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THE METHOD OF RANDOM BALANCE FOR STUDYING THE INFLUENCE OF EXCIPIENTS QUANTITIES ON TECHNOLOGICAL PARAMETERS OF TABLETS BASED ON *ORIGANUM VULGARE L.* DRY EXTRACT

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Abstract

The aim. The aim of the research was to study the influence of excipients amount on the technological parameters of the compression mixture and tablets based on dry extract of *Origanum vulgare L.* herb using the method of random balance.

Materials and methods. Objects of the study – *Origanum vulgare L.* herb dry extract, 8 excipients that have been studied at two quantitative levels. The tablets were prepared by direct compression method. The formulations were designed according to the method of random balance. The technological parameters of the compression mixture and tablets based on *Origanum vulgare L.* herb dry extract have been studied as a function of quantitative factors: silicon, magnesium carbonate basic, dioxide magnesium aluminometasilicate (Neusilin S1®), isomalt (GalenIQ™720), F-melt® Type C (co-spray dried excipients), sucralose, berry flavor and citric acid.

Results and discussion. The increase in the amount of Neusilin S1®, GalenIQ™720 and F-melt®, and the decrease in the amount of magnesium carbonate basic and silicon dioxide improved the flowability expressed by the Hausner ratio. Results of bulk density and tapped density of the compression mixture depended on the quantities of GalenIQ™720 and F-melt®. All formulations of the prepared tablets had the rapid disintegration and ranging from 6 to 15 minutes. Resistance for crushing and friability tablets' were improved with a decrease in the amount of silicon dioxide and increase in the amount of Neusilin S1®, F-melt® and sucralose. Higher resistance to moisture of tablets based on *Origanum vulgare L.* dry extract was obtained by using Neusilin S1®, F-melt® and sucralose on the upper levels.

Conclusions. The tablets based on *Origanum vulgare L.* herb dry extract were successfully manufactured by direct compression method. The random balance method enabled us to identify the most significant quantitative factors to optimize their composition in the tablets based on the dry extract of *Origanum vulgare L.* herb.

Keywords: *Origanum vulgare L.*, dry extract, excipients, compression mixture, tablets, method of random balance.

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1. Introduction

Seasonal influenza which is characterized by a fever, headache, dry cough, muscle and joint pain, feeling unwell, a runny nose and sore throat can cause severe illness or death especially in people at high risk. According to the WHO worldwide statistics, seasonal influenza annual epidemics result in about 3 to 5 million cases of severe illness, and about 290 000 to 650 000 respiratory deaths [1]. An acute sore throat may be caused by an inflammatory process in the pharynx, tonsils or nasopharynx at the acute respiratory disease due a bacterial agent [2]. The local use of the tablets with antimicrobial substances has the direct influence on the viral and inflammatory agents, which can cause local pain relief, rapid pharmacological and prolonged action, and effectiveness at the different types of sore throat that can help at the emotional problems associated with

a sore throat [3]. *Origanum vulgare L*. contains flavonoids, ascorbic acid, tannins, essential oil and has anti-inflammatory, wound-healing, hemostatic and antimicrobial properties [4–8]. We have developed technology of dry extract of this herb and have proved its antimicrobial activity and the anti-inflammatory effect [9]. According to results of analysis of the Ukrainian pharmaceutical market of medicines for the treatment of throat diseases the solid dosage forms are most commonly used dosage forms [10]. Thereof tablets based on *Origanum vulgare L*. herb dry extract are perspective for use in the treatment of the mucous membrane of the upper respiratory tract [11].

The aim of the research. The aim of our study was to analyze the influence of the amount of excipients on the technological parameters of compression mixture and tablets based on dry extract of *Origanum Vulgare L*. herb using the method of random balance.

In our study, we used the method of random balance, which is based on the fact that the significance of certain factor effects depends on their contribution to the response variance [12]. Primarily, the matrix of design of experiments was defined, the experiment took place and based on its results scatter diagrams were constructed. Significant factors are taken from scatter diagrams. The design construction of experiments matrix is preceded by coding the factors, selection of variation levels and by determining the experiment center [13].

2. Materials and methods

This research was performed in 2019–2020. The materials which we used for this study comprise a dry extract of *Origanum Vulgare L*. herb and excipients (silicon dioxide, magnesium carbonate basic, magnesium aluminometasilicate (Neusilin S2®), isomalt (GalenIQ™720), F-melt® Type C (co-spray dried excipients), sucralose, berry flavor and citric acid, microcrystalline cellulose (MCC). Excipients were kindly provided by Witec Industrial.

