ORIGINAL ARTICLE

Greco-Latin Square Design for Selection of Excipients in the Development of Metformin Orodispersible Tablets

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Abstract

Introduction: To provide the patient with the most convenient mode of administration, there is a need to develop fast-disintegrating tablets, which disintegrate and dissolve rapidly in the saliva, within a few seconds without drinking water. The aim of this study was to analyze the influence of the groups of excipients on technological parameters of metformin orodispersible tablets (ODTs). **Materials and Methods:** Greco-Latin squares design was used to establish the relations between independent variables such as type of disintegrant, type of diluent, type of sugar-based excipients, type of lubricant, and dependent variables. **Results:** Orally disintegrating tablets of metformin were prepared by direct compression method. Studying different groups of excipients, it was found that they provide good values of pre-compression parameters of powder mixture and uniformity of weight of tablets. The usage of excipients has provided lower disintegration time (<3 min) and wetting time of tablets. **Conclusion:** Using Greco-Latin squares design, the influence of four groups of excipients on technological characteristics of metformin ODTs was evaluated. According to the results of desirability function, the best values of technological parameters of metformin ODT were obtained when adding Polyplasdone XL-10 crospovidone, microcrystalline cellulose (MCC) Sanaq ®burst, MCC Vivapur® 200, lactose monohydrate, and Tablube Magnesium Stearate grade Micronized Vegetable to the tablets.

Key words: Fast-disintegrating tablets, Greco-Latin squares design, metformin, superdisintegrants

INTRODUCTION

Tablets and capsules are the most popular dosage forms. However, one important drawback of such dosage forms is dysphagia or difficulty in swallowing. Dysphagia is a common problem encountered in all age groups, especially for pediatrics, elderly, disabled or bedridden, and psychiatrists, resulting in patient's non-compliance, hence, ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attack or coughing, and unavailability of water, swallowing conventional tablets may be difficult.[1,2] To solve the above-mentioned problem, pharmaceutical technologists have done their best to develop a fast-dissolving drug delivery.

Mouth dissolving tablets disintegrate and dissolve rapidly in the saliva, within a few seconds without drinking water or chewing.[3] There are several synonyms for mouth dissolving tablets such as orodispersible, orally disintegrating tablets, quickly dissolving tablets, fast melt tablets, rapidly disintegrating tablets, and freeze dried.[4]

Their growing importance was underlined recently when European pharmacopoeia adopted the term "orodispersible tablet" (ODT) as the tablet which is placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the ODT should disperse/disintegrate in <3 min.[5]

ODTs are characterized by high porosity, low density, and low hardness when administered, an *in situ* suspension is obtained in the oral cavity as the tablet disintegrates and is subsequently swallowed.[6]

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Direct compression represents the simplest and the cheapest tablet manufacturing technique. ODT can be prepared using this technique because of the availability of improved excipients, especially superdisintegrants and sugar-based excipients.[7,8]

Metformin hydrochloride, a biguanide, is a highly water-soluble anti-hyperglycemic agent.[9] It is effectively used in the treatment of non-insulin-dependent diabetes mellitus.[10]

The aim of our study was to analyze the influence of groups of excipients on technological parameters of metformin ODT using Greco-Latin squares design.

Latin square designs, the related Greco-Latin square and Hyper-Greco-Latin square designs, are a special type of comparative design.[11,12] In our investigation, we used the Greco-Latin square, which is useful for the investigation of simultaneous effects of four factors in a single experiment. A Greco-Latin square is obtained by imposing the levels of the additional factor on a Latin square in the way any level of a factor appears at most once at each level of other factors. This method is used for analyzing the influence of independent factors on measured answers (dependent variables).[13,14]

