APPLICATION OF RESPONSE SURFACE METHODOLOGY TO OPTIMIZE THE TECHNOLOGY OF METFORMIN ORAL DISSOLVING TABLETS

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Abstract

To improve the compliance of patients with type 2 diabetes there is a need to develop metformin oral dissolving tablets, which disintegrate and dissolve rapidly in the saliva. The aim of this study was to optimize the composition of metformin orodispersible tablets. The central composite design was used to establish the relation between independent variables, such as, quantity of MCC Burst, quantity of Neusilllin US2, and dependent variables, such as, flowability, bulk density, tapped density, uniformity of weight, friability, tablet hardness, disintegration time, wetting time in order to obtain the optimal formulation using Response Surface Methodology. After generating the polynomial equations that relate the dependent and independent variables, the process was optimized for five responses. From the dissolution studies, it is confirmed that all formulations released more than 82% of the metformin within 3 min. It was found that the tablet containing 3% MCC Burst and 5% Neusilllin US2 was a better formulation in terms of hardness (72 N), uniformity of weight (1.09%), friability (0.75%), rapid disintegration (33 sec) and drug release (95.0%) when compared with all other formulations.

Rezumat

Pentru a îmbunătăți complianța pacienților cu diabet zaharat de tip 2, este nevoie de a dezvolta comprimate cu metformin cu dizolvare orală, care se dezintegrează și se dizolvă rapid în salivă. Scopul acestui studiu a fost de a optimiza compoziția comprimelor orodispersibile cu metformin. Am stabilit relația dintre variabile independente, cum ar fi, cantitatea de MCC Burst, cantitatea de Neusilllin US2 și variabilele dependente, cum ar fi curgerea, densitatea în vrac, densitatea la tasare, uniformitatea masei, friabilitatea, rezistența la rupere a comprimelor, timpul de dezintegrare, timpul de umectare pentru a obține formularea optimă folosind metodologia suprafeței de răspuns. După generarea ecuațiilor polinomiale care leagă variabilele independente și independente, procesul a fost optimizat pentru cinci răspunsuri. Studiile de dizolvare confirmă că toate formulările au eliberat mai mult de 82% din metformin în 3 minute. S-a constatat că tabletele care conțin 3% MCC Burst și 5% Neusilllin US2 au prezentat o formulare mai bună în ceea ce privește duritatea (72 N), uniformitatea masei (1.09%), friabilitatea (0.75%), dezintegrarea rapidă (33 sec) și eliberarea substanței active (95,0%) în comparație cu toate celelalte formulări evaluate.

Keywords: oral dissolving tablets, metformin, experimental design, response surface methodology

Introduction

Diabetes mellitus (DM) is a complex disease which has become one of the most serious public health problems based on its increasing incidence, devastating complications and even concerning the cost of anti-diabetic therapy. Type 2 diabetes is the most common type of diabetes, accounting for around 90% of all diabetes cases [10, 13, 20, 21]. It is a progressive disease that is treated with oral anti-diabetic medicines, and in some cases even insulin therapy will be needed to achieve the target blood glucose levels. Physicians usually prescribe metformin as the first-line therapy during the management of type 2 DM patients [5, 17]. In order to increase the bioavailability of oral dosage forms, as well as to solve the problem of dysphagia, which is common in the elderly, children, disabled or bedridden, pharmaceutical technologists have proposed oral dissolving tablets (ODT) [14]. Fast dissolving tablets disintegrate and dissolve rapidly in the saliva, within a few seconds without drinking water or chewing [7, 18]. In these cases, the bioavailability is significantly greater than the one observed with traditional solid forms such as tablets and capsules [16]. Response surface methodology (RSM) is often recommended to optimize experimental data in a multivariate system. A significant advantage is the possibility of decreasing the number of experimental tests to evaluate the impact of the independent variables and their interactions on dependent ones. RSM is useful in a variety of methods, including a central composite design [6, 11].
In our study, we aim to use RSM for analysing the influence of different amounts of excipients on technological parameters of metformin ODT and optimize the composition of metformin ODTs.

