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Original Article

THE METHOD OF RANDOM BALANCE FOR STUDYING THE INFLUENCE OF EXCIPIENTS' QUANTITIES ON TECHNOLOGICAL PARAMETERS OF METFORMIN ORODISPERSIBLE TABLETS

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ABSTRACT

Objective: The present investigation was undertaken with an objective of analyzing the influence of excipients' amount on the technological parameters of metformin orodispersible tablets using the method of random balance.

Methods: The tablets were prepared by using direct compression method. The formulations were designed according to the method of random balance. The technological parameters of metformin orodispersible tablets have been studied as a function of quantitative factors: crospovidone (Polyplasdone XL-10®), magnesium aluminometasilicate (Neusilin US2®), microcrystalline cellulose (MCC Sanaq®burst), lactose monohydrate, magnesium stearate (Tablube®MgSt micronized vegetable) and talc.

Results: The flowability results were ranging from excellent to good according to the quantities of Neusilin US2® and Polyplasdone XL-10® crospovidone, which used. Results of bulk density and tapped density of the powder mixtures for pressing depended from the quantities of Neusilin US2® and talc. The obtained tablets had uniform weight from 0.93 to 2.30 %. The increase in the amount of Polyplasdone XL-10® crospovidone and the decrease in the amount of talk improved the uniformity of tablets weights. All of the prepared tablets showed acceptable hardness and friability which were improved with a decrease in the amount of MCC Sanaq®burst and increase in the amount of Neusilin US2®. The rapid disintegration and wetting time for all formulations of tablets were obtained by using the Polyplasdone XL-10® crospovidone and MCC Sanaq®burst.

Conclusion: Oral disintegrating tablets of metformin were successfully prepared by direct compression method. The random balance method enabled us to identify the most significant quantitative factors and stabilize them at optimal values.

Keywords: Method of random balance, Oral disintegrating tablets, Metfomin

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INTRODUCTION

Diabetes is an important public health problem, one of the major causes of morbidity and mortality in the world [1, 2]. According to the data International Diabetes Federation (IDF) Diabetes Atlas, [3] there are 425 million people with diabetes in the world. Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, which has increased alongside cultural and societal changes. Around 90 % of patients with diabetes have T2DM. There is an increasing tendency in the number of patients with T2DM. The most common objectives of T2DM are overweight and obesity rates, lifestyle and dietary changes, and an aging population. Managing T2DM is complex and time-intensive. There are many clinical practice guidelines to manage T2DM. Now all the guidelines recommend metformin as the first choice for initiating pharmacological treatment of people with T2DM [4-6].

The pharmaceutical technologists have developed a new oral dosage form known as orodispersible tablets (ODT). They disperse rapidly in saliva before being swallowed, without the taking water (disintegrate within 3 min) [7, 8].

In the previous study, the effects of 16 different excipients on technological characteristics of metformin ODT were evaluated. Based on the obtained results related to the choice of excipients, the best excipients were chosen for the development of metformin ODT [9].

The aim of our study was to analyze the influence of the amount of excipients on the technological parameters of metformin ODT using the method of random balance.

In our investigation, 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 [10].

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, and their selection is proved by calculations. The design construction of experiments matrix is preceded by coding the factors, selection of variation levels and by determining the experiment center [11].

MATERIALS AND METHODS

The materials which we used for this study comprise metformin hydrochloride (Harman Finochem Limited, India), crospovidone (Polyplasdone XL-10®) (Ashland Specialty Chemical, USA), magnesium aluminometasilicate (Neusilin US2®) (Fuji Chemical Industry Co., LTD, Japan), microcrystalline cellulose (MCC Sanaq® burst) (Pharmatrans Sanaq AG, Switzerland), lactose monohydrate (Alpavit Kaserei Champignon Hofmeister GMBH and CO Ltd, Germany), magnesium stearate (Tablube® MgSt micronized vegetable) (Nitika Pharmaceutical Specialties Pvt. Ltd, India), talc powder (Liaoning Aihai Co LTD, China). Materials were kindly provided by Farmak JSC and Witec Industrial.

The formulations were designed according to the method of random balance. In this design, technological parameters of metformin ODT have been studied as a function of 6 quantitative factors. The names of factors, with their variation levels, are shown in table 1.

We studied Polyplasdone XL-10® crospovidone as a superdisintegrant in the metformin ODT. During tablets compression, crospovidone particles become highly deformed. After water penetration into the tablets, the deformed particles of Polyplasdone® recover their normal structure, then swell and cause hydrostatic pressures necessary to provide rapid disintegration in the mouth [12, 13].

MCC Sanaq®burst can be used as a disintegrant and filler in tableting. It has excellent compressibility. The outstanding plasticity

enables to produce tablets with high strength. Furthermore, the tablets have very short disintegration time [14].