MATERIALS AND METHODS

Materials used for the aim of this study consist of metformin hydrochloride (Harman Finochem Limited), sodium croscarmellose (Mingtai Chemical Co Ltd), sodium starch glycolate (SSG) (JRS Pharma GMBH & Co., Ltd.), Polyplasdone XL-10 crospovidone (Ashland Specialty Chemical), microcrystalline cellulose (MCC) Sanaq®burst (Pharmatrans Sanaq AG), MCC Vivapur® 102, MCC Vivapur® 112, MCC Vivapur® 200, Prosolv® SMCC HD 90 (JRS Pharma GMBH & Co. Ltd.), lactose monohydrate (Alpavit Kaserei Champignon Hofmeister GMBH & Co. Ltd.), mannitol (Getec Guanabara Quimica Industrial S.A.), sucrose Compri O (Südzucker GMBH), Ludiflash (BASF Global), Tablube magnesium stearate (MgSt) grades Superior Vegetable, Premium Vegetable, Micronized Vegetable (Nitika Pharmaceutical Specialties Pvt. Ltd), and calcium stearate (Magnesia GmbH). Materials were kindly provided by Farmac JSC and Witec Industrial.

The formulations were designed according to the method of 4 × 4 Greco-Latin squares. In this design, four groups of factors were evaluated, and experimental trials were performed in 16 possible combinations. To evaluate the reproducibility error, all experiments were duplicated.

The type of disintegrant (factor A), type of diluent (factor B), type of sugar-based excipients (factor C), and type of lubricant (factor D) were selected as independent variables. The list of independent variables is shown in Table 1.

Table 1: Independent variables and their levels selected to perform Greco-Latin squares design

Independent variables (factors)	Level of factor
A - type of disintegrant	a_1 - Sodium croscarmellose a_2 - SSG a_3 - Polyplasdone XL-10 crospovidone a_4 - MCC Sanaq® burst
B - type of diluent	b_1 - MCC Vivapur 102 b_2 - MCC Vivapur 112 b_3 - MCC Vivapur 200 b_4 - Prosolv SM HD 90 SMCC
C - type of sugar-based excipient	c_1 - Lactose monohydrate c_2 - Mannitol c_3 - Sucrose Compri O c_4 - Ludiflash
D - type of lubricant	d_1 - Tablube MgSt grade superior vegetable d_2 - Tablube MgSt grade premium vegetable d_3 - Tablube MgSt grade micronized vegetable d_4 - Calcium stearate

SSG: Sodium starch glycolate, MCC: Microcrystalline cellulose, MgSt: Magnesium stearate

The superdisintegrants provide instantaneous disintegration of a tablet after putting it on the tongue. Contacting with water, the superdisintegrants swell, hydrate, change volume or form, and make a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility and compatibility besides, they do not have any negative impact on the mechanical strength of formulations containing high-dose drugs.[15,16]

In the present investigation, such disintegrants as Polyplasdone XL-10 crospovidone, sodium croscarmellose, SSG, and MCC Sanaq® burst were studied. The total amount of disintegrant was fixed at 5% in the formulations.

Polyplasdone XL-10 crospovidone is a non-ionic and water-insoluble, but swellable cross-linked polyvinylpyrrolidone homopolymer. The high interfacial activity of Polyplasdone XL-10 crospovidone enhances the dissolution of poorly soluble drugs. Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures which are necessary for providing rapid disintegration in the mouth.[15,17]

MCC is used as a disintegrant, diluent, or binder in tablet formulations and is capable of undergoing plastic deformation at relatively low yield pressure, which allows preparation of compacts at low compression forces.[18] MCC Sanaq® burst has higher porosity than other standard MCC Avicel grades. The increase in porosity affects the capillary networks inside the tablet. It influences rapid passage of water into tablet

resulting in the instantaneous ruptures of the hydrogen bonds.[19,20]

Another modified cellulose excipient is sodium croscarmellose, which is cross-linked carboxymethylcellulose sodium. Sodium croscarmellose particles are long and narrow (fibrous) with curves and twists. Swelling, wicking, and strain recovery mechanisms are proposed for these superdisintegrants.[21]

SSG was chosen due to its ability to absorb water rapidly, resulting in swelling which leads to rapid disintegration of tablets.[22]

This class of disintegrants has been shown to be effective at the concentration as low as 2–10%.[21]

The sugar-based excipients display high aqueous solubility and sweetness, and hence impart taste masking property and provide pleasing mouthfeel.[23] The sugar-based excipients such as lactose, mannitol, sucrose Compri O, and Ludiflash were studied in this investigation. The total amount of grade of sugar-based excipients was fixed at 10% in the formulations.

