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A model design for managing technological parameters at the stage of the pharmaceutical development of antidiabetic drugs in the form of solid dosage forms

Aim. To develop a model for managing technological parameters at the stage of the pharmaceutical development of an antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin.

Materials and methods. In the study conducted, the methods of system and comparative analysis, generalization, statistical processing and synthesis were used in determining the projected prospects, design, modeling, mathematical modeling, tabular and graphic means of presenting the results. To implement the goals and objectives of the study, software and electronic resources of the Anatomical Therapeutically Chemical Classification System (ATC), Biopharmaceutical Classification System (BCS), Compendium, State Register of Medicines of Ukraine were used; statistical data and data from clinical studies of the content were as follows: https://www.wipo.int; https://www.dec.gov.ua; https://www.clinicaltrials.gov; https://www.ncbi.nlm. nih.gov; https://eacpt.org; https://bpspubs.onlinelibrary.wiley.com. The study was conducted on the modern equipment for determining the bulk density (ERWEKA SVM 202, Germany), the flowability of powders (ERWEKA GT, Germany), resistance to crushing (ERWEKA TBH-525 WTO, Germany), friability (ERWEKA TAR 200, Germany), disintegration (ERWEKA ZT 33, Germany). The active ingredient in tablets of the antidiabetic drug is API calculated with reference to the content of dapagliflozin, 5 mg. The following excipients from the groups of fillers (factor A) were used: a_1 – microcrystalline cellulose (MCC) of grade 200, a_2 – lactose monohydrate of grade 80, a_3 – a mixture of MCC of grade 102 with anhydrous lactose of grade 22 AN in the ratio of 3:1; disintegrants (factor B): b_1 – crospovidone XL-10, b2 – sodium croscarmellose, b_3 – sodium starch glycolate, glidants (factor C): c_1 – colloidal anhydrous silicon dioxide (aerosil 200), c_2 – talc, c_3 – polyethylene glycol (PEG) 8000, as well as magnesium stearate as a lubricant. The experimental data were subjected to statistical processing by the method of variance analysis.

Results and discussion. The development and introduction of new pharmaceuticals, effective analogs and generics is an important task as it contributes to the improvement of the quality of drug supply, treatment and safe use for patients with diabetes mellitus. A model for managing technological parameters at the stage of the pharmaceutical development has been developed; the target quality profile of the antidiabetic drug and tablets with API of SGLT-2 class – a derivative of gliflozin has been substantiated, and critical quality indicators have been determined. According to the model proposed, the optimal composition and technology of antidiabetic tablets with API of SGLT-2 class – a derivative of gliflozin calculated with reference to dapagliflozin, 5 mg, have been developed using an experiment planning matrix based on a 3*3 hyper-Greek-Latin square of the second order; the excipients have been selected; the effect of qualitative and quantitative factors and technological parameters on the pharmaco-technological properties of the tablet masses studied and tablet quality indicators, as well as critical indicators of the quality of the pharmaceutical product have been determined. Experimental studies and risk assessment have been carried out; based on the results, the optimal parameters of the technological process for the production of the antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin – dapagliflozin have been substantiated.

Conclusions. Based on the results of the system analysis of the application of mathematical models in the production of pharmaceutical forms, it has been determined that mathematical modeling is a key stage for ensuring the quality of the technological process at the stage of the pharmaceutical development of an antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin. The use of mathematical modeling in the course of the pharmaceutical development allows optimization at the stage of the experimental research of API, its polymorphic form, physico-chemical properties and pharmaco-technological indicators. A model for managing technological parameters at the stage of the pharmaceutical development has been proposed; the target quality profile of the antidiabetic drug and tablets with API of SGLT-2 class – a derivative of gliflozin has been substantiated; the optimal composition and technology of this pharmaceutical product has been developed.

Keywords: *antidiabetic tablets; mathematical modeling; statistical analysis; variance analysis; model of the technological parameters management; pharmaceutical development; target profile; core tablets; coated tablets; active pharmaceutical ingredient; pharmaco-technological indicators; quality indicators; pressing method; pressing effort; critical quality attributes; technological parameters; technological process variables*

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Проєктування моделі управління технологічними параметрами на етапі фармацевтичної розробки протидіабетичних засобів у вигляді твердих лікарських форм

Мета дослідження – розробити модель управління технологічними параметрами на етапі фармацевтичної розробки препарату протидіабетичної дії в таблетках з АФІ класу SGLT-2 – похідним гліфлозину.

