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FINDING THE OPTIMAL SOLUTION IN PHARMACEUTICAL TECHNOLOGICAL RESEARCH USING STATISTICAL METHODS WITH QUANTITATIVE FACTORS

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The aim. *Developing a methodological approach to determining the optimal solution using statistical methods in pharmaceutical and technological research with quantitative factors on the example of establishing the optimal content of filler in a solid dispersion in the manufacture of granules.*

Materials and methods. *The methodology for finding an optimal solution is shown in the example of the development of granules containing a solid dispersion of quercetin with polyethylene oxide 6000. To determine the optimal amount of filler, the method of mathematical modelling was applied using statistical analysis and multiple criterion optimization. Software tools such as MS Excel and Mathcad 14 spreadsheets were used to process the experimental data and perform calculations.*

Results. *The problem is formalized in a form suitable for solving by experimental and statistical methods. The issues of constructing mathematical models in the form of regression equations characterizing the effect of the quantitative content of the filler on several pharmacy-technological parameters of granules based on experimental data are considered. Attention is focused on the peculiarities of using static methods for processing experimental data in pharmaceutical research, namely, on establishing the structure of regression equations and assessing their adequacy. The criterion of multi-criteria optimization is proposed, which is formed based on the obtained regression equations, considering the restrictions imposed on each individual criterion.*

Conclusions. *A methodological approach to determining the optimal solution in pharmaceutical technological research with quantitative factors using experimental and statistical methods and the theory of multi-criteria optimization has been tested on the example of determining the optimal content of filler in a solid dispersion in the manufacture of granules. The optimal ratio of filler to solid dispersion was determined, which ensures the maximum approximation of all studied pharmacy-technological parameters of granules to their optimal values. None of the indicators exceeds the limits set by the researcher and has the minimum possible deterioration relative to the individually determined optimum*

Keywords: *statistical method, regression analysis, multiple-criterion optimization, optimization criterion, pharmacy-technological indicator*

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1. Introduction

A feature of the current stage of development of modern pharmacy is the widespread use of mathematical modelling, which can be applied at all stages of pharmaceutical development, starting with formulation development, continuing with the development of a technological process and its scaling, and ending with production monitoring and control of the commercial process [1, 2].

Statistical analysis and multiple-criteria optimization methods are integral parts of mathematical modelling. An important procedure of statistical analysis is establishing a regression equation and assessing its adequacy [3, 4]. However, in the context of pharmaceutical technological research with quantitative factors (PTRQF), problems arise with respect to compliance with the prerequisites and assumptions of classical regression analysis, which in some cases leads to the impossibility of making a decision or misinterpretation of the results obtained [5, 6].

The purpose of the article is to develop a methodological approach to determining the optimal solution using statistical methods in pharmaceutical and technological research with quantitative factors. It will use quantitative factors to establish the optimal filler content in a solid dispersion in the manufacture of granules.

2. Planning (methodology) of research

In modern pharmacy-technological research with quantitative factors, optimization is concerned with determining the optimal content of the excipients in the dosage form or the optimal technological parameters of its manufacture. As a rule, the decision is made using an interactive approach, taking into account the researcher's considerations of the hierarchy of pharmacy-technological characteristics under study (local criteria), the restrictions imposed on their values, and the analysis of equal yield lines for the criteria [7, 8]. Given the recent widespread use of regression analysis in pharmaceutical and technological research, we propose an approach to decision-making in a multiple-criteria space based on mathematical calculations, considering the optimal values of each local criterion. This approach does not require the use of information about preferences in a multi-criteria space defined by constraints. However, it considers the requirements for optimal values of local criteria established by analyzing regression dependencies. The most effective approach seems to be to find the optimal point in the space of feasible solutions that can provide a set of values of individual criteria that is closest to those determined by the researcher. Such an approach implies a preliminary solution of research tasks for each local criterion or the availability of expert opinion for them. The generalized criterion is the norm of approximation to the optimal values, according to which the sum of squared deviations of the functionalities from the established acceptable values will be minimal. The proposed method does not require the mandatory introduction of a gradation of individual criteria or their weighting coefficients. For the mathematical description of local criteria, mathematical statistics methods are used to describe experimental observations and build a probabilistic model of a random phenomenon [9, 10]. However, statistical regularity only helps to make optimal decisions and does not reject the researcher's experience and intuition. It can only be considered as one component of the decision-making process. Therefore, the obtained regression equations should be evaluated not only by their statistical significance but also, and above all, by their effectiveness.

