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Determination of the effect of the solid dispersion carrier on quercetin solubility

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The results of studying solid dispersions of quercetin aimed at improving its biopharmaceutical properties are presented. Quercetin belongs to Class IV of the Biopharmaceutics Classification System and is characterized by low solubility and permeability, which limits its bioavailability. To enhance its therapeutic effectiveness, solid dispersions were prepared with various polymeric carriers such as polyethylene glycol (PEG-4000), hydroxypropyl methylcellulose (HPMC), mannitol, polyvinylpyrrolidone K30 (PVP K30), and cetostearyl alcohol in 1:1 ratio. The physicochemical properties of the obtained samples were evaluated using spectrophotometry, X-ray diffraction analysis, thermal analysis, and scanning electron microscopy. It was found that the use of polymeric carriers promotes the amorphization of quercetin and improves its solubility. The highest degree of amorphization was achieved in the sample with PVP K30, as confirmed by both X-ray diffraction and thermal analysis. PEG-4000 and mannitol demonstrated moderate effectiveness, whereas cetostearyl alcohol proved unsuitable due to thermal instability and the formation of dense agglomerates, which slow down the release of the active substance. Biopharmaceutical studies demonstrated a significant increase in solubility and a reduction in the dose number in solid dispersions compared to the native substance. The most promising solid dispersions turned out to be those in which PVP K30 was used as a carrier for the gastric environment and mannitol for the intestinal environment. The obtained results indicate that the development of solid dispersions is an effective strategy for enhancing the bioavailability of poorly soluble compounds, particularly quercetin, and may be applied in the design of new oral dosage forms.

Key words: quercetin, polyvinylpyrrolidone, polyethylene glycol, mannitol, hydroxypropyl methylcellulose, solid dispersions, biopharmaceutical solubility.

Визначення впливу носія твердої дисперсії на розчинність кверцетину. *В.М. Верховод, І.В. Ковалевська, Т.Є. Колісник, В.О. Грудько, О.В. Ващенко, О.А. Рубан, О.В. Кутова*

Представлені результати досліджень твердих дисперсій кверцетину з метою покращення його біофармацевтичних властивостей. Кверцетин відноситься до IV класу біофармацевтичної класифікаційної системи і характеризується низькою розчинністю та проникністю, що обмежує його біодоступність. Для підвищення ефективності застосування було виготовлено тверді дисперсії з різними полімерними носіями, такими як ПЕГ-4000,

гідроксипропілметилцелюлоза (ГПМЦ), маннітол, полівінілпіролідон К30 (ПВП К30) та цетостеариловий спирт у співвідношенні 1:1. Фізико-хімічні властивості отриманих зразків оцінювали за допомогою спектрофотометрії, рентгеноструктурного аналізу, термічного аналізу та скануючої електронної мікроскопії. Встановлено, що використання полімерних носіїв забезпечує аморфізацію кверцетину та покращує його розчинність. Найвищий ступінь аморфізації досягнуто у зразку з ПВП К30, що підтверджується як рентгеноструктурним, так і термічним аналізом. ПЕГ-4000 та манітол продемонстрували помірну ефективність, тоді як цетостеариловий спирт виявився непридатним через термічну нестабільність та формування щільних агломератів, що уповільнюють вивільнення діючої речовини. Біофармацевтичні дослідження показали значне підвищення розчинності та зниження дозового числа у твердих дисперсіях у порівнянні з нативною субстанцією. Найбільш перспективними виявилися тверді дисперсії, де у якості носія використовували ПВП К30 (для шлункового середовища) та маннітол (для кишкового середовища). Отримані результати свідчать, що створення твердих дисперсій є ефективною стратегією підвищення біодоступності малорозчинних сполук, зокрема кверцетину, та можуть бути використані при розробці нових пероральних лікарських форм.

1. Introduction

Biopharmaceutical solubility studies focus on factors such as physicochemical properties, dosage form, and biological parameters that influence the bioavailability of drugs in the human body, as well as their pharmacokinetic profile. This knowledge is used to enhance the pharmacological and therapeutic effectiveness of medicinal products in clinical practice. The tools and scientific advances in this field are actively applied in the development of pharmaceutical products. The solubility and permeability of drugs are key indicators that determine bioavailability for oral dosage forms. Biopharmaceutical solubility indicator is used to determine the maximum absorbable dose of a drug, assess potential risks during formulation development, and optimize dosage form design. This approach allows for the identification of critical factors at early stages, thereby contributing to the improved clinical efficacy of new drugs [1]. This affects the drug effectiveness and plays a crucial role in determining the rate and extent of release of the active pharmaceutical ingredient (API) from the dosage form (DF), as well as its subsequent absorption in the gastrointestinal tract (GIT). Low solubility can limit the bioavailability of a drug, thereby reducing its therapeutic impact.

