СОЦІАЛЬНА МЕДИЦИНА І ФАРМАЦІЯ: ІСТОРІЯ, СУЧАСНІСТЬ ТА ПЕРСПЕКТИВИ РОЗВИТКУ

UDC 615.1:004.94 https://doi.org/10.24959/sphhcj.21.237

O. V. Kutova, O. A. Ruban, R. V. Sahaidak-Nikitiuk, I. V. Kovalevska, N. V. Demchenko

National University of Pharmacy of the Ministry of Health of Ukraine, Kharkiv

Construction of regression models for developing the technology to obtain tablets based on medicinal ginger

Scientific research in pharmacy, due to their multifactorial nature, is closely related to modeling of complex static systems. For this purpose, the so-called "input-output" mathematical models, which are built based on the results of the experiment, are widely used. Modeling of static systems based on the experimental data requires the solution of three interrelated tasks: planning of the experiment and its implementation; identification of the model structure and its parameters; approximation, if necessary, of a complex model to a simpler mathematical description.

Aim. To develop a methodological approach to the determination of regression equations in a two-factor experiment based on the analysis of the individual influence of factors on the target quality indicators of the dosage form.

Materials and Methods. The Mathcad computer environment (MathSoft Ins., USA) was applied in the study. The least squares method was used to determine the coefficients of regression equations. To develop a template, which automatically searched for the type and coefficients of the equation, the MS Excel application was used, namely the data analysis package (regression analysis); the possibility of creating macros; the VBA programming environment. The MS Word processor was used to edit the code.

Results. The methodological approach for determining a mathematical description of the influence of quantitative factors on targets at the experimental stage of the dosage form development has been developed. The method of constructing regression equations proposed makes some additions to the determination of the regression model based on the planned two-factor experiment and allows in certain cases to reduce the required number of experiments. A macro for MS Excel has been developed and tested to optimize calculations in order to obtain the coefficients of regression equations.

Conclusions. The algorithm developed for identification of two-factor mathematical models includes the stage of identifying the main consequences of the influence of individual factors on the target indicators; it allows analyzing the mechanism of action of factors. The method is effective for determining a mathematical description in the form of linear algebraic polynomials and making a decision about the need for additional experimental observations within the factor space. The method of processing experimental data described has been tested according to the results obtained when developing specific dosage forms.

Key words: two-factor experiment; separate influence of quantitative factors; regression equation; algebraic polynomial; function of the geometric average.

О. В. Кутова, О. А. Рубан, Р. В. Сагайдак-Нікітюк, І. В. Ковалевська, Н. В. Демченко

Національний фармацевтичний університет Міністерства охорони здоров'я України, м. Харків

Побудування регресійних моделей для розроблення технології отримання таблеток на основі імбиру лікувального

Наукові дослідження у фармації через їх багатофакторність тісно пов'язані з моделюванням складних статичних систем. Для цього широко використовуються так звані математичні моделі «вхід – вихід», які будуються за результатами експерименту. Моделювання статичних систем на основі експериментальних даних вимагає вирішення трьох взаємопов'язаних завдань: планування експерименту та його реалізація; визначення структури моделі та її параметрів; наближення, за необхідності, складної моделі до більш простого математичного опису.

Мета: розроблення методологічного підходу до визначення рівнянь регресії у двофакторному експерименті на основі аналізу індивідуального впливу факторів на цільові показники якості лікарської форми.

Матеріали та методи: використано комп'ютерне середовище Mathcad (MathSoft Ins., США); метод найменших квадратів – для визначення коефіцієнтів рівнянь регресії. Для розробки шаблону, в якому автоматично здійснюється пошук виду та коефіцієнтів рівняння, використано додаток MS Excel, а саме: пакет аналізу даних (регресійний аналіз); можливість створення макросів; середовище програмування VBA; для редагування коду – текстовий процесор MS Word.

Результати. Розроблено методологічний підхід до визначення математичного опису впливу кількісних факторів на цільові показники на технологічному етапі розроблення лікарської форми. Запропонований алгоритм математичного моделювання вносить деякі зміни у визначення рівнянь регресії на основі запланованого двофакторного експерименту та зменшує необхідну кількість експериментів. Розроблено і випробувано макрос для програми MS Excel з метою оптимізації обчислень для отримання коефіцієнтів алгебраїчних поліномів.

Висновок. Розроблений алгоритм ідентифікації двофакторних математичних моделей включає стадію виявлення основних наслідків впливу окремих факторів на цільові показники, що дозволяє проаналізувати механізм їх дії. Метод є ефективним для установлення математичного опису у вигляді лінійних алгебраїчних поліномів та прийняття рішення про необхідність проведення додаткових експериментальних спостережень всередині факторного простору. Описаний метод обробки експериментальних даних був випробуваний за результатами, отриманими під час розроблення специфічних лікарських форм.

***Ключові слова**:* двофакторний експеримент; окремий вплив кількісних факторів; рівняння регресії; алгебраїчний поліном; функція середнього геометричного.

О. В. Кутовая, Е. А. Рубан, Р. В. Сагайдак-Никитюк, И. В. Ковалевская, Н. В. Демченко

Национальный фармацевтический университет Министерства здравоохранения Украины, г. Харьков

Построение регрессионных моделей для разработки технологии получения таблеток на основе имбиря лекарственного

Научные исследования в фармации вследствие их многофакторности тесно связаны с моделированием сложных статических систем. Для этой цели широко применяются так называемые математические модели «вход – выход», которые строятся по результатам эксперимента. Моделирование статических систем на основе экспериментальных данных требует решения трех взаимосвязанных задач: планирование эксперимента и его реализация; идентификация структуры модели и ее параметров; приближение в случае необходимости сложной модели к более простому математическому описанию.

Цель: разработка методологического подхода к установлению уравнений регрессии в двухфакторном эксперименте на основе анализа индивидуального влияния факторов на целевые показатели качества лекарственной формы.

