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STUDY OF THE IDENTITY OF THE POLYMORPHIC FORM OF API-DAPAGLIFLOSIN DERIVATIVE AND OF ITS PERMANENCY STRUCTURE UNDER THE INFLUENCE OF THE TABLETING PROCESS

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The aim. *To investigate the polymorphic structure of the API-dapagliflozin propanediol monohydrate and to reveal the absence of an effect of the tabletting process on the polymorphic structure of the API in model compositions of tablets.*
Materials and methods. *Model mixtures of API-dapagliflozin propanediol monohydrate and excipients were studied. The research used the method of designing pharmaco-technological parameters of solid dosage forms, the method of quantum-chemical modelling of the mechanical properties of polymorphic modifications of APIs, the modelling of shear deformation, the nanoindentation method, the Rietveld method for calculating X-ray patterns, X-ray structural analysis of API and selected model compositions of tablets.*
Results. *The polymorphic structure of API-dapagliflozin propanediol monohydrate and its polymorphic structure in selected model compositions of tablets produced by the pressing method were studied and analyzed. An X-ray structural study was carried out, and the qualitative and phase composition of samples and polymorphic modifications of API and model series of tablets were determined. According to the results of the X-ray structural analysis, it was established that there is no polymorphic transition and that the polymorphic structure of API is invariant under the influence of pressing pressure, which ensures the quality of the tablet form.*
Conclusions. *The design of an experimental study was determined based on the application of the QbD concept, design of experiments – DoE, for designing and ensuring a high-quality technological process – tabletting of API-dapagliflozin propanediol monohydrate and excipients.*
To manage a critical technological parameter – the stability of the polymorphic structure of the API, which guarantees the quality of the tablet form, its bioavailability and bioequivalence, it is necessary to use a set of methods for studying structural changes and polymorphic modifications of the API during the tableting process.
According to the results of the X-ray structural study of API and selected model compositions of tablets, it was established that during the process of tabletting under pressure, the structure of the polymorphic modification of dapagliflozin propanediol monohydrate does not change, and no polymorphic transition is observed
Keywords: *polymorphism, critical technological parameter, tabletting, polymorphic transition, structural stability, bioequivalence*

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1. Introduction

According to the assessment of experts, in the realities of the modern world, companies that pay attention not only to the chemical composition of drugs but primarily to the bioavailability of active pharmaceutical ingredients (APIs) and bioequivalence to ensure their quality and therapeutic effectiveness will win to the competition in the pharmaceutical market.

Pharmaceutical manufacturing processes consist of a series of single operations designed to modulate certain properties of APIs and excipients being processed. To ensure an acceptable and reproducible modulation, the quality attributes of the input materials and their manufacturability should be considered for each unit operation.

To improve technological processes in the modern production of pharmaceutical products, the concept of Quality by Design (QbD) is implemented, which implements the basis of the "six sigma" approach to achieve process improvement, the comprehensive application of a system of practices that ensures the release of quality pharmaceutical products in accordance with the OOS – SOP for Out specification of Specification. The implementation of the QbD concept determines the design of experiments – Design of experiments (DoE), to obtain better results with a small number of experiments [1, 2].

The application of the QbD concept in pharmaceutical development guarantees the provision of a systematic and complete determination of product quality on the basis of a high-quality production process and control of critical technological parameters. The design space based on QbD is defined as a multidimensional combination and interaction of input variables and parameters of

the technological process that ensure the quality of the pharmaceutical product.

The progress achieved in the development of analytical methods for chemical attributes (for example, identity and purity) significantly affects the design of a high-quality technological process for the production of a pharmaceutical product. In general, the application of Processing Analytical Technology (PAT) is ensured by appropriate principles and tools.

The critical quality indicators (CQAs) of a pharmaceutical product are primarily related to the physical and chemical properties of the API, excipients, intermediates (in-process materials) and the pharmaceutical product.

CQAs for solid dosage forms for oral use, as a rule, are those characteristics that affect purity, therapeutic efficacy, drug release, and drug stability during transportation and storage. The pharmaceutical development of the drug and the technological process should be guided by the potential CQAs of the drug, determined on the basis of the target quality profile of the drug and experimentally confirmed scientific data [1–3].

However, certain physico-mechanical properties of pharmaceutical ingredients, such as API polymorphism, have not been fully investigated.

Polymorphic forms of APIs often show not only different mechanical, thermal, physical and chemical properties, which can significantly affect the bioavailability and pharmacotechnological parameters of the solid dosage form. An in-depth understanding of the relationship between the polymorphic form of an API and its functional properties is important for choosing the most effective method of administration and pharmaceutical form and developing a technological process for the production of a medicinal product. Studies of the physical and chemical properties of polymorphic forms of APIs acquire further importance for the high-quality serial pharmaceutical production of medicinal products. The focus of modern research is the dependence between the therapeutic effectiveness of the dosage form and the properties of the polymorphic form of API, in particular, the control of thermodynamic and kinetic indicators of polymorphic systems, the characteristics of polymorphs and the transformation between polymorphic forms.