Intestinal absorption of drugs is a key process that determines oral bioavailability and the systemic effects of medications. Along with the permeability of the intestinal mucosa, the concentration of drugs in intestinal fluids influences the rate and extent of their absorption. For poorly soluble drugs, intestinal absorption may be limited in the GIT. Even in cases where absorption is not solubility-limited, intestinal solubility remains an important factor affecting the dissolution rate and, in the case of supersaturation, the potential for precipitation. It is worth noting that aqueous solubility determined during screening does not always accurately reflect solubility in the intestine [2].

The most common route of drug administration is oral. This allows for self-administration, which improves patient acceptability, promotes adherence to the dosing regimen, and enables the pharmaceutical industry to meet this need by offering individualized and stable solid oral dosage forms [3]. However, the seemingly simple nature of this method conceals a complexity arising from the interaction of GIT anatomy and physiology with the physicochemical properties of the drug and its dosage form. It has been recognized that one of the key factors affecting drug absorption is intestinal solubility, which is determined not only by the intrinsic solubility of the drug in water but is also influenced by numerous factors within the GIT. Among these, pH plays an important role, as it can affect the ionization properties of the drug as well as the formation of mixed micelles composed of bile acids, phospholipids, and lipid digestion products [4]. Accordingly, the Biopharmaceutics Classification System (BCS) divides drugs into four classes based on their solubility and permeability. This classification helps to predict the behavior of drugs in the body and determine the necessary strategies to improve their bioavailability. The most challenging group is class IV. Substances in this category are characterized by low permeability and low solubility. Their absorption is unpredictable, resulting in consistently low bioavailability. Examples of such substances include quercetin and bifonazole [5].

For poorly soluble substances (classes II and IV), innovative technologies such as self-emulsifying drug delivery systems are being developed. The selection of base components,

including solvents and surfactants, significantly affects the biopharmaceutical properties of a prospective drug, promoting increased release rate and bioavailability of poorly soluble API. The evaluation of the biopharmaceutical properties of drugs involves analyzing their solubility and permeability [2, 6]. The determination of these parameters is carried out at the drug development stage and influences the selection of dosage forms, excipients, and manufacturing processes. In particular, factors such as the physical state of the API, its polymorphism, and dispersion can significantly affect dissolution and absorption processes, ultimately impacting bioavailability.

The use of the BCS in the development of new drugs allows for the optimization of their efficacy and bioavailability. The optimization is achieved by taking into account the characteristics of the active ingredient when selecting appropriate excipients and manufacturing methods [7].

Thus, drug solubility is a critical factor influencing the effectiveness of their therapeutic application. One of the priority directions in modern pharmacy remains the development of complex formulations based on biologically active compounds of plant origin for the prevention and treatment of atherosclerosis [8, 9]. Particular attention is drawn to quercetin, which is characterized by a broad spectrum of pharmaceutical activity. At the same time, it belongs to Class IV of the Biopharmaceutics Classification System, which is due to its low solubility and limited bioavailability. Therefore, it is advisable to use technologies aimed at enhancing the bioavailability of quercetin, in particular through the development of solid dispersions (SD) [10].

Thus, the aim of the work is to study solid dispersions of quercetin using physicochemical methods to select the optimal carrier for the active substance.

2. Materials and methods

Table 1 presents quercetin and its solid dispersions with various high-molecular compounds in a 1:1 ratio. The amount of dissolved substance was determined using infrared spectrophotometry in accordance with the State Pharmacopoeia of Ukraine (SPhU) specifications 2.1, p. 2.2.24. The study was conducted using an Evolution 60S spectrophotometer with cuvettes having a 10 mm path length at a wavelength of 367 nm.

The amount of substance dissolved, expressed in milligrams, was calculated using the following formula:

$$X = A \cdot \frac{C_{ss}}{A_{ss}} \cdot 100 + 5\%, \quad (1)$$

where A is the optical density of the test solution;

A_{ss} is the optical density of the reference solution;

C_{ss} is the concentration of the standard solution;

100 is the volume of the test solution;

5% is the the amount of substance removed from the solution during the sampling of the previous aliquot.

