute of Pharmacology n.a. V.V. Zakusov. ORCID ID: 0000-0003-3506-9051. E-mail: convieck@yandex.ru

Viktor K. Alekseev – Junior Researcher of the Laboratory of Finished Dosage Forms, Research Institute of Pharmacology n.a. V.V. Zakusov. ORCID ID: 0000-0003-3542-0024. E-mail: conwieck@yandex.ru

Dmitry I. Gavrilov – Junior Researcher of the Laboratory of Finished Dosage Forms, Research Institute of Pharmacology n.a. V.V. Zakusov. ORCID ID: 0000-0001-8821-4174. E-mail: dimagavrilov@list.ru