**Materials and Methods**

**Materials**
Metformin hydrochloride (Harman Finochem Limited), Polylplasdone XL-10 crosovidone (Ashland Specialty Chemical), Neusilin® US2 (Fuji Chemical Industry Co., LTD), microcrystalline cellulose (MCC) Sanaq® burst (Pharmatrans Sanaq AG), lactose monohydrate (Alpavit Kaserei Champignon Hofmeister GMBH & Co. Ltd.), Tabledue Magnesium stearate (MgSt) grade (Nitika Pharmaceutical Specialties Pvt. Ltd.), talc powder (Liaoning Aihai Co. Ltd.). Materials were kindly provided by Farmak JSC and Witec Industrial. Other used ingredients were of analytical grade.

**Experimental design**

The formulations were designed according to the central composite design [9]. A $2^2$ factorial design was utilized in the present study. In this design two independent factors were evaluated, each at five levels, and experimental trials were carried out at all possible combinations. $2^4$ 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 [1, 8].

The factors, the central point and range of the factors were selected based on preliminary study [3, 4]. The coded values of independent factors are shown in Table II.

**Preparation of tablets**

Fast dissolving tablets of metformin were prepared by direct compression method according to the matrix given in Table II. All the ingredients (powders of metformin hydrochloride, Polyplasdone XL-10 crosovidone, Neusilin US2, MCC Burst, lactose monohydrate) 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 designed formulations.

**Materials**
Metformin hydrochloride (Harman Finochem Limited), Polylplasdone XL-10 crosovidone (Ashland Specialty Chemical), Neusilin® US2 (Fuji Chemical Industry Co., LTD), microcrystalline cellulose (MCC) Sanaq® burst (Pharmatrans Sanaq AG), lactose monohydrate (Alpavit Kaserei Champignon Hofmeister GMBH & Co. Ltd.), Tabledue Magnesium stearate (MgSt) grade (Nitika Pharmaceutical Specialties Pvt. Ltd.), talc powder (Liaoning Aihai Co. Ltd.). Materials were kindly provided by Farmak JSC and Witec Industrial. Other used ingredients were of analytical grade.

| Factor | Level of factor | Variation interval | + α | ± 1 | 0 | -1 | ± α |
|--------|----------------|-------------------|-----|-----|---|----|-----|
| $x_1$ - quantity of MCC Burst, % | 1.0 | 4.414 | 6 | 3 | 2 | 1.586 |
| $x_2$ - quantity of Neusilin US2, % | 1.0 | 6.414 | 6 | 4 | 5 | 3.586 |

**Table I**

| № formula | $x_1$ | $x_2$ | $x_3$ | $x_4$ | $x_5$ | $x_6$ | $x_7$ | $x_8$ |
|------------|-----|-----|-----|-----|-----|-----|-----|-----|
| 1          | +   | +   | 9.8 | 0.544 | 0.687 | 1.32 | 0.67 | 80  | 35  | 42  |
| 2          | -   | +   | 7.4 | 0.521 | 0.728 | 0.77 | 0.88 | 75  | 42  | 45  |
| 3          | +   | -   | 9.0 | 0.558 | 0.739 | 1.24 | 0.86 | 81  | 40  | 47  |
| 4          | -   | -   | 5.7 | 0.564 | 0.749 | 0.95 | 0.52 | 76  | 45  | 38  |
| 5          | + α | 0   | 12.8| 0.546 | 0.749 | 1.22 | 0.88 | 84  | 40  | 48  |
| 6          | - α | 0   | 9.2 | 0.534 | 0.728 | 0.67 | 0.64 | 71  | 55  | 35  |
| 7          | 0   | + α | 5.7 | 0.519 | 0.711 | 1.15 | 0.80 | 65  | 45  | 40  |
| 8          | 0   | - α | 5.0 | 0.570 | 0.756 | 0.92 | 0.72 | 85  | 35  | 35  |
| 9          | 0   | 0   | 5.1 | 0.543 | 0.678 | 1.05 | 0.78 | 72  | 30  | 23  |
| 10         | 0   | 0   | 4.6 | 0.540 | 0.670 | 1.10 | 0.75 | 70  | 35  | 21  |
| 11         | 0   | 0   | 5.0 | 0.538 | 0.665 | 1.08 | 0.73 | 74  | 34  | 25  |
| 12         | 0   | 0   | 4.8 | 0.540 | 0.668 | 1.14 | 0.76 | 75  | 32  | 27  |