To determine the equilibrium moisture content of the studied samples depending on the relative humidity of the air (RH), a dynamic method with the construction of moisture sorption isotherms was applied. The SD samples were prepared using the solvent removal method. The hygroscopicity coefficient (K) was calculated using the formula [11]:

$$K = \frac{\Delta m_{100\%RH}}{100 - RH_{\text{the onset of growth}}} \approx \frac{\Delta m_{100}}{20} \quad (2)$$

(initiation of rapid growth ≈ 80% RH)

The dose number (D_0) allows evaluating whether a dose of a drug can be completely dissolved in the volume of liquid available for absorption, which directly affects its bioavailability. This parameter was calculated using the formula:

$$D_0 = \frac{D}{S \cdot V_0}, \quad (3)$$

where D is the API dose permitted for medical use, mg;

S is the solubility, mg/ml;

V_0 is the volume of fluid used to swallow the API dose (250 ml).

The dose-to-solubility ratio characterizes the ability of a substance to dissolve within the gastrointestinal environment at a single dose level, and was calculated using the following formula:

$$S_i = \frac{D}{S} \quad (4)$$

where, D is the the dose of the API approved for medical use;

S is the solubility, mg/ml.

Solubility values were considered high if the amount of solute was within 85–100%, the dose number ranged from 250.0 to 225.0, and the dose-to-solubility ratio was close to 1 [12].

Table 1. Composition of solid dispersion samples.

Sample No.	The excipient used as a carrier
No.1	PEG-4000
No.2	HPMC
No. 3	Mannitol
No. 4	PVP K30
No. 5	Cetostearyl alcohol

Thermal analysis (SPhU 2.1, p.2.2.34) was carried out using thermogravimetric and differential scanning calorimetry methods. This approach, depending on the temperature, makes it possible to identify the phase transitions of the studied substance, as well as the kinetics of its decomposition and the level of purity. The study was performed using a TG Q50 thermogravimetric analyzer (Thermogravimetric Analysis, TGA), model Q50, and a DSC Q20 differential scanning calorimeter (Differential Scanning Calorimetry, DSC), model Q20, according to a generally accepted methodology.

X-ray structural analysis is one of the most informative and effective methods for the identification of SD and the study of their structural characteristics [13]. The obtained diffraction patterns represent an individual «fingerprint» of the crystalline substance, consisting of a system of diffraction maxima. Each sample is characterized by a specific set of peaks that differ in number, intensity, and angular position, making it possible to accurately determine the phase composition and confirm the presence or absence of a crystalline form in the studied substance.

Scanning electron microscopy (SEM) is a technologically advanced analytical technique that enables the acquisition of highly detailed surface images with ultra-high spatial resolution and significant depth of field. By utilizing reflected and secondary electrons, SEM provides not only topographical analysis but also allows for the assessment of morphology, microstructural features, and elemental composition of the material.

For further studies, samples of quercetin solid dispersions with various carriers were prepared. The composition of the samples and the preparation method are presented in Table 1.

Quercetin was dispersed with the molten carrier at 55 °C (for samples No.1 and No. 5) and with the carrier solution at 40 °C (for samples No.2, No.3, and No.4) using an anchor stirrer at 350 rpm for 30 minutes. Drying was performed in a drying oven at 40 °C under vacuum conditions reaching a vacuum depth of −1 bar. After drying, the sample was milled and sieved.

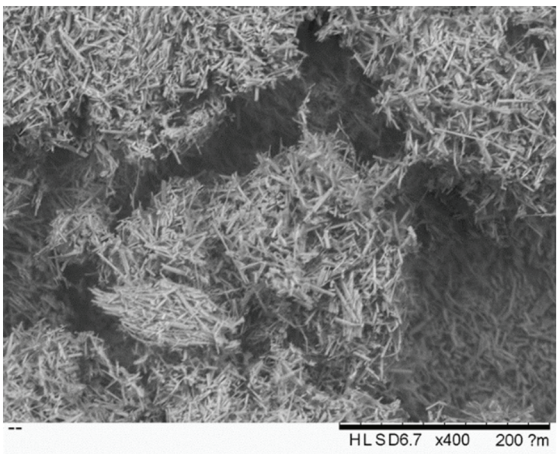

Fig. 1. Microscopic analysis of quercetin substance using SEM.