In addition, we studied diluents MCC Vivapur® 102, MCC Vivapur® 112, MCC Vivapur® 200, and Prosolv® SMCC HD 90. The total amount of diluent was fixed at 32% in the formulations.

Tablube MgSt grades Superior Vegetable, Premium Vegetable, Micronized Vegetable, and calcium stearate were used as lubricants in quantity of 1% in the formulations.

The flowability (y_1, y_1^1), bulk density (y_2, y_2^1), tapped density (y_3, y_3^1), compressibility (y_4, y_4^1), Hausner ratio (y_5, y_5^1), uniformity of weight (y_6, y_6^1), tablet hardness (y_7, y_7^1), friability (y_8, y_8^1), disintegration time (y_9, y_9^1), and wetting time (y_{10}, y_{10}^1) were selected as dependent variables. The data were interpreted using the method of 4 × 4 Greco-Latin squares (Microsoft Office Excel, 2010).

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. Then, lubricant and talcum powder (2%) (#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, tapped density, compressibility index, and Hausner ratio [Table 2].

Flowability

Flowability was determined using the fixed funnel method. The powder mixture (±100 g) was poured through the funnel.

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

Number formulation	Factor				Flowability, s/100 g		Bulk density, g/cm³		Tapped density, g/cm³		Compressibility index, %		Hausner ratio	
	A	B	C	D	y_1	y_1^1	y_2	y_2^1	y_3	y_3^1	y_4	y_4^1	y_5	y_5^1
1	a_1	b_1	c_1	d_1	29.10	29.22	0.585	0.575	0.745	0.751	21	23	1.27	1.31
2	a_1	b_2	c_2	d_4	25.92	26.32	0.568	0.557	0.716	0.726	21	23	1.26	1.30
3	a_1	b_3	c_3	d_2	44.02	46.18	0.584	0.572	0.738	0.734	21	22	1.26	1.28
4	a_1	b_4	c_4	d_3	34.44	22.12	0.554	0.560	0.683	0.688	19	19	1.23	1.23
5	a_2	b_1	c_2	d_3	27.46	27.18	0.585	0.576	0.731	0.737	20	22	1.25	1.28
6	a_2	b_2	c_1	d_2	29.20	28.36	0.592	0.587	0.753	0.749	21	22	1.27	1.28
7	a_2	b_3	c_4	d_4	48.58	49.78	0.586	0.597	0.732	0.738	20	19	1.25	1.24
8	a_2	b_4	c_3	d_1	48.80	49.61	0.577	0.567	0.698	0.691	17	18	1.21	1.22
9	a_2	b_1	c_3	d_4	57.33	57.45	0.580	0.576	0.723	0.727	20	21	1.25	1.26
10	a_2	b_2	c_4	d_1	36.11	36.35	0.565	0.555	0.690	0.700	18	21	1.22	1.26
11	a_3	b_3	c_1	d_3	43.34	43.54	0.566	0.574	0.683	0.689	17	17	1.21	1.20
12	a_3	b_4	c_2	d_2	28.71	28.95	0.520	0.521	0.639	0.642	19	19	1.23	1.23
13	a_4	b_1	c_4	d_2	47.49	46.43	0.582	0.578	0.729	0.730	20	21	1.25	1.26
14	a_4	b_2	c_3	d_3	26.46	24.46	0.567	0.574	0.733	0.737	23	22	1.29	1.28
15	a_4	b_3	c_2	d_1	38.24	36.96	0.593	0.585	0.732	0.731	19	20	1.23	1.25
16	a_4	b_4	c_1	d_4	40.98	40.14	0.591	0.585	0.720	0.726	18	19	1.22	1.24