The formulations were designed according to the method of random balance. In this design, technological parameters of tablets based on *Oregano vulgare L*. dry extract have been studied as a function of 8 quantitative factors. The names of factors, with their variation levels, are shown in the **Table 1**.

Table 1

Quantitative factors and their levels

Factors	Levels of factors			
	Variation interval	Upper level (+)	Basic level «0»	Lower level (–)
x_1 – mass of silicon dioxide in one tablet, g	0.005	0.020	0.015	0.010
x_2 – mass of magnesium carbonate basic in one tablet, g	0.010	0.130	0.120	0.110
x_3 – mass of Neusilin S1 in one tablet, g	0.010	0.030	0.020	0.010
x_4 – mass of GalenIQ™720 in one tablet, g	0.010	0.130	0.120	0.110
x_5 – mass of F-melt® C in one tablet, g	0.010	0.130	0.120	0.110
x_6 – mass of sucralose in one tablet, g	0.0002	0.005	0.0048	0.0046
x_7 – mass of berry flavor in one tablet, g	0.0005	0.005	0.0045	0.004
x_8 – mass of citric acid in one tablet, g	0.005	0.015	0.010	0.005

Matrix 2^3 of full factorial experiment has been used to make random balance matrix. The design of matrix and obtained results (responses) are shown in the **Table 2**. The bulk density (y_1), tapped density (y_2), Hausner ratio (y_3), friability of the tablets (y_4), resistance of the tablet's for crushing (y_5), disintegration (y_6) were evaluated.

Tablets based on *Oregano vulgare L*. dry extract have been obtained by direct compression method according to the matrix given in **Table 2**. All the ingredients were weighed and mixed to uniformity. Amount of *Oregano vulgare L*. dry extract in the one tablet was 0.125 g. MCC 200 was

added in the formulation to adjust tablets weight to 550 mg if factors were investigated at the lower levels. The compression mixture from each formula was evaluated by several parameters such as bulk density, tapped density, Hausner ratio. The mixtures were directly compressed using 12 mm semi-sphere round punches into tablets of 550 mg on a single tooling tablets machine. A batch of 50 tablets was prepared for all the designed formulations. Obtained tablets based on *Oregano vulgare L.* dry extract were evaluated for the following parameters: friability, resistance for crushing, and disintegration of the tablets.

Table 2

Design of matrix of the tablets based on *Oregano vulgare L.* dry extract formulations and technological parameters of compression mixtures and obtained tablets

No. formula	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	y_1	y_2	y_3	y_4	y_5	y_6
									Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Friability (%)	Resistance for crushing (N)	Disintegration (min)
1	+	+	+	+	+	+	+	+	0.382	0.423	1.107	0.016	47	15
2	–	+	+	+	–	–	–	+	0.389	0.527	1.355	0.210	46	15
3	+	–	+	+	–	–	+	–	0.360	0.517	1.434	1.800	30	9
4	–	–	+	+	+	+	–	–	0.408	0.538	1.318	0.280	57	16
5	+	+	–	+	–	–	–	–	0.366	0.441	1.203	1.550	23	9
6	–	+	–	+	+	+	+	–	0.396	0.528	1.333	0.390	54	11
7	+	–	–	+	+	+	–	+	0.372	0.542	1.454	0.800	32	10
8	–	–	–	+	–	–	+	+	0.429	0.537	1.250	1.700	30	8
9	+	+	+	–	–	+	–	–	0.340	0.432	1.272	1.550	37	9
10	–	+	+	–	+	–	+	–	0.366	0.496	1.354	0.180	78	13
11	+	–	+	–	+	–	–	+	0.344	0.485	1.408	0.660	52	10
12	–	–	+	–	–	+	+	+	0.395	0.515	1.304	0.160	78	9
13	+	+	–	–	+	–	+	+	0.337	0.472	1.400	1.170	27	8
14	–	+	–	–	–	+	–	+	0.364	0.527	1.444	1.160	44	7
15	+	–	–	–	–	+	+	–	0.345	0.486	1.408	0.150	43	11
16	–	–	–	–	+	–	–	–	0.390	0.561	1.435	1.060	36	6

Bulk density of the compression mixture was determined by pouring the mixture into the graduated cylinder. The bulk volume and weight of the mixture were also determined. The bulk density is the ratio of the total mass of the compression mixture to the bulk volume [14].

