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RESEARCH ON THE OPTIMIZATION OF THE COMPOSITION AND TECHNOLOGY OF COMBINED TABLETS OF BISOPROLOL FUMARATE WITH INDAPAMIDE

Nadia Malanchuk, Mariana Demchuk

The aim. *The study was focused on the development and optimization of a rational tablet formulation containing bisoprolol fumarate and indapamide by applying a response surface methodology to ensure the required pharmaco-technological and biopharmaceutical characteristics of the final dosage form.*

Materials and methods. *The central composite design was used to establish the relation between independent variables, such as, quantity of PEG 6000, quantity of Prosolv EASYtab SP, quantity of Sachelac 80 and dependent variables, such as flowability, bulk density, tapped density, angle of repose, Carr's index, uniformity of weight, friability, tablet hardness and disintegration time in order to obtain the optimal formulation using response surface methodology. Tablets were prepared by direct compression method. Quantitative determination of APIs in tablets was quantified by HPLC with UV detection at 220 nm.*

Results. *After generating the polynomial equations that relate the dependent and independent variables, the process was optimized for five responses. It was found that the tablet contained 1% PEG 6000, 37% Prosolv EASYtab SP, and 37% Sachelac 80 was a better formulation in terms of hardness (89 N), uniformity of weight (1.1%), friability (0.20%) and rapid disintegration (2.3 min). The experimental values of the dissolution of optimized tablets showed 95.6% release of bisoprolol fumarate and 99.7% release of indapamide. The quantitative content of active ingredients (bisoprolol fumarate and indapamide) in the developed tablets meets the requirements of the State Pharmacopoeia of Ukraine.*

Conclusions. *The study enabled the development of an optimized formulation and manufacturing process for combined bisoprolol fumarate and indapamide tablets, ensuring compliance with pharmaco-technological standards and demonstrating the applicability of response surface methodology for formulation design*

Keywords: *tablets, optimization, technology, excipients, direct compression, pharmaco-technological indicators, regression model, Quality by Design, response surface methodology*

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1. Introduction

According to the World Health Organization, cardiovascular diseases remain among the leading causes of reduced life expectancy worldwide. Arterial hypertension (AH) represents a major medical and social challenge, being a key contributor to the high rates of morbidity, disability, and mortality associated with cardiovascular disorders. Globally, more than 1.25 billion individuals aged 30–79 years are affected by elevated blood pressure [1, 2]. In developed countries, the prevalence of hypertension among adults ranges from 30 to 40%, whereas in certain developing nations it exceeds 45–50%. Notably, only about half of individuals with hypertension are aware of their condition, and fewer than one-third achieve adequate blood pressure control. In Ukraine, epidemiological studies indicate that approximately one in three adults has elevated blood pressure, with prevalence markedly increasing with age–exceeding 60–70% among individuals over 60 years. The progressive rise in hypertension prevalence is largely attributed to population aging, sedentary behavior, unbalanced diets, excessive salt and alcohol consumption, and persistently high levels of psychosocial stress [3, 4].

Hypertension rarely occurs in isolation, as patients with elevated blood pressure frequently present with concomitant conditions such as diabetes mellitus, heart failure, peripheral arterial disease, atrial fibrillation, or coronary artery disease. The presence of these comorbidities significantly influences therapeutic decision-making and necessitates individualized treatment strategies, particularly in patients with concomitant cardiovascular disorders [5].

According to the guidelines of the European Society of Hypertension (ESH), the extent of blood pressure reduction remains the primary determinant of improved clinical outcomes in the management of hypertension. Among the five principal classes of antihypertensive agents [3], any may be utilized as first-line pharmacotherapy. Additional agents can be introduced, as indicated, to achieve target blood pressure levels in individual patients.

The ESH further recommends initiating combination antihypertensive therapy in most patients, particularly those with stage 2 hypertension. The addition of a second agent to the therapeutic scheme generally results in a more rapid and effective attainment of target blood pressure compared with monotherapy dose escalation. Moreover, low-dose combinations are associated with

superior tolerability relative to high-dose monotherapy. The use of fixed-dose combinations in a single tablet has been shown to improve patient adherence and overall treatment efficacy [5, 6].

β-adrenergic blockers (β-blockers, β-ABs) play a significant role in the management of arterial hypertension. The clinical efficacy of this pharmacotherapeutic class has been well established, particularly in hypertensive patients with comorbid conditions such as heart failure, arrhythmias, and ischemic heart disease. Numerous clinical studies have demonstrated that β-blocker therapy significantly reduces the risk of cardiovascular complications, overall mortality, and sudden cardiac death [7–10].

Diuretics represent another fundamental class of antihypertensive agents recommended for both initial and combination therapy. Their inclusion in hypertension treatment schemes is pathogenetically justified and clinically rational, as they effectively lower blood pressure by decreasing circulating blood volume and peripheral vascular resistance. The combination of diuretics with other antihypertensive agents –particularly β-blockers – facilitates the achievement of target blood pressure levels and produces a pronounced synergistic effect. Furthermore, the use of diuretics enables dose reduction of concomitant medications and enhances overall treatment tolerability. Their efficacy is especially notable in elderly patients and in those with heart failure or edema syndrome [11, 12].

In combination antihypertensive therapy, indapamide, as a thiazide-like diuretic, and bisoprolol, as a highly selective β_1-adrenoreceptor blocker, are frequently employed. The combination of these agents is both rational and pathogenetically justified, as it provides complementary mechanisms of action that enhance the overall antihypertensive effect by targeting different pathways of blood pressure regulation. This therapeutic synergy promotes more consistent blood pressure control, reduces the risk of cardiovascular complications, and improves treatment tolerability.

Moreover, the daily dose and bioavailability of bisoprolol and indapamide are close, which allows achieving optimal therapeutic effect without the need to prolong the action of one of them. The use of fixed-dose combinations of indapamide and bisoprolol further enhances patient adherence, simplifies treatment regimens, and supports sustained long-term blood pressure control [13].

The aim of the study. Development and optimization of the tablet formulation containing bisoprolol fumarate and indapamide through a comprehensive pharmaceutical and technological approach.

2. Research planning (methodology)

The therapeutic performance of solid oral dosage forms, particularly tablets, depends on the complex interplay between the physicochemical properties of the active pharmaceutical ingredients (APIs), the functionality of excipients, and the overall formulation design. To achieve a robust, safe, and therapeutically effective tablet, it is essential to select appropriate active substances and optimize the composition and quantitative ratios of excipients. These formulation decisions ultimately determine the mechanical strength, stability, dissolution behavior, and bioavailability of the final product [14, 15].

Previous research evaluated 27 different excipients and their effects on the pharmaco-technological properties of combined bisoprolol fumarate and indapamide tablets. Based on these studies, the most suitable excipients were identified to support the development of an optimized formulation [16]. Building on this groundwork, the present study aimed to systematically design and refine a tablet formulation containing bisoprolol fumarate and indapamide through a structured experimental approach [16].