Матеріали та методи. У здійсненому дослідженні використано методи системного й порівняльного аналізу, узагальнення, статистичної обробки й синтезу у визначенні прогнозованих перспектив, проєктування, моделювання, математичне моделювання, табличні і графічні засоби презентації результатів. Для реалізації мети і завдань дослідження використано програмні та електронні ресурси ATC (Anatomical Therapeutically Chemical Classification System), BCS (Biopharmaceutical Classification System), Compendium, Державного реєстру лікарських засобів України; статистичні дані і дані клінічних досліджень контентів: https://www.wipo.int; https://www.dec.gov.ua; https://www.clinicaltrials.gov; https://www.ncbi.nlm. nih.gov; https://eacpt.org; https://bpspubs.onlinelibrary.wiley.com. Дослідження проведено на сучасному обладнанні для визначення насипної густини (ERWEKA SVM 202, Німеччина), сипкості порошків (ERWEKA GT, Німеччина), стійкості до роздавлювання (ERWEKA TBH-525 WTO, Німеччина), стираності (ERWEKA TAR 200, Німеччина), розпадання (ERWEKA ZT 33, Німеччина). Діючою речовиною таблеток лікарського засобу протидіабетичної дії є АФІ в перерахунку на вміст дапагліфлозину 5 мг. Використано допоміжні речовини, зокрема з груп наповнювачів (фактор А): a_1 – мікрокристалічна целюлоза (МКЦ) марки 200, a_2 – лактоза моногідрат марки 80, a_3 – суміш МКЦ марки 102 з лактозою безводною марки 22 AN у співвідношенні 3:1; розпушувачів (фактор В): b_1 – кросповідон XL-10, b_2 – натрію кроскармелоза, b_3 – натрію крохмальгліколят; ковзних речовин (фактор С): c_1 – кремнію діоксид колоїдний безводний (аеросил 200), c_2 – тальк, c_3 – поліетиленгліколь (ПЕГ) 8000, а також магнію стеарат як змащувальну речовину. Експериментальні дані піддавали статистичній обробці методом дисперсійного аналізу.

Результати та їх обговорення. Розробка та впровадження нових фармацевтичних препаратів, ефективних аналогів і генериків є важливим завданням, адже це сприяє покращенню якості лікарського забезпечення, лікування та безпечного застосування для пацієнтів, хворих на цукровий діабет. Розроблено модель управління технологічними параметрами на етапі фармацевтичної розробки, обґрунтовано цільовий профіль якості препарату протидіабетичної дії в таблетках з АФІ класу SGLT-2 – похідним гліфлозину, визначено критичні показники якості. Згідно із запропонованою моделлю розроблено оптимальний склад і технологію таблеток протидіабетичної дії з АФІ класу SGLT-2 – похідним гліфлозину, в перерахунку на дапагліфлозин 5 мг, з використанням матриці планування експерименту на основі 3*3 гіпер-греко-латинського квадрата другого порядку, здійснено відбір допоміжних речовин, визначено вплив якісних і кількісних факторів і технологічних параметрів на фармакотехнологічні властивості досліджуваних таблетмас і показники якості таблеток, а також критичні показники якості фармацевтичного продукту. Здійснено експериментальні дослідження та оцінено ризики, за результатами обґрунтовано оптимальні параметри технологічного процесу виготовлення препарату протидіабетичної дії в таблетках з АФІ класу SGLT-2 – похідним гліфлозину – дапагліфлозин.

Висновки. За результатами здійсненого системного аналізу застосування математичних моделей у виробництві фармацевтичних форм з'ясовано, що математичне моделювання є ключовим етапом для забезпечення якості технологічного процесу на етапі фармацевтичної розробки препарату протидіабетичної дії в таблетках з АФІ класу SGLT-2 – похідним гліфлозину. Використання математичного моделювання у ході фармацевтичної розробки дозволяє здійснити оптимізацію на етапі експериментальних досліджень АФІ, його поліморфної форми, фізико-хімічних властивостей та фармакотехнологічних показників. Запропоновано модель управління технологічними параметрами на етапі фармацевтичної розробки, обґрунтовано цільовий профіль якості препарату протидіабетичної дії в таблетках з АФІ класу SGLT-2 – похідним гліфлозину, розроблено оптимальний склад і технологію зазначеного фармацевтичного продукту.

