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# USING RANDOM BALANCE METHOD TO DEVELOP QUANTITATIVE COMPOSITION OF DAPAGLIFLOZIN TABLETS

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ІНФОРМАЦІЯ

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**Ключові слова:**
dapagliflozin,
tablets,
random balance method,
direct compression,
amount of excipient,
scatter plot,
quality attribute.

АНОТАЦІЯ

**The aim of the work** was to study the influence of excipients amount on the quality attributes of the tablet blend and tablets dapagliflozin using the random balance method.

**Materials and Methods.** The study used Dapagliflozin propanediol monohydrate, MCC 102, anhydrous lactose, crospovidone XL-10, colloidal anhydrous silicon dioxide (aerosil 200), magnesium stearate. The formulations were designed according to the random balance method. During the experiment, the appropriate amount of excipients was added to the Dapagliflozin propanediol monohydrate according to the planning matrix. Tablets were manufactured by direct compression. To characterize the quality of the resulting dosage form, there were analysed in accordance with the general pharmacopoeial articles for powders and tablets. The study was conducted on modern equipment.

**Results and Discussion.** The bulk density and tablet blend slope were improved with increase in the amount of lactose anhydrous 22 AN. Results of tablet blend slope and disintegration depended on amount of crospovidone XL-10. The decrease in the amount of aerosil 200 the bulk density and tapped density increase, improve flowability and tablet blend slope. Higher hardness of tablets dapagliflozin was obtained by using lower amount of magnesium stearate.

**Conclusions.** Using the random balance method, the amount of 4 excipients at 3 levels was studied. According to the results of the study, it was found that the advantages of quality attributes were obtained when using 30.365 mg of lactose anhydrous 22 AN, 5 mg of crospovidone XL-10, 1.25 mg of colloidal silicon dioxide anhydrous (aerosil 200) and 0.625 mg of magnesium stearate per tablet. As a result of the experimental studies, the optimal composition of Dapagliflozin, 5 mg tablet cores were proposed.

**Introduction.** In accordance with ICH Q8(R2) pharmaceutical development [1], modern pharmaceutical production and launch of new medicinal products on the market require a qualitatively new design of applied research at the stage of pharmaceutical development, nonclinical and clinical trials, and commercial implementation, including design, modelling and control of the manufacturing process using modern pharmaceutical technologies and industry innovations. To improve the manufacturing processes of pharmaceutical production, the company is implementing the QbD concept [2], which involves determining the target product quality profile, critical quality requirements (CQA) and risk assessment, which are the basis for developing

the composition and technological process to meet the product attributes [3].

Quality assurance of a pharmaceutical product involves the application of a combination of modern approaches to development: scientific, holistic, systematic, and risk-based approaches, and is a link between industry and drug regulatory authorities [4]. Based on QbD, a better understanding of the critical material attributes of raw materials is beneficial in guiding the improvement of tablet quality [5].

The implementation of QbD implies the use of drug design, which includes a set of statistical tools with a project screening and optimisation procedure, to obtain better results with a small number of experiments and guarantees the systematic and complete determination of the quality of a pharmaceutical product [6]. Drug design tools comprise methods of mathematical experiment planning, in particular: analysis of variance, desirability function, random balance method and regression analysis method. To establish the optimal ratio between excipients in the composition and technology of a product, regression analysis plans are used to obtain mathematical models and establish the relationship between the studied quantitative factors and pharmacological and process attributes [7]. The method of analysis of variance is used to study the impact of excipients on quality attributes [8]. The random balance method stochastically determines the most important features of a process, but it requires the values of the objective function at certain assigned points [9].

Most authors use only elements of drug design in pharmaceutical development. For example, the random balance method was used to study the influence of excipient quantities on the process parameters of tablets [10]. Using approaches of dispersion analysis, random balance method, regression analysis and neural networks the composition and technology of tablets were developed [11].

The aim of the work was to study the influence of excipients amount on the technological parameters of the tablet blend and tablets dapagliflozin using the random balance method.