In accordance with the goal and objectives of the study, the methodology for the development of the tablet formulation containing bisoprolol fumarate and indapamide included the following stages:

1. Optimization of the excipient ratio in the formulation using response surface methodology: establishing the optimal quantitative ratios of excipients to ensure maximum quality and stability of the final product.

2. Pharmaco-technological characterization: conducting comprehensive physicochemical and technological studies, including the evaluation of tablet disintegration time, uniformity of weight, hardness and friability, to verify compliance with pharmacopoeial standards.

3. Physicochemical analysis: determining the qualitative and quantitative content of the active ingredients in the developed tablets.

3. Materials and methods

The study used the following materials:

1. APIs: bisoprolol fumarate powder (Sypria Lifescience Ltd.); indapamide powder (KMP. RD. Dev. Lab. Com.17.In).

2. Excipients: sodium starch glycolate (SSG) trade name VivaStar (JRS Pharma GMBH & CO Ltd); magnesium aluminometasilicate, trade name Neusilin US 2 (Fuji Chemical Industry Co., LTD); polyethylene glycol (PEG) 6000 (Merck); high functionality excipient composite which including microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, sodium stearyl fumarate, trade name Prosolv EASY tab SP (JRS Pharma GMBH & CO Ltd); sieved alpha-lactose monohydrate, trade name Sachelac 80 (Meggle Excipients & Technology), and dibasic calcium phosphate anhydrous (Yunbo, China).

3. Model powder mixtures and tablet samples.

Formulation compositions used to generate experimental batches are presented in Table 2.

Formulations were developed using a central composite design (CCD) based on a 2^3 factorial structure [16]. In this design, three independent formulation variables were evaluated at five levels ($-\alpha$, −1, 0, +1, $+\alpha$). $2k$ factorial design is used to demonstrate the minimum number of tests needed for the central composite design. Whereas k indicates the number of variables used in specific design. Such variables are coded as 0, ± 1 and ± α for central, factorial and axial positions, respectively [17]. The inclusion of axial and center points allows for a quadratic

response surface to be constructed, facilitating the identification of optimal excipient ratios.

The choice of factors and their ranges was guided by preliminary experiments that identified plausible and technologically relevant boundaries for each variable. Coded levels of the independent factors are presented in Table 1.

Table 1

Experimental design variables

Factor	Level of factor					
	Variation interval	–α	–1	0	+1	+α
x_1 – quantity of PEG 6000, %	0.25	0.5795	0.75	1	1.25	1.4205
x_2 – quantity of Prosolv EASY tab SP, %	3	34.954	37	40	43	45.046
x_3 – quantity of SacheLac 80, %	3	30.954	33	36	39	41.046

According to the experimental plan, 20 trials were designed, including six replicates at the central points. The replicated runs were used to estimate pure experimental error, while randomization of the sequence minimized the possibility of systematic bias [18]. Mathematical models in the form of regression polynomial equations were generated for each response variable using Design-Expert software (version 12.0.0, Stat-Ease Inc., Minneapolis, USA). These models were applied to construct response surface and contour plots describing the influence of formulation factors. The obtained data were analyzed using a statistical model that included both interaction and quadratic terms to assess the behavior of the system. Analysis of variance (ANOVA) was carried out to evaluate the adequacy and significance of the models. A p-value below 0.05 was considered statistically significant at the 95% confidence level. For evaluating the model reliability, coefficient of determination (R^2), adjusted R^2, predicted R^2, lack of fit, and adequate precision were considered.

4. Preparation of tablets. Combined tablets of bisoprolol fumarate with indapamide were prepared by direct compression method according to the matrix given in Table 2. All ingredients were individually passed through a #60 mesh and weighed. The blending process was performed in stages: PEG 6000 was first pulverized in a separate mixer, after which predetermined amounts of Prosolv EASY tab SP, bisoprolol fumarate, indapamide, SacheLac 80, sodium starch glycolate (VivaStar), Neusilin US2, and the previously prepared PEG 6000 were successively added and thoroughly mixed after each addition. If necessary, anhydrous dibasic calcium phosphate was incorporated to adjust the final blend weight and enhance powder flowability. The resulting homogeneous mixture was directly compressed into tablets weighing 150 mg using 7 mm flat-faced punches on a TDP-1.5T tablet press, applying a compression force of approximately 70 kgf/cm^2. For each experimental formulation, a batch of 60 tablets was produced, with each unit containing 5 mg of bisoprolol fumarate and 2.5 mg of indapamide.

Before tablet compression, each powder blend was examined according to several parameters: flowability (y_1), angle of repose (y_2), bulk density (y_3), tapped density (y_4) and Carr's index (y_5).

Flowability was evaluated using the fixed funnel technique (EFT-01, Electrolab (India) PVT. LTD). Approximately 100 g of the powder blend was allowed to flow through the funnel, and the time required for the entire sample to pass was recorded as an indicator of its flow properties [19].

Angle of repose. A funnel with a 10 mm orifice was positioned 2 cm above a flat surface. The powder sample was gently poured along the inner wall of the funnel until the apex of the formed heap reached the outlet of the funnel. The radius of the conical base was measured, and the circumference of the powder pile was outlined. Powders exhibiting good flow properties formed a wide, low cone corresponding to a small angle of repose, whereas poorly flowing powders produced a narrow, steep cone with a higher angle value [20].

Bulk density was evaluated by gently pouring the powder blend into a graduated cylinder. Both the mass and the bulk volume of the powder were recorded. Bulk density was calculated as the ratio of the total powder mass to the measured bulk volume [19].

Tapped density was calculated as the ratio of the powder mass to its tapped volume. The measurement was performed using a Tap Density Tester (ETD 1020x, Electrolab (India) PVT. LTD). The powder sample was subjected to 500 taps, and the volume was recorded after every 100 taps. The final tapped volume was taken once two consecutive measurements showed no further change [19].

Carr's Index, also referred to as the compressibility index, is calculated using the measured bulk and tapped density values. This parameter indicates how easily a powder can be compressed. Because the same interparticle forces that influence compressibility also affect flow behavior, Carr's Index indirectly reflects flowability as well. Powders with good flow characteristics show weak interparticle interactions, meaning their bulk and tapped densities are nearly identical. Conversely, when a powder flows poorly, the difference between these density values increases, resulting in a higher Carr's Index. Generally, powders with a compressibility index below 20% are considered to have good flow properties [19].

Evaluation of tablets. The produced tablets were examined for several quality parameters, including weight uniformity (y_6), friability (y_7), hardness (y_8) and disintegration time (y_9).

Uniformity of weight. Twenty tablets were individually weighed, and their individual weights were compared with the calculated mean tablet weight. According to the acceptance criteria, tablets with a mass between 80 and 250 mg are allowed a maximum weight deviation of 7.5%. The batch complies with the requirement if no more than two tablets fall outside this range and none deviates by more than twice the permitted limit [19].