Материалы и методы: использована компьютерная среда Mathcad (MathSoft Ins., США); метод наименьших квадратов – для определения коэффициентов уравнений регрессии. Для разработки шаблона, в котором автоматически осуществляется поиск вида и коэффициентов уравнения, использовано приложение MS Excel, а именно: пакет анализа данных (регрессионный анализ); возможность создания макросов; среда программирования VBA; для редактирования кода – текстовый процессор MS Word.

Результаты. Разработан методологический подход к установлению математического описания влияния количественных факторов на целевые показатели на технологической стадии разработки лекарственной формы. Предлагаемый алгоритм математического моделирования вносит некоторые изменения к определению уравнений регрессии на основе планируемого двухфакторного эксперимента и позволяет в определенных случаях сократить необходимое количество опытов. Разработан и протестирован макрос для приложения MS Excel с целью оптимизации расчетов для получения коэффициентов алгебраических полиномов.

Выводы. Разработанный алгоритм идентификации двухфакторных математических моделей включает стадию выявления основных последствий влияния отдельных факторов на целевые показатели, что позволяет проанализировать механизм их действия. Метод эффективен для определения математического описания в виде линейных алгебраических полиномов и принятия решения о необходимости проведения дополнительных экспериментальных наблюдений внутри факторного пространства. Описанный метод обработки экспериментальных данных был испытан по результатам, полученным при разработке специфических лекарственных форм.

Ключевые слова: двухфакторный эксперимент; отдельное влияние количественных факторов; уравнение регрессии; алгебраический полином; функция среднего геометрического.

Statement of the problem. Scientific research in pharmacy, due to their multifactorial nature, is closely related to modeling of complex static systems [1-3]. For this purpose, the so-called "input-output" mathematical models, which are built based on the results of the experiment, are widely used [4]. In most cases, the relationship between input and output variables in such models is described by algebraic polynomials of the 1st or 2nd degree of both complete and incomplete form. Modeling of static systems based on the experimental data requires the solution of three interrelated tasks: planning of the experiment and its implementation; identification of the model structure and its parameters; approximation, if necessary, of a complex model to a simpler mathematical description.

The first stage of constructing a mathematical model of a pharmaceutical object is based on the results of the experiment. To estimate the coefficients of the regression equation approximating the experimental dependence, it is necessary to collect static data characterizing various states of the system. Taking into account the multifactorial nature of pharmaceutical research and its specific features experiments must be carried out in large numbers [5-7]. In this regard, the task of efficient processing of the minimum possible experimental base is very relevant.

Analysis of recent research and publications. The works of Groshovyi T. A., Gordienko O. I., Barchuk O. Z., Zaliska O. M., Shalata V. Ya., Maksimovich N. M., etc., are devoted to the determination of the influence of quantitative pharmaceutical factors on the main pharmacopoeial characteristics of drugs by the method of random balance [1-3]. Divak M. P. [4] paid attention to the methods of solving the problems of the experiment planning, parametric and structural identification of interval models and simplification of complex models under the condition of ensuring guaranteed accuracy. The studies related to mathematical planning of the experiment during scientific research in pharmacy were performed by Groshovyi T. A., Darzuli N. P., Martsenyuk V. P., Kucherenko L. I. and others [3, 5-7]. Consideration of solutions of engineering and technical problems using the MathCAD version 14 mathematical package is described in the works of Voskoboynikov Yu. E. [8-9]. The use of the Ms Excel computer program was studied by Voskoboynikov Yu. E., Zhuravsky A. A., Toryanyk E. I., Sinyaeva O. V. and Zavgorodniy O. I. [10, 11, 13].

Identification of aspects of the problem unsolved previously. One of the pressing issues in the research planning in pharmacy, which needs to be addressed, is the identification of mathematical models of systems with two dependent quantitative factors, which total value is determined by the quantitative composition of the mixture and fixed at a certain level.

Objective statement of the article. The aim of this article was to develop a methodological approach to the determination of regression equations in a two-factor experiment based on the analysis of the individual influence of factors on the target quality indicators of the dosage form.

Presentation of the main material of the research. This material considers an example, in which the output parameters of the system are studied depending on the quantitative content of two excipients in the drug mixture. Such a problem can arise in the case when the overall quantitative composition of the drug mixture is maintained by changing the content of the filler due to an increase or decrease in the amount of certain two independent mixture components.

The planning of the experiment was carried out according to the type of full-factor experiments 2^2 and 3^2.

It should be noted that the experimental data according to plan 2^2 is sufficient to determine the coefficients of the classical linear multiple regression model:

$$y_i(x1,x2) = a_0 + a_1x1 + a_2x2 \qquad (1)$$

It is also possible to determine a regression equation with the interaction of factors:

$$y_i(x1,x2) = a_0 + a_1x1 + a_2x2 + a_3x1x2 \qquad (2)$$

For this purpose, the means of modern computer programs with built-in functions are effective. A representative set of basic functions and algorithms that implement the least squares method (LSM) allow a researcher, without knowledge of special sections of higher mathematics, to technically quickly obtain an estimate of the regression coefficients. This article uses Mathcad (MathSoft Ins., USA), the most popular computer environment among users; it is one of the recognized world leaders in the number of universal mathematical systems [8, 9].

In some cases, the regression equations obtained have a high coefficient of determination and make it possible to carry out calculations with high accuracy at basic experimental points, thereby indicating the adequacy of the mathematical description. However, this result can be refuted by additional experiments within the factor space. In order not to conduct additional research, it is proposed to carry out the following sequence of actions. Based on the available experimental base 22 we determine and analyze linear dependences of the form:

$$y_i = f(x1)_{x2=min} \text{ and } y_i = f(x1)_{x2=max};$$
$$y_i = f(x2)_{x1=min} \text{ and } y_i = f(x2)_{x1=max}.$$

If these dependences have a unidirectional character at the minimum and maximum levels of the second factor, it is possible to create the final dependence as a geometric mean function of the form [8, 9]:

$$y_i(x1,x2) = \sqrt{(a_{01} + a_{11}x1)(a_{02} + a_{12}x2)}. \quad (3)$$

To obtain more accurate mathematical description, it is advisable to further refine the final dependence based on obtaining a correlation between the experimental and theoretical results [10]. The functional dependence can be defined as a linear or quadratic function. The correlation coefficients are determined by the least squares method using Mathcad tools. Thus, the adequate functional dependence obtained indicates the sufficiency of the experimental information for compiling a mathematical description.