Ключові слова: *таблетки протидіабетичної дії; математичне моделювання; статистичний аналіз; дисперсійний аналіз; модель управління технологічними параметрами; фармацевтична розробка; цільовий профіль; таблетки-ядра; таблетки, вкриті оболонкою; активний фармацевтичний інгредієнт; фармакотехнологічні показники; показники якості; метод пресування; зусилля пресування; критичні атрибути якості; технологічні параметри; змінні технологічного процесу*

Introduction. In modern conditions, diabetes mellitus (DM) is a chronic and complex metabolic disease, a problem which prevalence statistics is growing in the world. According to the World Health Organization (WHO) statistics, approximately 422 million people worldwide suffer from DM, and this number is expected to increase by 2050 (WHO, 2022). To date, different subtypes of DM have been identified, and specific clinical treatments have been developed to alleviate the complications associated with each subtype. A growing body of evidence suggests that type 2 diabetes or non-insulin-dependent diabetes accounts for nearly 90 % of all diabetes cases, while type 1 diabetes (T1DM) or insulin-dependent diabetes accounts for only 5 %, mixed diabetes statistics are also around 5 % [1].

The results of scientific research on transcriptomic, genomics and the development of metabolic processes have allowed scientists to reveal the molecular, cellular and physiological aspects of the etiology and pathogenesis of diabetes mellitus (DM), as well as to ensure the control and prevention of complications of this disease [2].

At the same time, the results of scientific research provide an opportunity to program artificial intelligence systems to provide a targeted rational pharmacotherapy using the patient's medical data.

Despite significant progress in the prevention of diabetes and overcoming the causes of complications, there is still no single therapeutic strategy that would completely stop the progression of diabetes [2].

FDA-approved indications for oral hypoglycemic agents focus primarily on the treatment of type 2 diabetes.

It should be noted that in modern industrial pharmacy the mass production of synthetic hypoglycemic drugs due to the fact that the active pharmaceutical ingredients are labile compounds requires specialized technological conditions at the pharmaceutical enterprise and significant financial resources.

To overcome such challenges, researchers have directed the search for new effective hypoglycemic drugs. The advent of advanced methods has provided a large amount of information about the molecular elements of the development of pathological conditions in patients with type 2 diabetes, including signaling pathways, enzymes, genes, transcription factors, and other key factors [3].

In addition, the rapid development of artificial intelligence, deep learning and innovative approaches have enabled scientists to develop sophisticated methods for the early diagnosis of type 2 diabetes and reliable healthcare management strategies to strengthen the control of the development of pathological conditions of type 2 diabetes and the implementation of the rational pharmacotherapy, which provide platforms to highlight new research. Researchers use an integrated approach that combines experimental analyses with computational studies [4].

The process of developing new pharmaceuticals is science-intensive and requires considerable resources and time. The pharmaceutical development requires innovative approaches and means. In this context, mathematical modeling becomes a powerful tool for optimizing research [5].

Mathematical modeling has an applied scientific value, allows to optimize the design of experimental studies without reducing their evidentiary value [6].

The analysis of innovative aspects of the use of mathematical modeling in the pharmaceutical industry allows us to generalize that mathematical modeling provides an opportunity to forecast and optimize various aspects of the pharmaceutical production, contributing to an increase in quality and a reduction in costs [6, 7].

In general, artificial intelligence has the potential to revolutionize the field of drug development [8].

According to the general conclusions of scientists, it is important to develop cost-effective strategies for the production of new hypoglycemic agents that minimize side effects and maximize the efficiency taking into account the molecular aspects of the progression of type 2 diabetes with the integrated use of artificial intelligence and mathematical modeling at the stage of the pharmaceutical development.

It should be summarized that the key advantage of using artificial intelligence to model new drugs is the speed of solving the problem since artificial intelligence can analyze large amounts of data in a short time. Another advantage is to ensure the representativeness of data as artificial intelligence can use complex algorithms for their analysis and allows predicting the effectiveness of the application. An application to provide the personalized rational therapy can be extremely effective as artificial intelligence can use the individual data of patients with diabetes.