The main goal of developing a new medicinal product is to obtain its storage-stable pharmaceutical form with optimal physico-chemical, pharmaceutical and biological properties.

Pharmaceutical companies and scientists modify APIs, which are often co-crystals, salts, or carefully selected polymorphs, to improve the properties of the parent drug. In order to find the best form of the drug, various advanced methods of determining these characteristics should be used.

Researchers discuss diffraction, spectroscopic, thermal, as well as pharmaceutical methods for determining characteristics. All of them are necessary to study the solid API in its complexity, from the mass to the molecular level, to obtain information about its structure, properties, purity and possible transformations, to make the characterization efficient, exhaustive and complete. In addition, these techniques can be used to monitor and investigate the physical processes involved in drug development in situ and in real-time [4, 5].

Current research and new regulatory guidance on pharmaceutical co-crystals have accelerated their development as effective approaches to improve the processing, storage stability, and bioavailability of poorly soluble APIs. The complex structure and the limited amount of available information related to their action may require development strategies that differ from those of single-component drugs to ensure their clinical safety and efficacy. Physical characterization of co-crystals should include elucidation of the structure of their objective crystalline form, as well as their possible variations (for example, polymorphs and hydrates). Some solids may also contain crystals of individual components. The methods of obtaining polymorphic forms of API and their further processing (for example, crystallization from solutions, grinding) differ in the applicable ingredients, scalability, and characteristics of the resulting solids.

Biopharmaceutical research and in vitro evaluation of properties that determine clinical efficacy is attracting more and more attention in the development of pharmaceuticals. Understanding and reducing the influence of possible factors that interfere with dissolution or dissolved states, including solution-mediated phase transformation and precipitation from supersaturated solutions, are important to ensure the bioavailability of orally administered APIs with lower solubility. In particular, the influence of polymeric excipients on the effectiveness of API emphasizes the relevance of formulation design for appropriate use [6].

Raw material variability for active pharmaceutical ingredients (APIs) is not always carefully considered during process design. The way in which the API is obtained and the parameters of the manufacturing process change during product development and the life cycle of the product, which leads to changes in physical characteristics, this can potentially affect its manufacturability. The need for a global approach to understanding the relationship between the synthesis and variability of APIs, the process and the quality of the pharmaceutical product is being updated. The conducted studies confirm the connection between the process of production of the medicinal substance, the physical and chemical properties of the API and the continuous process of the production of the medicinal product [7].

API polymorphism can also cause undetected variability of raw materials under the influence of the technological process, which can be detected in the final product and affect its bioavailability and therapeutic effectiveness.

The bioavailability of API for solid dosage forms for oral administration definitely depends on the polymorphic form and crystalline state of the substance – the active pharmaceutical ingredient [8].

One of the real dangers of pharmaceutical production is the ability of crystalline forms to change their structure under the influence of external influences, first of all, mechanical grinding or the action of pressure during the tabletting process.

Important during processing is the prevention of degradation of active pharmaceutical ingredients under the influence of external factors such as humidity, temperature or pressure. Synchronized nanomechanical measurements of the crystal structure of active pharmaceutical ingredients are essential for the rapid and efficient development of high-quality pharmaceuticals. Designing and controlling the nanomechanical properties of solid pharmaceuticals using nanoindentation as a function of crystal structure is a tool for developing fundamental knowledge in the structure-property relationship with implications for drug production and development [9].

The results of numerous studies have proven that enantiomeric crystalline forms of APIs have different levels of biological activity, but a clear pattern between the type of enantiomeric form and biological action has not been established.

For example, diuretic properties were stronger in enantiomeric crystal forms in all pairs containing one type of molecular conformation. At the same time, for the benzthiazine derivative with a cyclopropyl substituent, one enantiomeric crystalline form showed an antidiuretic effect, and the opposite one was three times stronger than hydrochlorothiazide, which was used as a comparison drug [10].

Scientists S. Shishkina and others proposed a developed methodology for studying crystal structures and modelling their deformation using quantum chemical methods. It was assumed that any deformation of the crystal is caused by the displacement of tightly bound fragments of the crystal packing with each other. This process can be studied using quantum chemical calculations in several stages. In the first stage, calculations of pairwise interaction energies between molecules are aimed at identifying the most tightly bound fragments of the crystal structure. The results of these calculations can be used to determine the crystallographic planes along which the crystal packing fragments shift most easily. The next step is a preliminary estimate of the direction of the easiest shear along the split plane. For this, a model system containing a fragment of one layer (immovable part) and a molecule or a dimer of molecules belonging to the adjacent layer (mobile part) was isolated from the crystal structure [10–12].