$x_1$ - quantity of MCC Burst, %; $x_2$ - quantity of Neusilin US2, %; $y_1$ - flowability, sec/100g; $y_2$ - bulk density, g/cm$^3$; $y_3$ - tapped density, g/cm$^3$; $y_4$ - uniformity of weight, %; $y_5$ - friability, %; $y_6$ - tablet hardness, N; $y_7$ - disintegration time, sec; $y_8$ - wetting time, sec.
**Pre-compression evaluation.** Before compression, the powder mixture from each formula was evaluated by several parameters such as flowability (\(y_1\)), bulk density (\(y_2\)), tapped density (\(y_3\)) (Table II). Flowability was determined using the fixed funnel method. The powder mixture (\(\pm 100\) g) was poured through the funnel. Time for the powder mixture to fall down through a funnel was used to calculate flowability of the powder [3, 19].

**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 determined. The bulk density is the ratio of total mass of the powder to the bulk volume of the powder [4, 19].

**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 500 times. The volume was determined every 100 intervals. Tapped volume was noted if the volume did not show the difference between two tapping intervals [4, 19].

**Evaluation of tablets.** All prepared tablets were evaluated for uniformity of weight (\(y_4\)), friability (\(y_5\)), tablet hardness (\(y_6\)), disintegration time (\(y_7\)), wetting time (\(y_8\)) and cumulative drug release (%).

**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 by more than twice the limit [4, 19].

**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 its 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 average value was documented [3, 19].

**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. Tablets should lose not more than 1% of their weight to be acceptable [3, 19].

**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 ± 2°C and the time taken for the entire tablet to disintegrate completely was noted [19].

**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 needed for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted [2].

**The Dissolution Test.** In vitro dissolution of tablets was performed using an USP Apparatus 2 (Erweka DT 600, Germany). The dissolution study was conducted in 900 mL volume of phosphate buffer solution (pH 6.8) at 37°C (± 0.5) using the paddle method. Aliquots of 2 mL were withdrawn at selected time intervals (30 sec, 1, 3, 5, 10 and 15 min), and the samples were replaced with the fresh dissolution medium [7, 19]. The concentrations of metformin in samples were determined using the proposed HPLC method. The HPLC system consisted of Agilent 1260 08-530.12 with spectrophotometric detector (Agilent technologies, USA). A column (µBondpak C18, 3.9 mm × 300 mm, 10 µm) was used for separation and quantification. The mobile phase was a mixture of acetonitrile and buffer solution (10:90, v/v). The buffer solution consisted of 0.5 g/L sodium heptanesulfonate solution and 0.5 g/L sodium chloride, adjusted to pH 3.85 with 0.06 M phosphoric acid solution. Analyses were run at the flow rate of 1.2 mL/min at the temperature maintained at 30°C, the injection volume was 2 µL and the detection wavelength was at 218 nm.

**Results and Discussion**

On the basis of the preliminary trials, 2\(^3\) full factorial design was employed to study the effect of independent variables, i.e. quantity of MCC Burst (\(x_1\)) and quantity of Neusilin US2 (\(x_2\)) on dependent variables. The results clearly indicate that all the dependent variables are strongly connected with the selected independent variables.

Optimization of formulation was performed using response surface quadratic model. The quadratic model showed a positive impact of such significant model terms as the linear variables \(A\) and \(B\) and quadratic variable \(A^2\) on the flowability. Finally, after ignoring the insignificant terms, the regression equation for flowability is:

\[
y_1 = 4.875 + 1.349x_1 + 0.436x_2 + 3.013x_1^2.
\]

As seen in Table III, the Model F-value of 162.14 implies that it is significant. There is only a 1.01% chance that an F-value this large could occur due to the noise. p-values less than 0.0500 indicate model terms are significant.