If the dependences $y_i = f(x1)$ and $y_i = f(x2)$ have a multidirectional character at the fixed values of the second factor, the creation of a geometric mean function will not be effective since the nonlinearity of the influence of factors on the target indicators studied will appear inside the factor space, and to determine it, additional experimental data are needed.

The nonlinear influence of two factors on the target functions can be described by various variants of the quadratic dependence. For all possible combinations, an equation is selected according to the equation by its static quality indicators. The most common least squares method is used to determine the coefficients of regression equations. From the technical point of view, such a method seems to be very difficult since the number of models that will need to be analyzed turns out to be extremely large.

One of the tasks of the work was to develop a template for the MS Excel application, in which the search of the type and coefficients of the equation would be carried out automatically. To achieve this goal, we used such MS Excel tools as the data analysis package (regression analysis); the possibility of creating macros; the VBA programming environment [11]. The MS Word processor was used to edit the code. For the equation obtained, a block of graphical interpretation of the calculation results is provided; with its help it is possible to compare the experimental and theoretical graphical dependencies. If there are several adequate options, the choice is made by the researcher based on his practical experience and taking into account the advantage of a simpler mathematical description.

When developing the formulation of tablets based on medicinal ginger the research was conducted to study the effect of excipients on the pharmacological and technological parameters of this dosage form at the Department of Industrial Technology of Drugs and the Department of Processes and Apparatuses for Chemical and Pharmaceutical Production of the National University of Pharmacy of the Ministry of Health of Ukraine [12]. According to the data of experiments to determine significant factors, kollidon K30 *(x1)* from the group of binders and neusilin as a moisture regulator *(x2)* were selected. The permissible amount of these components in the composition of tablets was determined by the variation intervals $2 \leq x1 \leq 5$ and $1 \leq x2 \leq 2$, respectively. The total amount of these excipients was not strictly limited, and the average tablet weight was controlled by the Galen IQ 721 filler, which was also selected on the basis of the previous studies.

To characterize the tablets obtained, such pharmacological and technological parameters as disintegration *(y1)*, resistance of tablets to crushing *(y2)* and friability *(y3)* were determined.

At the first stage of the experimental data processing a graphical dependence of the indicators studied on the factors analyzed was built (Fig. 1) based on the results of a full factorial experiment of type 2^2 with experiments at points corresponding to the maximum and minimum levels of factors (Tab. 1).

Tab. 1 contains the average results of two parallel experiments with the indication of the confidence interval of measurements.

The graphic interpretation made it possible to determine the intended type of regression

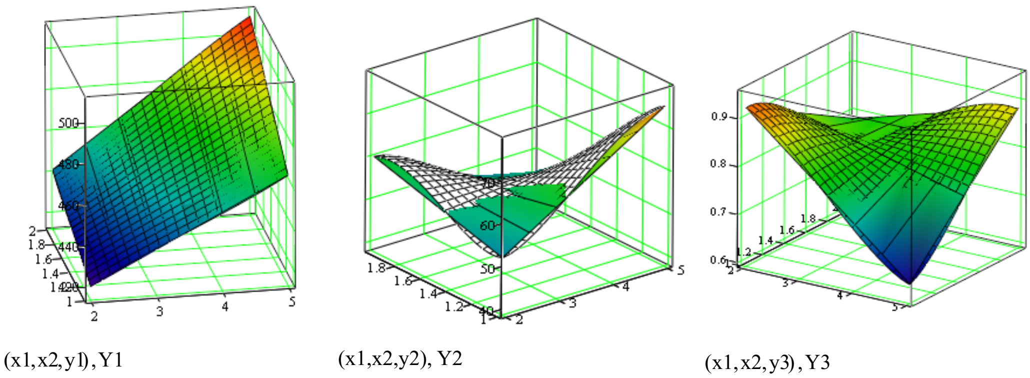


Fig. 1. The graphic interpretation of the experimental data

Table 1

THE MATRIX FOR PLANNING THE EXPERIMENT OF MODEL TABLETS ACCORDING TO PLAN 2^2

No. of the experiment	*x1*	*x2*	*y1*	*y2*	*y3*
1	5	2	509.5 ± 65.33	39 ± 4.17	0.873 ± 0.036
2	5	1	466.5 ± 45.87	75.25 ± 13.20	0.63 ± 0.028
3	2	2	441.5 ± 20.85	60.125 ± 104	0.783 ± 0.147
4	2	1	419 ± 2.78	51.25 ± 0.69	0.922 ± 0.022

equations. The behavior of the response surfaces obtained indicates the clear nonlinearity of the objective functions studied. This type of dependence can be a consequence of both the interaction of factors and their nonlinear impact on the target indicators.