Hardness testing determines the force required to break a tablet and reflects its mechanical strength. Adequate hardness is essential to ensure that tablets can with-

stand handling during storage, transportation, and routine use without crumbling or breaking. For each formulation, five tablets were tested, and their hardness was measured in Newtons using a tablet hardness tester (EH-01P, Electrolab (India) PVT. LTD). The mean hardness value for each batch was then recorded [19].

Friability was assessed by placing a pre-weighed sample of tablets into a friabilator (EF-2, Electrolab (India) PVT. LTD). The device was operated at 25 rpm for 4 minutes. After the test cycle, loose dust was removed from the tablets, and they were weighed again. A weight loss of no more than 1% is considered acceptable, indicating that the tablets possess sufficient mechanical durability [19].

The disintegration test for all tablet formulations was performed using a tablet disintegration apparatus (EDI-2, Electrolab (India) PVT. LTD). Six tablets were placed separately in the individual tubes of the apparatus, and discs were positioned on top of each tablet. The water bath was maintained at 37 ± 2°C, and the time required for each tablet to completely disintegrate was recorded [19].

The dissolution test. An RC-6D paddle apparatus (Tianjin Guoming Medicinal Equipment Co., Ltd., Guoming, China) was used. The dissolution medium was phosphate buffer solution pH 6.8; the medium volume was 900 ml, the temperature was maintained at 37 ± 0.5°C, the paddle rotation speed was 50 rpm, and the dissolution time was 45 minutes. The content of the API in the aliquot was determined according to the "Assay" method. According to the requirements of the State Pharmacopoeia of Ukraine [19], the degree of API release from the developed tablets must be at least 75% within 45 minutes of dissolution.

5. Assay of APIs. High-performance liquid chromatography (HPLC) (2.2.29) [19] was used for qualitative and quantitative analysis of bisoprolol fumarate and indapamide in tablets. The analysis was performed on a SHIMADZU LC-40XS chromatograph equipped with a UV detector. Chromatographic conditions: C18 column (0.15 × 4.6 mm, 5 μm) from Phenomenex filled with sorbent – octadecylsilyl endcapped silica gel for chromatography R, column temperature 25°C; flow rate 1.5 mL/min, injection volume 20 μL**.** The mobile phase consisted of buffer solution pH 7.0 R – acetonitrile R – water for chromatography R in the ratio 15:30:55. Detection was performed at λ = 220 nm.

Analytical procedure.

Test solution. Place up to 0.14 g (accurately weighed) of the crushed tablet powder into a 100 ml volumetric flask, add 70.0 ml of the mobile phase, keep the mixture in an ultrasonic bath at 25°C for 10 minutes, then adjust the volume of the solution to 100.0 ml, mix, and filter through a blue-ribbon paper filter.

Reference solution. 25.0 mg (accurate weight) of the standard sample of indapamide and 50.0 mg (accurate weight) of the standard sample of bisoprolol fumarate are placed in a 100 ml volumetric flask, dissolved in 20.0 ml of the mobile phase, mixed and the volume of the solution is adjusted to 100.0 ml with the mobile phase. Transfer 5.0 ml of this solution into a 50 ml volumetric flask and adjust the volume to 50.0 ml with the mobile phase.

Buffer solution pH 7.0. Place 17.9 g of potassium dihydrogen phosphate R, 7.8 g of dipotassium hydrogen phosphate R, and 4.0 g of tetrabutylammonium hydrogen sulphate R into a 1000 ml flask. Dissolve the substances in approximately 900 ml of water for chromatography R, then adjust the pH to 7.0 with phosphoric acid R. Make up the volume to the mark with water for chromatography R. Check the pH again and, if necessary, adjust it to 7.0 with phosphoric acid R.

System suitability:

– the efficiency of the chromatographic system, calculated from the peaks of indapamide and bisoprolol fumarate, must be at least 1000 theoretical plates;

– the peak symmetry coefficient, calculated from the peaks of indapamide and bisoprolol fumarate on the chromatograms of the reference solution, must be between 0.8 and 1.5;

– the separation factor must be not less than 1.5 for the peaks of indapamide and bisoprolol fumarate in the reference solution;

– the relative standard deviation (RSD), calculated for the peak areas of indapamide and bisoprolol fumarate from the chromatograms of the reference solution after three injections, must be ≤ 0.67% (2.2.46).

The content of indapamide (X_1) in one tablet, in milligrams, calculated per average tablet weight, is determined using the following formula

$$X_1 = \frac{S_1 \cdot 100 \cdot m_{0.1} \cdot 5 \cdot P \cdot b}{S_{0.1} \cdot m \cdot 100 \cdot 50 \cdot 100}, \quad (1)$$

where S_1 – the average peak area of indapamide calculated from the chromatograms of the test solution; $S_{0'1}$ – the average peak area of indapamide calculated from the chromatograms of the reference solution; m_0 – the mass of the indapamide standard sample, in milligrams; m – the mass of the drug sample, in milligrams; P – the content of indapamide in the standard sample, in percent; b – the average weight of the tablet, in milligrams.

The content of bisoprolol fumarate (X_2) in one tablet, in milligrams, calculated per average tablet weight, is determined using the following formula

$$X_2 = \frac{S_2 \cdot 100 \cdot m_{0.2} \cdot 5 \cdot 1{,}178 \cdot P \cdot b}{S_{0.2} \cdot m \cdot 100 \cdot 50 \cdot 100}, \quad (2)$$

where S_2 – the average peak area of bisoprolol fumarate, calculated from the chromatograms of the test solution; $S_{0.2}$ – the average peak area of bisoprolol fumarate, calculated from the chromatograms of the reference solution; $m_{0.2}$ – the mass of the bisoprolol fumarate standard sample, in milligrams; m – the mass of the drug sample, in milligrams; P – the content of bisoprolol fumarate in the sample, in percent; b – the average tablet weight, in milligrams; 1.178 – conversion factor of bisoprolol fumarate to bisoprolol.

According to the requirements of the State Pharmacopoeia of Ukraine, the acceptable deviation for each API in tablets is ±5%. Therefore, the proposed quality criterion for the developed tablets under the "Assay" indicator is a range of 4.75 mg to 5.25 mg for bisoprolol

fumarate and a range of 2.375 mg to 2.625 mg for indapamide per tablet.

4. Results

Combined bisoprolol fumarate and indapamide tablets were prepared by direct compression method according to the matrix given in Table 2.

Based on the results of preliminary experiments, a 2^3 full factorial design was utilized to evaluate the influence of independent factors, namely the amount of PEG 6000 (x_1), Prosolv EASYtab SP (x_2), and Sachelac 80 (x_3) on the dependent responses. The relationship between the studied factors and the quality attributes of bisoprolol fumarate tablets with indapamide were described by regression equations and 3D response surface plots.