The time for the powder mixture to fall down through the funnel was used to calculate flowability of the powder.[5,24]

Bulk density

Bulk density of the powder mixture was determined by pouring the powder into the graduated cylinder. The bulk volume (Vb) and weight of the blend (m) were also determined. The bulk density is the ratio of the total mass of the powder (m) to the bulk volume of the powder.[5,24]

Tapped density

Tapped density is the ratio of the total mass of the powder (m) to the tapped volume of the powder (Vt). The volume was measured by tapping the powder for 500 times. The volume was read every 100 intervals.[5,24] Tapped volume was noted if the volume did not show difference between two tapping intervals.

Compressibility index

Compressibility index is one of the methods to evaluate compressibility of the powder and flow property. Compressibility index can be calculated by comparing the bulk density (Db) and tapped density (Dt) of the powder.[5,24]

Hausner ratio

Hausner ratio is an indirect index of the ease of the powder flow. It is calculated as the ratio of the tapped density (Dt) to the bulk density (Db) of the powder. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).[5,24]

Evaluation of tablets

All the prepared tablets were evaluated for the following parameters [Table 3]:

Uniformity of weight

A total of 20 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 comply with the test if not more than two tablets are outside the limit, and no tablet differs by more than twice the limit.[5,24]

Tablet hardness testing

Tablet hardness testing 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 hardness tester (Tianjin Guoming Medicinal Equipment Co., Ltd.), and then, the average value was documented.[24]

The friability test

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 dust was brushed off the tablets and reweighed.

Table 3: Technological parameters of ODT metformin formulations

Number formulation	Uniformity of weight, %		Tablet hardness testing, N		The friability test, %		The disintegration time, s		Wetting time test, s		The desirability function	
	y_6	y_6^I	y_7	y_7^I	y_8	y_8^I	y_9	y_9^I	y_{10}	y_{10}^I	D	D^1
1	1.70	1.69	27	29	7.60	7.30	25	25	60	65	0	0
2	1.11	1.12	11	14	12.00	13.00	22	22	54	64	0	0
3	1.14	1.13	29	28	6.80	6.00	38	40	212	190	0	0
4	1.04	1.05	15	14	1.09	1.13	31	35	51	58	0.169	0.175
5	1.09	1.10	17	17	7.40	7.20	37	37	100	90	0	0
6	1.17	1.16	14	14	14.30	13.70	35	39	100	135	0	0
7	0.66	0.68	22	22	6.00	5.00	40	43	102	91	0	0
8	1.17	1.16	28	27	2.70	2.30	80	83	292	283	0.179	0.180
9	1.13	1.12	19	18	1.80	1.20	155	147	252	247	0.053	0.065
10	0.99	0.98	25	25	2.70	2.46	26	26	58	47	0.589	0.595
11	0.67	0.68	30	28	1.40	1.33	17	19	26	36	0.796	0.789
12	1.33	1.34	30	29	1.30	2.10	16	20	30	39	0	0
13	1.28	1.29	27	27	1.50	2.20	27	32	75	72	0	0
14	0.95	0.97	25	26	2.80	2.60	208	222	960	980	0.222	0.210
15	1.13	1.12	25	26	3.00	3.20	34	40	120	140	0.311	0.320
16	1.03	1.01	34	33	1.80	1.20	25	25	50	56	0.661	0.650

ODTs: Orodispersible tablets

Tablets should lose not more than 1% of their weight to be acceptable.[24]

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at the temperature of 37°C ± 2°C, and the time taken for the entire tablet to disintegrate completely was noted.[24]

Wetting time test

Wetting time test was conducted to predict the time required to complete wetting metformin ODT. A glass Petri dish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurs the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time.[25,26]