To select the optimal carrier and study the influence of the biopharmaceutical and physicochemical properties of quercetin, samples of solid dispersion of quercetin were prepared with a ratio of active pharmaceutical ingredient to carrier of 1:1.

3. Results and discussion

The most important parameters influencing the development and production of solid dosage forms are the physicochemical properties of substances, such as particle size, shape, surface microstructure, mechanical properties, and charge. Therefore, it is essential to first study the crystallographic properties of quercetin and its solid dispersions.

A microscopic study using SEM was conducted to identify morphological changes in the solid dispersions, and the results are illustrated in the accompanying images (Figs. 1,2).

According to the results of the microscopic study (Fig. 1), the quercetin substance is characterized by a high degree of particle agglomeration. The sample surface is covered with densely connected crystalline formations, which complicates the visualization of individual particles. The crystals are predominantly needle-shaped with variable lengths and small thicknesses, which is typical for this flavonoid. Aggregates composed of several interwoven crystals are also observed, making it difficult to achieve a uniform distribution of the substance in subsequent pharmaceutical forms. Such morphology may affect the technological properties of quercetin, particularly its solubility, release rate, and bioavailability.

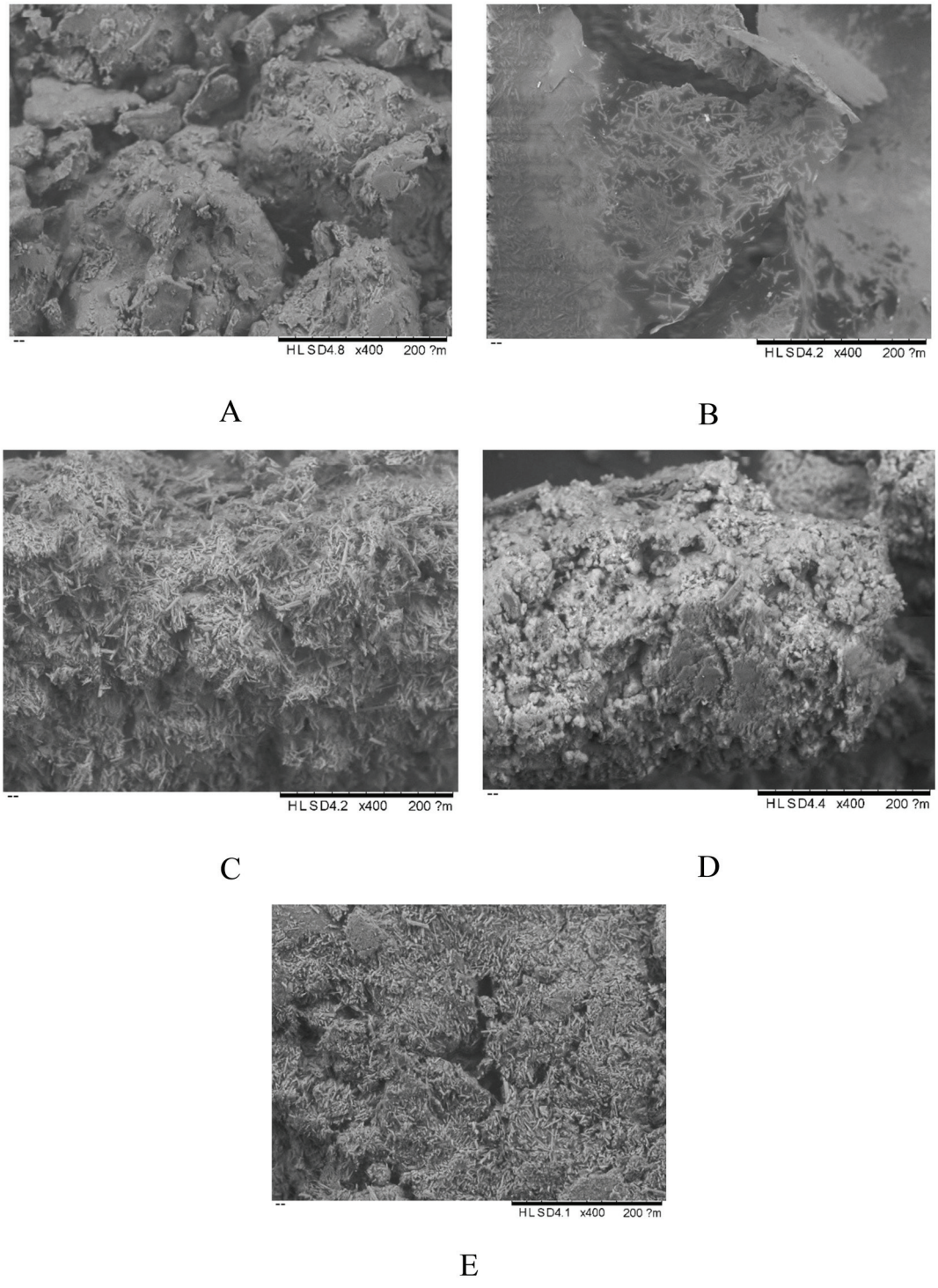

Fig. 2. Microscopic analysis of quercetin solid dispersions using SEM (sample A – No. 1, B – No. 2, C – No. 3, D – No. 4, E – No. 5).

Figs. 2A–E show the results of the microscopic analysis of quercetin solid dispersions, clearly demonstrating the uniform distribution of quercetin particles on the carrier surface. In sample No.2 (Fig. 2B), where HPMC was used as a carrier, a film formation around the substance particles is observed, indicating the gelling properties of the carrier. In sample No.4 (Fig. 2D), a homogeneous mass is formed, suggesting that quercetin is in a dissolved state. This morphology may be the result of complete or partial amorphization of the substance in the