It follows from the regression equation that with increasing of MCC Burst and Neusilin US2 quantities in the mass for tabletting, the time of pouring the mass through the funnel increases. The surface response plot reveal (Figure 1) that the lowest values of flowability are obtained when the quantity of MCC Burst (\(x_1\)) ranges from 2.5 to 3%, and the quantity of Neusilin US2 ranges from 4 to 4.5% in the composition of the mixtures for tabletting.
The equation of polynomial regression for bulk density after ignoring the insignificant terms is presented as follows:

\[ y = 0.541 + 0.004x_1 - 0.016x_2 + 0.007x_1x_2. \]

The adequacy of the model describing the influence of the studied factors on the bulk density of the mass for tableting was tested using the F-test. As seen in Table IV, the Model F-value of 31.26 implies that it is significant. There is only a 0.03% chance that an F-value this large could occur due to the noise. p-values less than 0.0500 indicate model terms are significant. In this case, linear variables A, B and the interactions of the variables AB, are significant model terms.

It follows from the regression equation that the greatest influence on the bulk density is demonstrated by the linear factor \( x_2 \). The surface response plot revealed (Figure 2) that the lowest values of bulk density of the mixtures of 0.52 g/cm\(^3\) are obtained by stabilizing the factor \( x_2 \) in the range from the main level to the level + \( \alpha \), when the factor \( x_1 \) is in the range from 2 to 3% in the composition of the mixtures for tableting. By increasing the quantity of MCC Burst to the upper level, the value of bulk density increases to 0.537 g/cm\(^3\).
Table IV  
Analysis of variance table for bulk density

| Source     | Sum of Squares | df | Mean square | F-value | p-value |
|------------|----------------|----|-------------|---------|---------|
| Model      | 0.0025         | 5  | 0.0005      | 31.26   | 0.0003  |
| A-MCC Burst| 0.0001         | 1  | 0.0001      | 9.03    | 0.0239  |
| B-Neusilin US2 | 0.0021 | 1  | 0.0021      | 130.47  | < 0.0001|
| AB         | 0.0001         | 1  | 0.0002      | 13.16   | 0.0110  |
| A²         | 3.600E-06      | 1  | 3.600E-06   | 0.2254  | 0.6518  |
| B²         | 0.0001         | 1  | 0.0001      | 3.61    | 0.1063  |
| Residual   | 0.0001         | 6  | 0.0000      | 2.58    | 0.2282  |
| Lack of Fit| 0.0001         | 3  | 0.0000      |         |         |
| Pure Error | 0.0000         | 3  | 8.917E-06   |         |         |
| Cor Total  | 0.0026         | 11 |             |         |         |

Figure 2.
Surface response plot for bulk density (g/cm³)

The final equation after ignoring the insignificant terms for tapped density is given by:

\[ y = 0.670 - 0.017x_2 + 0.029x_1^2 + 0.029x_2^2. \]

As seen in Table V, the Model F-value of 21.93 implies that it is significant. There is only a 0.09% chance that an F-value this large could occur due to the noise. p-values less than 0.0500 indicate model terms are significant. In this case, linear variable B and the quadratic variables A², B² are significant model terms.

Analysis of the regression equation shows that the studied parameter is significantly influenced by the linear factor x₂ and both quadratic factors. The surface response plot reveal (Figure 3) that the lowest values of tapped density 0.67 g/cm³ are obtained when the quantity of Neusilin US2 (x₂) ranges from 5 to 5.5% and the quantity of MCC Burst is 3% in the composition of the mixtures for tableting. The values of tapped density increase to 0.70 - 0.72 g/cm³ when the studied factors are noted at the lower (-1) level and the lower (-α) points.
After pressure, the obtained ODTs of metformin hydrochloride were investigated for uniformity of weight ($y_1$), friability ($y_5$), tablet hardness ($y_6$), disintegration time ($y_7$) and wetting time ($y_8$). The uniformity of weight in all investigated tablets ranged from 0.67% to 1.32%, which meets the pharmacopoeia's requirements [19]. 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. As seen in Table VI, the Model F-value of 6.36 implies that it is significant. In this case, linear variable $A$ is a significant model term. Final equation in terms of actual factors for uniformity of weight:

$$y_4 = 1.093 + 0.202x_1.$$  

The surface response plot reveal (Figure 4) that the corresponding decrease of the average weight of tablets from 1.3 to 0.80% is observed with the decrease of the quantity of MCC Burst from 1.3 to 0.8%.