As shown in Table 3, the regression models performed reasonably well, with suitable correlation coeffcients (R^2). Additionally, good agreement was observed between adjusted R^2 and predicted R^2, confirming that the obtained results were well fitted by the regression models. The generated mathematical models were helpful for recognizing the impact of the independent variables on the dependent response through quantitative comparison of the variable coefficients. The model fit summary statistics given in Table 3.

After verifying the statistical significance of the coefficients, using Student's t-test ($t_5 = 2.571$; $p = 0.05$), the adequacy of the models was assessed using the F-test ($F_{0.05;10;5} = 4.74$). The regression equations characterize the combined effects of the factors, while the magnitude and sign of each regression coefficient determine the nature of their influence.

Formulation optimization was carried out using a quadratic response surface model. The model F-value of 4.45 indicates statistical significance, suggesting that the model explains the observed variability. The probability that such a large F-value arises due to experimental noise is only 1.45%. P-values below 0.0500 confirm that the corresponding model terms are statistically significant.

Table 2

Design of tablets of bisoprolol fumarate with indapamide formulations matrix and results of technological parameters of powder mixtures and tablets

No. formula	x_1	x_2	x_3	y_1	y_2	y_3	y_4	y_5	y_6	y_7	y_8	y_9
1	+	+	+	13.81	31.6	0.562	0.745	24.62	1.50	0.07	96.6	3.6
2	–	+	+	10.10	31.3	0.554	0.724	23.49	1.45	0.14	96.1	2.5
3	+	–	+	9.17	32.0	0.589	0.787	25.2	1.60	0.24	82.3	1.8
4	–	–	+	9.17	30.0	0.583	0.751	22.26	1.57	0.07	73.3	1.5
5	+	+	–	12.44	33.7	0.553	0.740	21.00	1.34	0.14	95.8	2.0
6	–	+	–	10.38	33.0	0.563	0.724	22.25	1.38	0.17	94.8	2.1
7	+	–	–	9.14	32.0	0.583	0.751	22.26	1.56	0.07	95.4	2.0
8	–	–	–	9.37	32.7	0.583	0.751	22.26	1.39	0.20	100.8	2.3
9	+α	0	0	9.52	30.7	0.553	0.777	18.36	1.39	0.34	102.0	2.9
10	–α	0	0	10.32	33.3	0.578	0.677	25.68	1.41	0.03	91.0	1.8
11	0	+α	0	12.03	33.8	0.543	0.751	27.6	1.27	0.04	94.5	2.6
12	0	–α	0	8.51	27.7	0.568	0.751	24.26	1.13	0.26	99.2	2.3
13	0	0	+α	8.54	30.7	0.553	0.701	21.00	1.04	0.20	92.9	2.9
14	0	0	–α	11.56	35.0	0.565	0.751	24.66	1.43	0.03	99.0	2.4
15	0	0	0	9.02	31.5	0.562	0.751	24.56	1.05	0.11	97.7	2.8
16	0	0	0	9.62	30.5	0.564	0.745	24.29	1.00	0.15	97.4	2.6
17	0	0	0	9.65	30.0	0.569	0.751	23.41	1.00	0.07	94.1	2.7
18	0	0	0	9.05	30.0	0.57	0.721	21.28	1.003	0.10	98.8	3.0
19	0	0	0	9.65	30.0	0.565	0.761	23.33	1.007	0.15	94.6	2.7
20	0	0	0	9.11	31.0	0.563	0.751	25.14	0.92	0.11	93.3	2.6

Note: x_1 – quantity of PEG 6000,%; x_2 – quantity of Prosolv EASY tab SP,%; x_2 – quantity of Sachelac 80,%; y_1 – flowability, sec/100g; y_2 – angle of repose °; y_3 – bulk density, g/cm³; y_4 – tapped density, g/cm³; y_5 – Carr's Index,%; y_6 – uniformity of weight,%; y_7 – friability,%; y_8 – tablet hardness, N; y_9 – disintegration time, min.

Table 3

Model summary statistics

Response	Model	Standart deviation	R^2	Adjusted R^2	Predicted R^2	Adeq Precision	Significance
Flowability (y_1)	Quadratic	0.86	0.80	0.62	–0.45	6.75	Suggested
Angle of repose (y_2)	Quadratic	1.21	0.74	0.50	–0.81	6.32	Suggested
Bulk density (y_3)	Quadratic	0.01	0.69	0.4	–1.28	5.83	Aliased
	2fi	0.01	0.65	0.48	–0.47	7.05	Suggested
Tapped density (y_4)	Quadratic	0.02	0.57	0.18	–1.78	4.42	Aliased
	2 fi	0.02	0.49	0.26	–0.72	5.54	Aliased
	Linear	0.02	0.46	0.36	0.08	6.8	Aliased
Carr index (y_5)	Quadratic	2.23	0.39	–0.16	–2.94	3.61	Aliased
	2 fi	2.28	0.17	–0.22	–1.75	2.58	Aliased
	Linear	2.14	0.11	–0.06	–0.55	2.47	Aliased
Uniformity of weight (y_6)	Quadratic	0.16	0.74	0.51	–0.92	4.71	Suggested
Friability (y_7)	Quadratic	0.09	0.41	–0.12	–3.41	3.75	Aliased
	2 fi	0.08	0.35	0.05	–1.89	4.87	Aliased
	Linear	0.08	0.25	0.11	–0.35	4.61	Aliased
Tablet hardness (y_8)	Quadratic	5.16	0.67	0.37	–1.39	5.97	Aliased
	2 fi	4.72	0.64	0.47	–0.71	7.8	Suggested
Disintegration time (y_9)	Quadratic	0.26	0.86	0.73	0.05	11.37	Suggested

Finally, after ignoring the insignificant terms, the regression equation for flowability is

$$y_1 = 9.34 + 0.31x_1 - 0.30x_3 + \\ +0.75x_1x_2 + 0.24x_1x_3 + \\ +0.16x_2x_3 + 0.27x_1^2 + 0.39x_2^2 + 0.32x_3^2. \quad (3)$$

It follows from the regression equation that when all factors are maintained at their basic levels, the flow rate of the powder blend is 9.34 s/100 g. A decrease in the quantities of PEG 6000 (x_1) and Sachelac 80 (x_3) leads to a reduction in the pouring time of the powder mixture through the funnel, indicating an improvement in flowability. The interaction between PEG 6000 (x_1) and Prosolv EASYtab SP (x_2) was found to be statistically significant, as shown in Fig. 1. The optimal flowability value of 8.47 s/100 g was achieved when the amount of PEG 6000 (x_1) was 1.12%, and the amount of Prosolv EASYtab SP (x_2) was approximately 37.4% in the powder blend.