The desirability function

The desirability function approach is one of the most widely used methods in industry for the optimization of multiple response processes. It is based on the idea that the "quality" of the product or process has multiple quality characteristics. The method finds operating conditions x that provide the "most desirable" response values. For each response Yi(x), a desirability function di(Yi) assigns numbers between 0 and 1 to the possible values of Yi, with di(Yi) = 0 representing a completely undesirable value of Yi and di(Yi) = 1 representing a completely desirable or ideal response value. The individual desirabilities are then combined using the geometric mean, which gives the overall desirability D.[11,14]

RESULTS AND DISCUSSION

Based on the results of pre-compression parameter, it can be concluded that all formulas have good flowability. All formulas have flow velocity between 1.74 and 3.86 g/s, indicating good flowability for direct compression. 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.[22]

The obtained results of the study were subjected to variance analysis, the verification of the influence of factors on significance was carried out with the help of F-value. The test was performed to estimate the significance of the model. At 5% level of significance, a model is considered significant if the $F_{test} > F_{0.05}$.

Results of comparative design show that all four factors significantly affect on flowability of powder mixtures (y_1, y_1^I): B ≥ C > D > A [Table 4]. Comparison of excipients from the group of diluents (B) gives the following benefits: MCC Vivapur 112 (b_2) > Prosolv SM HD 90 SMCC (b_4) > MCC Vivapur 102 (b_1) > MCC Vivapur 200 (b_3). Among the investigated samples of sugars, mannitol and lactose monohydrate influenced the flow velocity of powder mixtures. A rank order of lubricants: Tablube MgSt grade Micronized Vegetable (d_3) > Tablube MgSt grade Premium Vegetable (d_2) > Tablube MgSt grade Superior Vegetable (d_1) > calcium stearate (d_4) was obtained for flowability of formulation, respectively.

The bulk density of powder metformin is 0.454 g/cm^3, the tapped density is 0.740 g/cm^3. Compressibility index of powder metformin is 39% that indicates a very poor flowability and inability to press.[5] Addition of excipients considerably improved flow properties of the powders. Parameters of bulk density in formulas change between 0.520 and 0.591 g/cm^3. Results of Greco-Latin square design show that all four factors are significant and effect on bulk density [Table 4]. The effect of different groups of excipients may be placed in the rank order: Factor A > factor B > factor C > factor D. Polyplasdone XL-10 crospovidone received a slight advantage over other excipients in the group of disintegrants. Among diluents Prosolv SM HD 90 SMCC and MCC Vivapur 112 have significantly influenced on the value of bulk density.

The rank order for the influence of the studied factors on the tapped density (y_3, y_3^I) has the following form: B > A > C > D [Table 4]. The value of this indicator was improved due to the diluents: Prosolv SM HD 90 SMCC 90 and MCC Vivapur 200. The best values of tapped density in powder mixtures were obtained using Polyplasdone XL-10 crospovidone or sodium croscarmellose as disintegrant, mannitol or Ludiflash as sugar-based excipients.

The rank order in the group of lubricants concerning the effect on tapped density is the following: Tablube MgSt grade Micronized Vegetable (d_3) > Tablube MgSt grade Premium Vegetable (d_2) > Tablube MgSt grade Superior Vegetable (d_1) > calcium stearate (d_4).

Furthermore, the flowability of powder mixtures was evaluated by the index of compressibility (Carr indicator) and Hausner ratio. These indicators allow us to estimate the relative importance of interactions between particles, by indicating the ability of the powders to settle and to be pressed.[27]

The value of the compressibility index changes from 17% to 20%, Hausner ratio fluctuates from 1.20 to 1.25 in formulas No. 4, 7, 8, 11, 12, 15, and 16, which indicates the satisfactory flowability of powder mixtures. In other formulas, the value of the compressibility index is slightly higher and fluctuates within 21–25%, which means that fluidity is satisfactory, although the powder may hang in the funnel.

The factors which are statistically significant for the impact on the compressibility index and Hausner ratio are B > A [Table 4]. The lowest values of the compressibility index received in formulas that contain Prosolv SM HD 90 SMCC or MCC Vivapur 200.