Tapped density is the ratio of the total mass of the compression mixture and its tapped volume. The volume was measured by tapping the compression mixture 500 times [14]. Tapped volume was noted if the volume did not show a difference between two tapping intervals.

The compression mixture had not ability to flow that is why we could not determine flowability using the funnel method. To express flowability we have used Hausner ratio. It expressed as the tapped density of the compression mixture divided by the bulk density [14].

The resistance of tablet's for crushing is used to test the hardness of the tablets. The hardness of each batch of tablets was measured in Newton, where five tablets from each formula were tested through Tablet's hardness tester (Electrolab Company), and then the average value was documented [14].

The friability test was conducted by placing pre-weighed tablets in the Friability Tester (Electrolab Company); the latter was operated at 25 rpm for 4 min. The dust was removed

from the tablets surface and the tablets weight loss caused by fracture or abrasion was recorded as the percentage weight loss. Tablets should lose not more than 1 % of their weight to be acceptable [14].

The disintegration test for all formulations was carried out using Disintegration Testers (Electrolab Company). Six tablets were placed individually in each tube of the disintegration test apparatus and discs were placed. The water was maintained at the temperature of 37 ± 2 °C and the time taken for the tablet disintegration was noted [14].

3. Results

According to the obtained results we have constructed scatter diagrams for each response in order to determinate the significant factors form these diagrams. The difference between the average values of the factor for the upper and lower levels determines the influence of the factor on the technological parameter of the compression mixture and obtained tablets. The difference between the average values of the parameter is shown through the median on scatter diagram. The value of the median indicates the significance of the factor.

The influence of quantitative factors on the bulk density of the compression mixture (y_1) is depicted in **Fig. 1**.

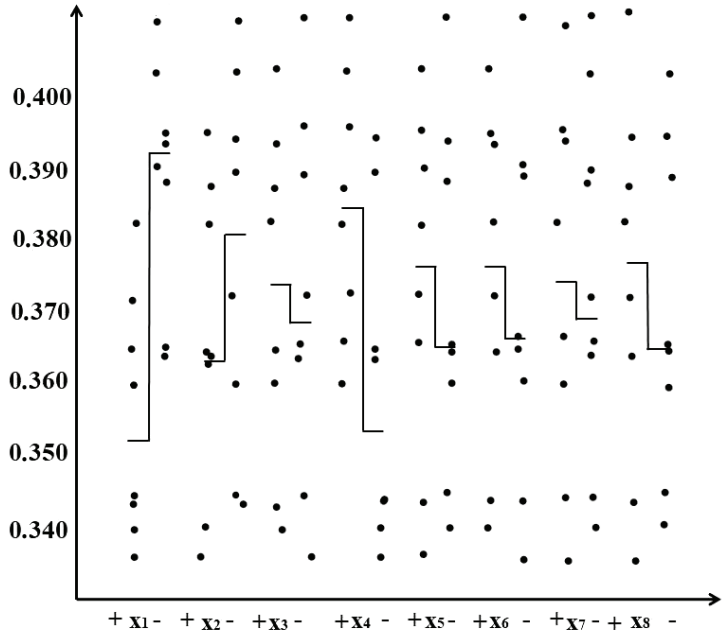

Fig. 1. Scatter diagram of bulk density results

Based on the analysis of the scatter diagram of bulk density results we have defined the statistically significant effects of factors x_1 and x_4. The decrease in the amount of silicon dioxide causes the increase in the value of the bulk density and vise versa, the bigger content of GalenIQ™720 is introduced in the compression mixtures, the larger the value of bulk density becomes. According direction of the medians, higher amount of magnesium carbonate basic (factor x_2) causes a reduction of the bulk density. Factors x_3, x_5, x_6, x_7 and x_8 have a slight positive effect on the studied parameters.

The dependence of tapped density on quantitative factors is shown in the **Fig. 2**.

Factors x_1, x_2 x_3 are statistical have been identified as statistically significant for studied parameter. The introduction of the silicon dioxide (factor x_1) and magnesium carbonate basic (factor x_2) at the lower level into the composition of the compression mixtures increase the value of the tapped density.

According to the scatter diagram in the **Fig. 3**, only factor x_5 has no influence on the Hausner ratio.