Mathematical processing of experimental data by Mathcad 14 allowed us to determine linear regression dependencies with the interaction of factors:

$$y1(x1,x2) = 378.5 + 9x1 + 8.833x2 + 6.833x1x2, \quad (4)$$

$$y2(x1,x2) = -3.708 + 23.042x1 + 38.958x2 - 15.042x1x2, \quad (5)$$

$$y3(x1,x2) = 1.516 - 0.227x1 - 0.399x2 + 0.13x1x2 \ (6) \quad (6)$$

Functions (1) – (3) in Mathcad 14 are given in Fig. 2.

$$z(a0,a1,a2,a3) := \sum_{i=0}^{3} \left[y1_i - \left[a0 + a1 \cdot x1_i \cdot x2_i + a2 \cdot (x1_i) + a3 \cdot (x2_i)\right]\right]^2$$

$a0 := 1$ $a1 := 1$ $a2 := 1$ $a3 := 1$ $a4 := 1$

Given

$\frac{d}{da0} z(a0,a1,a2,a3) = 0$ $\frac{d}{da1} z(a0,a1,a2,a3) = 0$ $\frac{d}{da2} z(a0,a1,a2,a3) = 0$ $\frac{d}{da3} z(a0,a1,a2,a3) = 0$

$Z := Find(a0,a1,a2,a3)$

$$Z = \begin{pmatrix} 378.5 \\ 6.833 \\ 9 \\ 8.833 \end{pmatrix}$$

$Y1(x1,x2) := 378.5 + 6.833 \cdot x1 \cdot x2 + 9 \cdot x1 + 8.833 \cdot x2$

Fig. 2. The example of determination of regression coefficients in Mathcad 14

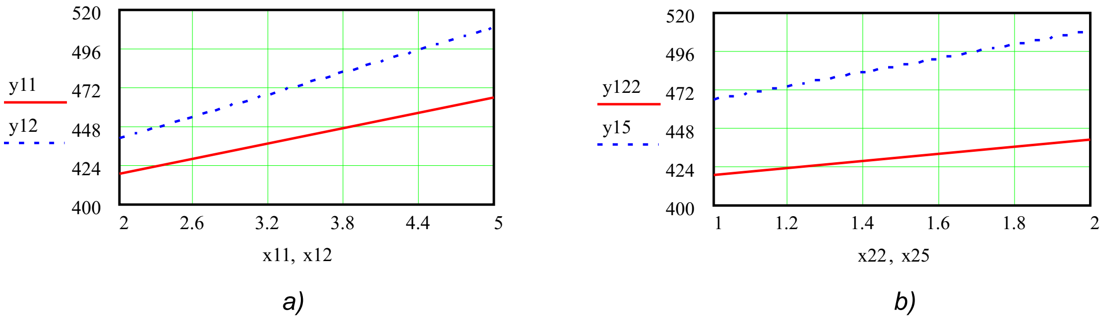


Fig. 3. The individual influence of factors on the target indicator y1:
a) $y1 = f(x1)_{x2=1}$ *and* $y1 = f(x1)_{x2=2}$*; b)* $y1 = f(x2)_{x1=2}$ *and* $y1 = f(x2)_{x1=5}$

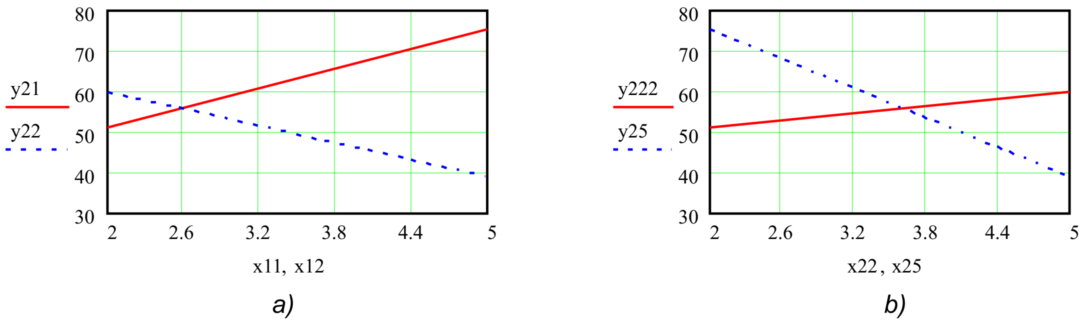


Fig. 4. The individual influence of factors on the target indicator y2:
a) $y2 = f(x1)_{x2=1}$ *and* $y2 = f(x1)_{x2=2}$*; b)* $y2 = f(x2)_{x1=2}$ *and* $y2 = f(x2)_{x1=5}$

To assess the adequacy of the equations obtained we calculated the coefficient of determination R^2. It shows that part of the variations depends on the variables due to variations of the objective function:

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(\tilde{y}_i - y_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y}_i)^2}$$

Such docking parameters as the experimental value – y_i, the theoretical value – $\tilde{y}_i$, and the average experimental value – $\bar{y}$ were determined.

All equations obtained had a high coefficient of determination $R^2 = 0.9999$. The average relative computation error was also determined:

$$\Delta = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{\tilde{y}_i - y_i}{y_i}\right| 100\ \%.$$

For regression equations (4) – (5) Δ=0, for (6) – 0.2 %.

In case of uncertainty of the researcher in the mechanism of the influence of factors, it is necessary to expand the experimental base on the basis of a full factorial experiment of type 3^2. The methodological approach proposed by the authors of the work to the experimental data processing according to plan 2^2 makes it possible not to carry out additional experiments in the factor space for making a decision regarding the mathematical description.

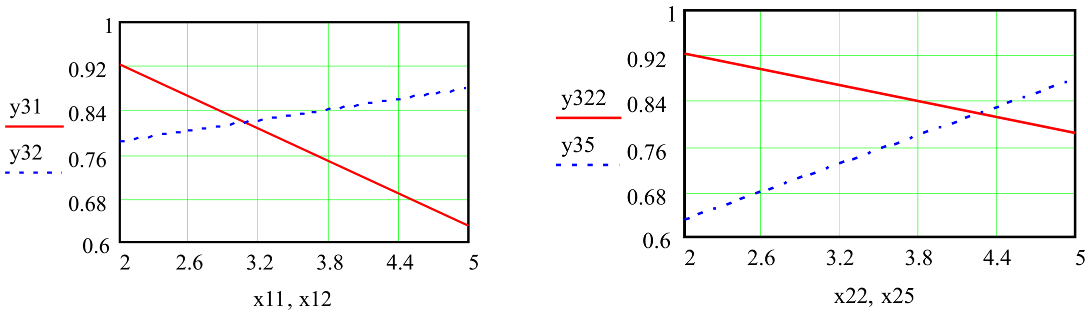
At the first stage the analysis of the individual influence of factors on the objective functions was performed, provided that the second variable remained fixed, and linear regression equations were determined. These dependences are shown in Fig. 3-5.

