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Research Article

Development of amlodipine and enalapril combined tablets based on quality by design and artificial neural network for confirming of qualitative composition

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Abstract

Using approaches of Quality by design, namely dispersion analysis, random balance method, regression analysis and neural networks, the composition and technology tablets based on amlodipine besylate and enalapril maleate have been developed. Using dispersion analysis was determined the effect of 30 excipients on 10 pharmaco-technological parameters of tablets. With the help of the desirability function, the leaders of the excipients were selected from 6 functional groups. It was confirmed that the composition with the best pharmaco-technological parameters, determined by using statistical methods, coincides with the results studies the synthesized Feed-forward neural network. The quantities of preferable excipients at 3 levels were identified by the random balance method. The relationship between the studied factors and the quality of the tablets was described by regression equations. Based on the placement of equal output lines, the optimal composition of amlodipine tablets with enalapril was established.

Keywords

amlodipine and enalapril tablets, artificial intelligence, pharmaceutical development, quality by design

Introduction

Every year 17 million people worldwide die from the cardiovascular disease, including heart attacks and strokes. Cardiovascular disease is the leading cause of death and disability in most countries. By 2030, more than 23 million people are expected to die from these diseases. They will be the leading cause of death on the planet (Virani et al. 2020). One of the first among this pathology is hypertension, that is a major risk factor for stroke, myocardial infarction, heart, and kidney failure. Therefore, the primary task of the pharmaceutical industry is the development and implementation in the production of highly effective cardiovascular medications (Kjeldsen 2018).

In order to increase the effectiveness of pharmacotherapeutic benefit and rise safety combined drugs are obtained. The main advantage of combined antihypertensive therapy is the merging of active pharmaceutical ingredients with different mechanisms of action to achieve additional antihypertensive activities and reduce side effects (Lopatowska et al. 2018). Usage of scientifically based drugs from different pharmacological groups in

one medicine is the most beneficial. Herewith, the safety and effectiveness of antihypertensive therapy is increased. Moreover, the cost of treatment is reduced and patient compliance is enhanced by single tablet regiment (Guerrero-García and Rubio-Guerra 2018).

Angiotensin-converting enzyme inhibitors (enalapril) and calcium antagonists (amlodipine) are the most often compounded in combination therapy (Pongpanich et al. 2018). The ACCOMPLISH study showed that mortality and morbidity from cardiovascular disease were reduced by amlodipine in combination with an ACE inhibitor. The progression of kidney disease was also decreased. (Okuda et al. 2018). Since the release of amlodipine in the early 1990s, it remains one of the world's top five pharmaceutical products with sales of $ 1 billion. Amlodipine is the best agent for both monotherapy and combination therapies to reduce the severity of cardiovascular disease worldwide (Khan et al. 2021). Combinations of active pharmaceutical ingredients and their concentrations are an important part of research when choosing a treatment for arterial hypertension.

The quality and bioavailability of tablets depends on many factors. The main are the physico-chemical properties of the active pharmaceutical ingredients, correctly selected excipients and obtaining tablets with a given quality and the stability of the drug in the future. The quality of the medicinal product is ensured primarily by compliance with the pharmaco-technological parameters and their indicators for each dosage form.

According to the pharmacopoeial requirements, the main pharmaco-technological indicators of powders are bulk density and tapped density. These indicators characterize the ability of raw materials to compact. They will allow further calculation of such indicators as the loading volume of technological equipment. The criterion for evaluating the flowability of the tableting blend is flowability. The flowability study will enables to investigate the ability to fill the appropriate press form. The angle of angle of repose is an additional characteristic of the flowability of the tableting blend or granulate. For well-flowing materials, its value is 25–40° (Council of Europe 2021).

The main pharmaco-technological indicators of tablet quality are: uniformity of mass, resistance of tablets to crushing, friability of uncoated tablets, disintegration. Uniformity of mass shows the deviation of each of the 20 tablets separately from the average weight and should not exceed 5%. The resistance of tablets to crushing characterizes their strength and is defined as the average value for 10 tablets. The pharmacopoeia describes the acceptance criteria for tablets with different diameters (for tablets with a diameter of 8 mm - at least 25 N). Friability of uncoated tablets is carried out in order to find out the resistance of tablets to the action of mechanical impact, or abrasion. Friability should not exceed 1% and tablets should not have chips or cracks. Disintegration allows you to determine the time of disintegration of tablets in a liquid environment, usually water. Disintegration requirements for each dosage form are different. Uncoated tablets should disintegrate as quickly as 15 minutes (Council of Europe 2021). In addition, the appearance of the tablets was investigated which is decisive for consumer compliance.

Quality by design (QbD) is a sound approach to pharmaceutical implementation. It is taken by the developers as a basis from the beginning of the formation of research objectives till the release of final drugs (Kadam et al. 2017). This is especially important when creating and researching tablet drugs because the process of developing the optimal composition and technology of tablets is multi-stage. The application of QbD principles in drug development ensures the quality of medicines for patients and doctors, as well as reducing risks at the production stages (Singh et al. 2018). It is possible to improve the quality of the drug and its production process (Schlindwein 2018) with the help of qualitative planning of the experiment, collection of preliminary data on the studied object, inclusion of all factors and control of the drug, taking into account all pharmacological indicators (Zhang and Mao 2017). QbD-based planning brings results that minimize the amount of research to develop the optimal composition and technology of the drug.

As a general rule, the practical implementation of QbD in the development of new pharmaceutical products can go through the following steps:

1. Define the desired performances of the product and identify the Quality Target Product Profile: including dosage form, delivery systems, dosage strength(s), etc;
2. Identification of the Critical quality attributes: including physical, chemical, biological, or microbiological properties or characteristics of an output material including finished drug product;
3. Identification of possible Critical Material Attributes: including physical, chemical, biological, or microbiological properties or characteristics of an input material and Critical Process Parameters: parameters monitored before or in process that influence the appearance, impurity, and yield of final product significantly;
4. Setup and execution of Design of experiment to link Critical Material Attributes and Critical Process Parameters to Critical quality attributes and get enough information of how these parameters impact Quality Target Product Profile. Thereafter, a process of Design Space should be defined, leading to an end product with desired Quality Target Product Profile;
5. Identify and control the sources of variability from the raw materials and the manufacturing process;
6. Continually monitor and improve the manufacturing process to assure consistent product quality (Zhang and Mao 2017).