Two-dimensional scanning of the displacement of the moving part relative to the stationary one and calculation of the minimum distances between atoms of molecules belonging to adjacent layers at each point of the trajectories allows for determining the most likely direction of deformation in the crystal. The next step is to move the moving part to the stationary part in the chosen direction to simulate the shifting of the layers towards each other. Calculations of the interaction energies between the moving and immobile parts at each point during the movement on the crystallographic translation make it possible to construct an energy profile and calculate the energy barrier for such deformation. Modelling of the shear deformation of tightly bound layers on the example of three polymorphic modifications of mefenamic acid showed that a polymorphic transition under pressure is not possible for these structures [11]

The proposed method consists of two stages: analysis of pairwise interaction energies between molecules in the structure, obtained by X-ray diffraction, with the separation of tightly bound fragments and subsequent quantum-chemical modelling of their displacement relative to each other. The application of this method to aspirin polymorphs I and II showed that they have a layered structure, and the crystallographic direction [001] in the (100) plane is the most likely for shear deformation, which correlates well with the data of the nanoindentation method [13].

The aim was to investigate the polymorphic structure of the API-dapagliflozin propane diol monohydrate and to reveal the absence of an effect of the tableting process on the polymorphic structure of the API in model compositions of finished tablets.

2. Research planning (methodology) of the research

The application of the proposed method of researching the crystal structure of the polymorphic form of API and modelling their deformation by a quantum chemical method is an acceptable tool for predicting the mechanical properties of the API Dapagliflozin propane diol monohydrate and pharmacotechnological parameters to ensure the quality of the technological process of tabletting.

To create effective drugs for the treatment of diabetes, pharmaceutically acceptable derivatives of gliflozin are new active pharmaceutical ingredients (APIs), and their solid dosage forms of immediate and prolonged action are just entering the pharmaceutical market.

Gliflozin as a basis represents a new class of oral hypoglycemic agents approved by the FDA for the treatment of diabetes with a unique mechanism of action – blocking SGLT-2 proteins from the area of the proximal convoluted tubule (PCT) in the kidneys, which leads to the prevention of reabsorption and allows the glucose molecule to be removed from the urine [14–16].

Thanks to this mechanism of action, drugs whose active substance is APIs – derivatives of gliflozin, reduce the level of blood glucose in the body and belong to the group of SGLT-2 inhibitors. For the gliflozin derivative – API Dapagliflozin propanediol monohydrate is characterized by polymorphism [17–19].

Therefore, the influence of the factors of the technological process of tabletting can cause a violation of the polymorphic structure of the API of Dapagliflozin propanediol monohydrate and, as a result, reduce the therapeutic effectiveness, which is unacceptable in the case of diabetes treatment [20].

The biological activity and bioavailability of the active substance – the active pharmaceutical ingredient (API) in tablet form is most strongly influenced by the technological process at the tabletting stage. During the compression process, the compression results in densification of the crystalline structure of the API due to conformational and orientational changes. The influence of pressure on a crystal structure can be studied by experimental methods such as nanoindentation (anisotropic

compression) or isotropic compression in a diamond anvil cell (DAC). Quantum chemical calculations are commonly used to explain or predict the results of experimental methods. The studies of the anisotropy of physical properties (modulus of elasticity, stiffness, etc.), as well as calculations of attachment energies or elastic constants, allow discussing structure-property correlations.

This approach to the organization of research design makes it possible to predict the possibility of a polymorphic transition of a certain crystalline form of API, to investigate the presence or absence of a polymorphic transition and the constancy of the polymorphic structure of API in a solid dosage form by X-ray structural analysis, and to adjust technological operations according to the obtained modeling data.

Therefore, the urgent task of our scientific group became to study a series of objects – model compositions of APIs and auxiliary substances, for which the crystalline structure of APIs was investigated by experimental methods, model mixtures under the action of pressing pressure and after it was investigated – measurements were carried out at different pressure values, in during the research, it was necessary to establish that the polymorphic transition did not occur. Therefore, the bioavailability of API in the form of tablets remains unchanged and predictable.

3. Materials and methods

Experimental research was conducted on the basis of SSI "Institute for Single Crystals" NAS of Ukraine in the period 2022–2023.

The object of the study: model mixtures of API-вapagliflozin propanediol monohydrate and excipients were studied, model series of tablets selected as promising in terms of qualitative and quantitative composition and the results of established pharmaco-technological indicators of tablet masses and tablets were produced.

The research used the method of constructing pharmacotechnological parameters of solid dosage forms for the production of tablets with appropriate quality indicators, the method of quantum-chemical modelling of mechanical properties of polymorphic modifications of API, simulation of shear deformation – to determine the stability of the polymorphic structure of API; nanoindentation method, Rietveld method for calculating X-ray pattern, X-ray structural analysis of API and selected model compositions of finished tablets – to confirm the stability of the polymorphic structure of API under the influence of the tabletting process.

4. Research results

The polymorphic structure of API-вapagliflozin propanediol monohydrate, its polymorphic structure in the composition of selected model compositions of tablets produced by the pressing method and the pressing method with preliminary compaction was studied and analyzed.

An X-ray structural research and analysis of API-вapagliflozin propanediol monohydrate and model series of tablets containing it was carried out.

The qualitative, phase composition of samples and polymorphic modifications of API and model series of tablets was determined (Table 1).