3. Materials and methods

Determination of the values of the studied pharmacopoeial indicators was carried out according to the appropriate methods of the State Pharmacopoeia of Ukraine [11]: abrasion (clause 2.9.7); bulk density and density after shrinkage of powders (clause 2.9.34); "Dissolution" test for solid dosage forms (clause 2.9.3); disintegration (clause 2.9.1); resistance to crushing (clause 2.9.8); liquidity (clause 2.9.16).

The procedure for finding the optimal solution is shown in the example of the development of granules containing a solid dispersion of quercetin and polyethylene oxide 6000. A mathematical modelling method was applied using statistical analysis and multiple-criteria optimization to determine the optimal amount of filler in a solid dispersion. Even though there are currently a number of computer software products that are capable of processing research results in order to determine optimal solutions in an experiment (Minitab, Stat Soft (Statistika), ANGLIB, etc.), for processing experimental data and performing calculations, they were used software tools such as MS Excel spreadsheets and Mathcad 14 [12, 13].

This approach was chosen due to the need to create an individual research algorithm considering the pharmaceutical approach.

The research was conducted from 2019 to 2022.

4. Results

In the context of research work [14], experiments were conducted to create preparations containing a solid dispersion of quercetin. One of the objectives of the study was to determine the optimal content of filler (d) in the composition of the solid dispersion used to make the granular mixture. The determination of the filler content is primarily related to its effect on the studied pharmacopeial characteristics of the granules, such as disintegration ($y1$), bulk density ($y2$), fluidity ($y3$), crushing strength ($y4$), abrasion strength ($y5$), and dissolution ($y6$).

Formalization of the problem consists of formulating the problem in a form suitable for solving by experimental and statistical methods:

$$y_i = f(d), \quad 0.33 \le d \ge 1,$$

$$180 \le y1(d) \le 318, \quad 0.79 \le y2(d) \le 0.86,$$

$$6.7 \le y3(d) \le 9.5, \quad 184 \le y4(d) \le 198,$$

$$0.47 \le y5(d) \le 0.95, \quad 5.15 \le y6(d) \le 5.44.$$

For multi-criterion optimization, an optimality criterion was proposed, which determines the coordinates of the point in the admissible decision domain that satisfies the condition of simultaneous equidistance and equal approximation of all individual criteria from their optimal values. Forming a generalized criterion and determining optimal values of individual pharmacy-technological characteristics were based on the empirical dependencies obtained in the regression analysis $y_i=f(d)$.

From the mathematical point of view, the established regression equations are functions of a single variable. In turn, each of them is a unit vector in a six-dimensional vector function $Y(d)=(y1(d), y2(d), y3(x), y4(d), y5(d), y6(d))$. Thus, the problem of one-parameter optimization finds its application in the implementation of multi-criteria optimization.

The use of statistical methods in PTRQF by researchers who are not experts in mathematical statistics can lead to multivariate and contradictory results. One of the problems is that researchers who use statistics to establish a mathematical description of the influence of technological factors on the pharmacy-technological indicators (PTI) under study believe that the regression equation should reflect the real structure of the relationships. Statisticians speak only about a certain set of statistical properties [3, 15].

We consider some features of regression analysis in PTRQF in the example of establishing regression equations for the dependencies of these PTI on the ratio of filler to solid dispersion (factor d).

As is well known, one of the most important prerequisites for classical regression analysis is the need to know the structure of the model, which determines the choice of the research plan and the calculation of the coefficients of the regression equation. It is impossible to know for sure how factor d will affect PTI – linearly or non-linearly. Therefore, we form a matrix with the minimum number of experiments for this case [8, 16]. Choosing factor levels ($d1$=1; $d2$=0,33; $d3$=0,5) were based on the availability of a priori information and the experimenters' own experience.