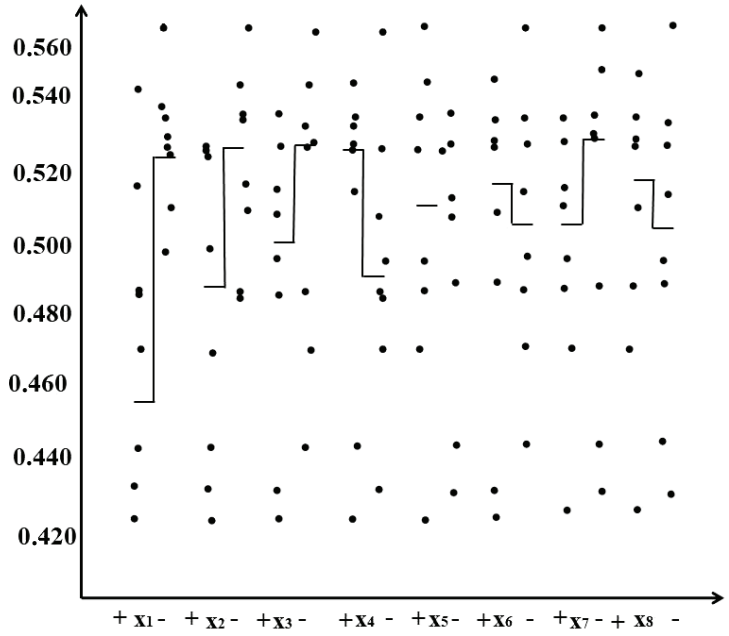

Fig. 2. Scatter diagram of tapped density results

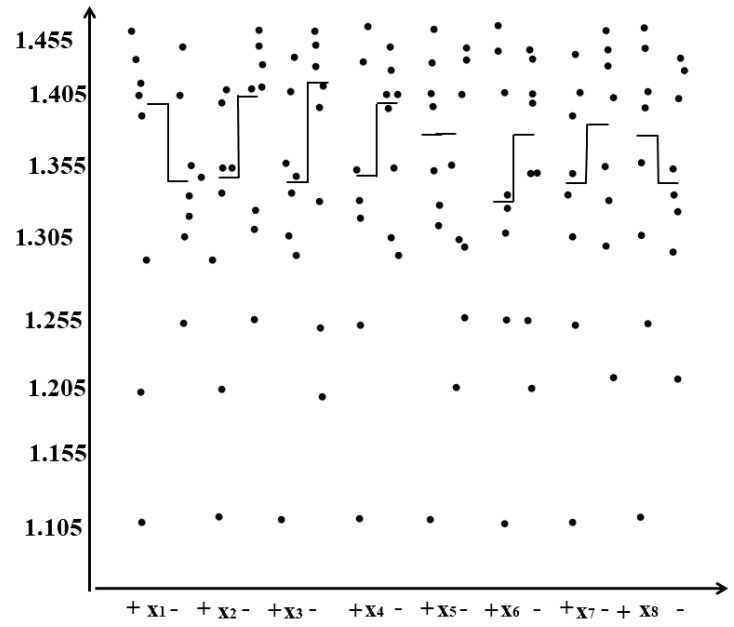

Fig. 3. Scatter diagram of Hausner ratio results

The increase in the amount of silicon dioxide (x_1) and citric acid (x_8) cause the increase in the value of the Hauster ratio. This means that the flowability of the compression mixture becomes worse. At the upper level the factors x_2, x_3, x_4, x_6, and x_7 value of the Hausner ratio decreases and flowability gets better.

The influence of the investigated factors on the friability of the tablets based on the *Oregano vulgare L.* dry extract is shown in **Fig. 4**.

We have discovered the statistical significance of the factors x_1, x_3, x_5, x_6, and x_7 for studied parameter of the tablets. Introduction of Neusilin S1, F-melt® C, sucralose, and berry flavor on the upper level in the tablets makes better the friability of the tablets. The decrease in the amount of silicon dioxide in the tablets enables to improve the studied parameter. The dependence of resistance for crushing obtained tablets on quantitative factors is shown in the **Fig. 5**.