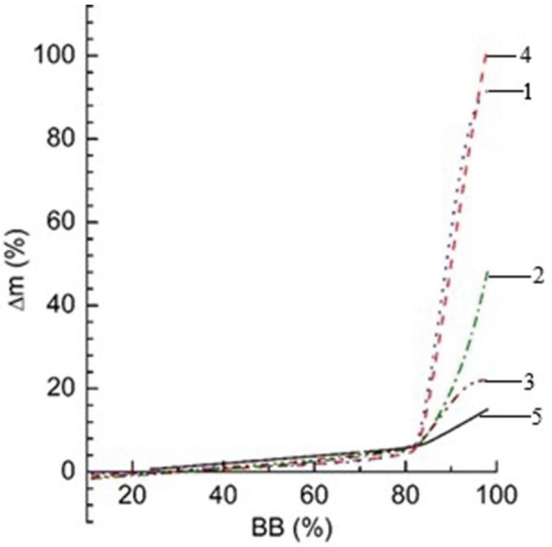

Fig. 3. Specific mass increase of samples No. 1–5 depending on the relative air humidity

presence of the respective carrier, namely PVP K30, which helps to improve the homogeneity of the composition and potentially its solubility. In all other cases, this phenomenon was not observed, except for sample No.5 (Fig. 2E), where, due to the amorphous state, dense clusters of cetostearyl alcohol with quercetin are formed, which may potentially slow the release of the active substance from the solid dispersion.

Subsequent analysis (Fig. 3) determined the mass gain of the solid dispersion samples. The carriers used were as follows: sample No.1 – PEG-4000, No.2 – HPMC, No.3 – mannitol, No. 4 – PVP K30, and No.5 – cetostearyl alcohol. Based on preliminary findings, quercetin was classified as a compound with low hygroscopicity [14]. The experimental results, reflecting the actual increase in sample mass as a function of relative humidity (RH), are presented in Fig. 3. As shown, the type of carrier has a significant effect on the equilibrium humidity, especially at relative humidity above 80%. The lowest moisture absorption was observed for sample No.5, while the highest values were recorded for samples No.1 and No. 4. Sample No.2 exhibited intermediate behavior. Notably, in sample No.1, at saturated vapor pressure, the equilibrium moisture content was comparable to the dry mass of the sample.

In Fig. 3, a sharp deviation of the sorption curves for the solid dispersions is clearly visible, indicating a change in the absorption surface associated with a change in the particle dispersion state. Samples No.1 and No.4 exhibit the highest hygroscopicity, which correlates with

Table 2. Hygroscopicity coefficient values of the samples.

Sample	Δm (%)	K (evaluation)
No.1	90	4.5
No.2	25	1.25
No. 3	70	3.5
No.4	110	5.5
No.5	15	0.75

a high degree of amorphization and improved solubility.