Neusilin US2® is a multifunctional excipient which can be used for direct compression. It has a porous structure which improves flowability of powder mixtures and hardness of obtained tablets. In addition, low concentrations of Neusilin US2® can improve the hardness of other filler and binder excipients [15, 16].

The sugar-based excipients display high aqueous solubility and sweetness and hence have a taste masking property and provide pleasing mouth feel [17, 18]. Lactose was used as the sugar-based excipients. Tablube® MgSt micronized vegetable was used as a lubricant. Talc was used as a glidant and lubricant.

Matrix 2^3 of full factorial experiment has been used in constructing random balance matrix. The design matrix by the method of random balance with experimental results is shown in table 2. The flowability (y_1), bulk density (y_2), tapped density (y_3), uniformity of weight (y_4), tablet's hardness (y_5), friability (y_6), disintegration time (y_7) and wetting time (y_8) were evaluated.

Table 1: Quantitative factors and their levels

Factor	Level of factor			
	Variation interval	Upper level (+)	Basic level «0»	Lower level (-)
x_1-quantity of Polyplasdone XL-10® crospovidone, %	1	5	4	3
x_2-quantity of microcrystalline cellulose Sanaq®burst, %	1	4	3	2
x_3-quantity of Neusilin US2®, %	1	4	3	2
x_4-quantity of lactose monohydrate, %	1	10	9	8
x_5-quantity of Tablube® magnesium stearate micronized vegetable, %	0.25	1.00	0.75	0.50
x_6-quantity of talc powder, %	0.5	2.0	1.5	1.0

Preparation of tablets

Fast dissolving tablets of metformin were prepared by direct compression method according to the matrix given in table 2.

All the ingredients were passed through #60 mesh separately, weighed and mixed. MCC 200 was added in the amount of 24 % of tablet's weight. Then lubricant and talc powder (# 200 mesh) were added and mixed for further 5 min. The mixture was directly compressed using 12 mm flat round punches into tablets of 500 mg on a single tooling tablet compression machine. A batch of 60 tablets was prepared for all the designed formulations.

Pre-compression evaluation

Before compression, the powder mixture from each formula was evaluated by several parameters such as flowability, bulk density and tapped density. The results of the pre-compression parameters were shown in table 2.

Flowability

Flowability was determined using the fixed funnel method. The powder mixture (±100 g) was poured through the funnel. The time for the powder mixture to fall down through the funnel was used to calculate flowability of the powder [19].

Bulk density

Bulk density of the powder mixture was determined by pouring the powder into the graduated cylinder. The bulk volume and weight of the blend were also determined. The bulk density is the ratio of the total mass of the powder to the bulk volume of the powder [20].

Tapped density

Tapped density is the ratio of the total mass of the powder to the tapped volume of the powder. The volume was measured by tapping the powder for 500 times. The volume was read every 100 intervals [20]. Tapped volume was noted if the volume did not show a difference between two tapping intervals.

Evaluation of tablets

The results of the technological parameters of obtained metformin ODT were shown in table 3. All the prepared tablets were evaluated for the following parameters:

Uniformity of weight

Twenty tablets were weighed individually, and the average weight was compared with the individual tablet weights. As per the specifications, for tablets weighing 250 mg and more, the allowed weight variation deviation is 5 %. The tablets meet the test if not more than two tablets are outside the limit and no tablet differs the limit by more than twice [21].

The tablet's hardness is used to test the breaking point. The resistance of tablets to shipping, breakage, under conditions of storage, transportation, and handling before usage depends on their hardness. The hardness of each batch of tablets was measured in Newton, where five tablets from each formula were tested through tablet's hardness tester (Tianjin Guoming Medicinal Equipment Co., LTD), and then the average value was documented [21].

The friability test was conducted by placing pre-weighed tablets in the friabilator (Tianjin Guoming Medicinal Equipment Co., LTD); the latter was operated at 25 rpm for 4 min. The tablets were deducted and the 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 [19, 21].

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. 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 entire tablet to disintegrate completely was noted [19, 21].

Wetting time

A piece of circular tissue paper (8 cm) folded twice was placed in a Petri dish containing 10 ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted [20, 22].

RESULTS AND DISCUSSION

Scatter diagrams were constructed based on the results from table 2 and table 3. Determination of significant factors was carried out using scatter diagram. 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. 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. Then, the significance check of the obtained effects is done by the Students t-criterion.

Based on the results of the pre-compression parameter, it can be concluded that all formulas have good flowability. The flow velocity of the powder blend has the predictive power for its ability to fulfill the dies during the compression stage. The homogeneity of powder flow will decrease the variation in the tablet weight.