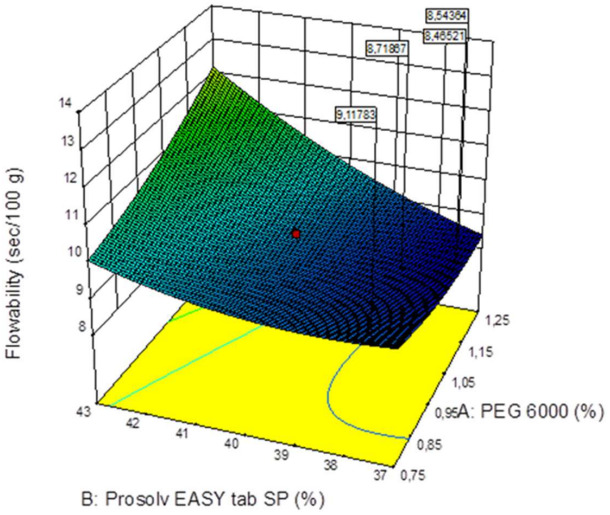

Fig. 1. Surface response plot for flowability (sec/100 g)

The regression equation describing the influence of the studied factors on the angle of repose of the powder mass (y_2) has the form

$$y_2 = 30.5 - 0.15x_1 + 0.96x_2 - 1.101x_3 - \\ -0.037x_1x_2 + 0.29x_1x_3 - 0.14x_2x_3 + \\ +0.55x_1^2 + 0.11x_2^2 + 0.85x_3^2. \quad (4)$$

The Model F-value of 3.12 indicates that the model is statistically significant. There is only a 4.53% probability that an F-value of this magnitude could occur due to random noise. P-values less than 0.0500 indicate model terms are significant. In this case, all linear variables, their interactions and the quadratic variables are significant model terms.

The angle of repose of the powder blend is influenced by the amounts of Prosolv EASYtab SP (x_2) and Sachelac 80 (x_3). The interactions between x_2 (Prosolv EASYtab SP) and x_3 (Sachelac 80), as well as between x_1 (PEG 6000) and x_3 (Sachelac 80), have a significant effect on the evaluated parameter.

The lowest angle of repose value, 29.45°, was obtained when factor x_2 (Prosolv EASYtab SP) was maintained at its lower level, and factor x_3 (Sachelac 80) was within the range of 37.5–38.5% in the powder mixture. The response surface plot (Fig. 2) showed the interaction between factors x_1 (PEG 6000) and x_3 (Sachelac 80). The minimum angle of repose value of 30.3° was observed when factor x_1 (PEG 6000) was maintained at its central level and factor x_3 (Sachelac 80) was present at 37% in the formulation.

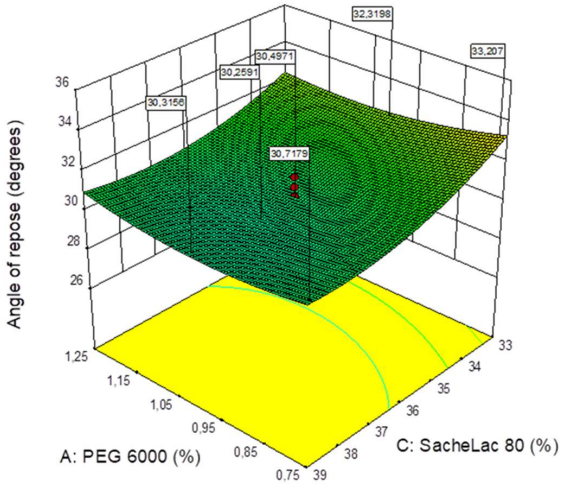

Fig. 2. Surface response plot for angle of repos

The equation of polynomial regression for bulk density after ignoring the insignificant terms is presented as follows

$$y_3 = 0.57 + 0.003x_1 - 0.001x_3 + 0.001x_1x_2 + \\ + 0.003x_1x_3 + 0.0007x_2x_3. \quad (5)$$

The adequacy of the model describing the effect of the studied factors on the bulk density of the powder mass was evaluated using the F-test. The model F-value of 3.94 indicates that the model is statistically significant, with only a 1.82% probability that such a high F-value could be attributed to random noise. P-values below 0.0500 confirm the significance of model terms. In this case, the linear factors A and C, as well as the interaction terms AB, AC, and BC, were identified as significant contributors.

According to the regression equation, the linear factor x_1 exerts the most pronounced effect on bulk density. The response surface plot (Fig. 3) shows that the lowest bulk density value of 0.563 g/cm^3 is achieved when factor x_1 is maintained between its central level and the +α level, while factor x_3 is within the range of 33–34% in the powder mixture.

The regression equations describing the effect of the studied factors on the tapped density (y_4) and Carr's index (y_5) are represented as constants:

$$y_4 = 0.741; \quad (6)$$

$$y_5 = 23.69. \quad (7)$$

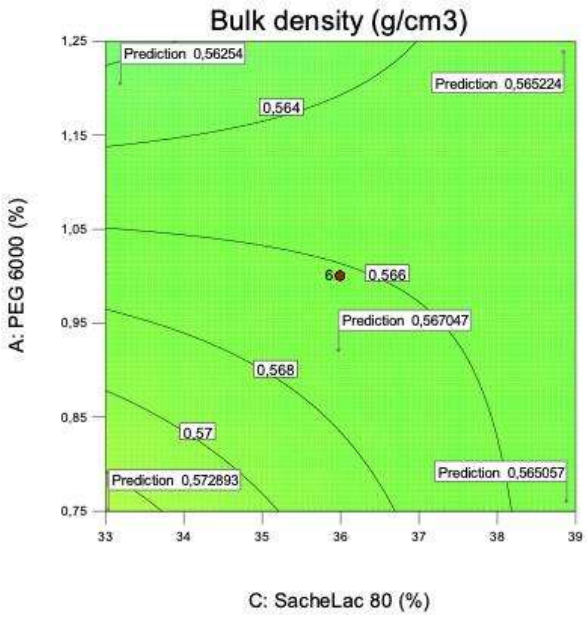

Fig. 3. Surface response plot for bulk density (g/cm^3)

These results indicate that the tapped density (0.741 g/cm^3) and Carr's index (23.69%) do not significantly depend on the quantities of the investigated excipients, as the corresponding F-values confirm the absence of a statistically significant relationship.

After pressure, the obtained combined tablets of bisoprolol fumarate with indapamide were investigated for uniformity of weight (y_6), friability (y_7), tablet hardness (y_8) and disintegration time (y_9).

The uniformity of weight in all investigated tablets ranged from 0.92 to 1.60%, which meets the pharmacopoeia's requirements [16]. Using the F-test, the adequacy of the model describing the influence of the studied factors on the homogeneity of the tablet weight was checked. The Model F-value of 3.16 implies that it is significant.

$$y_6 = 0.99 + 0.013x_1 - 0.014x_2 - 0.014x_3 - \\ -0.023x_1x_2 - 0.0005x_1x_3 + 0.0005x_2x_3 + \\ +0.18x_1^2 + 0.12x_3^2. \quad (8)$$

According to the obtained regression equation, the average value of mass uniformity is 0.99%. The interaction between factors x_1 (PEG 6000) and x_2 (Prosolv EASYtab SP) exerts the most pronounced effect on this parameter. Both the amounts of Prosolv EASYtab SP and Sachelac 80 influence mass uniformity to a similar extent, the increase of which will lead to a deterioration of the studied indicator. According to the response surface plot (Fig. 4), the optimal mass uniformity value (0.99%) was achieved for tablets containing PEG 6000 in the range of 0.95–1.05% and Prosolv EASYtab SP in the range of 40–42%.