We interpreted the experimental data graphically to form a general idea of the mathematical description of the studied dependencies. All the objective functions have a nonlinear dependence on the factor d, but only the bulk density ($y2$) has an extreme value in the specified factor space.

The graphical comparative analysis of the experimental and theoretical dependencies of PTI on factor d using regression analysis demonstrates the possibility of mathematical description by various functions. For example, the disintegration time of granules can be effectively described by linear, exponential, quadratic, and logarithmic dependencies with a high coefficient of determination (Fig. 1).

According to the regression equation established by experiments at three levels (results from three parallel experiments were used) – $y1(d)=378.05-200.08d$ – high accuracy at the basic points of the experiment, which does not exceed 3 %. This calculation error is acceptable. However, the calculation of statistical indicators indicates the insignificance of the equation as a whole and its coefficients (Fig. 2).

The inclusion of the fourth test point leads to an increase in the relative calculation error at one of the base points to 4.28 %, which is not acceptable. However, the statistical characteristics of the equation indicate its significance and the significance of its coefficients (Fig. 3).

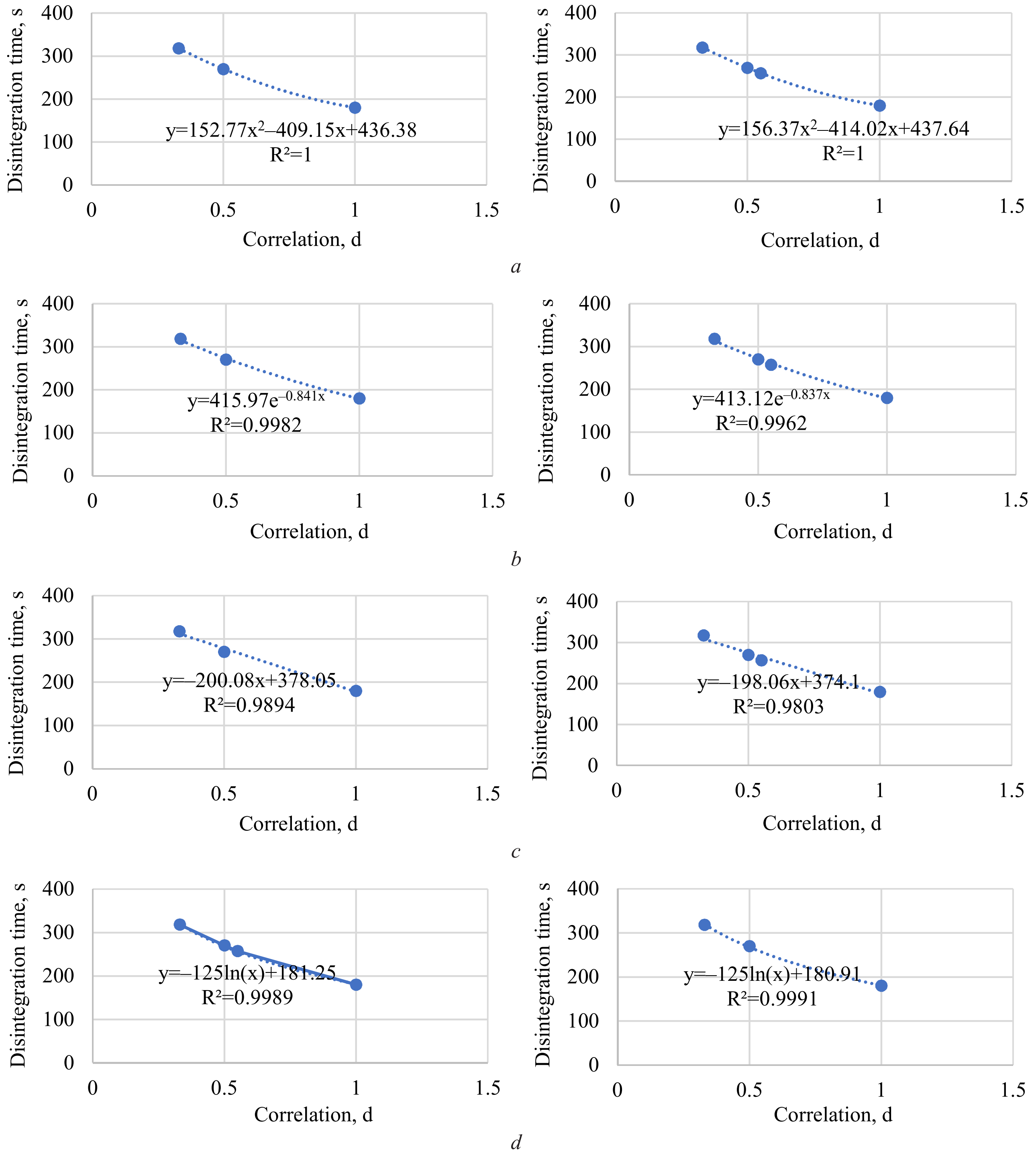


Fig. 1. Graphical comparative analysis of the experimental and theoretical $y1=f(d)$ dependencies using some types of mathematical equations, performed using MS Excel: *a* – quadratic; *b* – exponential; *c* – linear; *d* – logarithmic

The logarithmic version of the regression equation – $y1(d)=180.91-125\cdot\ln(d)$ – is statistically significant (Fig. 4). The maximum relative error of the calculation at the base points does not exceed 0.8 %. The equation is effective and, based on practical experience, correctly describes the flow of the studied factor.