| Source        | Sum of Squares | df | Mean square | F-value | p-value |
|---------------|----------------|----|-------------|---------|---------|
| Model         | 0.0120         | 5  | 0.0024      | 21.93   | 0.0009  |
| A-MCC Burst   | 0.0002         | 1  | 0.0002      | 1.92    | 0.2147  |
| B-Neusilin US2| 0.0023         | 1  | 0.0023      | 21.27   | 0.0036  |
| AB            | 0.0002         | 1  | 0.0002      | 2.19    | 0.1895  |
| $A^2$         | 0.0054         | 1  | 0.0054      | 48.84   | 0.0004  |
| $B^2$         | 0.0057         | 1  | 0.0057      | 52.27   | 0.0004  |
| Residual      | 0.0007         | 6  | 0.0001      |         |         |
| Lack of Fit   | 0.0006         | 3  | 0.0002      | 6.10    | 0.0859  |
| Pure Error    | 0.0001         | 3  | 0.0000      |         |         |
| Cor Total     | 0.0127         | 11 |             |         |         |
Table VI

| Source   | Sum of Squares | df | Mean square | F-value | p-value |
|----------|----------------|----|-------------|---------|---------|
| Model    | 0.3689         | 5  | 0.0738      | 11.02   | 0.0055  |
| A-MCC Burst | 0.3272       | 1  | 0.3272      | 48.87   | 0.0004  |
| B-Neusilin US2 | 0.0063     | 1  | 0.0063      | 0.9476  | 0.3679  |
| AB       | 0.0169         | 1  | 0.0169      | 2.52    | 0.1632  |
| A²       | 0.0185         | 1  | 0.0185      | 2.76    | 0.1476  |
| B²       | 0.0005         | 1  | 0.0005      | 0.0732  | 0.7958  |
| Residual | 0.0402         | 6  | 0.0067      |         |         |
| Lack of Fit | 0.0359       | 3  | 0.0120      | 8.40    | 0.0570  |
| Pure Error | 0.0043       | 3  | 0.0014      |         |         |
| Cor Total | 0.4091         | 11 |             |         |         |

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

The friability of metformin ODTs ranged from 0.52 to 0.88%, which meets the pharmacopoeia's requirements [19]. Moreover, it is also observed from Table VII, that the Model F-value of 15.64 implies the model is significant. There is only a 0.22% chance that an F-value this large could occur due to the noise. In this case linear variables A, B, and the interactions of the variables AB are significant model terms.

The final equation after ignoring the insignificant terms for friability is the next:

\[ y_5 = 0.755 + 0.059x_1 + 0.035x_2 - 0.138x_1x_2. \]

The surface response plot (Figure 5) reveal that the corresponding decrease of the friability is observed when the quantities of MCC Burst and Neusilin US2 are at the lower (-α) points.

The hardness results of metformin ODTs were from 65 N to 85 N, which meets the pharmacopoeia's requirements [19].