Table 1

Qualitative composition for determining the phase composition of samples and polymorphic modifications

No. exsp.	No. samples	Samples	Quality composition of samples
584	1	API	Dapagliflozin propanediol monohydrate
585	4	Model series tablets MS23	Dapagliflozin propanediol monohydrate A mixture of microcrystalline cellulose102 and Anhydrous lactose 3:1 Croscarmellose sodium Talc
586	3	Model series tablets MS22	Dapagliflozin propanediol monohydrate A mixture of microcrystalline cellulose102 and anhydrous lactose 3:1 Crospovidone Talc
587	5	Model series tablets MS27	Dapagliflozin propanediol monohydrate A mixture of microcrystalline cellulose102 and anhydrous lactose 3:1 Sodium starch glycolate PEG 8000
588	2	Model series tablets MS20	Dapagliflozin propanediol monohydrate Lactose 80 Crospovidone PEG 8000

Powder diffractograms were taken on a Siemens D500 diffractometer (filtered CuKα copper radiation, Bragg-Brentano geometric scheme).

After grinding, the sample was placed in a glass cuvette with a working volume of 2'1'0.1 cm^3 for taking an X-ray pattern (interval $3<2\theta<60°$ with a step of 0.01°). The obtained diffractograms are presented in Fig. 1, 2.

Calculations of radiographs according to the Rietveld method were performed using the structural data of the Cambridge and Bonn banks (Table 2).

Lanthanum hexaboride was used as an external standard for calibrating the diffractometer and calculating the instrumental profile function.

The results of refining the diffractogram of the studied samples using the Rietveld method are shown in Fig. 3–7.

Analysis of the X-ray pattern of sample 584 showed that it contains only one crystalline phase – Dapagliflozin propanediol monohydrate, the structure of which corresponds to the Cambridge Bank data, that is, it is in the same polymorphic modification as the already known structure. The substance is chemically pure, impurity lines are not observed on the X-ray image.