The reference drug is Forxiga, 5 mg film-coated tablets from AstraZeneca UK Limited. It belongs to the group of diabetes mellitus inhibitors of the sodium-dependent glucose cotransporter type 2. According to the instructions for medical use, 1 film-coated tablet contains 6.15 mg of dapagliflozin propandiol monohydrate as calculated on dapagliflozin 5 mg, excipients: microcrystalline cellulose (MCC), anhydrous lactose, crospovidone, silicon dioxide, magnesium stearate and Opadry II yellow. These are yellow, biconvex, round, film-coated tablets with “5” engraved on one side and “1427” engraved on the other side. The average weight of a tablet is 130 mg. The tablets are packed in a blister of polyvinyl chloride and polyamide laminated foil and aluminium foil with thermal varnish. The shelf life is 3 years. Keep out of the reach of children at a temperature below 25°C [12].

To minimise the risks associated with compatibility, stability and bioequivalence, a less risky strategy for developing a generic drug is to use a similar quality composition to the original drug. Therefore, the study included excipients that are part of the reference drug. Lactose and MCC are among the most commonly used excipients in tablet formulations [13]. Because of lactose water solubility and acceptable flowability, it is generally added into tablet formulations to improve wettability and undesirable flowability. At present, numerous grades of MCC are available for pharmaceutical manufacturing and significantly differ in particulate and powder properties [14]. All of the MCC successfully reduced the tablet friability and disintegration time values. The improvement effect of MCC on tablet disintegration followed the descending order: PH 200 > PH 102SCG > PH 302 > PH 102 > PH 112. When comparing superdisintegrants, tablets with crospovidone were the best in terms of disintegration rate [15]. Commercially available crospovidone is available in XL-10 and XL grades, which differ in particle size, so Polyplasdone XL-10 provides twice the disintegration time of Polyplasdone XL [16]. The most commonly used glidant in tablets is colloidal anhydrous silicon dioxide with a surface area of 300 $m^2$/g for Aeroperl®300 and 200 $m^2$/g for Aerosil®200 [17], [18]. Most pharmaceutical formulations also include magnesium stearate as a lubricant to improve their flowability and prevent their adhesion to the surfaces of processing equipment. It is able of forming films on other tablet excipients during prolonged mixing, leading to a prolonged drug release time, a decrease in hardness, and an increase in disintegration time. Depending on the amount of magnesium stearate added, differences in drug release from tablets are observed and may cause differences in therapeutic response [19].

**Materials and Methods.**

**Materials.** Dapagliflozin propanediol monohydrate powders from Fuxin Long Rui Pharmaceutical Co., Ltd., China, were used for the study. The tablets contained 6.15 mg of dapagliflozin propandiol monohydrate as an API (as calculated on dapagliflozin 5 mg). MCC 102 or MCC 200 from JRS PHARMA, Germany and anhydrous lactose 22 AN by the trademark SuperTab®22AN from DFE Pharma, Germany were added as fillers. Crospovidone XL-10 from ISP Technologies Inc, USA was used as a disintegrant. Colloidal anhydrous silicon dioxide of the aerosil 200 from Evonik Industries, Germany, was used as a sliding agent. Magnesium stearate from Faci Metalest S.L.U., Spain, was added as a lubricant.

**Methods.**

*Random balance method*

The formulations were designed according to the random balance method. For this purpose, the selected excipients were classified into 4 factors, which were studied at the lower “-“, basic “0” and upper “+” levels according to Table 1.

During the experiment, the appropriate amounts of excipients were added to dapagliflozin propanediol monohydrate according to the planning matrix, shown in Table 2. To achieve an average weight of 125 mg, MCC 102 was added in different amounts ranging from 80.37 mg to 88.85 mg per tablet.