Table 4: Analysis of variance of pre-compression parameters of powder mixtures

Source	Degrees of freedom	Sum of squares	Mean squares	F_{test}	$F_{0.05}$
Flowability					
Factor A	3	364.25	121.4179	23.23	3.2
Factor B	3	942.15	314.0485	60.09	3.2
Factor C	3	911.45	303.8176	58.14	3.2
Factor D	3	597.84	199.2789	38.13	3.2
Residual	3	276.82	92.2718		
Total	31	3176.12			
Bulk density					
Factor A	3	0.00361	0.001204	35.88	3.2
Factor B	3	0.00255	0.000849	25.30	3.2
Factor C	3	0.00144	0.000479	14.28	3.2
Factor D	3	0.00082	0.000273	8.13	3.2
Residual	3	0.00080	0.000266		
Total	31	0.00975			
Tapped density					
Factor A	3	0.01002	0.003339	201.95	3.2
Factor B	3	0.01088	0.003628	219.47	3.2
Factor C	3	0.00216	0.000719	43.51	3.2
Factor D	3	0.00109	0.000362	21.91	3.2
Residual	3	0.00124	0.000414		
Total	31	0.02565			
Compressibility index					
Factor A	3	18.63	6.21	6.62	3.2
Factor B	3	44.13	14.71	15.69	3.2
Factor C	3	4.63	1.54	1.64	3.2
Factor D	3	4.38	1.46	1.56	3.2
Residual	3	9.13	3.04		
Total	31	95.88			
Hausner ratio					
Factor A	3	0.00494	0.00165	6.93	3.2
Factor B	3	0.01061	0.00354	14.89	3.2
Factor C	3	0.00086	0.00029	1.21	3.2
Factor D	3	0.00071	0.00024	1.00	3.2
Residual	3	0.00226	0.00075		
Total	31	0.02320			

The rank order among disintegrants according to the influence on the investigated parameters is as follows: Polyplasdone XL-10 crospovidone > SSG > MCC Sanaq® burst > sodium croscarmellose.

As the mixture for pressing was characterized by satisfactory flow velocity, the obtained tablets were uniform weight with acceptable variation (<5%). On the basis of the conducted dispersion analysis, it was established that the influence groups of excipients on this parameter can be placed in range B > D > A > C [Table 5].

The least deviation from the average weight of the tablets was observed when using MCC Vivapur 200, which has an advantage over MCC Vivapur 112 and Prosolv SM HD 90 SMCC.

The lubricants (group D) have a determinative effect on uniform weight of tablets. The least deviation from the average weight of the tablets was observed when using Tablube MgSt grade Micronized which has a slight advantage over calcium stearate.

A rank order in group of disintegrants: SSG > Polyplasdone XL-10 crospovidone > MCC Sanaq®Burst > sodium croscarmellose

Table 5: Analysis of variance of technological parameters of ODT metformin formulations

Source	Degrees of freedom	Sum of squares	Mean squares	F_{test}	$F_{0.05}$
Uniformity of weight					
Factor A	3	0.25981	0.086603	1108.52	3.2
Factor B	3	0.66493	0.221645	2837.05	3.2
Factor C	3	0.13468	0.044895	574.65	3.2
Factor D	3	0.60341	0.201136	2574.55	3.2
Residual	3	0.06201	0.020670		
Total	31	1.72610			
Tablet hardness testing					
Factor A	3	331.093	110.365	141.27	3.2
Factor B	3	271.344	90.448	115.77	3.2
Factor C	3	133.094	44.365	56.79	3.2
Factor D	3	144.344	48.114	61.59	3.2
Residual	3	343.344	114.448		
Total	31	1235.719			
The friability test					
Factor A	3	206.52843	68.84281	416.91	3.2
Factor B	3	158.75473	52.91824	320.47	3.2
Factor C	3	77.80628	25.93543	157.06	3.2
Factor D	3	40.13338	13.37779	81.01	3.2
Residual	3	1.58148	0.527161		
Total	31	487.44637			
The disintegration time					
FactorA	3	8883.09	2961.03	239.88	3.2
FactorB	3	8728.84	2909.61	235.72	3.2
Factor C	3	51544.09	17181.36	1391.91	3.2
Factor D	3	9318.34	3106.11	251.63	3.2
Residual	3	10339.59	3446.53		
Total	31	89011.47			
Wetting time test					
Factor A	3	244642.84	81547.61	777.34	3.2
Factor B	3	207579.84	69193.28	659.57	3.2
Factor C	3	758558.59	252852.90	2410.27	3.2
Factor D	3	175429.34	58476.45	557.42	3.2
Residual	3	187236.84	62412.28		
Total	31	1575125.97			
The desirability function					
FactorA	3	0.67	0.22	11602.48	3.2
Factor B	3	0.34	0.11	5882.15	3.2
FactorC	3	0.38	0.13	6652.98	3.2
Factor D	3	0.43	0.14	7517.02	3.2
Residual	3	0.31	0.10		
Total	31	2.13			