The principles of QbD are enshrined in the regulations of pharmaceutical development (ICH Q8 (R2)), quality

risk management (ICH Q9) and pharmaceutical quality system (ICH Q10) (Sangshetti et al. 2017). Successful use of QbD has been demonstrated in the development of quetiapine fumarate prolonged-release matrix tablets (Gavan et al. 2017), during the simultaneous quantification of telmisartan, amlodipine and chlorthalidone (Palakurthi et al. 2020), and in the use of a 3D printer for printing immediate-release tablets (Than and Titapiwatanakun 2021).

One of the modern methods of medicines manufacturing is an area of artificial intelligence known as artificial neural networks. Artificial neural networks use personalized knowledge and learn from experimental data to solve complex problems. Technologies involving artificial intelligence have become universal tools that can be used everywhere at different stages of drug development, such as the identification and verification of target medicine, developing of new drugs, drug reprofiling, improving the research and development efficiency, aggregating, and analyzing biomedical information and refining the decision-making process for involving patients in clinical research (Das et al. 2016). This potential use of artificial intelligence makes it possible to counteract the inefficiencies and uncertainties that arise in classical drug development methods, minimize bias and human interference in the process (Mak and Pichika 2019; Pu et al. 2019). Artificial intelligence was used to simulate the release of a drug from tablets containing lignin as an excipient (Pishnamazi et al. 2019) and for forecasting of disintegrating oral tablets (Han et al. 2018). It was applied in the manufacture of optimized mucoadhesive buccal tablet containing flurbiprofen and lidocaine for the treatment of toothache (Hussain et al. 2016), in the development of a floating tablet containing rosiglitazone maleate (Güler et al. 2017) and in optimization of the formulation of a self-emulsifying drug delivery system containing rosuvastatin (Vu et al. 2020).

In connection with the above, the creation of medicine based on QbD for the treatment of hypertension, namely the combined tablets based on antihypertensive substances of different pharmacological groups is relevant for pharmaceutical science and practice.

The aim of the work was to develop the qualitative and quantitative composition of amlodipine and enalapril combined tablets based on QbD using an artificial neural network.

Materials and methods

Materials

Enalapril maleate from Zhejiang Huahai Pharmaceutical Co., Ltd, China and Amlodipine besylate from Anek Prayog, India were used as APIs for the development of the drug.

For the study, excipients were grouped into 6 factors by functional purpose (Table 1).

Table 1. Factors and their levels studied in the development of amlodipine and enalapril combined tablets.

Factor	Factor level
A – filler	a_1 – microcrystalline cellulose 101
	a_2 – sucrose
	a_3 – calcium hydrogen phosphate
	a_4 – corn starch
	a_5 – pregelatinized starch
B – disintegrant	b_1 – croscarmellose sodium
	b_2 – povidone K17
	b_3 – crospovidone XL-10
	b_4 – sodium starch glycolate
	b_5 – potato starch
C – binder	c_1 – pregelatinized starch
	c_2 – macrogol 20
	c_3 – povidone K17
	c_4 – povidone K30
	c_5 – hypromellose E5
D – glidant	d_1 – aerosil 200
	d_2 – aeroperl 300
	d_3 – talc
	d_4 – neusilin US-2
	d_5 – aerosil 200 + talc (1:1)
E – lubricant	e_1 – magnesium stearate
	e_2 – calcium stearate
	e_3 – stearic acid
	e_4 – sodium stearyl fumarate
	e_5 – polyethylene glycol 4000
F – stabilizing	f_1 – sodium bicarbonate
	f_2 – maleic acid
	f_3– citric acid monohydrate
	f_4 – magnesium carbonate
	f_5 – lactic acid

Statistical methods

A generalized scheme of research on the development of amlodipine and enalapril combined tablets is shown in Fig. 1.

To implement the experiment mathematical and statistical methods of planning the experiment and processing the results of the study were used.

Method of dispersion analysis

Method of dispersion analysis based on the second-order hyper-Greek-Latin square. Analysis of variance is a statistical method used to divide the total sum of squares of observations into components due to the influence of various factors, their interactions and random variables. Dispersion analysis was used to be able to statistically identify the influence of various factors on the variability of the studied feature (Hroshovyi et al. 2008). The second order hyper-Greek-Latin square made it possible to reduce the number of studies from 7776 to 27. The plan of the experiment is shown in Table 2.

Statistical processing of the results of experimental studies of intermediates and tablets was performed by the method of dispersion analysis. Ranked batches of advantages were built for each parameter using Duncan's criterion. It is one of the multiple comparison procedures that