The regression equation describing the effect of the studied factors on the friability (y_7) is expressed as follows

$$y_7 = 0.13. \quad (9)$$

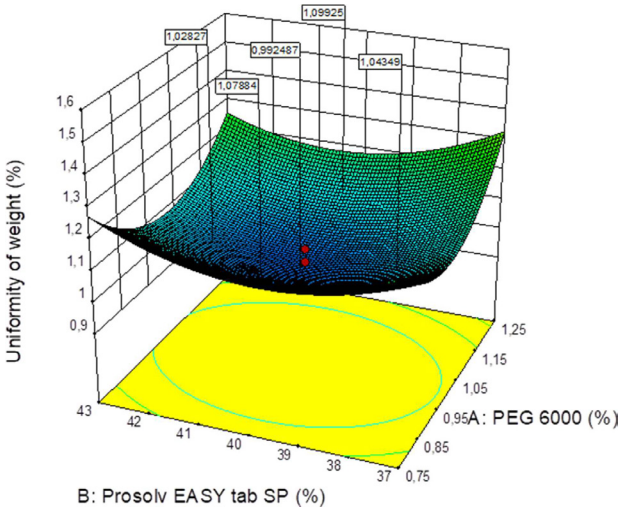

Fig. 4. Surface response plot for uniformity of weight (%)

This result indicates that the average tablet abrasion value is 0.13% and is not affected by variations in the quantitative content of the investigated excipients in the tablet formulation. The friability of combined tablets of bisoprolol fumarate with indapamide ranged from 0.03 to 0.34%, which meets the pharmacopoeia's requirements [19].

The hardness results of combined tablets of bisoprolol fumarate with indapamide were from 73 to 102 N, which meets the pharmacopoeia's requirements [19].

Final equation of tablets hardness in terms of actual factors is presented as follows

$$y_8 = 94.49 + 1.73x_1 + 1.72x_2 - 3.56x_3 - \\ - 0.26x_1x_2 + 1.75x_1x_3. \quad (10)$$

The Model F-value of 3.79 implies the model is significant. There is only a 2.09% chance that an F-value this large could occur due to the noise. In this case linear variables A, B, C, the interactions of the variables AB and AC are significant model terms.

When all factors were maintained at their central levels, the tablet hardness was 94.49 N. The factor x_3 (Sachelac 80) greatly influenced on this parameter as increase in its content led to decrease in tablet strength. In contrast, higher amounts of PEG 6000 and Prosolv EASYtab SP resulted in increase in tablet hardness. The interaction between PEG 6000 (x_1) and Sachelac 80 (x_3) was also found to have a significant effect on this response. Analysis of Fig. 5 shows that reducing the amount of Sachelac 80 to 33% and increasing the PEG 6000 content to 1.25% leads to an increase in tablet strength up to 97.9 N.

The disintegration time of combined tablets of bisoprolol fumarate with indapamide was less than 15 minutes, which meets the established requirements [19]. The final equation after ignoring the insignificant terms for disintegration time is the next

$$y_9 = 2.74 + 0.23x_2 + 0.13x_3 + \\ +0.12x_1x_2 + 0.22x_1x_3 - 0.19x_1^2 - \\ -0.15x_2^2 - 0.08x_3^2. \quad (11)$$

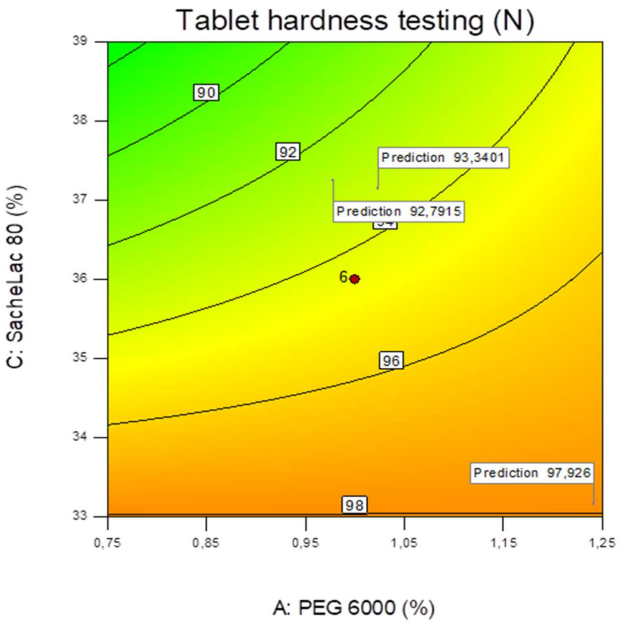

Fig. 5. Surface response plot for tablet hardness (N)

When all factors were maintained at basic levels, the obtained tablets disintegrated within 3 minutes. Increasing the amounts of factors x_2 (Prosolv EASYtab SP) and x_3 (Sachelac 80) in the tablet formulation resulted in prolonged disintegration time. Significant interactions were also observed between factors x_1 (PEG 6000) and x_2 (Prosolv EASYtab SP), as well as between x_1 (PEG 6000) and x_3 (Sachelac 80). As shown in Fig. 6, when PEG 6000 was present in quantities ranging from 0.95% to 1.05% and Sachelac 80 in amounts between 33% and 37%, the disintegration time varied from 2.54 to 2.78 minutes. The introduction of Prosolv EASY tab SP at the lower level gives the best disintegration time of bisoprolol fumarate and indapamide tablets.

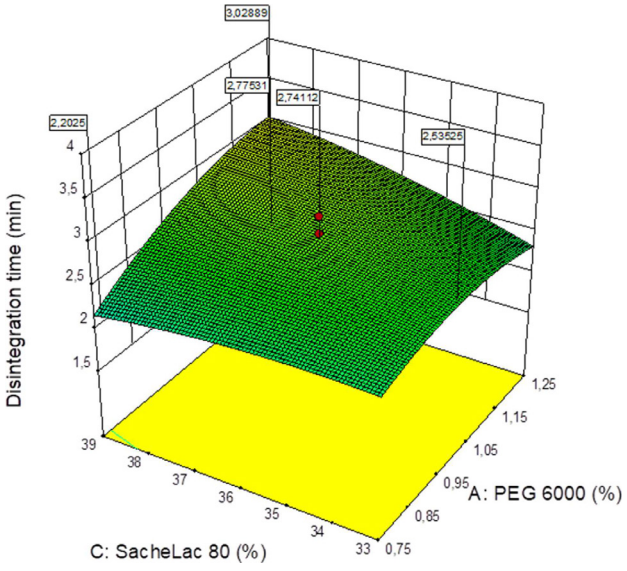

Fig. 6. Surface response plot for disintegration time (min)

Optimization of composition tablets of bisoprolol fumarate with indapamide. After generating the model polynomial equations relating the dependent and independent variables, the process was optimized for five responses (Fig. 7–9). The optimum formulation was selected based on the constraints set on independent variables: y_1 – flowability (7.49–8.71 sec/100g), y_2 – angle of repose (27–29°), y_6 – uniformity of weight (0.92–1.60%), y_8 – tablet hardness (73–93 N), y_9 – disintegration time (2–5 min).