The **aim** of the study was to develop a model for managing technological parameters at the stage of the pharmaceutical development of an antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin.

Materials and methods. In the study conducted, the methods of system and comparative analysis, generalization, statistical processing and synthesis were used in determining the projected prospects, design, modeling, mathematical modeling, tabular and graphic means of presenting the results. To implement the goals and objectives of the study, software and electronic resources of the Anatomical Therapeutically Chemical Classification System (ATC), Biopharmaceutical Classification System (BCS), Compendium, State Register of Medicines of Ukraine were used; statistical data and data from clinical studies of the content were as follows: https://www.wipo.int; https://www.dec.gov.ua; https://www.clinicaltrials.gov; https://www.ncbi.nlm.nih.gov; https://eacpt.org; https://bpspubs.onlinelibrary.wiley.com, by keywords – names of APIs of SGLT-2 class – gliflozin derivatives. The study was conducted on the modern equipment for determining the bulk density (ERWEKA SVM 202, Germany), the flowability of powders (ERWEKA GT, Germany), a tablet press (Korsh XL-100, Germany), resistance to crushing (ERWEKA TBH-525 WTO, Germany), friability (ERWEKA TAR 200, Germany), disintegration (ERWEKA ZT 33, Germany). The active ingredient in tablets of the antidiabetic drug is API calculated with reference to the content of dapagliflozin, 5 mg. The following excipients from the groups of fillers (factor A) were used: a_1 – microcrystalline cellulose (MCC) of grade 200, a_2 – lactose monohydrate of grade 80, a_3 – a mixture of MCC of grade 102 with anhydrous lactose of grade 22 AN in the ratio of 3:1; disintegrants (factor B): b_1 – crospovidone XL-10, b2 – sodium croscarmellose, b_3 – sodium starch glycolate, as well as glidants (factor C): c_1 – colloidal anhydrous silicon dioxide (aerosil 200), c_2 – talc, c_3 – polyethylene glycol (PEG) 8000, as well as magnesium stearate as a lubricant. The experimental data were subjected to the statistical processing by the method of the variance analysis.

Results and discussion. The development and introduction of new pharmaceuticals, effective analogs and generics is an important task as it contributes to the improvement of the quality of medical supply, treatment and safe use for patients with diabetes.

In experimental studies, mathematical modeling is used to evaluate the effectiveness and safety of new drugs. At various stages of the pharmaceutical development, mathematical modeling helps to reduce the time and costs of developing new drugs, as well as increase their effectiveness and safety for patients.

Using mathematical modeling, it is possible to establish the prospects for the use of APIs and their polymorphic forms and carry out a rational selection of excipients at the early stages, develop the optimal composition of the future dosage form.

In the modern world, advanced pharmaceutical campaigns use a new method of modeling drug development based on the application of artificial intelligence [7].

We present a selective review of the main approaches to modeling the development of medicinal products

based on the results of the analysis of the use of artificial intelligence systems.

So, *Google AI* has developed an artificial intelligence system that can predict the effectiveness of new drugs using data from patients' genomes to identify new targets for treatment. *IBM Watson Health* has worked out an artificial intelligence system that helps make diagnoses for effective treatment of diseases using patients' medical data. *Berg Health* has developed an artificial intelligence system that can help patients search for appropriate prescription drugs with recommendations for use. *Insilico Medicine* has developed an artificial intelligence system that can generate new drug molecules using protein structure data to identify new molecules that can bind to target proteins. The development of *Recursion Pharmaceuticals* is an artificial intelligence system that can identify new disease targets using protein structure data to identify marker proteins that may be associated with specific diseases.

Leading pharmaceutical companies use various approaches to modeling new medicines based on artificial intelligence and strive to use artificial intelligence to improve the process of developing new medicines.

In order to substantiate the target profile of the antidiabetic drug in tablets with an API of SGLT-2 class – a derivative of gliflozin to ensure the effective use based on the personalized rational therapy of patients with diabetes, we offer the application of artificial intelligence programs, which are an important component of our technological parameter management model at the stage of the pharmaceutical development, Figure1.