The analysis of the scatter diagram of flowability results shows the significance of the effects of factors x_3 and x_1 (fig. 1). Increasing the quantity of Neusilin US2® (x_3) from 2 to 4 % in powder mixtures leads to the reduction of the flow time of powder from the funnel. Better flowability results are obtained when Polyplasdone XL-10® crospovidone is introduced in an amount of 3 % in powder mixtures.

Significance check of obtained effects of factors x_3 and x_1 are quantitatively checked by t-criterion. Calculations are shown in table 4. For the threshold or significance level α=0.05 and for f=4 we have the tabular value of Students criterion t=2.78. Since the calculated values are above the tabular value for the T-test, the separated effects are statistically significant with 95 % confidence. A check of Fisher's criterion offered the value F_R=0.104 (table 3). Since the tabular value is higher than F_R, further process of screening factors is stopped. The analysis of the influence of other factors showed an insignificant effect on this indicator.

Although the statistical significance of other factors within the studied intervals has not been confirmed, the medians of the factors x_2 and x_4 are visually distinguished on the scatter diagram of flowability results. The flow rate of the investigated powders is better in those formulations, which contain less quantity of MCC Sanaq®burst (2 %) and lactose (8 %).

Table 2: Design of ODT metformin formulations matrix and pre-compression parameters of powder mixtures

№ formula	x_1	x_2	x_3	x_4	x_5	x_6	Flowability (s/100 g)		Bulk density (g/cm³)		Tapped density (g/cm³)	
							Experimental responses	Corrected responses	Experimental responses	Corrected responses	Experimental responses	Corrected responses
							y_1	y_1^I	y_2	y_2^I	y_3	y_3^I
1	+	+	+	+	+	+	16.9	15.95	0.527	0.541	0.684	0.698
2	-	+	+	-	-	-	13.3	23.85	0.528	0.568	0.625	0.712
3	+	-	+	-	-	+	16.1	15.15	0.538	0.578	0.671	0.758
4	-	-	+	+	+	-	13.2	23.75	0.537	0.551	0.682	0.696
5	+	+	-	-	+	-	24.2	13.65	0.567	0.528	0.719	0.633
6	-	+	-	+	-	+	17.7	18.65	0.547	0.533	0.717	0.703
7	+	-	-	+	-	-	23.4	12.85	0.545	0.531	0.677	0.663
8	-	-	-	-	+	+	13.4	14.35	0.578	0.539	0.750	0.664
9	o	o	o	o	o	o	13.3	-	0.526	-	0,646	-
$\overline{yi}$							16.8	17.28	0.544	0.546	0.686	0.691
S_R^2								19.23		0.0003		0.0014
S_y^2								184.34		0.0442		0.0779
$F= S_R^2/S_y^2$								0.104		0.0074		0.0184

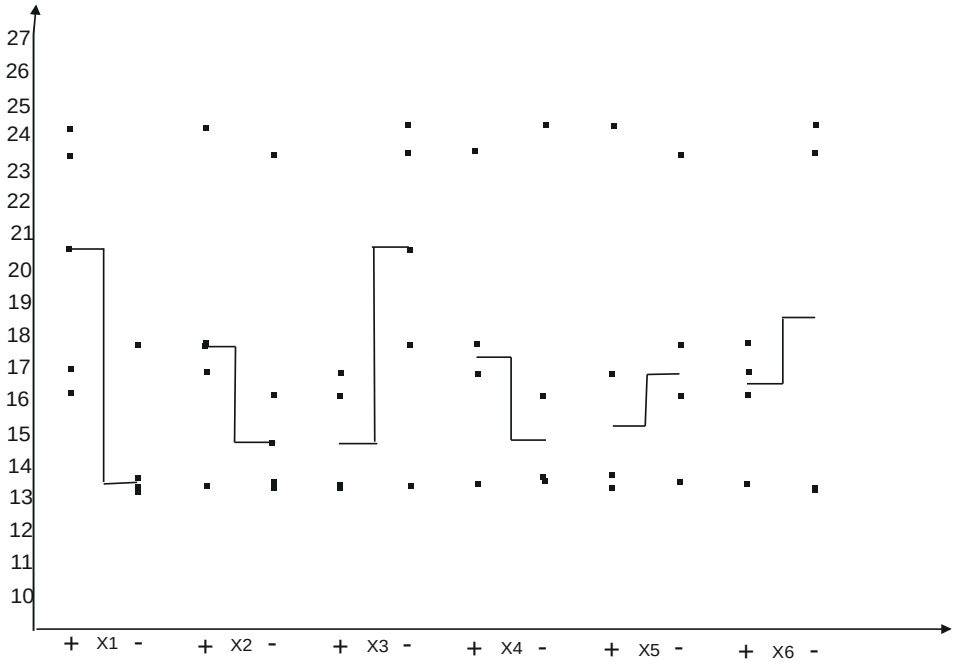

Fig. 1: Scatter diagram of flowability results

The influence of quantitative factors on the bulk density (y_2) is depicted in fig. 2. The analysis of the scatter diagram of bulk density results and significance check of obtained effects show the statistically significant effects of factors x_3 and x_6. The smaller the content of Neusilin US2® is in the powder mixtures for pressing, the larger the value of bulk density becomes. The introduction of the talk on the lower level (factor x_6) into the composition of the powder mixtures reduces the value of the studied parameter.