As can be seen from the presented figures, both factors at the boundaries of the variation interval affect the tablet disintegration in one direction, namely the dependences *y1 = f(x1)* and *y1 = f(x2)* increase monotonically.

In the case of two other indicators, there is a multidirectional influence of factors at the levels studied: $y2 = f(x1)_{x2=1}$, $y2 = f(x2)_{x1=5}$, $y3 = f(x2)_{x1=5}$, $y3 = f(x1)_{x2=2}$ – increasing; $y2 = f(x1)_{x2=2}$, $y2 = f(x2)_{x1=2}$, $y3 = f(x1)_{x2=1}$, $y3 = f(x2)_{x1=2}$ – decreasing.

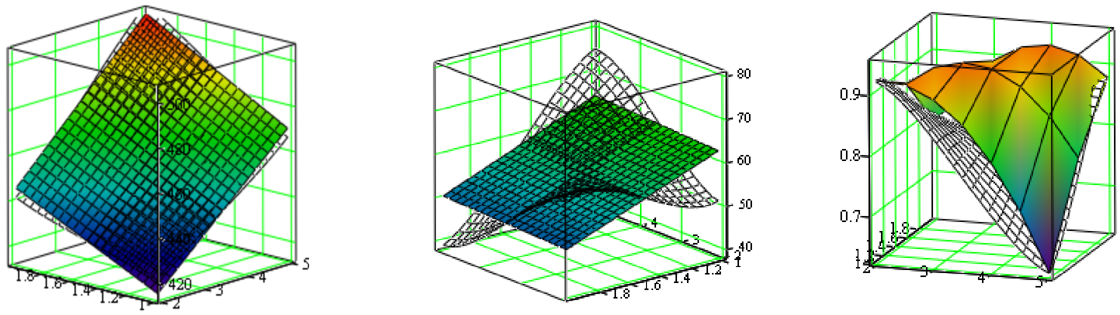
This fact is the key moment for making a decision on the need for additional research.

To determine the interaction of factors such a mathematical technique as multiplying



a) b)

Fig. 5. The individual influence of factors on the target indicator y3:
a) $y3 = f(x1)_{x2=1}$ and $y3 = f(x1)_{x2=2}$; b) $y3 = f(x2)_{x1=2}$ and $y3 = f(x2)_{x1=5}$



a) b) c)

Fig. 6. The graphic interpretation of geometric mean dependencies:
a) y1 = f(x1,x2); b) y2 = f(x1,x2); c) y3 = f(x1,x2)

these equations by each other is used. All functions will reflect the interaction of factors at the *x1x2* level. We get the final equations of geometric mean expressions of the form:

$$y1(x1,x2) = \sqrt{(391.75 + 19.25x1)(410 + 32.75x2)}, \quad (7)$$

$$y2(x1,x2) = \sqrt{(54.729 + 0.479x1)(76.937 - 13.687x2)}, \quad (8)$$

$$y3(x1,x2) = \sqrt{(0.907 - 0.032x1)(0.72 + 0.056x2)}. \quad (9)$$

To obtain more accurate mathematical description, it is advisable to carry out an additional refinement of the final dependence based on obtaining the correlation dependence between the experimental and theoretical results. The functional dependence can be defined as a linear or quadratic function. The correlation coefficients are determined using the least squares method.

For the objective function *y1 = f(x1,x2)*, the geometric mean dependence with the corresponding correction is the mathematical description with a relative calculation error at the base points of no more than 1 % and a good coincidence of the experimental and theoretical response surfaces (Fig. 6*a*):

$$\begin{aligned} y1(x1,x2) &= -2.426 + \\ &+ 0.002191(391.75 + \\ &19.25x1)(410 + 32.75x2) = \\ &= 349.326 + 17.28x1 + 28.097x2 + \\ &+ 1.38x1x2 \end{aligned} \quad (10)$$

For the objective functions *y2 = f(x1,x2)* and *y3 = f(x1,x2)* the response surfaces obtained from the geometric mean dependences with the corresponding correction do not coincide with the experimental ones (Fig. 6*b,c*). This result indicates the nonlinear nature of the influence of factors on the target indicators and the need to expand the experimental base to determine an adequate mathematical description of these dependencies.

The graphic interpretation of the experimental data according to plan 3^2 (Tab. 2) shown

Table 2

THE MATRIX FOR PLANNING THE EXPERIMENT OF MODEL TABLETS ACCORDING TO PLAN 3²

No.	*x1*	*x2*	*y1*	*y2*	*y3*
1	5	2	509.5 ± 65.33	39 ± 4.17	0.881 ± 0.036
2	5	1	466.5 ± 45.87	75.25 ± 13.20	0.63 ± 0.028
3	2	2	441.5 ± 20.85	60.125 ± 1.04	0.783 ± 0.147
4	2	1	419 ± 2.78	51.25 ± 0.69	0.922 ± 0.022
5	3.5	2	474.25 ± 27.10	79 ± 5.56	0.736 ± 0.061
6	3.5	1	437.75 ± 61.85	93.5 ± 6.95	0.652 ± 0.086
7	3.5	1,5	456.5 ± 51.43	118.75 ± 0.69	0.528 ± 0.0
8	5	1,5	487.99 ± 5.53	89.62 ± 3.34	0.60 ± 0.03
9	2	1,5	430.25 ± 11.12	88.18 ± 4.5	0.69 ± 0.028