Final equation in terms of actual factors is presented as follows:

\[ y_6 = 75.67 + 3.55x_1 - 3.79x_2. \]

The F-value Model of 5.59 implies that it is significant. (Table VIII). There is only a 2.64% chance that an F-value this large could occur due to the noise. In this case, linear variables A and B are significant model terms.
Table VI

Analysis of variance table for friability

| Source       | Sum of Squares | df | Mean square | F-value | p-value |
|--------------|----------------|----|-------------|---------|---------|
| Model        | 0.1134         | 5  | 0.0227      | 15.64   | 0.0022  |
| A-MCC Burst  | 0.0275         | 1  | 0.0275      | 19.00   | 0.0048  |
| B-Neusilin US2 | 0.0100       | 1  | 0.0100      | 6.91    | 0.0391  |
| AB           | 0.0756         | 1  | 0.0756      | 52.17   | 0.0004  |
| A²           | 0.0001         | 1  | 0.0001      | 0.0845  | 0.7811  |
| B²           | 0.0001         | 1  | 0.0001      | 0.0845  | 0.7811  |
| Residual     | 0.0087         | 6  | 0.0014      |         |         |
| Lack of Fit  | 0.0074         | 3  | 0.0025      | 5.69    | 0.0936  |
| Pure Error   | 0.0013         | 3  | 0.0004      |         |         |
| Cor Total    | 0.1221         | 11 |             |         |         |

The highest results of tablet hardness (80 N) are obtained when the quantity of MCC Burst is 4.414% and the quantity of Neusilin US2 ranges from 4 to 4.5%. The disintegration time of metformin ODTs ranges from 30 - 55 sec, which meets the established requirements [7].

Final equation in terms of actual factors is the following:

\[ y_7 = 32.75 - 4.15x_1 + 6.56x_1^2. \]

The Model F-value of 4.84 implies that it is significant (Table IX). There is only a 4.05% chance that an F-value this large could occur due to the noise. In this case, A and A² are significant model terms.
The surface response plot (Figure 7) reveal that the optimal value of disintegration time is obtained when the studied factors are stabilized at the central points. The metformin ODTs were investigated by the wetting time in phosphate buffer solution (pH 6.8), which corresponds to the value of salivary acidity [2]. The obtained values of the studied indicator range from 21 to 48 sec. The Model F-value of 42.37 implies that it is significant (Table X). There is only a 0.01% chance that an F-value this large could occur due to the noise.
p-values less than 0.0500 indicate that model terms are significant. Final equation in terms of actual factors is the next: \[ y_8 = 24 + 4.04x_1 + 2.13x_2 - 5x_1x_2 + 9.12x_1^2 + 7.13x_2^2. \]

The surface response plot (Figure 8) reveal that the corresponding decrease of the wetting time is observed when the quantities of MCC Burst and Neusilin US2 are stabilized at the central points.

![Figure 7. Surface response plot for disintegration time (sec)](image)

![Figure 8. Surface response plot for the wetting time (sec)](image)
Dissolution test. The metformin ODTs were subjected to the dissolution test using phosphate buffer (pH 6.8) as the dissolution media. The results of the cumulative release of metformin ODTs are shown in Table XI. Dissolution profiles are shown in Figure 9. The drug release from the tablet formulations was almost 75% within 1 min (except for formula №4). However, all tablets released more than 82% of the drug within 3 min. The fast-dissolving tablets containing MCC Burst (3%) and Neusilin US2 (5%) showed the most appropriate drug release (95%) within 3 min.