Gliflozin represents a new class of oral hypoglycemic agents approved by the Food and Drug Administration (FDA) in 2013 for the treatment of diabetes with the unique mechanism of action of blocking SGLT-2 proteins from the proximal convoluted tubule (PCT) region of the kidney, resulting in the reabsorption prevention and allows the glucose molecule to be excreted in the urine. Thanks to this mechanism, drugs which active pharmaceutical ingredient (API) are gliflozin derivatives reduce the blood glucose level in the body and belong to the group of SGLT-2 inhibitors [9, 10].

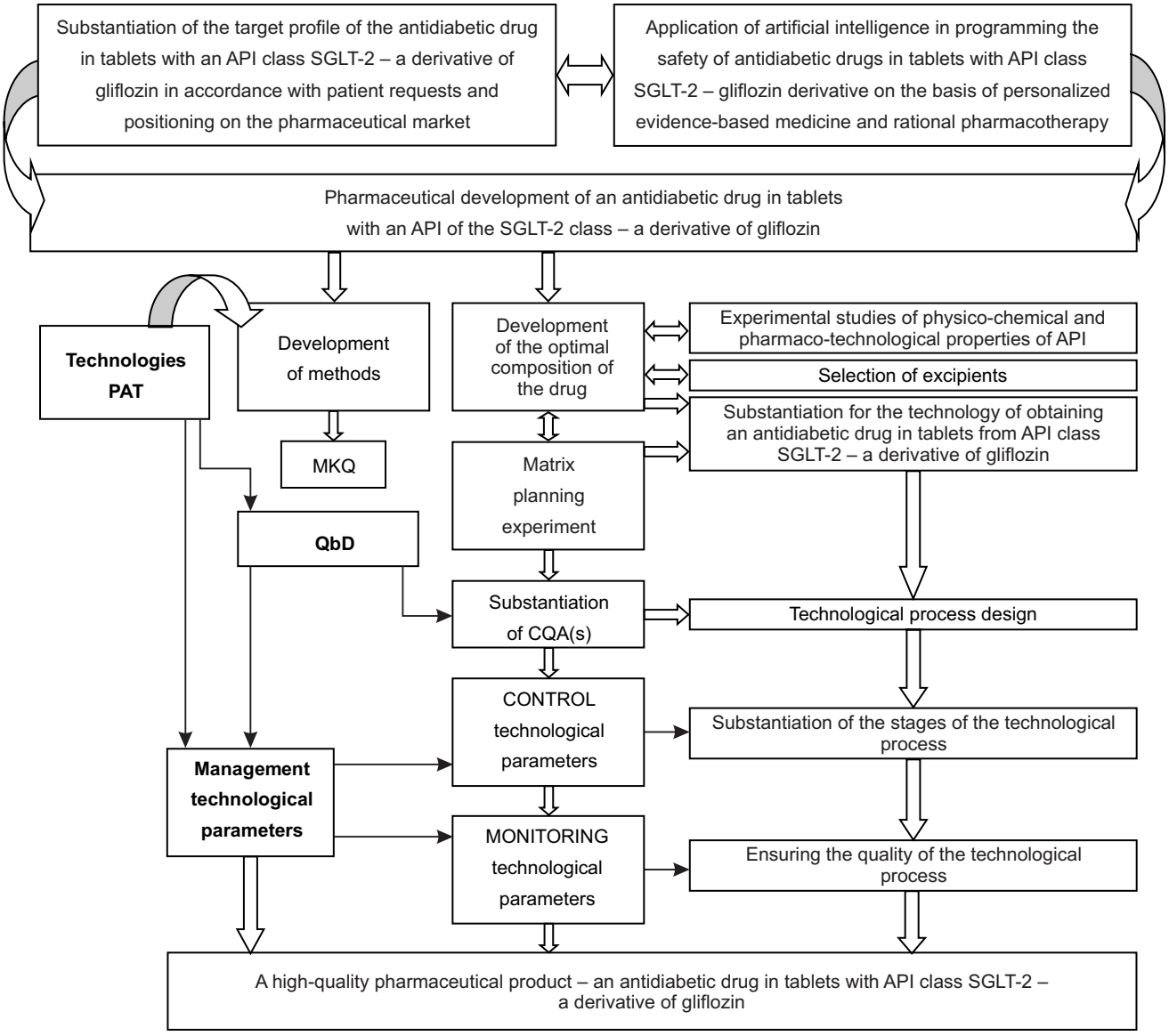

Fig. 1. A model of the technological parameter management at the stage of the pharmaceutical development of an antidiabetic drug in tablets with an API of SGLT-2 class – a derivative of gliflozin.