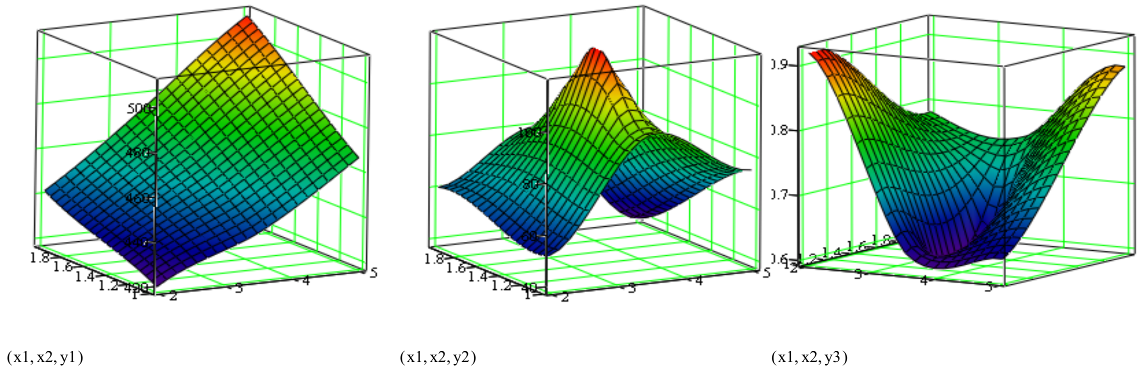


Fig. 7. The graphic interpretation of the experimental data according to plan 2³

in Fig. 7 confirms that the quantitative factors studied have a nonlinear effect on the objective functions *y2 = f(x1,x2)* and *y3 = f(x1,x2)*, and for *y1 = f(x1,x2)* the nature of influence of the variables has not changed.

Tab. 2 contains the average results of two parallel experiments with the indication of the confidence interval of measurements.

Determination of the corresponding quadratic dependences for *y2* and *y3* requires the mathematical processing of the additional data within the factor space.

Based on the plan of experiment 2^3 the following regression dependencies were determined:

$$y2(x1,x2) = -395.941 + 115.889x1 + 428.687x2 - 15.042x1x2 - 13.264x1^2 - 130x2^2, \quad (11)$$

$$y3(x1,x2) = 3.288 - 0.574x1 - 2.347x2 + 0.13x1x2 + 0.05x1^2 + 0.658x2^2, \quad (12)$$

and dependence (4) was corrected:

$$y1(x1,x2) = 375.64 + 9x1 + 10.08x2 + 6.83x1x2. \quad (13)$$

The results of evaluating the adequacy of the regression equations are presented in Tab. 3.

The p-values of the coefficients for all the regression equations obtained do not exceed 0.05, it shows their significance. Significance coefficients with a reliability of 0.95 % correspond to the calculated ones. The intervals that with a probability of 95 % fall into the

Table 3

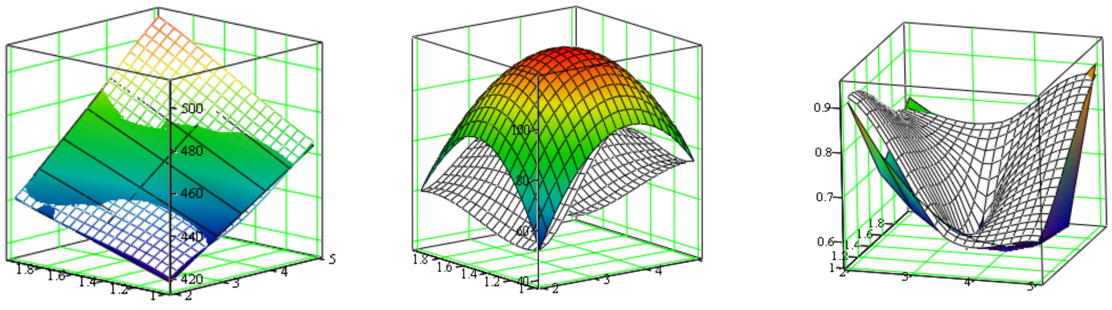
ESTIMATION OF SIGNIFICANCE OF REGRESSION EQUATIONS

Equation	R^2	Significance of criterion F	*Δ*, %	Conclusion
13	0.9995	0.000001 < 0.05	0.28	The equation is significant
11	0.9976	0.000385 < 0.05	0.23	The equation is significant
12	0.9967	0.000001 < 0.05	1.22	The equation is significant

Table 4

INTERVAL ESTIMATES OF THE VALUES OF THE REGRESSION EQUATIONS

Regression equation	Confidence intervals
$y1(x1,x2) = 375.64 + 9x1 + 10.083x2 + 6.833x1x2$	y1(5;2) ± 23.65; y1(5;1) ± 16.77; y1(2;2) ± 10.12; y1(2;2) ± 13.14; y1(3,5;2) ± 18.3; y1(3,5;1) ± 13.38; y1(3,5;1.5) ± 15.7; y1(5;1.5) ± 20; y1(2;1,5) ± 11.55
$y2(x1,x2) = -395.941 - 0.574x1 - 2.347x2 + 0.13x1x2 + 13.64x1^2 + 130x2^2$	y2(5;2) ± 8.8; y2(5;1) ± 8.3; y2(2;2) ± 2.35; y2(2;2) ± 3; y2(3,5;2) ± 5.24; y2(3,5;1) ± 4.7; y2(3,5;1.5) ± 4.9; y2(5;1.5) ± 8.5; y2(2;1.5) ± 2.6
$y3(x1,x2) = 3.288 + 115.889x1 + 428.687x2 - 15.042x1x2 + 0.05x1^2 + 0.658x2^2$	y3(5;2) ± 0.62; y3(5;1) ± 0.58; y3(2;2) ± 0.16; y3(2;2) ± 0.2; y3(3,5;2) ± 0.37; y3(3,5;1) ± 0.3; y3(3,5;1.5) ± 0.34; y3(5;1.5) ± 0.6; y3(2;1.5) ± 0.18



a) b) c)

Fig. 8. Comparison of graphical interpretation of experimental and theoretical response surfaces: a) y1 = f(x1,x2); b) y2 = f(x1,x2); c) y3 = f(x1,x2)

individual values of functions (1), (5), (6) are presented in Tab. 4 [13].