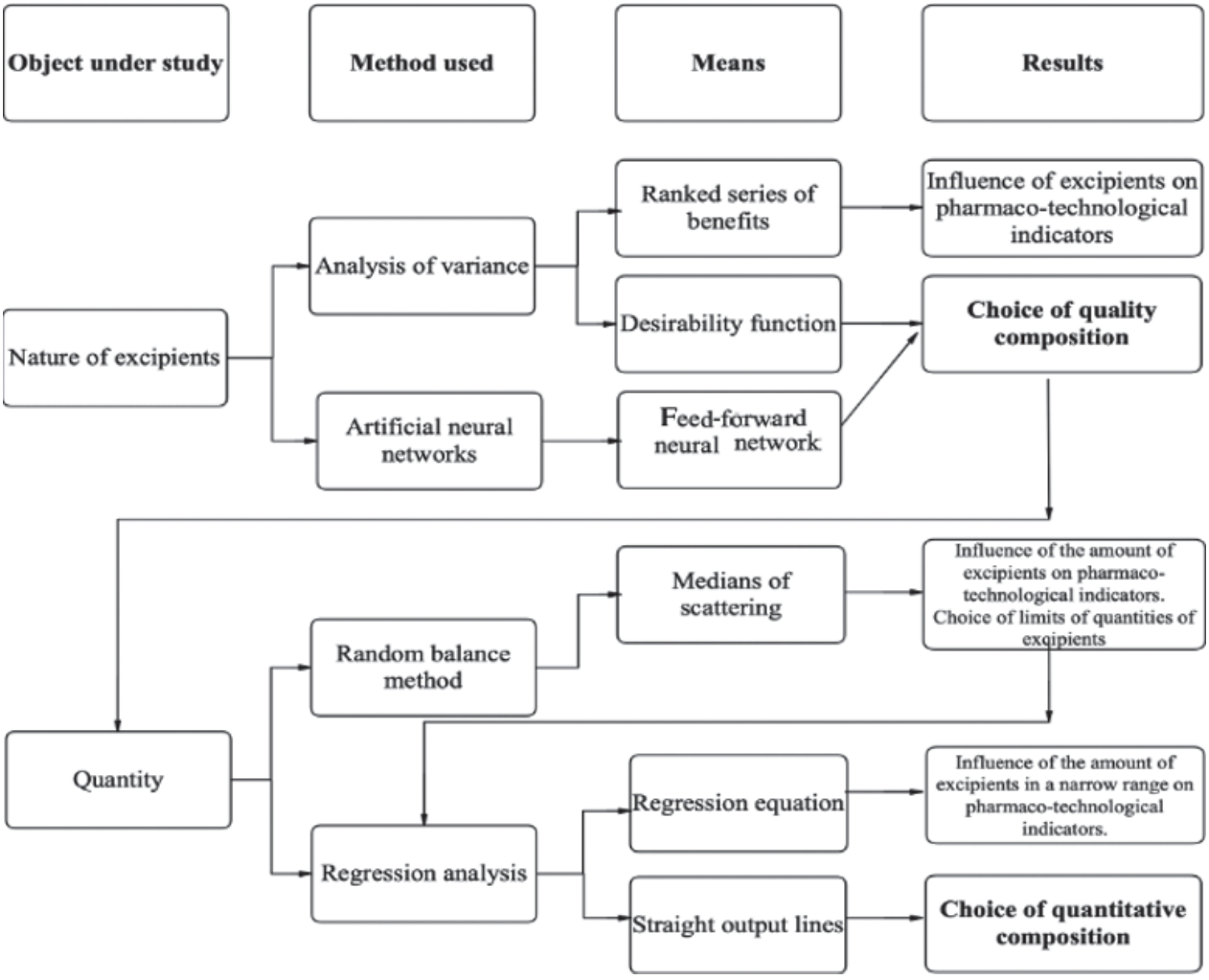

Figure 1. Research algorithm for the development of qualitative and quantitative composition of amlodipine and enalapril combined tablets.

are used in statistical analysis. Duncan's multiple range test or Duncan's test, or Duncan's new multiple range test, provides significance levels for the difference between any pair of means (Bewick et al. 2004), therefore every indicator was studied twice. Based on them, the influence of excipients on the studied pharmaco-technological parameters was determined.

Desirability function

The leaders in all respects were selected from each group of excipients for further studies on the selection of the optimal quality composition of amlodipine and enalapril combined tablets. The choice of the best combinations of excipients in the production of tablets was carried out using a generalized quality indicator such as the desirability function. The research results were converted into dimensionless values from 0 to 1 by using the scale shown in Fig. 2. The 10^{th} root of the product of the obtained values (D, D' in Table 7) was subjected to variance analysis.

The root of the tenth degree of the product of the obtained values was subjected to dispersion analysis. Based on these results, ranked batches of benefits for each functional group of excipients were built. That allowed to identify leaders among them for the introduction of tablets.

Principles of the artificial neural networks

In applied fields of science, the problem of approximating experimental data often arises. For a qualitative solution to this problem, feed-forward neural networks (multilayer perceptron). They are often called universal approximators. It is mathematically proven that with a sufficiently large number of neurons in the hidden layer, the feed-forward neural network is able to approximate any vector nonlinear function with a limited number of breakpoints with a given accuracy. The minimum required number of neurons in the hidden layer is determined heuristically based on the permissible approximation error.

The ability of neural network to high-quality approximation of complex dependencies is achieved due to the

Table 2. Experimental plan based on the second-order hyper-Greek-Latin square.

Factor / Batch	A	B	C	D	E
1	a_1	b_1	c_1	d_1	e_1
2	a_1	b_2	c_2	d_2	e_2
3	a_1	b_3	c_3	d_3	e_3
4	a_1	b_4	c_4	d_4	e_4
5	a_1	b_5	c_5	d_5	e_5
6	a_2	b_1	c_2	d_3	e_4
7	a_2	b_2	c_3	d_4	e_5
8	a_2	b_3	c_4	d_5	e_1
9	a_2	b_4	c_5	d_1	e_2
10	a_2	b_5	c_1	d_2	e_3
11	a_3	b_1	c_3	d_5	e_2
12	a_3	b_2	c_4	d_1	e_3
13	a_3	b_3	c_5	d_2	e_4
14	a_3	b_4	c_1	d_3	e_5
15	a_3	b_5	c_2	d_4	e_1
16	a_4	b_1	c_4	d_2	e_5
17	a_4	b_2	c_5	d_3	e_1
18	a_4	b_3	c_1	d_4	e_2
19	a_4	b_4	c_2	d_5	e_3
20	a_4	b_5	c_3	d_1	e_4
21	a_5	b_1	c_5	d_4	e_3
22	a_5	b_2	c_1	d_5	e_4
23	a_5	b_3	c_2	d_1	e_5
24	a_5	b_4	c_3	d_2	e_1
25	a_5	b_5	c_4	d_3	e_2

segmentation of the input space into subspaces by the action of non-linear functions of neuron activation and the subsequent interpolation of neuron data on each segment. The analysis of the work of neural network proves that in some cases input signals, some neurons work and others are passive, however, other neurons are already working for other input signals.