The development of modern tableted antidiabetic drugs with a high therapeutic efficacy is due to the need to ensure quality based on the implementation of the concept of Quality by Design (QbD) in the pharmaceutical development, which determines the Design of Experiments (DoE), in order to obtain better results with the optimal number of experiments, guarantees ensuring a systematic and complete determination of the quality of the pharmaceutical product.

The achieved progress in the development of analytical methods has a significant impact on the design of a high-quality technological process, provided by appropriate principles and tools with the use of Processing Analytical Technology (PAT). To ensure the quality of the pharmaceutical drug development and the technological process, it is necessary to be guided by the potential critical quality attributes (CQAs) of the medicinal product, determined on the basis of the quality target profile (QTP) of the drug and experimentally confirmed scientific data.

Based on the model developed, the QTP of the antidiabetic drug and tablets with API of SGLT-2 class – a derivative of gliflozin – dapagliflozin was determined (Table 1).

Critical quality indicators were determined, taking into account the established limits of indicators, such as description, average weight, dissolution, related impurities, uniformity of dosage units, assay, etc. An initial risk assessment was carried out.

The critical quality attributes (CQAs) of the antidiabetic tablets and API of SGLT-2 class – gliflozin derivative – dapagliflozin, 5 mg, film-coated tablets are listed in Table 2.

The results of the initial assessment of the risks of variables of the manufacturing technology of the antidiabetic tablets with API of SGLT-2 class – a derivative of gliflozin – dapagliflozin, 5 mg, film coating tablets are shown in Table 3.

The use of mathematical modeling in the course of the pharmaceutical development allows optimization at the stage of the experimental research of API, its polymorphic form, physico-chemical properties and pharmaco-technological indicators.

The use of mathematical models increases the quality and efficiency of the pharmaceutical development as it allows predicting the bioavailability of APIs, analyzing pharmacokinetic and pharmacodynamic indicators of release from a solid pharmaceutical form – tablets, which helps to optimize the dosage, apply a film coating and minimize side effects.

In order to substantiate the optimal composition of a tableted medicine, the effective selection of the input ingredients, the application of mathematical modeling and dispersion analysis provides the opportunity to determine

Table 1

The quality target profile of the antidiabetic drug and tablets with API of SGLT-2 class – a derivative of gliflozin – dapagliflozin, 5 mg, film-coated tablets

An element of the quality target profile	Criterion	Substantiation
Medicinal form	Film-coated tablets	Pharmaceutical equivalence requirements: the same dosage form
Administration route	Oral dosage form	Pharmaceutical equivalence requirements: the same route of administration
Dosage	Each tablet contains API,5 mg of dapagliflozin, respectively	Pharmaceutical equivalence requirements: the same route of administration
Pharmacokinetics	API of class III of BSC	According to literature sources, the product belongs to class III of BSC with high solubility and low permeability
Stability	The shelf life is 3 years. Keep out of reach of children at temperatures up to 25 °C	The shelf life based on data from stability studies
Signs of the quality of the medicinal product	Description	The requirements of the European Pharmacopoeia, the monograph "Tablets", as well as other quality standards. Requirements to be established compared to the reference drug
	Identification	
	Average weight	
	Dissolution	
	Related impurities	
	Uniformity of dosage units	
	Assay	
	Microbiological purity	
Container/packing system	Foil laminated with PVC and polyamide and aluminum foil with thermal varnish	It is necessary to achieve the target shelf life and ensure the integrity of the tablets during transportation
Application	Tablets should be taken orally once a day at any time regardless of the meal. Tablets should be swallowed whole	Equivalent drug

Table 2

Critical Quality Attributes (CQAs) of the antidiabetic tablets and API of SGLT-2 class – gliflozin derivative – dapagliflozin, 5 mg, film-coated tablets