The experimental and theoretical response surfaces obtained using equations (5) – (7) are compared in Fig. 8. The results of the comparative graphical analysis correspond to the estimates of the adequacy of the equations.

The method proposed for processing the data of a two-factor experiment of type 2^2 allows with a minimum amount of the experimental data to draw a conclusion of the possibility of using linear regression with the interaction of factors.

The method of processing experimental data described in two-factor experiments was tested on the results obtained when developing specific dosage forms, and it proved its effectiveness.

In the case of an obvious absence of the extremum of the function within the factor space, as determined during the research, it is possible not to carry out the planned experiment, but to use the values of the quantities studied, which do not change uniformly in the corresponding range.

The formation of the geometric mean function will be an effective solution for displaying the linear influence of factors and their possible interaction. Moreover, the use of the geometric mean function as a mathematical description in these conditions is possible for any number of factors.

The VBA programming environment made it possible to quickly create a program skeleton for determining the type and coefficients of various modifications of the quadratic equation with two variables. It can be used for further block modifications of the template, such as adding analyzing blocks for cubic equations.

The algorithm developed for regression equations for pharmaceutical research can be used to determine the influence of quantitative factors on target indicators in any other field of research.

Conclusions and prospects of further research. Based on the methodological approach developed the regression equations, which characterize the quantitative effect of a binder and a moisture regulator in the composition of ginger-based tablets on the pharmacopoeial parameters of this dosage form, have been determined. These equations can be used in further studies to optimize the technology for obtaining tablets.

Conflict of interests: authors have no conflict of interests to declare.

References

1. Гордієнко О. І., Грошовий Т. А. Вивчення впливу кількісних факторів на фармакотехнологічні властивості порошкових мас і таблеток із рослинними екстрактами та ефірною олією. *Фармацевтичний журнал*. 2021. № 1. С. 35–42. DOI: https://doi.org/10.32352/0367-3057.1.21.04.
2. Вивчення впливу кількісних факторів при створенні таблеток екстрактів листя чорниці і трави козлятника та таурину методом прямого пресування / О. З. Барчук та ін. *Фармацевтичний часопис*. 2018. № 4. С. 42–48. DOI: https://doi.org/10.11603/2312-0967.2018.4.9706.
3. Дарзулі Н. П., Грошовий Т. А. Дослідження впливу кількісних факторів на фармако-технологічні властивості порошкових мас та таблеток екстракту грушанки круглолистої. *Фармацевтичний часопис*. 2018. № 3. С. 45–51. DOI: https://doi.org/10.11603/2312-0967.2018.3.9377.
4. Дивак М. П. Задачі математичного моделювання статичних Д–44 систем з інтервальними даними. Тернопіль : ТНЕУ Економічна думка, 2011. 216 с.
5. Математичне планування експерименту при проведенні наукових досліджень у фармації / Т. А. Грошовий та ін. Тернопіль : Укрмедкнига, 2008. 367 с.
6. Песков К. В. Математическое моделирование при разработке лекарств. *Вестник «Росздравнадзора»*. 2013. № 1. С. 57–60. URL: https://www.researchgate.net/publication/259397341_Mathematical_modeling_in_drug_development.
7. Zivorad R. L. Design of experiments in chemical engineering. A practical guide. Weinheim : Wiley-VCH, 2004. 610 p.
8. Воскобойников Ю. Е. Решение инженерных задач в пакете MathCAD : учеб. пособие. Новосибирск : НГАСУ Сибстрин, 2013. 120 с.
9. Воскобойников Ю. Е. Регрессионный анализ данных в пакете MATHCAD. Санкт-Петербург : Лань, 2011. 224 с.
10. Свідоцтво про реєстрацію авторського права на твір № 47998 від 25.02.2013. Комп'ютерна програма для автоматичної побудови математичної моделі функціювання довільного об'єкту / А. О. Журавський та ін. *Авторське право і суміжні права. Офіційний бюлетень.* 2013. № 30. С. 364–365.
11. Берндт Г., Каинка Б. Измерение, управление и регулирование с помощью макросов VBA в Word и Excel (+CD). Киев : МК-Пресс, Санкт-Петербург : Корона-Век, 2008. 256 с.
12. Optimization of tablet formulation containing ginger dry extract / W. A. A. Malek et al. *Current Issues in Pharmacy and Medical Sciences*. 2020. Vol. 33, Iss. 2. P. 90–93. DOI: https://doi.org/10.2478/cipms-2020-0018.
13. Воскобойников Ю. Е. Эконометрика в Excel : учеб. пособие. Новосибирск : НГАСУ, 2011. 215 с.

References

1. Hordiienko, O. I., Hroshovyi, T. A. (2021). *Farmats. zhurn.*, *1,* 35–42. doi: https://doi.org/10.32352/0367-3057.1.21.04.
2. Barchuk, O. Z., Hroshovyi, T. A, Zalis'ka, O. M., Shalata, V. Ya., Maksymovych, N. M. (2018). *Farmats. zhurn.*, *4,* 42–48. doi: https://doi.org/10.11603/2312-0967.2018.4.9706.
3. Darzuli, N. P., Hroshovyi, T. A. (2018). *Farmats. zhurn.*, *4,* 42–48. doi: https://doi.org/10.11603/2312-0967.2018.4.9706.
4. Dyvak, M. P. (2011). *Zadachi matematychnoho modeliuvannia statychnykh D-44 system z interval'nymy danymy*. Ternopil': Ekonomichna dumka, 216.
5. Hroshovyi, T. A., Martseniuk, V. P., Kucherenko, L. I. et al. *Matematychne planuvannia eksperymentu pry provedenni naukovykh doslidzhen' v farmatsii.* Ternopil': Ukrmedknyha, 2008.
6. Peskov, K. V. (2013). *Vestnik "Roszdravnadzora", 1,* 57–60.
7. Zivorad, R. (2004). *Lazic. Design of experiments in chemical engineering. A practical guide.* Weinheim: Wiley-VCH, 610.
8. Voskoboinikov, Yu. Ye. (2013). *Reshenie inzhenernykh zadach v pakete MathCAD.* Novosibirsk: NGASU (Sibstrin), 120.
9. Voskoboinikov, Yu. Ye. (2011). *Regressionnyi analiz dannykh v pakete MATHCAD.* Saint Petersburg: Lan', 224.