In this work the set task is to design a feed-forward neural network that approximates the complex nonlinear dependence of ten pharmaco-technological indicators of tablets on their six-factors qualitative composition.

Design of the feedforward neural network

The design of the artificial neural network was carried out using the commercially available Matlab software product the Neural Network Toolbox through the following five main steps: 1 - training data set collection, 2 - data processing, 3 - selection of network architecture, 4 - network training, 5 - evaluation of the quality of learning.

The training set of data was the result of 25 experiments for different level combinations of 6 qualitative factors - A, B, C, D, E, F. Each of factors had 5 levels - 1, 2, 3, 4, 5. As a result of each experiment, 10 pharmaco-technological indicators of tablets y1 ... y10 were determined. So, the set of data for training the network includes an input array of size 6×25=150 and an output array of size 10×25=250. Such a set of data is not large. However, it is representative since it was obtained based on the mathematical theory of experiment planning. As is well known the representativeness

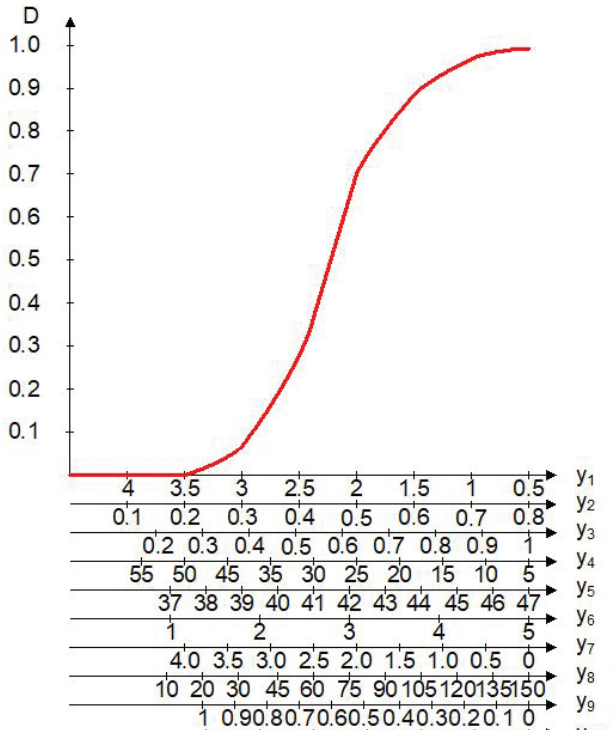

Figure 2. Desirability function.

of the training data set is fundamentally necessary for the successful synthesis of a neural network.

The architecture of a neural network includes the number of inputs and outputs of the network, the number of neurons in the hidden and output layers, and the type of their activation function. The inputs to the network are 6 factors, so it will have 6 inputs. The output values of the network are 10 indicators of the tablets, so it will have 10 outputs. Accordingly, there will be 10 neurons in the output layer. To date, there is no theoretically justified method for choosing the number of neurons in the hidden layer of the S1 network. Some practical recommendations are known, but they are rather inaccurate. In general, the choice of S1 must satisfy 2 conditions. First, S1 should be small enough to avoid the phenomenon of over-learning, when the network remembers the training data but does not generalize it. Second, S1 must be large enough for the network to be able to approximate complex functional dependence.

Taking into account the specified conditions, the number of neurons in the hidden layer S1=11 was empirically selected with an activation function of the hyperbolic tangent ("tansig") type. Neurons of the output layer usually have a linear activation function. However, we applied the "tansig" activation function because the network had higher accuracy in this case. The scheme of the synthesized feed-forward neural network with the architecture of the 6-11-10 type is shown in Fig. 3.

The learning quality of the designed neural network was evaluated by regression analysis. The results are shown in Fig. 4, where along the abscissa axis of the graphs, the experimental values of the indicators of the tablets are plotted,

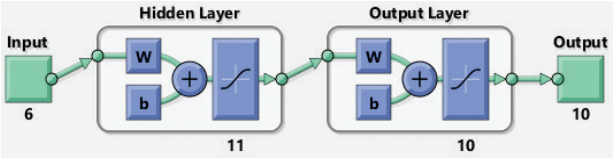

Figure 3. Scheme of the synthesized neural network.

and along the ordinate axis - the estimates of these indicators, which are formed by the neural network. These graphs show that the training quality of the network is not perfect when the regression coefficient R=1 is reached. However, the obtained training results can be qualified as pretty good.

With the help of the synthesized neural network, estimates of indicators of tablets for all possible combinations of 5 levels of 6 factors by quantity $5^6 = 15625$ were obtained. From the obtained data, variants of the combination of investigated excipients that ensure finding of all 10 pharmaco-technological indicators in the established ranges were selected.

Method of random balance

The method of random balance was used in the study of many quantitative factors that significantly affect the object of research. The use of this method makes it possible to reduce the number of test subjects and to make a research plan to optimize the processes of tablet technology. Construction of the experimental plan was performed by random mixing of complete factor plans. Significant factors were determined using scatter plots. The significance of the selected factors was checked using the t-test (Hroshovyi et al. 2008).

Based on the results of previous studies, the excipients that showed the best results were allocated in 7 factors, that were studied at the lower «-», basic «0» upper «+» according to Table 3. The list of studied quantitative factors is given in Table 3.

Table 3. Quantitative factors and their levels studied in the development of amlodipine and enalapril combined tablets.