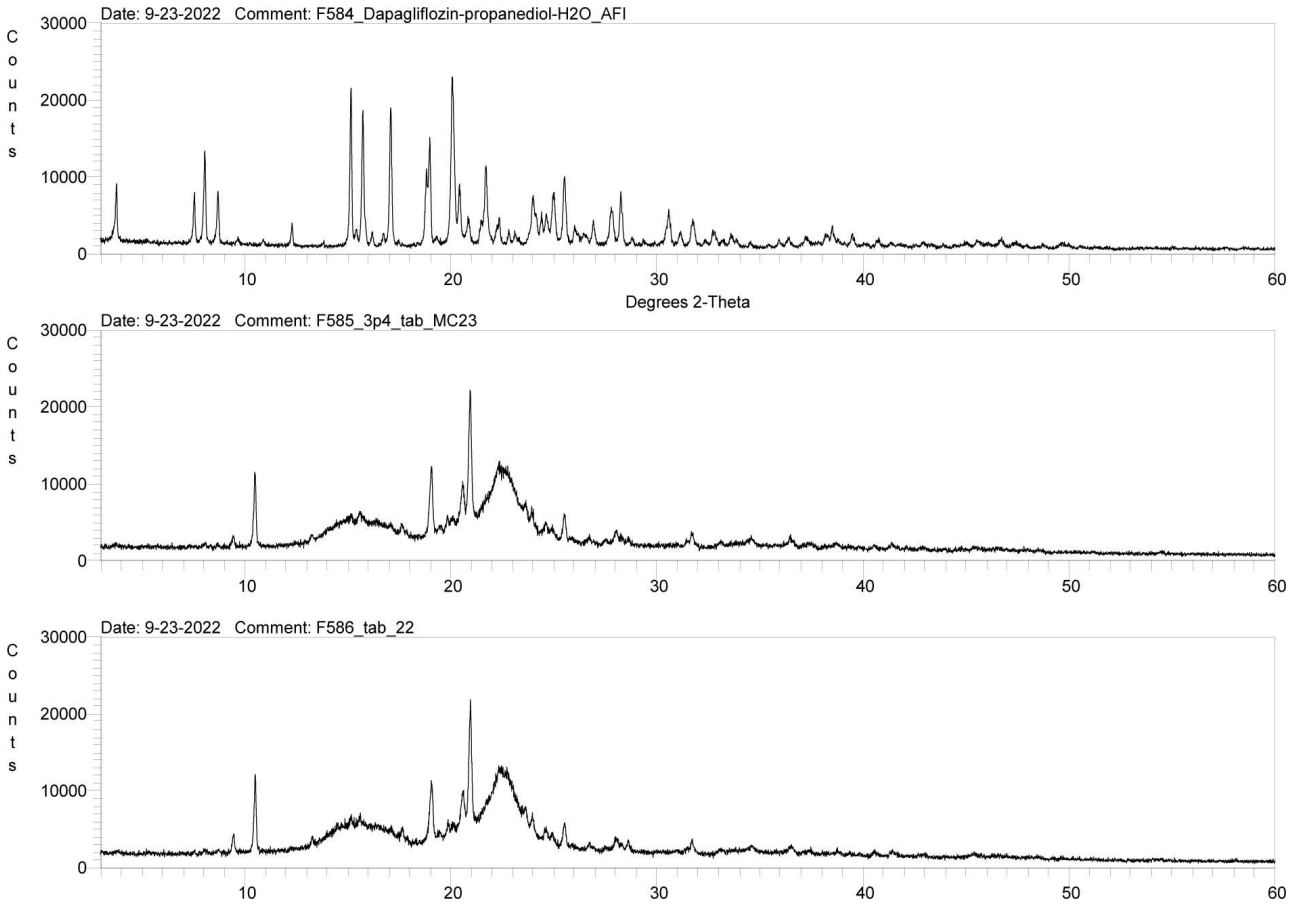

Fig. 1. Renthenograms of samples 584–586

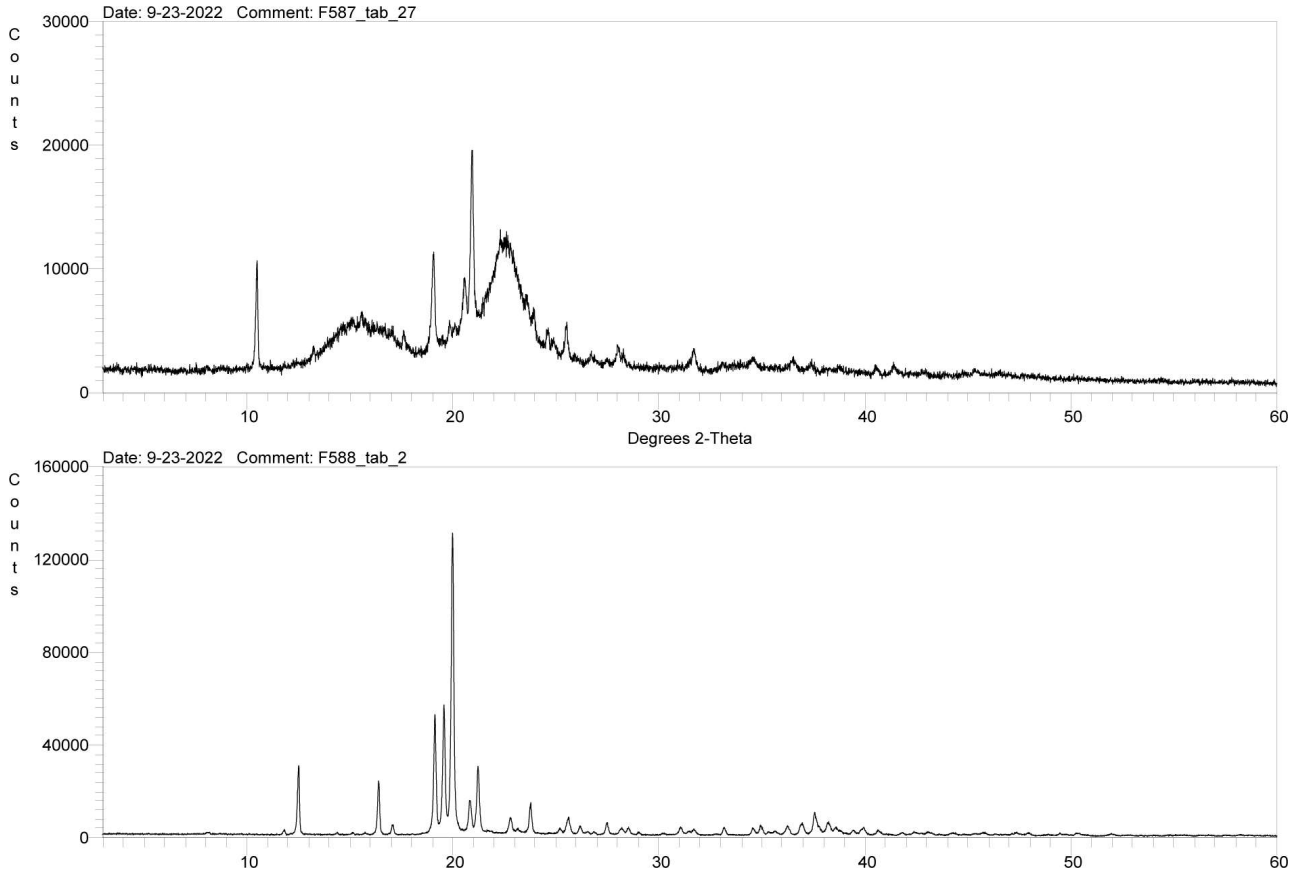

Fig. 2. Renthenograms of samples 587–588

Table 2

Single-crystal data and the result of analysis by the Rietveld method

Samples	*a*, Å	*b*, Å	*c*, Å	α, β, γ, °	Spatial symmetry group	Content (wt.%)	Ser. size of crystallites, nm
Single crystal data							
Dapagliflozin propanediol monohydrate	11.269	4.809	46.723	90 90 90	$P2_12_12_1$	CCDC=CIMNUJ	
α-lactose monohydrate	7.982 (2)	21.562 (3)	4.824 (1)	90 109.57(3) 90	$P2_1$	CCDC=LACTOS10	
β-lactose	10.839 (6)	13.349 (6)	4.954 (5)	90 91.31(9) 90	$P2_1$	CCDC=BLACTO	
Cellulose-1β	7.784 (8)	8.201 (8)	10.38 (1)	90 90 96.55(5)	$P112_1$	CCDC=JINROO01	
Talc 1A	5.290 (3)	9.173 (5)	9.460 (5)	90.46(5) 98.68(5) 90.09(5)	C-1	ICSD=100682	
Powder samples							
F584 dapagliflozin propanediol monohydrate	7.8439 (6)	33.861 (2)	8.2984(5)	90 109.393 90	$P2_1/c$	100 (1)	97
F585 β- lactose	10.8426(7)	13.3409 (10)	4.96683 (18)	90 91.449 (3) 90	$P2_1$	14.8 (2)	61
Cellulose -1β	7.9542 (9)	8.158 (3)	10.606(6)	90 90 96.03 (2)	$P112_1$	83.1 (5)	3