10. Zhuravs'kyi, A. O., Torianyk, E. I., Siniaieva, O. V., Zavhorodnii, O. I. (2013). Svidotstvo pro reyestratsiyu avtors'koho prava na tvir No. 47998. Kompiuterna prohrama dlia avtomatychnoyi pobudovy. Avtorske pravo i sumizhni prava. *Ofitsiinyi biuleten, 30,* 364–365.
11. Berndt, G.-Y., Kainka, B. (2008). *Izmerenie, upravlenie i rehulirovanie s pomoshch'iu makrosov VBA v Word i Excel (+CD).* Kiev: MK-Press; Saint Petersburg: Korona-Vek, 256.
12. Malek, W. A. A., Ruban, O. A., Kutova, O. V., Herbina, N. A. (2020). Optimization of tablet formulation containing ginger dry extract Issues Pharm. *Med. Sci., 33 (2),* 90-93. doi: http://doi.org/10.2478/cipms-2020-0018.
13. Voskoboinikov, Yu. Ye. (2011). *Ekonometrika v Excel.* Novosibirsk, 215.

Information about authors:
Kutova O. V., Candidate of Engineering Sciences (Ph.D.), associate professor of the Department of Pharmaceutical Product Technology, National University of Pharmacy of the Ministry of Health of Ukraine (https://orcid.org/0000-0002-3761-2831). E-mail: paxtoxt@gmail.com
Ruban O. A., Doctor of Pharmacy (Dr. habil.), professor, head of the Department of Industrial Technology of Drugs, National University of Pharmacy of the Ministry of Health of Ukraine. E-mail: ruban_elen@ukr.net
Sahaidak-Nikitiuk R. V., Doctor of Pharmacy (Dr. habil.), professor of the Department of Management and Public Administration, National University of Pharmacy of the Ministry of Health of Ukraine (https://orcid.org/0000-0002-9337-7741). E-mail: management@nuph.edu.ua
Kovalevska I. V., Doctor of Pharmacy (Dr. habil.), associate professor of the Department of Industrial Technology of Drugs, National University of Pharmacy of the Ministry of Health of Ukraine (https://orcid.org/0000-0001-5610-8334). E-mail: inga.kovalevskaya@gmail.com
Demchenko N. V., Candidate of Economics (Ph.D.), associate professor of the Organization and Economy of Pharmacy Department, National University of Pharmacy of the Ministry of Health of Ukraine (https://orcid.org/000-0001-5915-0087). E-mail: demchenata@ukr.net
Відомості про авторів:
Кутова О. В., кандидатка технічних наук, доцентка кафедри технології фармацевтичних препаратів, Національний фармацевтичний університет Міністерства охорони здоров'я України (https://orcid.org/0000-0002-3761-2831). E-mail: paxtoxt@gmail.com
Рубан О. А., докторка фармацевтичних наук, професорка, завідувачка кафедри заводської технології ліків, Національний фармацевтичний університет Міністерства охорони здоров'я України. E-mail: ruban_elen@ukr.net
Сагайдак-Нікітюк Р. В., докторка фармацевтичних наук, професорка кафедри менеджменту та публічного адміністрування, Національний фармацевтичний університет Міністерства охорони здоров'я України (https://orcid.org/0000-0002-9337-7741). E-mail: management@nuph.edu.ua
Ковалевська І. В., докторка фармацевтичних наук, доцентка кафедри заводської технології ліків, Національний фармацевтичний університет Міністерства охорони здоров'я України (https://orcid.org/0000-0001-5610-8334). E-mail: inga.kovalevskaya@gmail.com
Демченко Н. В., кандидатка економічних наук, доцентка кафедри організації та економіки фармації, Національний фармацевтичний університет Міністерства охорони здоров'я України (https://orcid.org/000-0001-5915-0087). E-mail: demchenata@ukr.net
Сведения об авторах:
Кутовая О. В., кандидат технических наук, доцент кафедры технологии фармацевтических препаратов, Национальный фармацевтический университет Министерства здравоохранения Украины (https://orcid.org/0000-0002-3761-2831). E-mail: paxtoxt@gmail.com
Рубан О. А., доктор фармацевтических наук, профессор, заведующая кафедрой заводской технологии лекарств, Национальный фармацевтический университет Министерства здравоохранения Украины. E-mail: ruban_elen@ukr.net
Сагайдак-Никитюк Р. В., доктор фармацевтических наук, профессор кафедры менеджмента и публичного администрирования, Национальный фармацевтический университет Министерства здравоохранения Украины (https://orcid.org/0000-0002-9337-7741). E-mail: management@nuph.edu.ua
Ковалевская И. В., доктор фармацевтических наук, доцент кафедры заводской технологии лекарств, Национальный фармацевтический университет Министерства здравоохранения Украины (https://orcid.org/0000-0001-5610-8334). E-mail: inga.kovalevskaya@gmail.com
Демченко Н. В., кандидат экономических наук, доцент кафедры организации и экономики фармации, Национальный фармацевтический университет Министерства здравоохранения Украины (https://orcid.org/000-0001-5915-0087). E-mail: demchenata@ukr.net

Надійшла до редакції 16.09.2021 р.