Factor	Factor level		
	lower «-»	basic «0»	upper «+»
x_1 – amount of calcium hydrogen phosphate, g	0.14	0.15	0.16
x_2 – amount of croscarmellose sodium, g	0.006	0.008	0.010
x_3 – amount of povidone K17, g	0.004	0.005	0.006
x_4 – amount of aerosil 200, g	0.001	0.0015	0.002
x_5 – amount of talc, g	0.001	0.0015	0.002
x_6 – amount of sodium stearyl fumarate, g	0.001	0.0015	0.002
x_7 – amount of citric acid monohydrate, g	0.004	0.005	0.006

Using the method of random balance, an experimental plan was drawn up to study seven factors (Table 4).

10 batches of experiments were performed, that differed in the quantitative ratio of excipients. The active substances were added to all batches in equal amounts, the amount of sucrose was added to obtain an average weight of 0.2 g per 1 tablet.

Method of regression analysis

The method of regression analysis was used to analyze and process experimental data when influencing the response of only quantitative factors. Regression analysis allows you to get a mathematical model of the process in the form of a regression equation and analyze this equation.

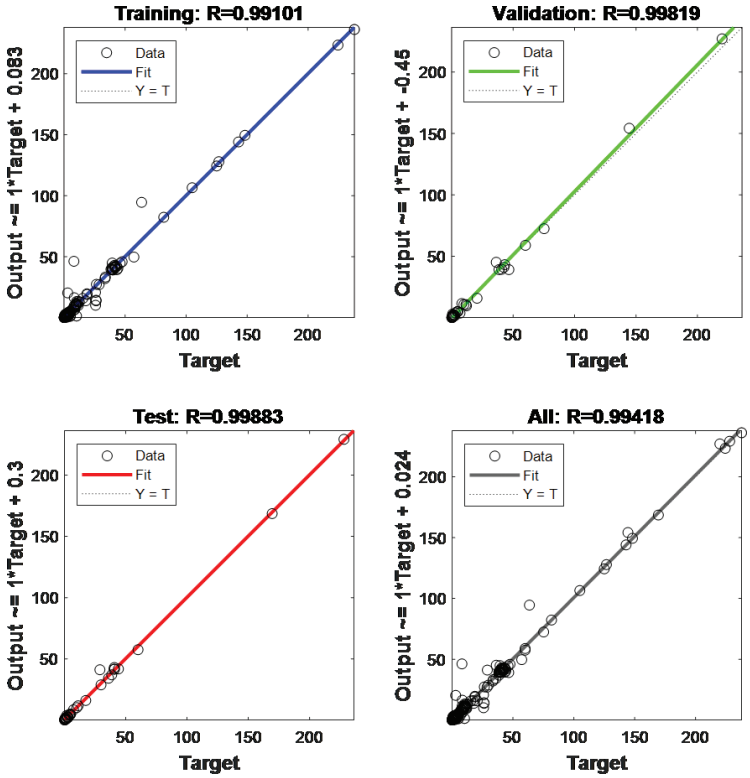

Figure 4. Regression assessment of the quality of neural network training with S1 = 19.

Table 4. Experimental plan for the development of amlodipine and enalapril combined tablets.

Batch	x_1	x_2	x_3	x_4	x_5	x_6	x_7
26	–	–	–	+	+	+	–
27	–	+	–	+	–	+	–
28	+	–	–	–	–	–	+
29	+	+	–	–	+	–	+
30	–	–	+	+	–	–	+
31	–	+	+	–	+	+	–
32	+	–	+	+	+	–	–
33	+	+	+	–	–	+	+
34	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0

For a detailed study of the impact of excipients, croscarmellose sodium, povidone K17 and anhydrous citric acid were selected. A list of three quantitative factors, each of which was studied at five levels, is given in Table 5.

Table 5. Factors and their levels studied in the development of amlodipine and enalapril combined tablets.

Factor	Lower star point «-α»	Lower level «-1»	Basic level «0»	Upper level «+1»	Upper star point «+α»
x_1 – amount of croscarmellose sodium, mg	4.318	5	6	7	7.682
x_2 – amount of povidone K17, mg	4.318	5	6	7	7.682
x_3 – amount of citric Acid monohydrate, mg	3.659	4	4.5	5	5.341

A symmetrical rotatable uniforms composite plan with second order was used for the study. The planning matrix of the experiment of amlodipine and enalapril combined tablets is shown in Table 6.

Table 6. Experiment planning matrix based on symmetrical rotatable uniforms composite plan with second order.

Batch	x_1	x_2	x_3
36	+	+	+
37	–	+	+
38	+	–	+
39	–	–	+
40	+	+	–
41	–	+	–
42	+	–	–
43	–	–	–
44	+α	0	0
45	–α	0	0
46	0	+α	0
47	0	–α	0
48	0	0	+α
49	0	0	–α
50	0	0	0
51	0	0	0
52	0	0	0
53	0	0	0
54	0	0	0
55	0	0	0

The relationship between the studied factors and the quality of amlodipine and enalapril combined tablets was described by regression equations. After checking the statistical significance of the coefficients, taking into account the Student's test (t_5 = 2.571; p = 0.05), the adequacy of the models was checked using the F-test ($F_{0.05;\ 10;\ 5}$ = 4.74). The regression equations were adequate if $F_{experimental} < F_{tabular}$.

The nature of the influence of the studied factors is determined by the values and signs of regression coefficients. The second-order model for three factors is:

$$y=b_0x_0+b_1x_1+ b_2x_2+ b_3x_3+ b_{12}x_1x_2+ b_{13}x_1x_3+ b_{23}x_2x_3+ b_{11}x_1^2+ b_{22}x_2^2+ b_{33}x_3^2 \quad (1),$$

where y is the value of the response (indicator);

b_0 – zero regression equation coefficient;

b_1, b_2, b_3 – factorial regression equation coefficients;

b_{12}, b_{13}, b_{23} – interaction coefficients of independent factors;

b_{11}, b_{22}, b_{33} – quadratic regression equation coefficients;

x_0 – zero factor;

x_1, x_2, x_3 - independent factors.

The magnitude of the coefficients and the signs in front of them indicate the nature and strength of the influence of the studied factors (Hroshovyi et al. 2008).