The influence of the investigated factors on the tapped density is shown in fig. 3. The impact of the factors x_3 and x_6 on the tapped density is significant at the level α=0.05 and α=0.10, respectively (table 4). Adding the factor x_3 at the upper level in the powder mixtures decreases the value of tapped density. The median of the effect of the factor x_6 shows that the decrease in the amount of talk causes the reduction in the value of the tapped density.

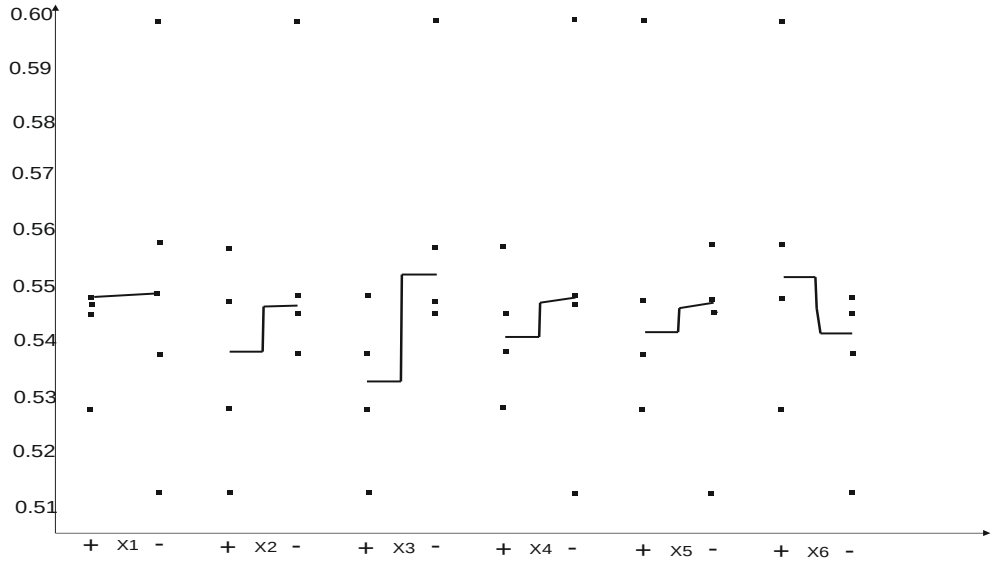

Fig. 2: Scatter diagram of bulk density results

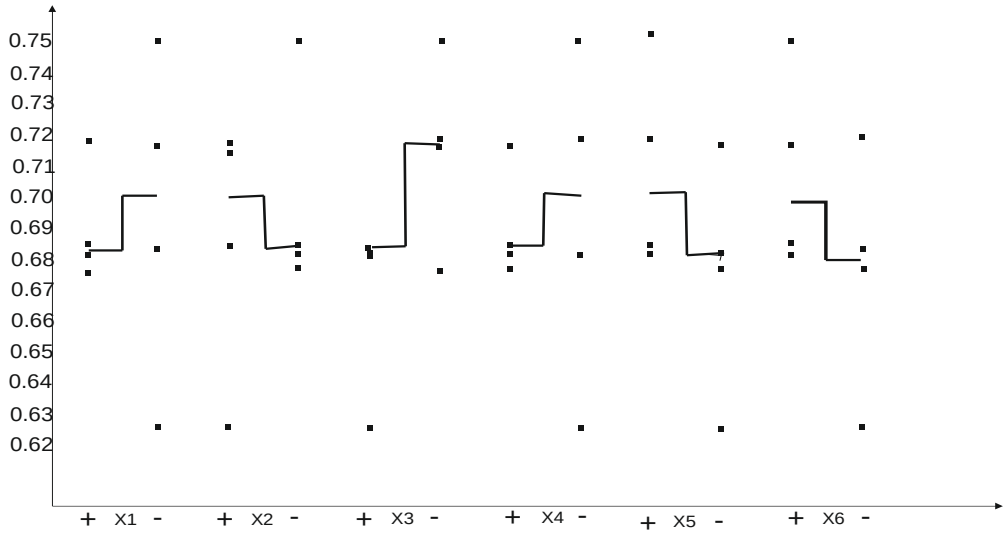

Fig. 3: Scatter diagram of tapped density results

Table 3: Technological parameters of ODT metformin formulations

№ formula	Uniformity of weight (%)		Tablet's hardness test (N)		Friability test (%)		Disintegration time (s)		Wetting time test (s)	
	Experimental responses	Corrected responses	Experimental responses	Corrected responses	Experimental responses	Corrected responses	Experimental responses	Corrected responses	Experimental responses	Corrected responses
	y_4	y_4^I	y_5	y_5^I	y_6	y_6^I	y_7	y_7^I	y_8	y_8^I
1	1.15	1.320	50.0	49.8	0.24	0.290	15.0	10	21.5	21.00
2	1.40	1.230	54.2	54.0	0.31	0.360	11.5	10	22.5	23.00
3	1.45	1.620	62.4	42.4	0.18	0.405	8.5	10	17.0	23.25
4	1.54	1.370	59.2	39.2	0.23	0.455	9.0	14	26.0	19.75
5	1.10	1.835	41.7	61.7	0.39	0.165	10.5	9	21.5	21.00
6	1.80	1.065	39.9	59.9	0.47	0.245	13.0	8	19.5	20.00
7	0.95	1.685	49.1	49.3	0.34	0.290	9.0	14	19.5	25.75
8	1.72	0.985	54.7	54.9	0.31	0.260	10.5	12	23.0	16.75
9	2.30	-	82.3	-	0.48	-	13.0	-	24.0	-
$\overline{yi}$	1.49	1.389	54.8	51.4	0.33	0.309	11.1	10.9	21.6	21.31
S_R^2		0.091		62.0		0.009		4.98		7.35
S_y^2		1.689		1705.7		0.102		56.25		123.57
$F=S_R^2/S_y^2$		0.054		0.036		0.088		0.089		0.059