ODTs: Orodispersible tablets

was obtained by the influence on uniform weight for formulas, respectively. The group of sugar-based excipients showed the slightest influence on the results of this indicator: Ludiflash > sucrose Compri O > lactose monohydrate > mannitol.

The tablets showed a high friability >1% and a low hardness < 30 N, which refer to an inadequate resistance against abrasion. For the influence on tablet hardness, the group of excipients can be placed in next order: A > B > D ≥ C [Table 5].

The harder tablets were obtained in formulas containing MCC Sanaq® burst, as well as Polyplasdone XL-10 crospovidone. The higher value of hardness for metformin tablets was observed when using MCC Vivapur 200 or Prosolv SM HD 90 SMCC. Tablube MgSt grades Superior Vegetable or Premium Vegetable has shown better influence on this indicator. In sugar-based excipients group, lactose monohydrate and sucrose Compri O have the benefits over mannitol and Ludiflash.

The most significant effect on the friability of metformin tablets has been made by the group of disintegrants [Table 5]. In this case, the most resistant to abrasion were the tablets containing Polyplasdone XL-10 crospovidone and MCC Sanaq® burst. Prosolv SM HD 90 SMCC has the most significant impact on the abrasion resistance, which has the advantage over MCC Vivapur 101 and MCC Vivapur 200.

The disintegration time <3 min observed in all formulations except #15, meets the requirements of the European Pharmacopoeia and State Pharmacopoeia of Ukraine for ODT.

The influence of the factors on the disintegration time of metformin tablets can be displayed as follows: C > D ≥ A ≥ B [Table 5]. The tablets containing the following examples of sugars: Lactose monohydrate or mannitol disintegrated the fastest.

Other groups of factors influenced on the disintegration of metformin tablets. Hence, in the group of lubricants, the leader in the influence was Tablube MgSt Premium Vegetable, which was significantly inferior to other factors. Sodium croscarmellose among the studied disintegrants allows us to get pills with a minimum decomposition time.

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 minimal quantity of water, which represents the amount of moisture available in the oral cavity.[21] The wetting time for all formulations of tablets was <60 s, except #5–9, 13–15. The faster wetting time of the tablets produces better disintegration time.

The results of the dispersion analysis of the data on the absorption time in water showed that all factors are statistically significant: C > A > B > D [Table 5]. As for the influence on the investigated parameter, samples of sugars can be placed in the following sequence: Lactose monohydrate > Ludiflash > mannitol > sucrose Compri O. Polyplasdone XL-10 crospovidone and sodium croscarmellose play a decisive role in the group of disintegrants. The absorption time in water was optimal when using Prosolv SM HD 90 SMCC, which was slightly inferior to MCC Vivapur 200.

Since according to the variance analysis, different factors have better effect on different indicators, so it is necessary to transfer them into dimensionless quantities, using the desirability function, a generalized quality indicator.[11,14]

The results were subjected to dispersion analysis [Table 5]. Emerging influence on the descriptive function indicators was shown by disintegrants. The second place in the ranking was taken by the group of lubricants. Samples of sugars and diluents followed them with a slight difference.