To be able to obtain information about the interaction between factors and to obtain the optimal composition of amlodipine and enalapril combined tablets, it is necessary to determine whether there is an extremum. If so, to find its coordinates. For this regression equation, obtained by the results of the experiment, was led to the canonical (standard) expression. The canonical transformation consists in choosing a coordinate system in which the geometric analysis of the equation is greatly facilitated. When making decisions on the model of the second order, the regression equation is transformed into a model for two factors with the stabilization of others at the optimal levels for the study area. Instead of the factor corresponding to the condition $b_{ii}>0$ i $|b_i|-\Sigma|-b_{ij}|>2|b_{ii}|$ the optimal value was entered, and the equation was converted into an expression with two variables. Based on the transformed regression equations, equal exit lines were constructed. According to the location of the lines, the optimal amounts of the other two studied factors were chosen.

Technology and methods of analysis

Amlodipine and enalapril combined tablets were made by wet granulation. This method of obtaining tablets includes the following stages: 1) mixing powders of active pharmaceutical ingredients with excipients from groups A and B; 2) moistening the mixture of powders with solutions of binders and stabilizing substances (groups C and F) to obtain a mass that sticks to the lump, but does not stick to the fingers; 3) obtaining wet granules, i.e. wiping the wet mass through the perforated plates; drying of wet granules; 4) obtaining dry granules, for which the dry mass is wiped

through perforated plates to destroy lumps and obtain homogeneous granules; 5) dusting of dry granules with substances from groups D and E; 6) compression of tablets.

The obtained granulate was investigated for loss of drying (Council of Europe 2021). The tablet mass was tested by bulk density and tapped density of powders, flowability, angle of repose according to pharmacopoeial methods. The following pharmaco-technological indicators were determined for tablets: uniformity of mass, resistance to crushing of tablets, friability of uncoated tablets and disintegration. Research methods are described in the European Pharmacopoeia.

Results

The results of the study of pharmaco-technological parameters of intermediates and tablets, and data of the desirability function, obtained on the basis of the dispersion analysis are shown in Suppl. material 1: The results of the study of pharmaco-technological parameters of intermediates and amlodipine tablets with enalapril, data of the desirability functions. By comparative analysis, it was confirmed that obtained by statistical methods of pharmaco-technological indicators of tablets are among the 10 best results (Table 7), which were determined by the synthesized feed-forward neural network.

The results of the study of the amounts of excipients by random balance in the development of amlodipine and enalapril combined tablets are shown in Table 8.

The results of the study of the amounts of excipients by regression analysis in the development of amlodipine and enalapril combined tablets are shown in Table 9.

Discussion

Based on the dispersion analysis of experimental data, the significance of the studied factors on the pharmaco-technological properties of powder masses and tablets was determined (responses). An analysis of these reviews revealed that the same excipient may improve one response but worsen another response at the same time. For example, when one of the studied excipients (povidone XL-10) has the best effect on the resistance of tablets to crushing but gives the worst result of the abrasion of tablets.

Statistical processing of the summary results obtained by the desirability function shows that the factors in the study sequence have the greatest influence on the studied indicators: A > E > D > F > C > B. According to the results of the desirability function among calcium fillers anhydrous dihydrogen phosphate (a_3) and sucrose (a_2) have the same effect. Unequivocal leader among lubricants is sodium stearyl fumarate (e_4). Aerosil 200 + talc (1:1) (d_5) was preferred in the group of glidants. Among the stabilizing substances, citric acid predominates (f_3). Of the selected binders, povidone K17 (c_3) had the greatest effect on amlodipine and enalapril combined tablets. Analyzing studies on the use of these leavening agents, croscarmellose sodium is preferred (b_1).

Table 7. Top 10 best formulations and corresponding pharmaco-technological indicators of tablets determined by means of an artificial neural network.

Batch	y_1	y_2	y_3	y_4	y_5	y_6	y_7	y_8	y_9	y_{10}
$a_2b_1c_3d_5e_4f_3$	0.6231	0.7027	0.7854	8.1976	40.9032	4.7546	0.9079	215.3673	0.0689	1.1836
$a_2b_1c_1d_3e_4f_1$	0.5992	0.7145	0.7942	8.2304	38.7178	4.0668	1.1343	208.9395	0.0436	1.3524
$a_2b_1c_1d_4e_4f_1$	0.6164	0.6072	0.8266	8.8173	37.1463	3.9409	1.2119	176.8341	0.0332	2.4224
$a_2b_1c_2d_3e_4f_1$	0.6085	0.6980	0.7948	8.2771	43.4693	4.3995	1.2394	218.2921	0.0505	2.1201
$a_2b_1c_4d_1e_5f_2$	0.7954	0.7412	0.7512	7.6007	40.8676	4.7813	0.6644	236.1660	0.0674	2.0053
$a_2b_2c_4d_1e_5f_2$	0.7917	0.6909	0.7545	7.8050	39.6801	4.5692	0.6215	224.3214	0.0596	2.4497
$a_2b_3c_2d_2e_5f_2$	0.6685	0.7295	0.8038	8.5070	37.6365	4.9435	0.7308	193.9313	0.0669	2.8729
$a_1b_1c_1d_2e_4f_1$	0.6021	0.6917	0.8049	8.3470	41.9503	4.1000	0.9881	212.3585	0.0699	2.5884
$a_1b_2c_2d_1e_5f_2$	0.6679	0.7069	0.7687	7.8222	38.3734	4.9176	0.6228	229.7394	0.0512	1.9746
$a_1b_3c_1d_1e_5f_2$	0.8319	0.7510	0.7294	8.1947	37.2146	5.1709	0.6183	218.0585	0.0573	2.4652

Table 8. The results of the study of the amounts of excipients by random balance.