The most successful mathematical description is the quadratic regression equation $-y1(d)=436.383-409.148d+152.766d^2$, which has the maximum coefficient of determination (Fig. 1). There is no relative error in the calculations based on the equation at the base points. To evaluate the statistical characteristics, it is necessary to add another experimental point – $y1(0.55)=257$. The coefficients of the equation slightly change: $y1(d)=437.64-414.02d+156.37d^2$. The significance of the regression equation according to Fisher's criterion is proved (significance of F=0.00367<0.05), and its coefficients (p-values of the coefficients are less than 0.05) (Fig. 5).

ANOVA						
	df	SS	MS	F	Significance F	
Regression	1	9712,001649	9712,001649	93,386112	0,06564414	
Residua	1	103,9983512	103,9983512			
Total	2	9816				
	Coefficients	Standart Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	378,0502885	13,93480676	27,12992687	0,023455	200,991781	555,1088
X Variable 1	-200,08244	20,70464692	-9,663648988	0,0656441	-463,159923	62,995042

Fig. 2. The results of variance analysis of the linear equation obtained from three experiments, performed using MS Excel

ANOVA						
	df	SS	MS	F	Significance F	
Regression	1	9622,919792	9622,919792	99,292261	0,00992164	
Residua	2	193,8302079	96,91510395			
Total	3	9816,75				
	Coefficients	Standart Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	374,0978394	12,81014561	29,20324646	0,0011705	318,980231	429,21545
X Variable 1	-198,063596	19,87682247	-9,964550213	0,0099216	-283,58666	-112,5405

Fig. 3. The results of the analysis of variance of the linear equation obtained from four experiments, performed using MS Excel

ANOVA						
	df	SS	MS	F	Significance F	
Regression	1	9806,958476	9806,958476	1084,6577	0,01932415	
Residua	1	9,041524233	9,041524233			
Total	2	9816				
	Coefficients	Standart Error	t Stat	P-value	Lower 95%	Upper 95,0%
Intercept	180,9106901	2,865688007	63,12993239	0,0100834	144,498672	217,32271
X Variable 1	-125,023146	3,796156242	-32,93414118	0,0193241	-173,257884	-76,78841

Fig. 4. The results of the analysis of variance of the logarithmic equation obtained from three experiments, performed using MS Excel