Dapagliflozin propanediol monohydrate	11.2552	4.8085	46.735	90 90 90	$P2_12_12_1$	1.54 (7)	104
Talc	5.290	9.173	9.460	90.46 98.68 90.09	C-1	0.59 (3)	89
F586 β- lactose	10.8460 (8)	13.3396 (11)	4.96584 (20)	90 91.452 (3) 90	$P2_1$	13.8 (2)	61
Cellulose-1β	7.9580 (9)	8.123 (3)	10.631 (6)	90 90 96.18 (2)	$P112_1$	84.0 (3)	3
Dapagliflozin propanediol monohydrate	11.2552	4.8085	46.735	90 90 90	$P2_12_12_1$	1.50 (7)	96
Talc	5.290	9.173	9.460	90.46 98.68 90.09	C-1	0.75 (3)	94
F587 β- lactose	10.8444 (8)	13.3416 (12)	4.9647 (2)	90 91.437 (3) 90	$P2_1$	12.8 (2)	61
Cellulose-1β	7.9533 (9)	8.110 (3)	10.668 (6)	90 90 96.10 (2)	$P112_1$	86.3 (5)	3
Dapagliflozin propanediol monohydrate	11.2552	4.8085	46.c735	90 90 90	$P2_12_12_1$	0.94 (10)	122
F588 α-lactose monohydrate	7.9425 (2)	21.5899 (4)	4.81736 (8)	90 109.7736 (10) 90	$P2_1$	97.9 (6)	73
Dapagliflozin propanediol monohydrate	11.2552	4.8085	46.735	90 90 90	$P2_12_12_1$	2.1 (3)	124

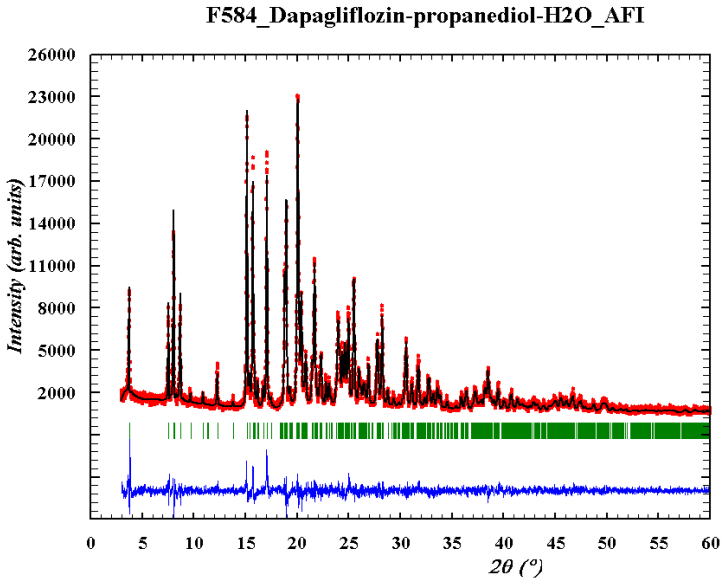

Fig. 3. Results of refinement of the diffractograms of sample 584 by the Rietveld method