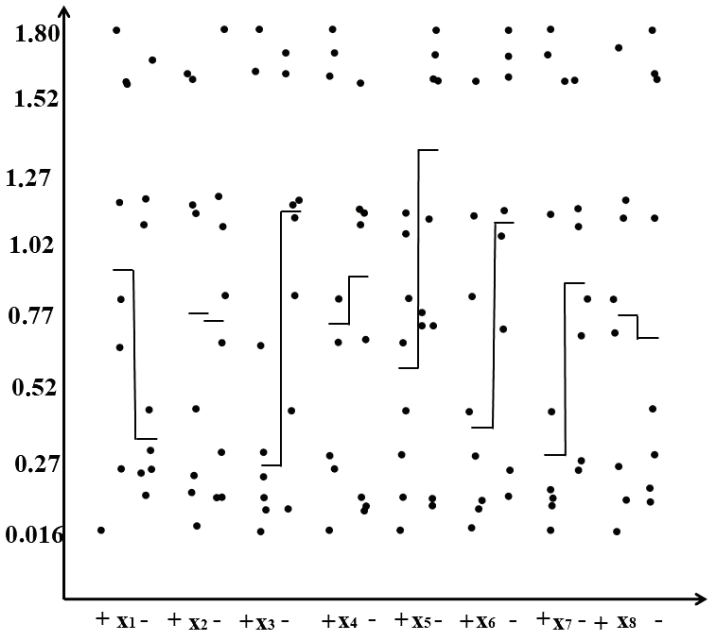

Fig. 4. Scatter diagram of tablets friability results

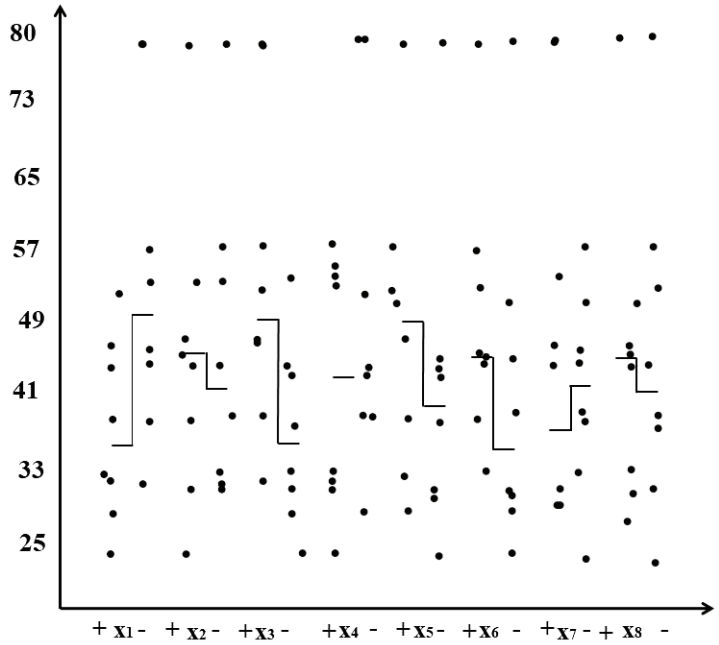

Fig. 5. Scatter diagram of tablets resistance for crushing results

Based on the analysis of the scatter diagram we have defined the statistically significant effects of factors x_1, and x_3. The better results of resistance for crushing tablets based on the *Oregano vulgare L.* dry extract were obtained at the lower levels of silicon dioxide and berry flavor. Increase in the amount of Neusilin S1, F-melt® C, and sucralose in the tablets have improved the hardness of the tablets.

The dependence of disintegration tablets on quantitative factors is shown in the **Fig. 6**.

The influence of the quantitative factors on the disintegration tablets based on the *Oregano vulgare L.* dry extract allowed us to reveal the statistical significance of the factors x_3 and x_6. The decrease in the amount of Neusilin S1 and sucralose in the tablets composition enables to reduce their disintegration time.

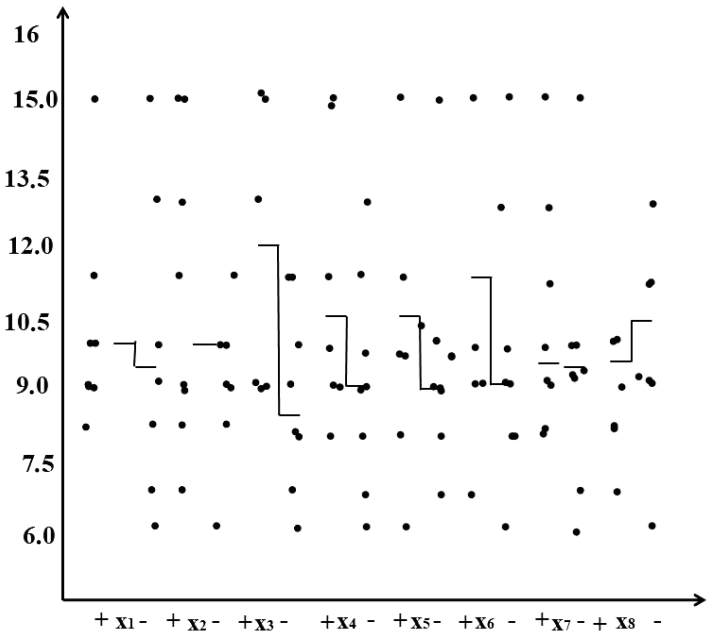

Fig. 6. Scatter diagram of disintegration tablets results

4. Discussion

We used excipients that are widely used in the development of the composition and technology of tablets [15–18], as well as new excipients.