**Table 1**
Quantitative factors and their levels studied in the development of the composition of dapagliflozin 5 mg tablet cores, per 1 tablet

| Factor designation | Factor | Factor level | | |
|---|---|---|---|---|
| | | Lower "-" | Basic "0" | Upper "+" |
| $x_1$ | amount of lactose anhydrous 22 AN, mg | 25.0000 | 27.6825 | 30.3650 |
| $x_2$ | amount of crospovidone XL-10, mg | 2.50 | 3.75 | 5.00 |
| $x_3$ | amount of colloidal anhydrous silicon dioxide (aerosil 200), mg | 1.25 | 1.87 | 2.49 |
| $x_4$ | amount of magnesium stearate, mg | 0.6250 | 0.9375 | 1.2500 |

**Table 2**
Matrix for planning the experiment using the random balance method and results of the study of quantitative factors

| Batch | $x_1$ | $x_2$ | $x_3$ | $x_4$ | $y_1$ | $y_2$ | $y_3$ | $y_4$ | $y_5$ | $y_6$ | $y_7$ | $y_8$ | $y_9$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | – | – | – | + | 0.393 | 0.524 | 34.1 | 39.4 | 5 | 5 | 104.40 | 0.02 | 4.07 |
| 2 | – | + | – | + | 0.405 | 0.526 | 38.4 | 40.9 | 5 | 5 | 102.05 | 0.03 | 2.15 |
| 3 | + | – | – | – | 0.409 | 0.524 | 37.0 | 39.8 | 5 | 5 | 116.00 | 0.02 | 3.50 |
| 4 | + | + | – | – | 0.411 | 0.533 | 39.7 | 39.8 | 5 | 5 | 121.90 | 0.01 | 2.38 |
| 5 | – | – | + | + | 0.380 | 0.500 | 61.0 | 40.6 | 5 | 5 | 113.65 | 0.02 | 4.51 |
| 6 | – | + | + | – | 0.367 | 0.477 | 78.4 | 41.9 | 5 | 5 | 115.75 | 0.01 | 1.47 |
| 7 | + | – | + | + | 0.391 | 0.495 | 63.9 | 40.5 | 5 | 5 | 98.45 | 0.06 | 3.13 |
| 8 | + | + | + | – | 0.367 | 0.490 | 68.9 | 40.9 | 5 | 5 | 113.40 | 0.01 | 1.56 |
| 9 | 0 | 0 | 0 | 0 | 0.386 | 0.514 | 53.0 | 40.1 | 5 | 5 | 109.25 | 0.03 | 2.20 |
| 10 | 0 | 0 | 0 | 0 | 0.396 | 0.521 | 55.5 | 41.1 | 5 | 5 | 108.10 | 0.03 | 2.12 |

*Notes: $y_1$ – bulk density of tablet blend, g/ml; $y_2$ – tapped density, g/ml; $y_3$ – flowability of tablet blend, s/100 g; $y_4$ – slope of tablet blend, °; $y_5$ – evaluation of the compression process, points; $y_6$ – appearance of tablets, points; $y_7$ – hardness, N; $y_8$ – friability, %; $y_9$ – disintegration, min*

Significant factors were selected using scatter plots. The difference in mean values on the diagrams was expressed as medians. When quantifying the selected effects, the significance was tested using the t-test. The experimental values of the t-test were compared with the tabulated values ($t_{0.05} = 2.44$). Factors for which $t_{experimental} > t_{tabular}$ were considered significant and their influence on the studied attribute was judged. To summarise the results obtained, the optimal amounts of the study substances in the formulation were determined by the sum of the prevailing amounts of significant factors.

*Technology and methods of analysis*

Dapagliflozin tablets were manufactured by direct compression. This method of obtaining tablets includes the following steps: 1) MCC, lactose anhydrous 22 AN, crospovidone XL-10 were mixed with dapagliflozin propanediol monohydrate; 2) the resulting blend was mixed with silicon dioxide colloidal anhydrous; 3) the mixture was lubricated with magnesium stearate; 4) the resulting tablet blend was pressed into round, biconvex tablet cores with a diameter of 7 mm and an average weight of 0.125 g ± 5%.