Table 4: Calculation of variance and summarized results

Number of cells	n_i	Σy_i	$(\Sigma y_i)^2$	Σy_i^2	S_r^2	S_r^2/n	Effect values	t_R
Flowability								
1	2	33.0	1089.00	544.82	0.320	0.1600	Ex_1=5.75	5,17
2	2	47.6	2265.76	1133.20	0.320	0.1600		
3	2	26.5	702.25	351.13	0.005	0.0025	Ex_3=-4.80	-4,32
4	2	31.1	967.21	492.85	9.245	4.6225		
Σ	8					4.9450		
Bulk density								
1	2	1.064	1.132	0.566	5E-05	2.5E-05	Ex_3=0.027	-5.94
2	2	1.066	1.136	0.568	5E-05	2.5E-05		
3	2	1.145	1.311	0.656	6,05E-05	3.02E-05	Ex_5=-0.013	2.83
4	2	1.092	1.192	0.596	2E-06	1E-06		
Σ	8							
Tapped density								
1	2	1.366	1.866	0.933	2E-06	1E-06	Ex_3=0.050	-2.94
2	2	1.296	1.680	0.841	0.001058	0.000529		
3	2	1.469	2.158	1.079	0.000481	0.00024	Ex_5=-0.036	2.12
4	2	1.394	1.943	0.972	0.0008	0.0004		
Σ	8							
Uniformity of weight								
1	2	2.600	6.760	3.425	0.045	0.0225	Ex_1=0.453	-4.86
2	2	2.050	4.203	2.113	0.011	0.0056		
3	2	3.520	12.390	6.198	0.003	0.0016	Ex_6=-0.283	3.04
4	2	2.940	8.644	4.332	0.010	0.0049		
Σ	8							
Tablet's hardness								
1	2	104.2	10857.64	5437.64	8.82	4.41	Ex_2=9.9	-5.01
2	2	81.6	6658.56	3330.90	1.62	0.81		
3	2	121.6	14786.56	7398.40	5.12	2.56	Ex_3=-10.1	5.11
4	2	103.8	10774.44	5402.90	15.68	7.84		
Σ	8							
Friability								
1	2	0.550	0.303	0.154	0.0025	0,0012	Ex_2=-0.0875	2.89
2	2	0.860	0.740	0.373	0.0032	0,0016		
3	2	0.410	0.168	0.085	0.0013	0.0006	Ex_3=0.1375	-4.54
4	2	0.650	0.423	0.212	0,0005	0.0002		
Σ	8							
Disintegration time								
1	2	28	784	394.0	2.0	1.00	Ex_2=-3.25	4.33
2	2	22	484	242.5	0.5	0.25		
3	2	19	361	182.5	2.0	1.00	Ex_6=-1.75	2.33
4	2	18	324	162.0	0	0		
Σ	8							
Wetting time								
1	2	43.0	1849.00	924.50	0	0	Ex_1=2.88	-2.34
2	2	36.5	1332.25	669.25	3.1	1.6		
3	2	49.0	2401.00	1205.00	4.5	2.3	Ex_5=-3.38	2.74
4	2	42.0	1764.00	886.50	4.5	2.3		
Σ	8							