Batch	y_1	y_2	y_3	y_4	y_5	y_6	y_7	y_8	y_9	y_{10}
26	2.03	0.720	0.787	9.3	40.4	4.5	1.48	157	0.043	10.8
27	2.62	0.704	0.790	9.6	42.6	4.5	2.05	125	0.003	8.6
28	2.81	0.643	0.693	9.2	39.3	4	0.86	104	0.006	6.3
29	2.61	0.659	0.807	8.8	40.2	5	1.17	103	0.126	6.2
30	1.73	0.721	0.831	8.6	41.0	4	1.15	135	0.009	5.2
31	2.65	0.658	0.750	9.1	37.9	5	1.26	119	0.011	7.3
32	2.30	0.692	0.764	9.5	40.6	4.5	0.73	123	0.004	6.0
33	1.30	0.646	0.778	11.1	42.0	5	1.49	60	0.100	5.5
34	2.16	0.666	0.788	10.4	42.0	5	1.42	126	0.009	7.8
35	2.16	0.711	0.807	10.3	42.3	5	1.51	123	0.028	8.0

Notes: 1. y_1 – loss of drying of the granules, %; 2. y_2 - bulk density of the tableting blend, g/ml; 3. y_3 – tapped density of the tableting blend, g/ml; 4. y_4 – flowability of the tableting blend, s/100 g; 5. y_5 – angle of repose of the tableting blend, °; 6. y_6 – appearance of tablets, points; 7. y_7 – uniformity of mass, %; 8. y_8 – resistance of tablets to crushing, N; 9. y_9 – friability of uncoated tablets, %; 10. y_{10} – disintegration, min.

Table 9. The results of the study of the amounts of excipients by regression analysis.

Batch	y_1	y_2	y_3	y_4	y_5	y_6	y_7	y_8	y_9	y_{10}
36	1.44	0.642	0.768	11.6	40.6	5	1.13	146	0.139	8.05
37	0.90	0.687	0.801	10.6	41.2	5	1.21	151	0.163	8.88
38	2.43	0.626	0.767	14.4	41.0	5	0.79	142	0.165	6.48
39	2.92	0.677	0.792	14.8	39.0	5	0.79	177	0.163	6.23
40	2.07	0.630	0.793	18.6	41.8	5	1.16	125	0.173	6.60
41	1.16	0.668	0.781	13.4	41.6	5	0.92	153	0.161	8.23
42	2.33	0.639	0.819	18.5	41.0	5	0.86	121	0.197	5.62
43	1.75	0.665	0.774	13.8	42.0	5	0.92	152	0.172	7.38
44	1.87	0.655	0.786	19.5	42.8	5	0.86	127	0.172	5.93
45	1.67	0.655	0.791	14.8	41.0	5	1.29	140	0.167	7.42
46	2.04	0.687	0.793	13.7	40.8	5	1.11	142	0.153	7.18
47	1.34	0.653	0.818	18.2	42.2	5	1.17	104	0.219	5.10
48	1.27	0.642	0.768	14.7	42.6	5	0.82	128	0.139	6.78
49	1.06	0.635	0.775	16.8	41.3	5	1.31	119	0.181	6.22
50	1.75	0.639	0.799	14.9	41.0	5	1.19	118	0.210	5.83
51	1.17	0.649	0.777	16.2	41.3	5	0.81	131	0.180	6.15
52	1.08	0.643	0.790	12.0	40.5	5	0.99	133	0.181	6.53
53	1.58	0.646	0.781	15.2	41.9	5	1.30	118	0.219	6.10
54	1.50	0.646	0.774	14.4	41.2	5	0.77	135	0.146	6.95
55	1.71	0.661	0.780	13.2	41.4	5	0.90	136	0.162	6.17

Notes: 1. y_1 – loss of drying of the granules, %; 2. y_2 - bulk density of the tableting blend, g/ml; 3. y_3 – tapped density of the tableting blend, g/ml; 4. y_4 – flowability of the tableting blend, s/100 g; 5. y_5 – angle of repose of the tableting blend, °; 6. y_6 – appearance of tablets, points; 7. y_7 – uniformity of mass, %; 8. y_8 – resistance of tablets to crushing, N; 9. y_9 – friability of uncoated tablets, %; 10. y_{10} – disintegration, min.

Among the top 10 combinations with optimal pharmaco-technological parameters that were shown by the artificial neural network, the composition of $a_2b_1c_3d_5e_4f_3$ coincides with the results of previous studies using statistical methods of dispersion analysis and the desirability function. The obtained data confirm that for the selection of the qualitative composition of the drug statistical processing of the experimental results can be analyzed using statistical methods of dispersion analysis and desirability function or as an alternative using artificial neural networks.

The method of random balance made it possible to reduce the number of experimental batches to 10. Using scattering diagrams, the dependence of the studied quality indicators on the change in the quantities of excipients is shown and significant factors are selected. In order to select the amounts of excipients that provided indicators in accordance with pharmacopoeial requirements, Table 10 is constructed.

As a result of the research conducted by the method of random balance, the amount of investigated excipients in general for all quality indicators was determined.

Croscarmellose sodium, povidone K17 and anhydrous citric acid were selected for detailed study of the effect of excipients. The relationship between the studied factors and the loss in mass during drying of the granulate (y_1) is described by the regression equation ($F_{Experimental} = 1.95$): $y_1=1.45-0.20x_2-0.27x_2x_3$.

The regression equation describing the relationship between the studied factors and the bulk density of the tableting blend (y_2) is as follows ($F_{Experimental} = 2.19$): $y_2=0.647-0.012x_1+0.006x_2+0.08x_2^2$.

The nature of the influence of the quantities of the studied factors on the tapped density of the tableting blend (y_3) is expressed by the regression equation ($F_{Experimental} = 0.50$): $y_3=0.783-0.014x_1x_3+0.007x_2^2$.

Table 10. The results of the analysis of scattering diagrams are summarized.