To characterise the quality of the resulting dosage form, there were analysed in accordance with the general pharmacopoeial articles for powders for the following parameters: bulk density, tapped density, flowability (n=3), slope (n=3) [20]. To evaluate the compression process, a composite index (using a five-point scale) was used, which took into account the uniformity of filling the matrix, the ability to stick, and the ejection force. The appearance of the tablets was determined visually in daylight by examining their surface against a white background. Attention was paid to the integrity, smoothness and gloss of the surface, evenness of the edges, gloss and condition of the edge, presence of inclusions, and a five-point scale was assigned to the tablets. According to pharmacopoeial methods, the resistance of tablets to crushing (n=20), friability and disintegration (n=6) were studied [20].

Modern equipment was used in the course of the work: device for determining bulk density (Erweka SVM 202, Germany), device for determining the flowability of powders (Erweka GTB, Germany), rotary tablet press (Korsch XL 100, Germany), device for determining strength and geometric dimensions (Erweka TBH-525 WTO, Germany), single blade drum type tablet friability tester (Erweka TAR 200, Germany), tablet disintegration tester (Erweka ZT 33, Germany).

**Results and Discussion.**

***Development of the quantitative composition of the core***

The results of the study of dapagliflozin tablet blends and tablet cores are shown in Table 2.

For bulk density ($y_1$), the highest median values are observed for factors $x_1$ and $x_3$ (Fig. 1).

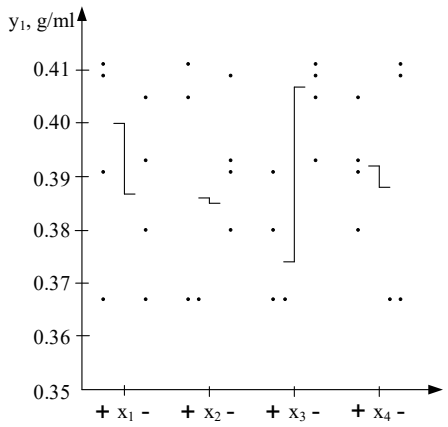


**Figure 1.** Scatter diagram of the results of the bulk density of tablet blend

The calculations of the t-test confirm the significant effect of the amounts of lactose anhydrous 22 AN ($x_1$) and aerosil 200 ($x_3$) on the bulk density of the tablet blend. With an increase in the content of lactose anhydrous 22 AN, the bulk density increases, and the addition of a larger amount of aerosil 200 leads to a significant decrease in this attribute.

The influence of quantitative factors on the tapped density ($y_2$) was considered using a scatter plot (Fig. 2).

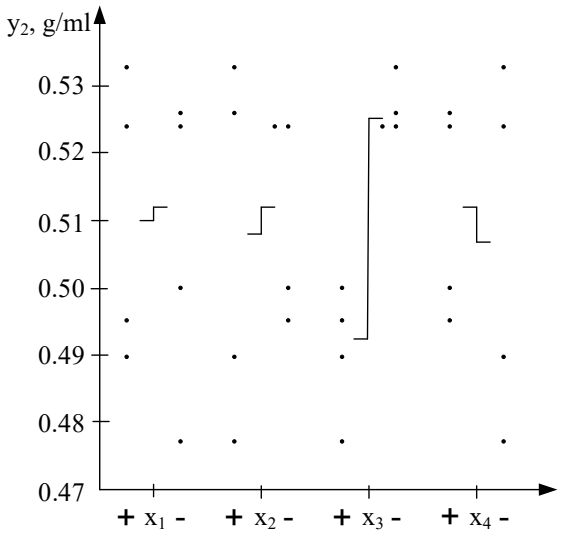


**Figure 2.** Scatter plot of the results of the tapped density of the tablet blend

For the tapped density, the highest median value is observed for the $x_3$ factor. Lower levels of lactose anhydrous 22 AN, crospovidone XL-10 and aerosil 200 significantly improve this value. The results of the tapped density also increase with the addition of more magnesium stearate.

The amount of aerosil 200 ($x_3$) has a significant effect on the flowability of the tablet blend ($y_3$), and a decrease in its content in the composition leads to an improvement in the studied attribute (Fig. 3).