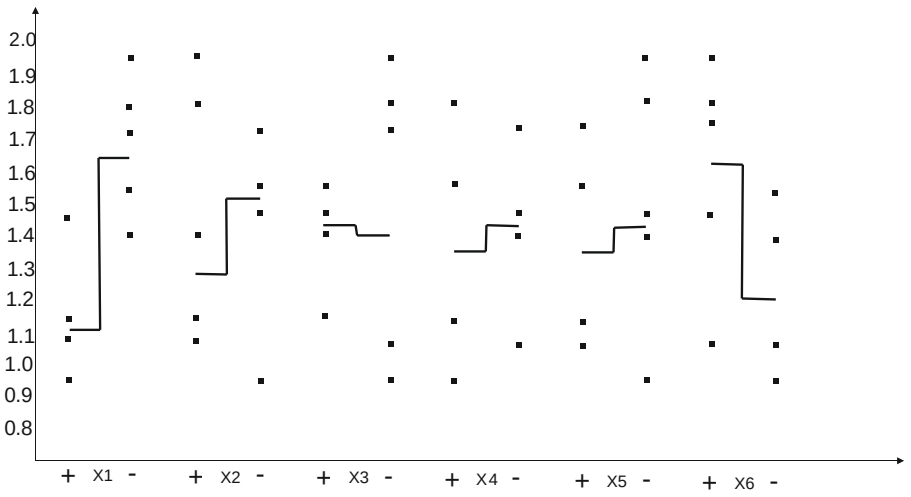

Fig. 4: Scatter diagram of uniformity of weight results

As the mixture for pressing was characterized by satisfactory flow velocity, the obtained tablets had uniform weight from 0.93 to 2.30 % (table 3). The impact of factors x_1 and x_6 on the uniformity of tablets' weight was significant on the level of 95 %. The increase in the amount of Polyplasdone XL-10® crospovidone improves the uniformity of tablets' weights**.** The decrease in the amount of talk (x_6) in the formulations causes a reduction in the percentage deviation from the average weight of tablets. From fig. 4, we can observe that a median of the effect of x_2 on the uniformity of tablets' weight is noticeable. An increase in the amount of MCC Sanaq®burst in the formulations improves tablets' uniformity.

The metformin ODTs were characterized by satisfied hardness, except the formulations # 5-7, values of which were less than 50 N (table 3). The impact of factors x_2 and x_3 were significant. The decrease in the amount of MCC Sanaq®burst in the tablets leads to an increase of hardness. Adding Neusilin US2® by 4 % (upper level) to the tablets causes an increase of hardness. From fig. 5, it is observed that the medians of the effect of x_1 and x_4 on the tablet hardness are noticeable. The decrease in the amount of Polyplasdone XL-10®crospovidone and lactose in the formulations causes an increase in this indicator.

The friability of metformin tablets less than 1 % observed in all formulations, meets the requirements of the European Pharmacopoeia and State Pharmacopoeia of Ukraine for tablets. The impact of factors x_2 and x_3 on the friability of tablets was significant on the level of 95 %. The tablets containing Neusilin US2® on the upper level were the most resistant to abrasion. The better results of friability were obtained in formulations, which contain less quantity of MCC Sanaq®burst (2 %).

From fig. 6, we can observe that the medians of the effect of x_5 and x_6 on the friability of metformin tablets are noticeable. The percentage deviation from the average weight of tablets after friability is less in formulations, which contain Tablube® MgSt (1 %) and talc (2 %).