The influence of the studied disintegrants on the generalized indicator, the function of desirability, is depicted in Figure 1. The leading role in this group is given to Polyplasdone XL-10 crospovidone and MCC Sanaq® burst, which were selected for future research.

Among the studied samples of lubricants, the influence on the generalized quality index of Tablube MgSt grade Micronized Vegetable, which has the advantage over Tablube MgSt grade Superior Vegetable, and also significantly exceeds calcium stearate, has been determined. Therefore, for further research, the Tablube MgSt grade Micronized Vegetable was chosen.

The effect of various samples of sugars on the function of desirability is shown in Figure 2.

As for the influence on the generalized indicator of the quality of tablets in the group of diluents, MCC Vivapur 200 became the leader. It prevails over other investigated factors [Figure 3].

CONCLUSION

Based on the obtained results concerning the choice of excipients, the best excipients were chosen for the

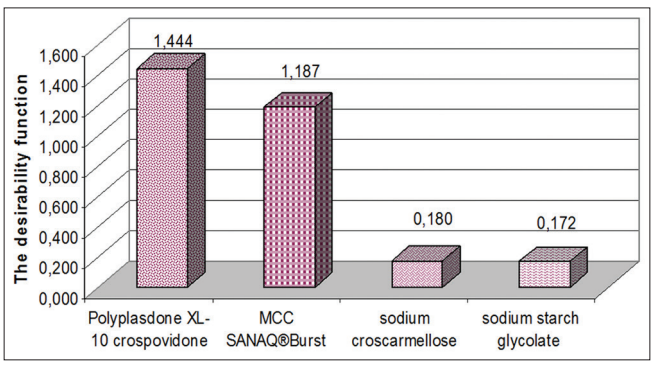

Figure 1: The influence of the studied disintegrants on the generalized indicator, the function of desirability

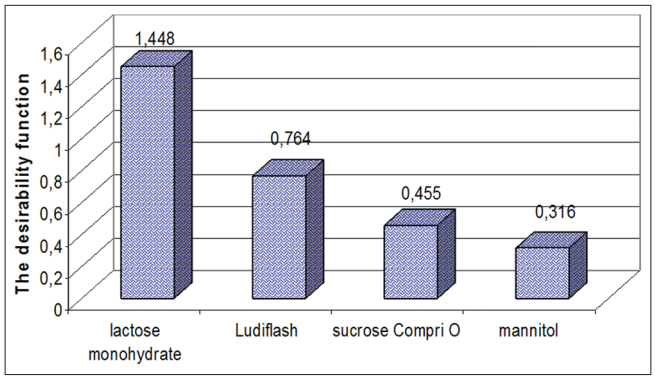

Figure 2: The influence of various samples of sugars on the function of desirability

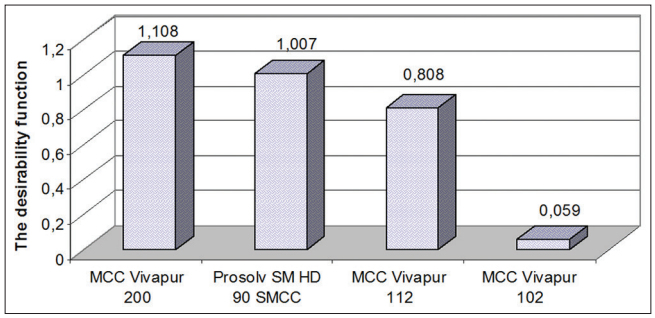

Figure 3: The effect of various samples of diluents on the function of desirability

development of metformin ODTs. According to the results of desirability function, the best values of technological parameters of metformin ODT were obtained when adding Polyplasdone XL-10 crospovidone, MCC Sanaq® burst, MCC Vivapur® 200, lactose monohydrate, and Tablube MgSt grade Micronized Vegetable to the tablets.

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