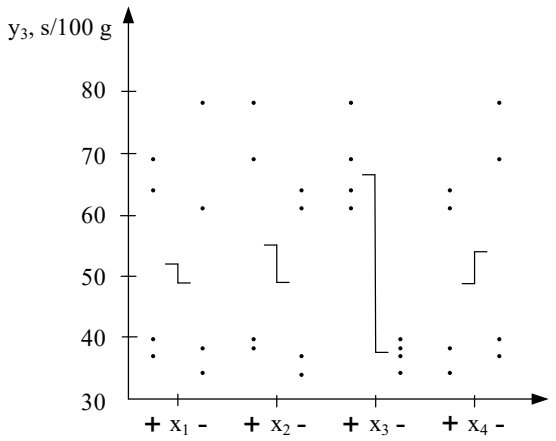


**Figure 3.** Scatter plot of the results of the tablet blend flowability study

The influence of quantitative factors on the tablet blend slope ($y_4$) is shown in Figure 4.

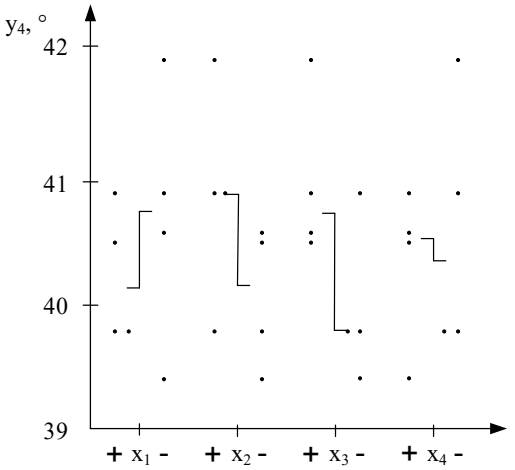


**Figure 4.** Scatter diagram of the results of the tablet blend slope study

The results of statistical processing of the study data for this attribute confirm the statistical significance of the factor $x_1$, $x_2$ and $x_3$. With a decrease in the amount of crospovidone XL-10 ($x_2$), aerosil 200 ($x_3$) and magnesium stearate ($x_4$), the slope decreases. An increase in the content of lactose anhydrous 22 AN ($x_1$) in the tablet blend is accompanied by an improvement in the slope.

For the assessment of the pressing process ($y_5$) and the appearance of tablets ($y_6$), all the factors studied are minor, as all batches of tablets received a score of 5.

The results of statistical processing of the data on the study of tablet hardness ($y_7$) showed the statistical significance of the factor $x_4$ (Fig. 5).

When the amount of magnesium stearate ($x_4$) in dapagliflozin tablets is reduced, their tablet hardness increases significantly. The introduction of larger amounts of lactose anhydrous 22 AN ($x_1$), crospovidone XL-10 ($x_2$) and aerosil 200 ($x_3$) is accompanied by improved results in tablet hardness.

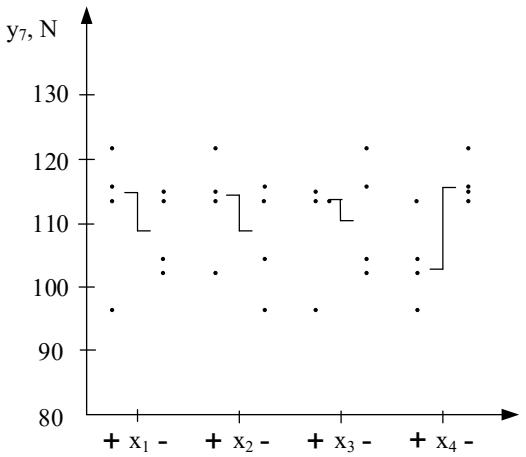


**Figure 5.** Scatter plot of the results of the study of tablet hardness

The scatter plot of the friability test results ($y_8$) shows that the tested amounts of excipients are minor for this attribute (Fig. 6).