Factor / Indicator	x_1	x_2	x_3	x_4	x_5	x_6	x_7
y_1	–	–	+*	+	–	+	+
y_2	–*	–*	–	+*	0	+	–*
y_3	–	+	–	+	–	–	+
y_4	–	–	–	–	+	–	+
y_5	–	+	+	+*	–*	+*	+
y_6	+	+*	+	–	+*	+*	0
y_7	+	–*	+	–	+	–*	+
y_8	–*	–*	+	+*	+	+	–*
y_9	–*	–*	+	+*	–	–	–*
y_{10}	+*	–	+*	–	–	–*	+*
general	–	–	+	+	0	0	–

Note: * - significant factor

The flowability of the tableting blend (y_4) depends on the amount of test excipients as follows ($F_{Experimental} = 0.80$): $y_4=14.4+1.3x_1-1.1x_2-1.2x_3$.

The regression equation describing the angle of repose of the tableting blend (y_5) has the form: $y_5 = 41.2$ ($F_{Experimental} = 2.66$).

The appearance of the tablets on a 5-point rating system was excellent in all batches studied.

The regression equation for uniformity of mass ($F_{Experimental} = 0.63$) has the form: $y_7 = 1.00$. Therefore, this indicator is not affected by the studied factors, and the average value of uniformity of mass is 1.00%.

The influence of the studied factors on the resistance of tablets to crushing (y_8) illustrates the regression equation ($F_{Experimental} = 2.47$): $y_8 = 127.828-8.850x_1+5.868x_3+5.838x_1^2$.

The studied factors do not have a significant effect on the friability of uncoated tablets index (y_9), as $y_9 = 0.18$ ($F_{Experimental} = 0.32$).

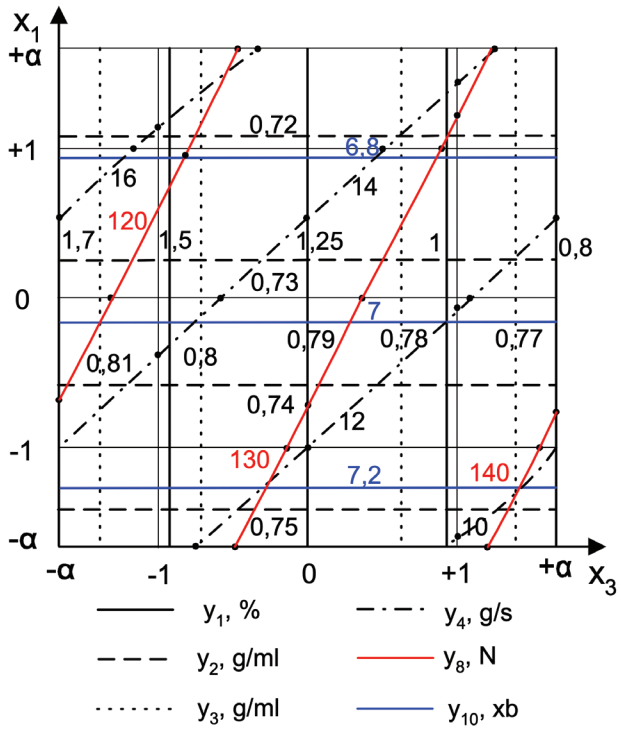

Figure 5. Lines of equal exit in the coordinate system x_1x_3.

The relationship between the studied factors and the disintegration (y_{10}) is described by the following regression equation: $y_{10}= 6.262-0.474x_1+0.699x_2+0.292x_1^2$.

To translate the regression equations to the canonical standard expression instead of x_2 in the model enter +1. We are building new models. On the basis of the transformed models, equal exit lines were built in the x_1x_3 coordinate system (Fig. 5).

Taking into account the results of placement of equal output lines, the optimum point is set at x_1 = -α and x_3 = + α is established. This allowed us to calculate the optimal composition of amlodipine and enalapril combined tablets (Table 11).

The proposed composition was tested experimentally and the following results were obtained: loss of drying of the granules 0.81%, bulk density of the tableting blend of 0.753 g / ml, tapped density of the tableting blend of 0.807 g / ml, flowability of the tableting blend of 10.3 s / 100 g, angle of repose of the tableting blend of 41.3°, appearance of the tablets 5 points, uniformity of mass of 1.18%, resistance of tablets to crushing 142.77 N, friability of uncoated tablets of 0.17%, disintegration of 7 minutes 27 seconds.

Table 11. Optimal composition of tablets with enalapril and amlodipine.

Ingredient	Amount	
Enalapril maleate	6.950 mg	3.48%
Amlodipine besylate	5.010 mg	2.51%
Croscarmellose Sodium	4.318 mg	2.16%
Calcium Hydrogen Phosphate	166.381 mg	83.19%
Povidone K17	7.000 mg	3.50%
Citric Acid Monohydrate	5.341 mg	2.67%
Aerosil 200	2.000 mg	1.00%
Talc	1.500 mg	0.75%
Sodium Stearyl Fumarate	1.500 mg	0.75%
Total	200.000 mg	100.00%

Conclusions

The composition and technology of amlodipine and enalapril combined tablets by wet granulation were developed with the help of QbD. The effect of 25 excipients on the pharmaco-technological parameters of amlodipine tablets with enalapril was studied. The desirability function was used to select the best combinations of excipients in the tablets. Qualitative composition is confirmed by an artificial neural network. The choice of the quantities of excipients is made by the method of random balance. Using the method of regression analysis, the optimal amount of excipients for tablets was determined: amlodipine besylate - 5.010 mg, enalapril maleate - 6.950 mg, croscarmellose sodium - 4.318, calcium dihydrogen phosphate - 166.381 mg, K17 - 7 mg, citric acid anhydrous - 5 mg aerosil 200 – 2.000 mg, talc – 1.500 mg, sodium stearyl fumarate – 1.500 mg.

The authors report there are no competing interests to declare.

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Supplementary material 1

The results of the study of pharmaco-technological parameters of intermediates and amlodipine tablets with enalapril, data of the functions of desirability

Authors: Nataliia Behei

Data type: pharmaco-technological parameters in the table

Explanation note: Results of the study of pharmaco-technological parameters of intermediates and amlodipine tablets with enalapril.

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