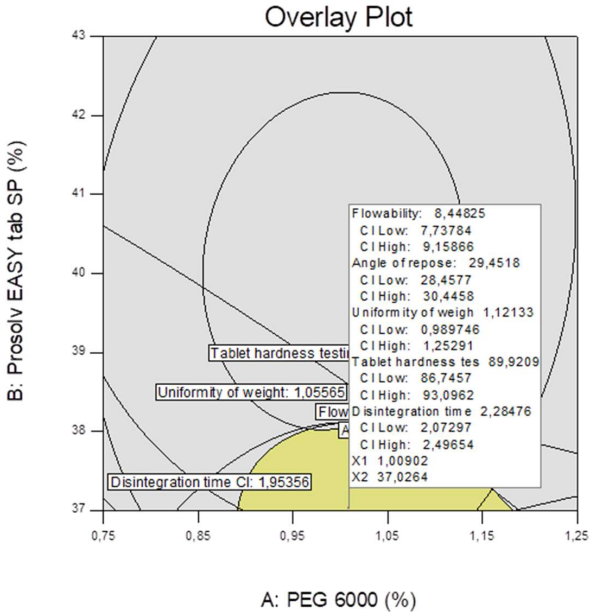

Fig. 7. Interaction of PEG 6000 and Prosolv EASY tab SP in determining the optimal composition of tablets

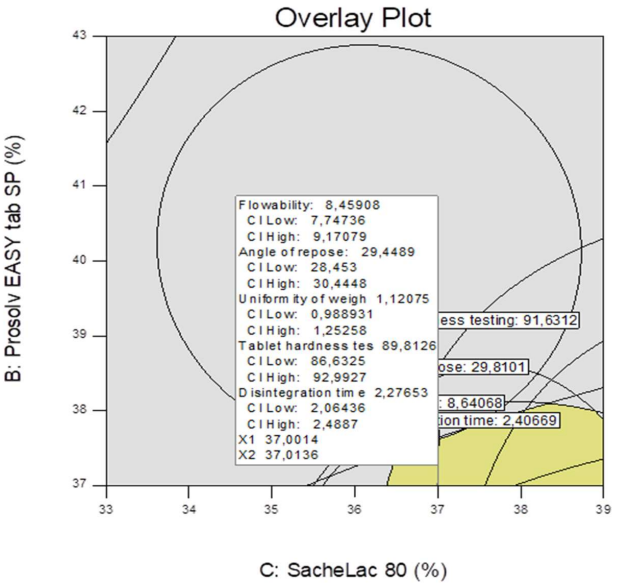

Fig. 8. Interaction of Sachelac 80 and Prosolv EASY tab SP in determining the optimal composition of tablets

Analysis of the obtained data revealed that the optimal quality characteristics of the powder mass (flowability of 8.45 s/100 g and an angle of repose of 29°) and the optimal pharmaco–technological properties of the tablets (uniformity of weight – 1.1%, tablet hardness – 89 N, and disintegration time – 2.3 minutes) were achieved with a formulation containing 1% PEG 6000, 37% Prosolv EASYtab SP, and 37% Sachelac 80. Based on these results, the optimal qualitative and quantitative composition of bisoprolol fumarate and indapamide tab-

lets prepared by direct compression with an average tablet mass of 150 mg are presented in Table 4.

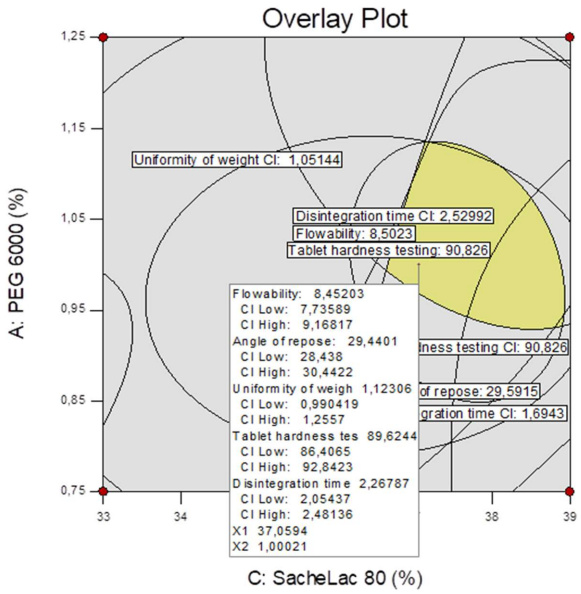

Fig. 9. Interaction of Sachelac 80 and PEG 6000 in determining the optimal tablet composition

The proposed formulation was evaluated experimentally. The results of the obtained data are presented in Table 5.

Table 4

Optimal composition of bisoprolol fumarate with indapamide tablets

Component	Ratio (%)	Weight per 1 tablet (mg)
Bisoprolol fumarate	3.33	5
Indapamide	1.67	2.5
Sodium starch glycolate VivaStar	6	9
Neusilin US 2	2	3
PEG 6000	1	1.5
Prosolv EASY tab SP	37	55.5
Sachelac 80	37	55.5
Dibasic calcium phosphate anhydrous	12	18
Total	100.00	150.00

Table 5

The results of the study of the physicochemical and pharmaco-technological properties of the combined tablets of bisoprolol fumarate with indapamide

Indexes	Results
Average weight, mg*	145.67 ± 1.66%
Friability, %*	0.20 ± 0.015%
Hardness, N*	72.0 ± 3.5 N
Disintegration Time, min*	2.5 ± 0.5 min
Dissolution, %*:	
Bisoprolol fumarate	95.6±1.15%
Indapamide	99.7±1.30%
Assay, mg:	
Bisoprolol fumarate	5.05±0.08 mg
Indapamide	2.49±0.03 mg

*Note: * – Mean ± S.D., n = 3 (Values are the average of three measurements).*

Thus, the selected qualitative and quantitative composition of excipients ensured the production of combined tablets of bisoprolol fumarate with indapamide, which meets the requirements of the State Pharmacopoeia of Ukraine, according to the main pharmaco-technological indicators (deviation from the average weight, friability, hardness, disintegration time, dissolution and assay of APIs).