Quality indicators	Requirements	Substantiation
Dissolution	At least 75 % (Q) in 15 min	It affects the efficiency as it indirectly reflects the release of API over a certain period of time
Related impurities	They must meet the established requirements: Related impurities: any unidentified impurity ≤ 0.2 %; total impurities ≤ 1.0 %	The limit of the decomposition product is crucial for the safety of the medicinal product. The API degradation product standardization complies with ICH Q3B
Uniformity of dosage units	According to the requirements of SPhU and EP, AV ≤ 15	Variability affects the efficacy as it indirectly reflects the quantitative content of API
Quantitative content	It must meet the established requirements: from 4.75 to 5.25 mg per 1 tablet	The variability of the quantitative assessment affects the patient's safety or effectiveness

Table 3

The results of the initial risk assessment of technology variables

Critical quality indicators	Technological process variables				
	Preparation of materials	Preparation of the tablet mass	Tableting	Film coating	Packaging, packing and labeling
Dissolution	Low	Low	Average	Low	Low
Related impurities	Low	Low	Average	Low	Low
Uniformity of dosage units	Low	High	Low	Low	Low
Quantitative content	Low	Average	Low	Low	Low

the optimal ratio of the dose of the active substance – the active pharmaceutical ingredient and excipients used in the development of the pharmaceutical form. The optimal composition and technology of antidiabetic tablets with API of SGLT-2 class – a derivative of gliflozin calculated with reference to dapagliflozin, 5 mg, was developed using an experiment planning matrix based on a 3*3 hyper-Greek-Latin square of the second order; the excipients were selected; the effect of qualitative and quantitative factors and technological parameters on the pharmaco-technological properties of the tablet masses studied and tablet quality indicators, as well as critical indicators of the quality of the pharmaceutical product were determined.

The research stage on the stability and safety of a drug in tablets also requires the use of a mathematical model that allows predicting and controlling stability during storage and transportation, as well as assessing the impact of various environmental factors on the choice of primary packaging.

The application of mathematical models in the production of pharmaceutical forms is a key stage for ensuring the quality of the technological process and optimizing the serial production of a tableted medicine.

Let us define the key aspects of the application of mathematical modeling to ensure the quality of the technological process and optimize serial production at the stage of the pharmaceutical development of the antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin.

At the stage of mixing the incoming ingredients – API and introducing excipients according to their functional purpose – fillers, lubricants, disintegrants, mathematical modeling allows analyzing and optimizing the mixing processes to ensure uniform distribution of ingredients and reduce losses.

Mathematical modeling allows prediction of tablet compression parameters, such as their hardness and size. This is important to ensure consistent tablet quality during production. The technological stage of compression and repulsion of tablets is a critical stage in the production of forms since it depends on the quality, stability and safety of the medicinal product – an antidiabetic drug in tablets with an API of SGLT-2 class – a derivative of gliflozin. It allows determining the optimal parameters of the compression process, such as pressure, speed, time and shape of the matrix, helps to achieve the desired hardness and size of tablets, minimizing losses during compression. Modeling the process of tablet repulsion helps to reduce losses and selectivity, ensuring the stability of the quality of the manufactured products.

Therefore, it is necessary to generalize that the use of mathematical modeling allows to optimize various aspects of production, as well as to substantiate the effective application of pharmaceutical engineering and management of technological parameters.

Mathematical modeling is an effective tool for predicting quality indicators and implementing quality control in the production process and at various stages of storage of the antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin as it programs the assurance of high quality of the pharmaceutical product. The effective use of modeling allows to develop methods of the quality control of tablets during production, which helps to detect and eliminate possible defects in time.

Table 4

Indicators of the quality of core tablets obtained at different pressing forces

Pressing force (кN)	Appearance of tablets, points	Tablet height, mm	Resistance of tablets to crushing, H	Friability, %	Disintegration, min
5	4	2.37	75.90 (59-83)	0.09	2.20
10	5	2.32	82.95 (64-89)	0.03	2.50
15	5	2.26	85.21 (69-91)	0.02	2.85
20	5	2.23	97.05 (78-105)	0.01	3.30
25	5	2.18	110.75 (98-116)	0.01	3.57
30	5	2.15	125.50 (101-132)	0.01	3.83

To ensure a high-quality technological process and optimize the technological parameters, the application of the model allows you to enter certain optimal technological parameters, such as the raw material supply speed, temperature and humidity, and ensure the process stability and the product quality.