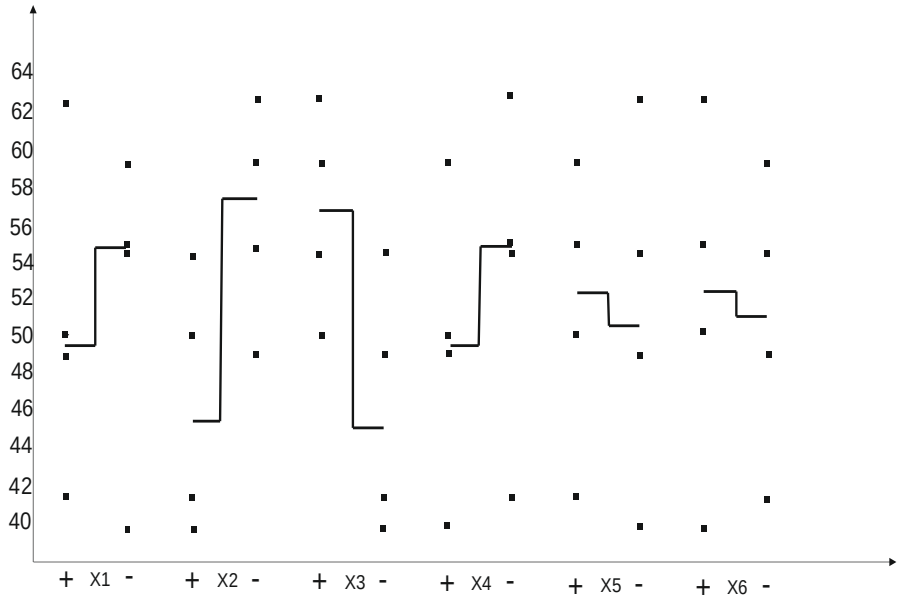

Fig. 5: Scatter diagram of tablet's hardness results

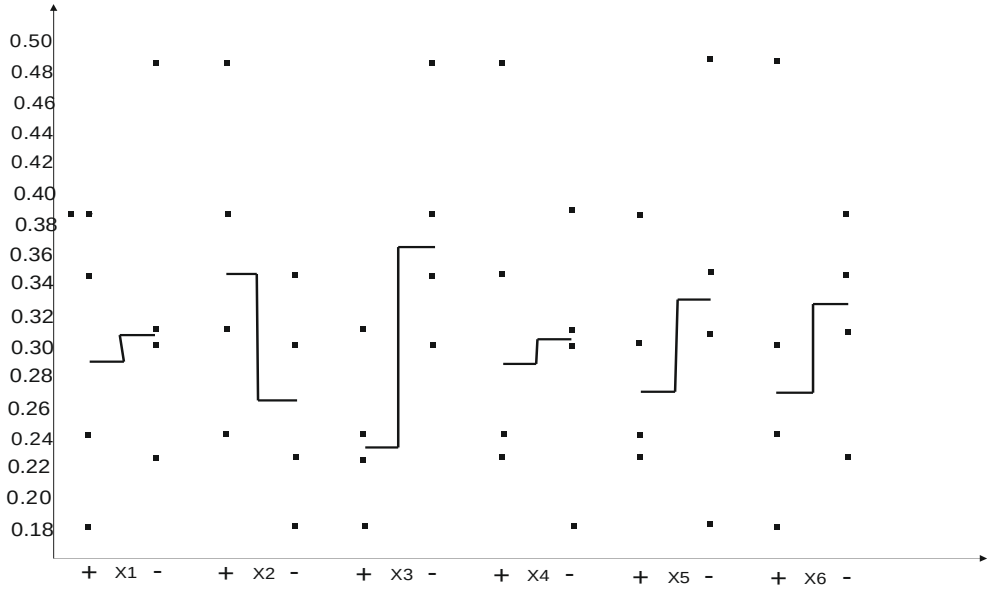

Fig. 6: Scatter diagram of friability results

The most important technological parameter of ODT is the disintegration time. The disintegration time was changed from 9 to 15 s in all formulations, which meets the Pharmacopoeia requirements for ODT. The impact of factors x_2 and x_6 on the disintegration time of tablets was significant on the level α=0.05 and α=0.10, respectively (table 4). The decrease in the amount of MCC Sanaq® burst in the tablets lead to a decrease of disintegration time.