ANOVA						
	df	SS	MS	F	Significance F	
Regression	2	9816,61785	4908,308925	37142,079	0,00366901	
Residua	1	0,132149547	0,132149547			
Total	3	9816,75				
	Coefficients	Standart Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	437,6444216	1,725914328	253,5725062	0,0025106	415,714601	459,57424
X Variable 1	-414,01953	5,688283265	-72,78461895	0,0087461	-486,296022	-341,743
X Variable 2	156,3673979	4,084288533	38,28510073	0,0166246	104,471592	208,2632

Fig. 5. The results of the analysis of variance of the quadratic equation obtained from four experiments, performed using MS Excel

The results of the interval estimation of the quadratic regression at the baseline points are fully acceptable:

$y1(1)=180.00\pm0.81$ s; $y1(0.5)=269.72\pm0.45$ s;

$y1(0.33)=318.04\pm0.62$ s; $y1(0.55)=257.23\pm0.43$ s.

The confidence interval for the mean value with 95 % reliability is $y1(0.595)=256.25\pm0.94$ s. The standard error of the average result determining (P=0.95) – ±0.37 %, is within acceptable limits.

The regression analysis results show that the researcher has a choice regarding the regression equation. Statistical characteristics are not always decisive when making the final choice in PTI, but they cannot be completely neglected.

In this case, we choose the quadratic regression equation based on the simplicity of the mathematical expression and the correspondence to the researcher's understanding of the process under study. The minimum number of experiments that constitutes a rich experiment plan for establishing this type of equation does not objectively allow for its analysis of variance, but is completely acceptable for a particular study [17].

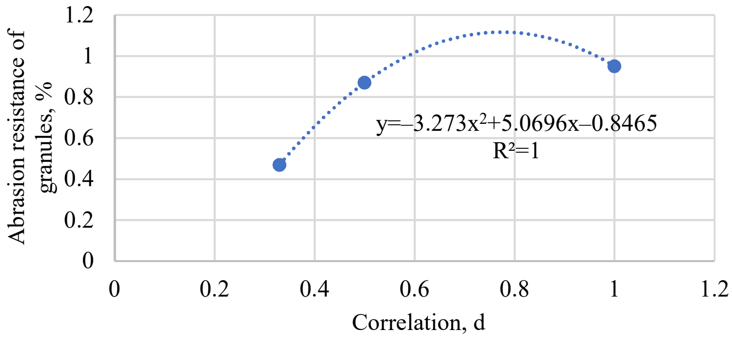
The processing of experimental data on the effect of filler content on the strength of granules showed that using the quadratic regression equation $y5=f(d)$, high accuracy can be achieved at the basic points of the experiment (Fig. 6). However, in the intervals between the experimental points, the values calculated by the quadratic model will differ from the real situation, despite acceptable statistical characteristics (Fig. 7) using an additional experimental point within the factor space. The abrasion resistance cannot exceed 1 %. In such cases, the statistical characteristics that prove the significance of the equation, as well as the model coefficients, are irrelevant.

The coefficients of the regression equations obtained at three points – $y5(d)=-0.847+5.07d-3.273d^2$ and for the four points – $y5(d)=-0.843+5.055d-3.262d^2$ do not differ significantly. However, the first equation cannot be objectively analyzed for significance by statistical characteristics. However, it can be effectively used as a mathematical description of the relationship $y5=f(d)$ with a value limit of 0.95, despite the impossibility of obtaining adequacy estimates using standard statistical indicators.

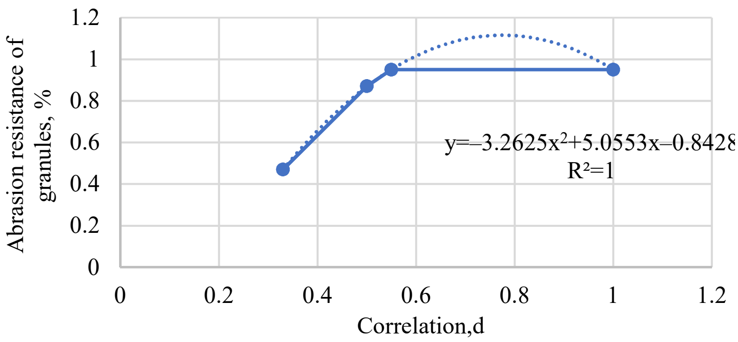
If necessary, they can be calculated using an additional test point. The confidence interval of the average value of the function with a reliability of 95 % for the equation established by four points is 0.95±0.0027 %. The standard error of the average result (P=0.95) is within acceptable limits of ±0.3 %.