To increase productivity, using the model in the long term provides an opportunity to increase the performance of the compression and repulsion line, reducing the time of these processes and improving the use of equipment.

Therefore, the effective use of modeling provides a reduction in the cost of production since the optimization of the compression and repulsion processes allows to reduce production costs, such as raw material and energy costs, resource and time savings, which contributes to reducing the overall costs of the tablet production and allows to ensure the product quality.

In order to minimize risks at the tableting stage, the study of the impact of pressing parameters on the control of quality indicators of the drug was conducted. Biconvex tablets with a diameter of 7 mm were used to determine the impact of the amount of a pressing force. The pharmaco-technological indicators of core tablets obtained at different pressing forces are shown in Table 4.

The use of a pressing pressure of 30 kN was accompanied by the operation of the press with a force exceeding the maximum allowable pressure level for the press, which could lead to damage to the moving elements of the equipment. The results obtained show a direct relationship – with an increase in the pressing force, the height decreases, the resistance of tablets to crushing increases, friability decreases, and the time of disintegration increases.

Table 5

The results of the study dapagliflozin tablets, 5 mg, obtained at different pressing forces

Pressing force (кN)	Disintegration (minute)	Dissolution, %
5	3.68	99.8
10	4.03	94.3
15	4.58	81.4
20	4.87	73.9
25	5.12	69.2
30	5.38	61.0

After applying the film coating, disintegration and dissolution were determined. The results of the study of dapagliflozin tablets obtained at different pressing forces are shown in Table 5.

The data demonstrate that the indicators of disintegration and dissolution depend significantly on the pressing force. At a pressing force of 10 kN, the tablet disintegrates similarly to the original drug. The use of a pressing force in the range from 5 kN to 15 kN ensures the release of dapagliflozin in 15 min by more than 80 %. Increasing the pressing force leads to dissolution results exceeding the established limits.

Therefore, for tableting, the pressing force (10±5) kN was chosen as optimal. With these parameters, tablets were characterized by pharmaco-technological indicators closest to the reference drug. Taking into account the research results when developing, the risk analysis of the technology variability was updated. The data are given in Table 6.

Table 6

The risk assessment of technology variables

Critical quality Indicators	Technological process variables				
	Preparation of materials	Preparation of the tablet mass	Tableting	Film coating	Packaging, packing and labeling
Dissolution	Low	Low	Low	Low	Low
Related impurities	Low	Low	Average	Low	Low
Uniformity of dosage units	Low	Low	Low	Low	Low
Quantitative content	Low	Low	Low	Low	Low

* – the level of risk was reduced

Based on the risk assessment and the experimental studies conducted, the optimal parameters of the manufacturing process of the antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin – dapagliflozin were substantiated.

Conclusions and prospects for further research. Based on the results of the system analysis of the application of mathematical models in the production of pharmaceutical forms, it has been determined that mathematical modeling is a key stage for ensuring the quality of the technological process at the stage of the pharmaceutical development of an antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin. It allows ensuring the product quality. The use of mathematical modeling in the course of the pharmaceutical development allows optimization at the stage of the experimental research of API, its polymorphic form, physico-chemical properties and pharmaco-technological indicators.

A model for managing technological parameters at the stage of the pharmaceutical development has been developed; the target quality profile of the antidiabetic drug and tablets with API of SGLT-2 class – a derivative of gliflozin has been substantiated, and critical quality indicators have been determined.

The optimal composition and technology of antidiabetic tablets with API of SGLT-2 class – a derivative of gliflozin calculated with reference to dapagliflozin, 5 mg, have been developed using an experiment planning matrix based on a 3*3 hyper-Greek-Latin square of the second order; the excipients have been selected; the effect of qualitative and quantitative factors and technological parameters on the pharmaco-technological properties of the tablet masses studied and tablet quality indicators, as well as critical indicators of the quality of the pharmaceutical product have been determined.

Based on the results of the experimental studies and risk assessment, the optimal parameters of the technological process for the production of the antidiabetic drug in tablets with API of SGLT-2 class – a derivative of gliflozin – dapagliflozin have been substantiated.

Prospects for further research are the development of SGLT-2 class API drugs – gliflozin derivatives in modified-release tablets.

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