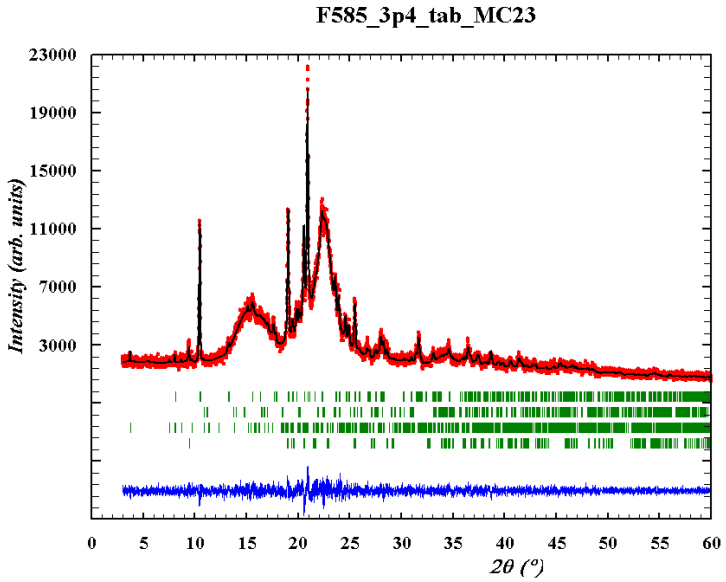

Fig. 4. Results of refinement of the diffractograms of sample 585 by the Rietveld method

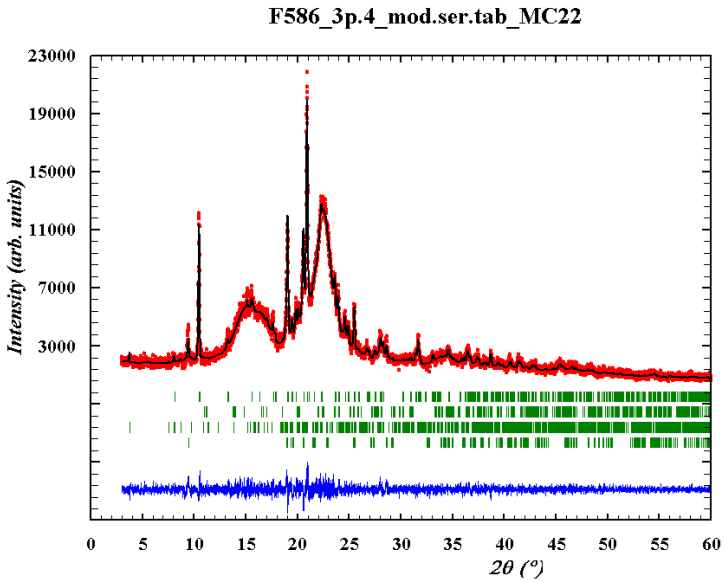

Fig. 5. Results of refinement of the diffractograms of sample 586 by the Rietveld method

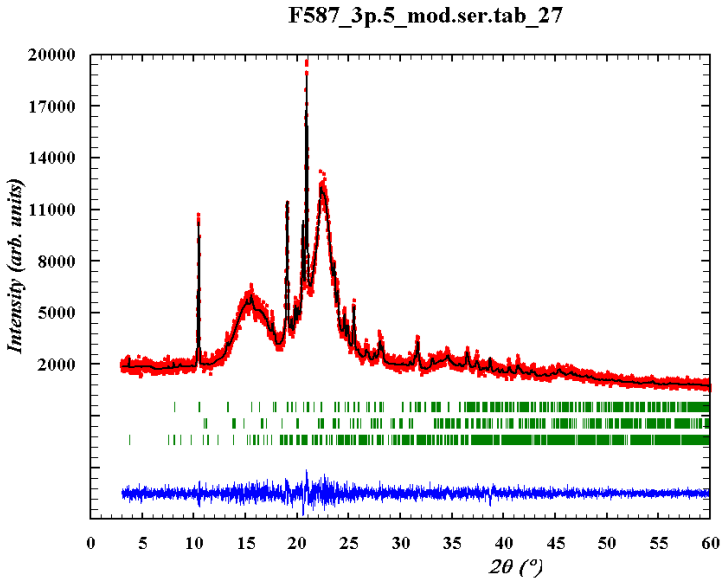

Fig. 6. Results of refinement of the diffractograms of sample 587 by the Rietveld method

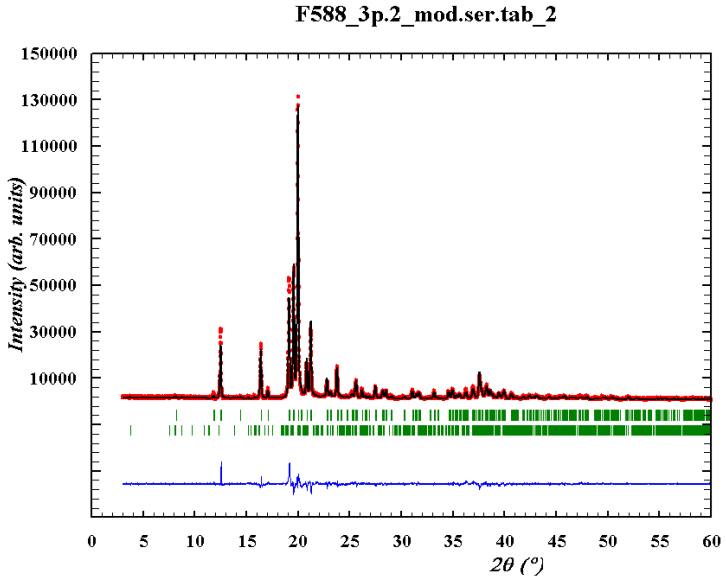

Fig. 7. Results of refinement of the diffractograms of sample 588 by the Rietveld method

The analysis of radiographs of samples 585–586 showed that the tablets of series MS22 and MS23 (samples 585, 586) have a similar composition and contain 4 crystalline phases: lactose anhydrous, microcrystalline cellulose, Dapagliflozin propane diol monohydrate and talc in the ratios shown in the Table 1.