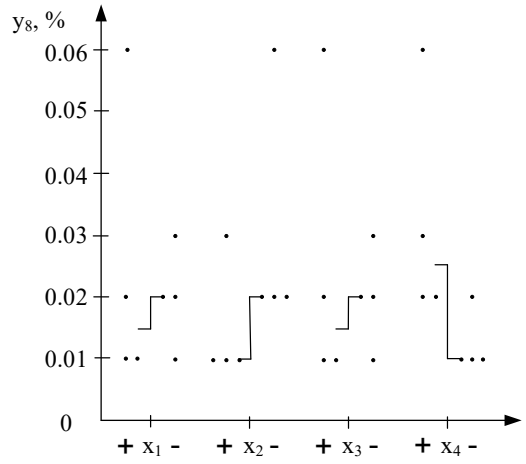


**Figure 6.** Scatter plot of the friability test results

The disintegration time of dapagliflozin tablet cores can be used to predict the dissolution of the drug. The disintegration time dependence ($y_9$) on the amounts of excipients studied is shown in Figure 7.

The figure shows that the largest difference in medians is observed for factors $x_2$ and $x_4$. Increasing the amounts of lactose anhydrous 22 AN ($x_1$), crospovidone XL-10 ($x_2$) and aerosil 200 ($x_3$) reduces the disintegration time. Adding less magnesium stearate ($x_4$) to dapagliflozin tablets promotes faster disintegration of the finished dosage form.

Thus, the use of the random balance method made it possible to reduce the number of batches to 10. As a result of the experiment, the effect of the amounts of the excipients studied on the main pharmacological and process characteristics of dapagliflozin tablet blends and tablet cores was determined, and major factors were identified. Based on the analysis of Figs. 1–7, the amounts of excipients that improve each quality attribute under study were determined by the position of the scattering medians. The summary data of the study of quantitative factors for achieving better quality attributes are presented in Table 3.

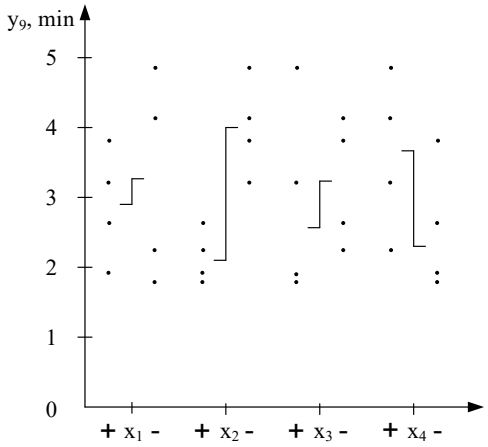


**Figure 7.** Scatter plot of the disintegration study results

**Table 3**
Summary results of the study of the amounts of excipients in the development of dapagliflozin tablet cores

| Attribute/factor | $x_1$ | $x_2$ | $x_3$ | $x_4$ |
|---|---|---|---|---|
| $y_1$ | +* | + | –* | + |
| $y_2$ | – | – | –* | + |
| $y_3$ | – | – | –* | + |
| $y_4$ | +* | –* | –* | – |
| $y_7$ | + | + | + | –* |
| $y_8$ | + | + | + | – |
| $y_9$ | + | +* | + | –* |
| summarised | + | + | – | – |

*Note: * – major factor*

According to the results of the study, it was found that the advantages of quality attributes were obtained when using factors $x_1$ and $x_2$ at the upper level, and factors $x_3$ and $x_4$ at the lower level. Therefore, it is advisable to add 30.365 mg of lactose anhydrous 22 AN, 5 mg of crospovidone XL-10, 1.25 mg of colloidal silicon dioxide anhydrous (aerosil 200) and 0.625 mg of magnesium stearate per tablet to the composition of dapagliflozin tablet cores.

As a result of the experimental studies, the optimal composition of the product was proposed (Table 4).