Finally, the pharmaco-mathematical description of the dependence of the abrasion strength of the granules on the filler content is written in the form:

$$\begin{cases} y5(d)=\text{if}\left(\begin{matrix} d\le 0.55,-0.847+ \\ +5.07d-3.273d^2,0.95 \end{matrix}\right), \\ 0.33\le d\ge 1, \\ 0.47\le y5(d)\le 0.95. \end{cases} \quad (1)$$



a



b

Fig. 6. Graphical comparative analysis of the experimental and theoretical dependences of $y5=f(d)$, performed using MS Excel: *a* – 3 experiments; *b* – 4 experiments

ANOVA						
	df	*SS*	*MS*	*F*	*Significance F*	
Regression	2	0,158398873	0,079199436	70268,51611	0,002667492	
Residua	1	1,1271E-06	1,1271E-06			
Total	3	0,1584				
	Coefficients	*Standart Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	-0,842838756	0,005040424	-167,215853	0,003807128	-0,90688341	-0,7787941
X Variable 1	-3,262527662	0,011927907	-273,520557	0,002327492	-3,41408609	-3,11096924
X Variable 2	5,0553439	0,016612272	304,3138192	0,002091977	4,844264973	5,26642283

Fig. 7. Results of the analysis of variance of the quadratic equation obtained from four experiments, performed using MS Excel

The regression equations for the rest of the dependencies were established in a similar way, taking into account the above points:

$$\begin{cases} y1(d)=436.383-409.148d+152.766d^2, \\ y2(d)=0.912-0.437d+0.385d^2, \\ y3(d)=13.556-14.969d+8.112d^2, \\ y4(d)=202.752-12.255d-6.497d^2, \\ y5(d)=\text{if}\begin{pmatrix} d\le 0.55,-0.847+ \\ +5.07d-3.273d^2,0.95 \end{pmatrix}, \\ y6(d)=\text{if}\begin{pmatrix} d\le 0.676,4.594+ \\ +2.098d-1.252d^2,5.44 \end{pmatrix}. \end{cases} \quad (2)$$

Establishing the optimal composition of the dispersion is associated with the condition of ensuring the desired values of the studied pharmacy-technological indicators of granule quality, which are defined in the problem statement. According to the conditions of the study and considering a priori information, it is recommended to approximate the analyzed indicators to the values from the corresponding experimental intervals: decay – to the minimum; bulk density – to a minimum; flowability – to the maximum; crushing strength – up to the maximum; abrasion resistance – to the minimum; dissolution – to the maximum.

The obtained regression equations establish the domain of acceptable solutions for solving the optimization problem, taking into account the existing constraints for each individual PTI (Fig. 8).

At the next stage, the proposed generalized function (optimality criterion) is formed to determine from the region of admissible values the coordinate of the point whose minimization will fulfil the condition of both equidistant [18, 19] and equal approximation of all functions from their optimal values, which were identified during the regression analysis [20]:

$$R(d)=\left(\frac{y1(d)}{180}-1\right)^2+\left(\frac{y2(d)}{0.788}-1\right)^2+\left(\frac{y3(d)}{9.5}-1\right)^2+\left(\frac{y4(d)}{198}-1\right)^2+\left(\frac{y5(d)}{0.47}-1\right)^2+\left(\frac{y6(d)}{5.44}-1\right)^2. \quad (3)$$