| Time, min | №1 | №2 | №3 | №4 | №5 | №6 | №7 | №8 | №9 | №10 | №11 | №12 |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 0.5       | 42.8 ± 0.02 | 57.6 ± 0.03 | 72.7 ± 0.03 | 39.4 ± 0.02 | 55.4 ± 0.03 | 75.2 ± 0.03 | 60.3 ± 0.03 | 77.3 ± 0.03 | 56.0 ± 0.04 | 57.0 ± 0.04 | 58.0 ± 0.04 | 56.0 ± 0.04 |
| 1         | 78.8 ± 0.04 | 75.7 ± 0.04 | 91.0 ± 0.05 | 67.2 ± 0.04 | 83.3 ± 0.04 | 91.5 ± 0.05 | 96.7 ± 0.06 | 90.8 ± 0.05 | 93.4 ± 0.05 | 92.5 ± 0.06 | 92.5 ± 0.06 | 93.0 ± 0.06 |
| 3         | 90.1 ± 0.04 | 88.5 ± 0.04 | 98.7 ± 0.06 | 82.6 ± 0.05 | 91.2 ± 0.04 | 97.7 ± 0.04 | 99.3 ± 0.05 | 98.5 ± 0.05 | 95.5 ± 0.06 | 95.0 ± 0.06 | 94.5 ± 0.06 | 95.0 ± 0.06 |
| 5         | 94.3 ± 0.05 | 98.1 ± 0.05 | 101.3 ± 0.05 | 98.4 ± 0.05 | 99.8 ± 0.05 | 99.1 ± 0.06 | 101.5 ± 0.06 | 99.6 ± 0.05 | 101.3 ± 0.06 | 99.5 ± 0.06 | 98.5 ± 0.06 | 100.5 ± 0.06 |
| 10        | 100.7 ± 0.06 | 99.5 ± 0.05 | 102.1 ± 0.04 | 101.2 ± 0.04 | 101.5 ± 0.06 | 101.3 ± 0.06 | 102.4 ± 0.05 | 101.8 ± 0.06 | 102.2 ± 0.04 | 101.5 ± 0.06 | 102.0 ± 0.04 | 101.5 ± 0.06 |
| 15        | 101.6 ± 0.05 | 99.6 ± 0.04 | 103.6 ± 0.04 | 103.2 ± 0.05 | 102.9 ± 0.04 | 102.1 ± 0.03 | 103.8 ± 0.06 | 102.4 ± 0.04 | 103.8 ± 0.04 | 103.0 ± 0.05 | 102.8 ± 0.04 | 103.5 ± 0.06 |

All the values are represented by mean ± SD (n=3). SD: Standard deviation.

Table XI
Cumulative drug release of metformin ODTs

Optimization of metformin ODTs’ ingredients. After generating the model polynomial equations which relate the dependent and independent variables, the process was optimized for five responses (Figure 10). The optimum formulation was selected based on the constraints set on independent variables: $y_4$ – uniformity of weight (0.7 - 1.2%), $y_5$ – friability (0.5 - 0.8%), $y_6$ – tablet hardness (68 - 80 N), $y_7$ – disintegration time (30 - 50 sec), $y_8$ – wetting (absorption) time (25 - 50 sec).

The present study of metformin ODTs by direct compression method was performed using MCC Burst and Neusilin US2. It was found out that the tablet containing 3% MCC Burst and 5% Neusilin US2 was a better formulation in terms of hardness (72 N), uniformity of weight (1.09%), friability (0.75%), rapid disintegration (33 sec) and the most appropriate drug release (95.0%) when compared with all other formulations.

Figure 9.
Dissolution profiles of metformin ODTs' formulations
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 MCC Burst, quantity of Neusillin US2, on the dependent variables and for predicting the optimal formulation of metformin ODTs. According to the experimental results, the proposed formulation for metformin ODTs obtained by direct compression is: metformin 250 mg, 3% MCC Burst, 5% Neusillin US2, 4% Polyplesdone XL-10, 8% lactose monohydrate, 27% MCC 102, 1% magnesium stearate, 2% talcum, providing good tablet properties: hardness (72 N), uniformity of weight (1.09%), friability (0.75%), disintegration time (33 sec) and drug release (95.0%).

Conflict of interest

The authors declare no conflict of interest.