The tablet blend of the proposed formulation was characterised by a bulk density of 0.366 g/ml, tapped density of 0.476 g/ml, flowability of 74.7 s/100 g, and a slope of 41.1°. The tablet cores were pressed without any complications, and the compression process was excellent. The resulting tablet cores had a smooth, shiny surface, with smooth edges and no scratches. Their hardness was 117.25 N, friability was 0.02%, and disintegration was 2 min. Thus, the studies made it possible to determine the optimal amounts of the investigated excipients that provide the best quality attributes.

**Table 4**
Optimal composition of Dapagliflozin, 5 mg tablet cores

| Ingredients | Quantity | |
|---|---|---|
| | mg/tablet | % |
| Dapagliflozin propanediol monohydrate (as calculated on dapagliflozin content) | 6.150 (5.000) | 4.92 |
| MCC grade 102 | 81.610 | 65.29 |
| lactose anhydrous grade 22 AN | 30.365 | 24.29 |
| crospovidone XL-10 | 5.000 | 4.00 |
| colloidal silicon dioxide anhydrous (aerosil 200) | 1.250 | 1.00 |
| magnesium stearate | 0.625 | 0.50 |
| Total (weight of tablet core) | 125.000 | 100.00 |

**Conclusion.** Using the random balance method, the amount of 4 excipients at 3 levels was studied. According to the results of the study, it was found that the advantages of quality attributes were obtained when using to the composition of dapagliflozin tablet cores 30.365 mg of lactose anhydrous 22 AN, 5 mg of crospovidone XL-10, 1.25 mg of colloidal silicon dioxide anhydrous (aerosil 200) and 0.625 mg of magnesium stearate per tablet. As a result of the experimental studies, the optimal composition of Dapagliflozin, 5 mg tablet cores were proposed. The studies made it possible to determine the optimal amounts of the investigated excipients that provide the best quality attributes.

**Conflicts of interest:** The authors declare that they have no conflict of interest.

## ВИКОРИСТАННЯ МЕТОДУ ВИПАДКОВОГО БАЛАНСУ ДЛЯ РОЗРОБКИ КІЛЬКІСНОГО СКЛАДУ ТАБЛЕТОК ДАПАГЛІФЛОЗИНУ

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**Метою роботи** було вивчення впливу кількості допоміжних речовин на показники якості таблетмас та таблеток дапагліфлозину методом випадкового балансу.
**Матеріали і методи.** Для дослідження використовували дапагліфлозину пропандіолу моногідрат, МКЦ 102, лактозу безводну, кросповідон XL-10, кремнію діоксид колоїдний безводний (аеросил 200), магнію стеарат. Рецептури розроблені за методом випадкового балансу. Таблетки дапагліфлозину 5 мг виготовляли методом прямого пресування. Для характеристики якості отриманої лікарської форми їх аналізували відповідно до загальних фармакопейних статей на порошки і таблетки. Дослідження проведено на сучасному обладнанні.
**Результати і обговорення.** Насипна густина і густина після ущільнення таблетмас покращувалися зі збільшенням кількості безводної лактози 22 AN. Результати кута природного відкосу та розпаду таблеток залежали від кількості кросповідону XL-10. Зменшення кількості аеросилу 200 збільшує насипну густину і густину після ущільнення, покращує сипучість і кут природного відкосу таблетмас. Вищу стійкість таблеток дапагліфлозину до роздавлювання досягали у разі застосування меншої кількості магнію стеарату.
**Висновки.** За допомогою методу випадкового балансу вивчено кількість 4 допоміжних речовин на 3 рівнях. За результатами дослідження встановлено, що переваги за ознаками якості отримані у разі використання 30,365 мг лактози безводної 22 АН, 5 мг кросповідону XL-10, 1,25 мг діоксиду кремнію колоїдного безводного (аеросил 200) та 0,625 мг магнію стеарату в розрахунку на 1 таблетку. В результаті експериментальних досліджень запропоновано оптимальний склад таблеток-ядер дапагліфлозин 5 мг.
**Ключові слова:** дапагліфлозин, таблетки, метод випадкового балансу, пряме пресування, кількість допоміжних речовин, діаграми розсіювання, показники якості.

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