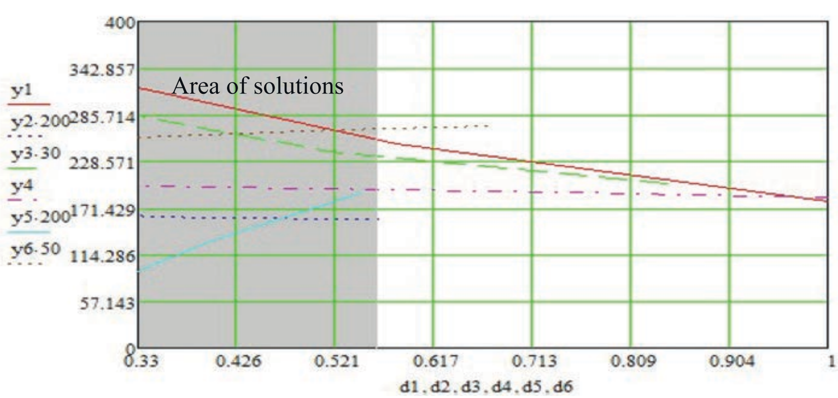


Fig. 8. Graphical representation of the area of acceptable values using Mathcad 14

The calculations were performed in Mathcad 14. The minimum value of the optimality criterion corresponds to the optimal filler content. This value is 0.364 and ensures the disintegration time of the granules ($y1$) – 307.694 s (compared to 180 s, a deviation of 71 %), bulk density ($y2$) – 0.804 g/ml (compared to 0.79 g/ml a deviation 2 %), friability ($y3$) – 9.182 s^{-1} (compared to 9.5 s^{-1} a deviation 3 %), crushing strength ($y4$) – 197.43 H (compared to 198 H a deviation 0.3 %), abrasion strength ($y5$) – 0.565 % (compared to 0.47 % a deviation 17 %), dissolution ($y6$) – 5.192 % (compared to 5.44 % a deviation 5.4 %). For all indicators, the conditions set by the researchers are met, and all indicators are equally close to their respective values. None of the indicators exceeds the limits set by the researcher and has the minimum possible deterioration relative to the individually determined optimum.

5. Discussion

It is shown that the use of statistical methods in PTRQF is an effective direction in solving the issues of multiple-criteria optimization. The proposed generalized optimization criterion, constructed using statistical methods, is a simple and flexible mathematical method for establishing an optimal solution that fulfils the condition of equal approximation of all studied individual optimization criteria from their optimal values revealed in the course of regression analysis.

However, the effectiveness of statistical methods in PTRQF is due to a number of objective reasons related to the peculiarities of pharmaceutical research objects. It is not always possible to comply with the prerequisites of classical regression analysis due to the uncertainty of the model structure, which directly determines the choice of the research plan and the calculation of the coefficients of the regression equation, and the attempt to minimize the size of the experimental base. These points lead to the need to move from mathematical statistics to data analysis. In this regard, it is advisable for the researcher not to use statistical software tools for processing experimental data but to choose the algorithm of actions and methods of their evaluation independently [21].

Practical importance. The proposed methodology generalizes the approach to determining optimal technological parameters in the development of drug technology. It helps the researcher to prevent subjective erroneous or ineffective decisions in the multiple-criteria space formed by the studied pharmacotechnological parameters.

Study limitations. The process of establishing regression equations, based on which a generalized optimization criterion is formed, becomes more complicated with an increase in the number of factors under study. As a result, there is a need to consider single-factor dependencies, provided that other factors are fixed to predict the structure of regression equations, which objectively leads to a significant increase in experiments.

Prospects for further research. It is planned to continue testing the methodology for determining the optimal technological parameters of medicines in the development of technology for various dosage forms.

6. Conclusions

A methodological approach to determining the optimal solution in pharmaceutical technological research with quantitative factors using experimental and statistical methods and the theory of multiple-criteria optimization has been tested on the example of determining the optimal content of filler in a solid dispersion in the manufacture of granules. The optimal ratio of filler to solid dispersion was determined, which ensures the maximum approximation of all studied pharmacy-technological parameters of granules to their optimal values. None of the indicators exceeds the limits set by the researcher and has the minimum possible deterioration relative to the individually determined optimum.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this study, including financial, personal, authorship, or other, that could affect the study, and its results presented in this article.

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Data availability

Data will be provided upon reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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