Neusilin US 2 was used at the development of technology of tablets based on the extracts of goat's rue herb, extracts of bilberry leaves and taurine by direct compression method. It improved the homogeneity of the mass, increased the resistance to crushing, reduced friability and slightly reduced the disintegration time of the tablets [15]. The influence of the amounts of Neusilin US 2 on the technological indicators of the quality of compression mixture and the tablets with round-leaved wintergreen extract was determined. According to results increase in the amount of Neusilin US 2 improves Carr index of compression mixture, resistance to crushing, and friability of the tablets [16].

Neusilin of two brands, US 2 and UFL-2, have been studied as moisture regulators at the development of composition and technology of the tablets based on the *Malva sylvestris L*. and *Plantago lanceolata L*. dry extracts [17]. Neusilin US 2 has provided the best results.

Neusilin® UFL2 has been studied to increase solubility of poorly soluble drugs in the composition of an amorphous drug composites preparation [19].

Corn Starch-Neusilin UFL2 conjugates improved powder flow properties and disintegration of domperidone tablets [20].

The comparative evaluation of GalenIQ 721, against known excipients such as Pharmatose M200 and Alfacel type 102 has been performed. The influence of these excipients on compatibility properties, disintegration time and flowability has been studied. GalenIQ 721 gave better results than Pharmatose M200 but it inferior of Alfacel 102. Scientists predicted that the GalenIQ 721 characteristics, could be more stable to changes in composition and process conditions than those of Alfacel 102 [21].

Usage of F-melt have helped in solving formulation problems at the development of orally disintegrating dosage forms and improved flowability, compressibility, palatability, dissolution, disintegration, and dust generation [22].

In our research the increase of Neusilin S1 and sucralose amount makes better almost all investigated parameters but increase disintegration time of tablets. Hence, on the next stage of our research, we have decided to investigate more detailed the impact of these excipients on the main technological parameters of tablets based on the *Oregano vulgare L*. dry extract. To define the optimal quantity of GalenIQ™720 and F-melt® C in the composition of the investigated tablets we have include them in the next stage of the experiment too. These excipients improved most of

the studied parameters, but we have made decision to define the influence of their amount on the tablets quality more details in the narrower range because these substances are novel and very little information we have about their usage in the pharmaceutical technology.

The amount of berry flavor has been decided to stabilize at the upper level of 0.005 g in the one tablet.

The increase of silicon dioxide and magnesium carbonate basic amount had negative influence on most investigated parameters; citric acid have been defined as statistically insignificant factor. Hence, on the next stage of our research, we have decided to not use these excipients at development composition of the tablets based on the *Oregano vulgare L.* dry extract.

Therefore, excipients such as Neusilin S1, GalenIQ™720, F-melt® C, and sucralose will be used to optimize the composition of the tablets based on the *Oregano vulgare L.* dry extract with anti-inflammatory and antimicrobial properties for use in the treatment of a sore throat.

Study limitations. The study did not investigate the influence of excipients' amount on the dissolution of the tablets and wetting time.

Prospects for further research. Further research is aimed at optimization of the composition of excipients for the development tablets based on dry extract of *Origanum Vulgare L.* herb.

5. Conclusion

Tablets based on the *Oregano vulgare L.* dry extract were successfully obtained by direct compression method.

1. Based on the random balance method it is established the most significant quantitative factors influenced on the technological parameters of compression mixture and tablets based on the *Oregano vulgare L.* dry extract.

2. Taking into account the results of technological research we made decision to decrease amount of excipients in the composition of the tablets.

3. Considering that excipients such as Neusilin S1, GalenIQ™720, F-melt® C, and sucralose improved most of the technological parameters of the compression mixture and tablets with dry extract of *Origanum Vulgare L.* herb, they were included to the next experimental stage to develop the composition and technology of the tablets based on the *Oregano vulgare L.* dry extract with anti-inflammatory and antimicrobial properties for use in the treatment of a sore throat.

Conflict of interests

The authors declare that they have no conflicts of interest.

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