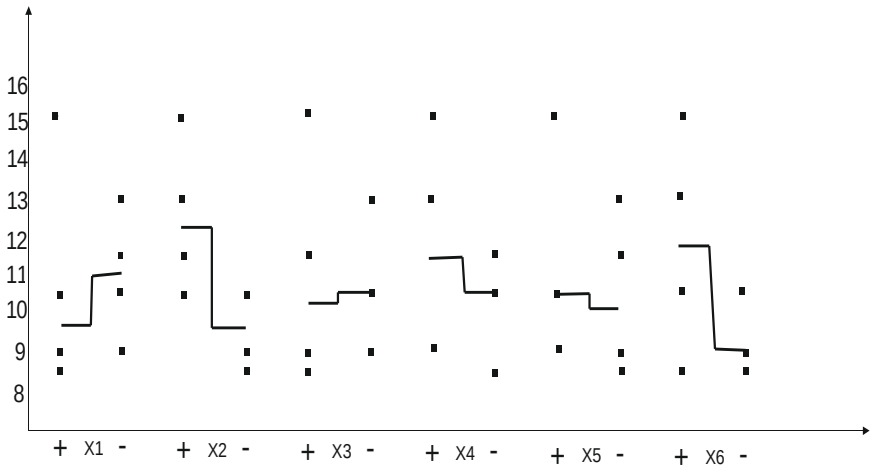

Fig. 7: Scatter diagram of disintegration time results

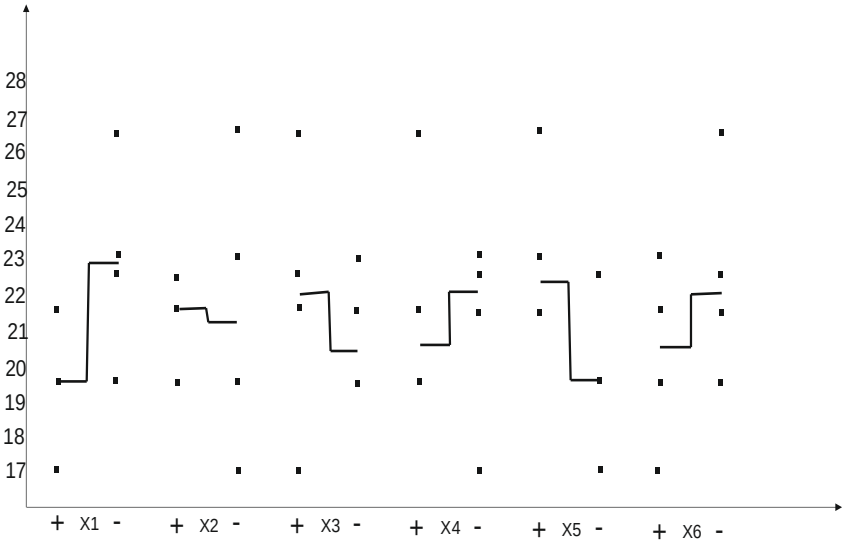

Fig. 8: Scatter diagram of wetting time results

Wetting time test is not a standard test, but it is useful for quality control and provides a correlative evaluation of water absorption. The wetting test uses a minimal quantity of buffer solution simulating saliva pH 6.8, which represents the amount of moisture available in the oral cavity [20]. The wetting time for all formulations of tablets was less than 25 s. The faster wetting time of the tablets produces better disintegration time.

The impact of the investigated factors allowed us to discover the statistical significance of the factors x_1 and x_5. The decrease in the amount of Tablube® MgSt grade micronized vegetable and the increase in the amount of Polyplasdone XL-10® crospovidone in tablets enable to reduce the absorption time in phosphate buffer (pH 6.8).

As the reduction of the amount of Polyplasdone XL-10® crospovidone in the powder mixtures improves flowability and tablet's hardness but simultaneously worsens uniformity of weight, disintegration and absorption time in the phosphate buffer (pH 6.8). Hence, the amount of Polyplasdone XL-10® crospovidone (x_1) was stabilized at a basic level of 4 % in the formulations.

The impact of the amount MCC Sanaq®burst (x_2) on the technological parameters of the metformin ODT is ambiguous. The decrease of its amounts accelerates the flowability of powder mixtures, but increases the uniformity of tablets weight, and improves mechanical strength and disintegration time. Hence, on the next stage of research, we have decided to investigate more detailed the impact of the amount of MCC Sanaq®burst on the main technological parameters of metformin tablets.

The amount of Neusilin US2® in the powder mixtures has the greatest impact on the technological parameters of the tablets. Thus, the reduction of its amount in the powder mixtures improves flowability, bulk density, and tapped density. However, the increase of its amount allows us to obtain tablets with higher hardness and friability. Hence, on the next stage of research, we have decided to investigate the impact of the amount of Neusilin US2® on the main indicators of metformin ODT.

We have decided to stabilize the amount of lactose monohydrate at a lower level of 8 % in the powder mixtures. The amount of Tablube® MgSt grade micronized vegetable has been decided to stabilize at the

upper level in the amount of 1 %. As with the increase of its amount we have obtained the better flowing properties of the powder mixtures, tablet's hardness and friability. The amount of talc has been decided to stabilize at the upper level of 2 %.

CONCLUSION

Oral disintegrating tablets of metformin were successfully prepared by direct compression method. All the oral disintegrating tablets possessed good physicochemical and dissolution properties. The random balance method enabled us to identify the most significant quantitative factors and stabilize them at optimal values, except the two factors of MCC Sanaq®burst and Neusilin US2®. For these factors, an additional stage of optimization will be conducted at the next stage of the studying.

ABBREVIATIONS

IDF: International Diabetes Federation; T2DM: Type 2 diabetes mellitus; ODT: Orodispersible tablets; MCC: microcrystalline cellulose; MgSt: Magnesium stearate.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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