References

1. Ali H, Zafar F, Khan S, Yasmeen R, Bushra R, Baloch SA. Design and optimization of fast dispersible formulations of multi strength meloxicam tablets using response surface methodology. Farmacia, 2019; 67(4): 709-721.
2. Bhardwaj P, Chauhan SB. Formulation and evaluation of orodispersible tablets of Metformin hydrochloride using agar as natural super disintegrant. Int J Pharm Sci & Res., 2018; 9(10): 4220-4228.
3. Demchuk M, Chubka M, Grochovuy T. The method of random balance for studying the influence of excipients’ quantities on technological parameters of metformin orodispersible tablets. Int J App Pharmaceut., 2019; 11(3): 168-175.
4. Demchuk M, Grochovuy T, Chubka M, Stechyshin I. Greco-Latin square design for selection of excipients in the development of metformin orodispersible tablets. Asian J Pharm., 2018; 12(3): 211-220.
5. Demchuk M, Pokotylo O, Denys A, Hroshovy T, Ravliv Y. Nationwide trends in antidiabetic drugs (Type-2) utilization, Ukraine, 2014-2016. Int J Green Pharmaceut., 2018; 12: 181-187.
6. Durakovic B. Design of experiments application, concepts, examples. State of the Art Periodicals of Engineering and Natural Sci., 2017; 5(3): 421-439.
7. European Pharmacopoeia, 10th ed. EDQM, European Pharmacopoeia, Council of Europe, 2019, www.edqm.eu/en/european-pharmacopoeia.
8. Elyemni M, Louaste B, Ouadrhiri FE, Bouia A, Eloutassi N. Application of response surface methodology to optimize the extraction of essential oil from Rosmarinus officinalis using microwave-assisted
9. Grochovuy TA, Martsenyuk VP, Kucherenko LI, Vronskya LV, Hurveyeva CM. Mathematical planning of experiment in pharmacy. Ternopil: Ternopil State Medical University; 2008, (available in Ukrainian).
10. Hevko U, Kozak K, Krynytska I, Marushchak M. Diagnostic value of a complete blood count in type 2 diabetes mellitus and comorbidities. *Archives of the Balkan Medical Union*, 2020; 55(4): 601-607.
11. Iancu V, Roncea F, Cazacincu RG, Lupu CE, Miresan H, Dănăilă CN, Rosca C, Lupuleasa D. Response surface methodology for optimization of diclofenac sodium orodispersible tablets (ODTs). *Farmacia*, 2016; 64(2): 210-216.
12. Killivalavan P, Kumaravelrajan R, Gopi M, Suba V. Development of nifedipine timed-release spansule dosage form by extrusion spheronization technology. *Asian J Pharmaceut.*, 2017; 11(3): 192-200.
13. Krynytska I, Marushchak M. The indices of nitric oxide system in rats with carrageenan-induced enterocolitis combined with diabetes mellitus. *Rom J Diabetes Nutr Metab Dis.*, 2018; 25(3): 283-288.
14. Kumar RS, Yagnesh TNS, Kumar VG. Optimization of ibuprofen fast dissolving tablets employing starch xanthate using 2³ factorial design. *Int J Appl Pharmaceut.*, 2017; 9: 51-59.
15. Montgomery DC. Design and analysis of experiments. John Wiley & Sons, Hoboken, NJ, 2017.
16. Muntean AC, Negoi Olu, Rus LL, Veronica AL, Tornață I. Formulation of orodispersible tablets containing paracetamol and their *in vitro* characterization – a QBD approach. *Farmacia*, 2020; 68(3): 436-446.
17. Okafo SE, Alalor CA, Ordu JI. Design and in vitro evaluation of sustained release matrix tablets of metformin produced using Detarium Microcarpum gum. *Int J Appl Pharmaceut.*, 2020; 12(5): 131-137.
18. Roy H, Rahaman ASk. Box-Behnken design for optimization of formulation variables for fast dissolving tablet of urapidil. *Asian J Pharmaceut.*, 2018; 12(3): 946-954.
19. State Pharmacopoeia of Ukraine: In 3 tons, State Enterprise “Ukrainian Scientific Pharmacopoeia Centre for the Quality of Medicines”. – 2nd kind. Kharkiv: State Enterprise “Ukrainian Scientific Pharmacopoeias Centre for Quality of Medicines”; 2015. 1128, (available in Ukrainian).
20. Stechynshyn I, Pavliuk B. The quercetine containing drugs in pharmacological correction of experimental diabetes with myocardial injury. *Rom J Diabetes Nutr Metab Dis.*, 2020; 26(4): 393-399.
21. Stechynshyn I, Pavliuk B, Demchuk M, Chubka M. Changes in mass measurement indices, cardiointervalogram parameters and duration of swimming in animals with experimental Type 2 Diabetes Mellitus treated with drugs exerting antioxidant properties. *Rom J Diabetes Nutr Metab Dis.* 2020; 27(2): 146-152.