Analysis of the X-ray pattern of sample 587 showed that tablets of the MS27 series (sample 587) have a similar composition but differ in that talc lines are not observed in the X-ray pattern. It should be noted that only crystalline phases are determined by X-ray phase analysis; amorphous substances (crospovidone, sodium starch glycolate, PEO) are not identified by this method.

The experimental radiograph is shown in red, and the theoretical one is in black. The rows of vertical dashes show the Bragg positions of the peaks for each phase in the same order as in Table 1, the blue curve below shows the difference between the experimental and theoretical curves at each point.

5. Discussion of research results

Based on the results of the theoretical analysis of scientific publications [15, 17–20], which highlight the experimental studies of APIs – derivatives of gliflozin, it was established that their polymorphism, the influence of technological parameters on the polymorphic structure of APIs and the quality of the dosage form and therapeutic effectiveness are insufficiently studied.

The application of a set of methods of quantum chemical modelling of mechanical properties, simulation of shear deformation and the method of nanoindentation of polymorphic modifications of API, X-ray structural analysis of the crystal structure of the polymorphic form of API is an acceptable tool for predicting the mechanical properties of API-dapagliflozin propanediol monohydrate and pharmacotechnological parameters to ensure the quality of the technological process of tabletting.

Based on the results of the X-ray structural analysis, it was confirmed that the composition of tablets

MC22, MC23 and MC27 corresponds to that indicated in Table 1.

The content of microcrystalline cellulose relative to anhydrous lactose in the ratio given in Table 1. Since MCC is a nanocrystalline substance, this must be taken into account when refining similar phases using the Rietveld method.

Unlike tablets MS22, MS23, MS27, tablets MS20 (sample 588) have a composition that contains lactose monohydrate as an auxiliary substance – filler and does not contain microcrystalline cellulose, giving a diffraction pattern that does not differ from the background given by amorphous substances.

According to the results of the conducted research, it was established that the API Dapagliflozin propane diol monohydrate (DPM) (sample 584) has a structure that corresponds to literature data, is chemically pure and does not contain impurities or other polymorphs.

According to the results of the conducted research, it was established that during the production of core tablets of the model series under the action of pressing pressure, the polymorphic modification of API Dapagliflozin propanediol monohydrate does not change, and no polymorphic transition is observed.

Practical relevance. The practical relevance of the conducted research lies in the fact that the complex application of methods of quantum-chemical modelling of mechanical properties, modelling of shear deformation and the method of nanoindentation of polymorphic modifications of API to detect the presence or absence of a polymorphic transition is justified. According to the obtained results, it was established and confirmed that in the process of manufacturing core tablets of the model series under the action of pressing pressure, the polymorphic modification of API Dapagliflozin propanediol monohydrate does not change, and no polymorphic transition is observed. Therefore, this approach is promising for the control of a critical technological parameter – the stability of the polymorphic structure of ARI in the process of pharmaceutical development, which guarantees the quality of the tablet form, bioavailability of ARI and bioequivalence.

Study limitations. The limitation of this work is that only one polymorphic modification of API was used – dapagliflozin propanediol monohydrate.

Prospects for further research. Further studies will investigate the release of the API Dapagliflozin propanediol monohydrate from selected coated tablet formulations and demonstrate predicted bioequivalence.

The results of the work can be used to design a high-quality technological process and predict critical technological parameters for the production of coated tablets with API-вapagliflozin propanediol monohydrate.

6. Conclusions

On the basis of the performed theoretical analysis, the design of an experimental study was determined based on the application of the QbD concept, design of experiments – DoE, for designing and ensuring a high-quality technological process – tabletting of core tablets with API-вapagliflozin propanediol monohydrate and excipients. The stability of the polymorphic structure of API is defined as a critical technological parameter.

In order to control the critical technological parameter – the stability of the polymorphic structure of the API, which guarantees the quality of the tablet form, the bioavailability of the API, and bioequivalence, it is necessary to comprehensively use the methods of quantum chemical modelling of mechanical properties, simulation of shear deformation and the method of nanoindentation of polymorphic modifications of the API to detect the presence or absence of structural changes polymorphic modifications of the API, which could have occurred under the influence of pressure during the tabletting process and confirm the polymorphic transition.

According to the results of X-ray structural research and analysis of API and selected model compositions of ready-made tablets, it was established that in the process of manufacturing core tablets of model series under the action of pressing pressure, the polymorphic modification of API Dapagliflozin propanediol monohydrate does not change, the polymorphic transition is not observed.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

Finding

The authors declare that they have no conflicts of interest.

Data availability

Data will be made available at a reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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