5. Discussion of research results

Quality by Design (QbD) involves the purposeful development and optimization of pharmaceutical formulations and manufacturing processes to ensure that the final product consistently meets predefined quality criteria. The core principle of this approach is the transition from a "quality-by-testing" concept to a "quality-by-design" strategy, which enables a deeper understanding of product characteristics and process behavior. This enhances product quality, improves manufacturing efficiency and provides greater regulatory flexibility [21].

Quality by Design requires systematic identification, evaluation and management of risks, acknowledging that every stage of production may introduce potential deviations. During risk assessment, it is essential to determine how the formulation composition, physicochemical properties of active and excipient substances and process parameters may influence critical quality attributes and critical process parameters, which must be tightly controlled to ensure the final product's quality [22].

The response surface methodology was used to study the effect of critical factors on various attributes of combined tablets of bisoprolol fumarate with indapamide. The quantity of PEG 6000 (X_1), quantity of Prosolv EASY tab SP (X_2), quantity of Sachelac 80 (X_3) were selected as independent factors. The response variables were flowability, angle of repose, bulk and tapped density, Carr's Index, uniformity of weight, friability, tablet hardness, disintegration time. ANOVA and lack of fit test illustrated that selected independent variables had significant effect on the response variables, and excellent correlation was observed between actual and predicted values.

The flow characteristics of powder blends play a crucial role in selecting an appropriate tablet manufacturing method. As consolidated stress increases, the bulk density of the powder also rises, which directly affects powder handling and blending. Variations in this parameter may promote segregation, ultimately causing inconsistencies in dose uniformity. Moreover, powders with low bulk density require higher compression forces during tableting, while powders with elevated bulk density may receive insufficient pressure. Both conditions can result in defects such as capping or tablet breakage. The results show that combined tablets have passable flow properties to be compressed directly by tablet machine with the angle of repose range of (27–35°) and Carr's index range of (18–27%).

The analysis of the regression equations for flowability, bulk density and angle of repose showed that the incorporation of PEG 6000 at 1% (basic level), Prosolv EASYtab SP at 37% (lower level) and Sachelac 80 at 36% (basic level) provides optimal values of these techno-

logical parameters. The introduction of Prosolv EASY tab SP in the amount of 37% (lower level) has a positive effect on the disintegration time of the tablets. Increasing the amount of Sachelac 80 from 33% to 37% improved the crushing resistance but slightly worsened the uniformity of the tablet mass. The pharmaco-technological characteristics of the obtained tablets, namely uniformity of mass, hardness, friability, and disintegration time, meets the requirements of the State Pharmacopoeia of Ukraine.

Previous studies have demonstrated that incorporating the excipient Sachelac 80 into formulations enhances granule flowability, improves their organoleptic properties, and increases the dissolution rates of orodispersible tablets [23].

PEG 6000, due to its plasticizing properties, improves the compression process and tablet strength by reducing intermolecular forces in the tablet matrix [24].

The application of PEG 6000 as a carrier aligns with earlier research demonstrating that its hydrophilic character effectively improves the solubility of a wide range of active pharmaceutical ingredients [25, 26].

Prosolv EASY tab SP is a uniform, lubricated high-functionality excipient composite. Its specific particle morphology provides significantly improved flow characteristics compared with a simple physical blend of its individual constituents. The material's porous surface facilitates the adhesion of low-dose, micronized active ingredients, which enhances content uniformity both in the powder mixture and in the final tablets [27].

In previous studies on the pharmaceutical development of tablets, it was found that the introduction of Prosolv EASY tab SP® into the formulation allowed better disintegration time values [28, 29].

After generating polynomial equations for each model to describe the relationship between the independent and response variables, the formulation was simultaneously optimized for five responses.

To obtain the optimal composition, both numerical and graphical optimization methods available in the Design-Expert software were used. The main objective of the optimization process was to improve the flowability and angle of repose of the powder mass, reduce the disintegration time and deviation from the average mass and increase the tablet hardness within the pharmacopoeial range.

The optimization explores the design space using the developed regression model to identify factor settings that optimize one or more objectives. This method determines the point at which the predicted optimal response values and their corresponding factor levels are achieved. The area identified by yellow colour was preferred to be a representative of the optimized area corresponding to 1% of PEG 6000, 37% of Prosolv EASY tab SP and 37% of Sachelac 80. With these conditions, the software predicts a flowability of 8.44–8.46 s/100 g, an angle of repose of 29°, a uniformity of weight of 1.12%, tablet hardness value of 89–90 N and disintegration time of 2.3 minutes.

The optimized formulation was evaluated for its tablet properties. As presented in Table 4, the formulation ensured the production of tablets with quality parameters that complied with the pharmacopoeial specifications.

Practical relevance. The findings of the study provide a theoretical foundation for the development of combined tablets using direct compression technology.

Study limitations. During the pharmaceutical development of the combined bisoprolol fumarate and indapamide tablets, the solubility and the quantitative content of the active substances in the optimized formulation were evaluated. However, as a tool for formulation optimization to achieve the desired release profile, as well as during stability studies and for routine quality monitoring of the medicinal product, conducting an *in vitro* dissolution test is essential.

Prospects for further research. Further research should be directed at the technological transfer of the optimized formula from the laboratory level to industrial equipment, using Design of Experiments approaches to justify scaling parameters and ensure reproducibility of quality indicators in serial production conditions.

6. Conclusions

In the current research, the RSM on based the central composite design was successfully applied for evaluating the influences of independent variables, such as, quantity of PEG 6000, quantity of Prosolv EASY tab SP and quantity of Sachelac 80, on the dependent variables and for predicting the optimal formulation of combined tablets of bisoprolol fumarate with indapamide. Accordingly, the desired optimum condition was obtained at 1% of PEG 6000, 37% of Prosolv EASY tab SP and 37% of Sachelac 80. The tablets obtained with these optimum excipient quantities demonstrated the friability of 0.2%, the hardness of 72 N and the disintegration time of 2.5 minutes. The experimental values of the dissolution of optimized tablets showed 95.6% release of bisoprolol fumarate and 99.7% release of indapamide. The developed tablet composition ensured the production of tablets that complied all pharmacopoeial specifications.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

The manuscript has no associated data.

Use of artificial intelligence

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

Authors' contributions

Nadia Malanchuk: Visualization, Software, Writing – original draft; **Mariana Demchuk:** Conceptualization, Methodology, Writing – review & editing, Supervision.

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Nadia Malanchuk, Assistant**,** Department of Pharmacy Management, Economics and Technology**,** I. Horbachevsky Ternopil National Medical University**,** Voli sq., 1, Ternopil, Ukraine, 46001

Mariana Demchuk, PhD, Associate Professor, Head of Department, Department of Pharmacy Management, Economics and Technology**,** I. Horbachevsky Ternopil National Medical University**,** Voli sq., 1, Ternopil, Ukraine, 46001

***Corresponding author:** Malanchuk Nadia, e-mail: malanchuc_nv@tdmu.edu.ua*