It was established that the sample with cetostearyl alcohol does not have a significant effect on solubility, making further investigation of its impact on the substances unnecessary.

Based on the determination of the increase in specific mass of the samples (Table 2), the hygroscopicity coefficient K was calculated using Eq. (2).

Thus, the improvement in solubility is closely associated with an increase in hygroscopicity, which serves as an indirect marker of API amorphization in the dispersions. Therefore, the high hygroscopicity of the studied samples is primarily due to the presence of hydroxyl groups that are not fully involved in intermolecular interactions. This, in turn, can serve as an indicator of the internal state of the solid dispersions and the degree of their compaction. The amount of adsorbed moisture under specific conditions depends on the structure of the carrier and the absorption mechanism accompanying the sorption process. Additionally, it is known that hygroscopicity increases with a decrease in particle size, which suggests that the particles of the solid dispersions are significantly smaller compared to the original substance.

The influence of high temperature can alter the structure of quercetin, which may cause certain difficulties in the formation of solid dispersions. Therefore, to determine the behavior of the substance during possible processes of crystallization, melting, or amorphous transformations, thermoanalytical studies and differential scanning calorimetry were carried out (Figs. 4, 5).

Fig. 4 demonstrates several characteristic thermal events. In the temperature range of 101.19–136.25 °C, a sample mass loss of 10.66% was observed (according to thermogravimetric analysis, TGA), which was accompanied by the appearance of a broad endothermic peak on the DSC thermogram starting at 121.02 °C. This is likely associated with moisture evaporation

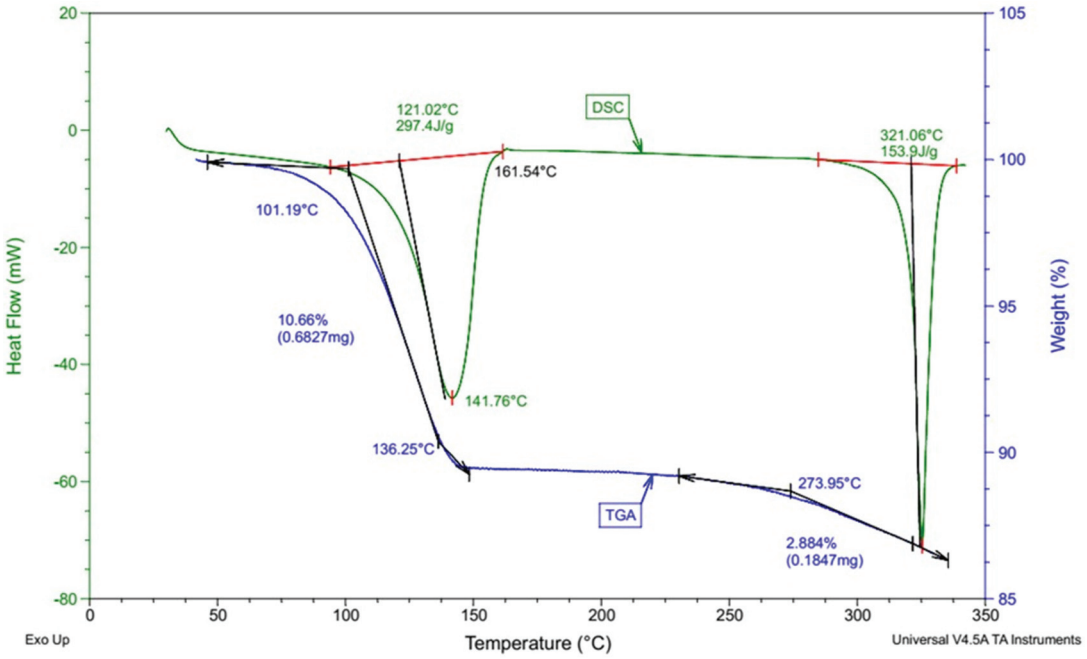

Fig. 4. Results of thermographic analysis of quercetin substance.

from the studied substance. The next event is thermal degradation, which begins at 273.95 °C according to TGA data. However, by the time the final scanning temperature was reached, the sample mass had decreased by only 2.88%, indicating the relative thermal stability of the main substance at this heating stage. The last recorded event is the melting of quercetin, manifested as a sharp endothermic peak on the DSC curve starting at 321.06 °C. The corresponding enthalpy of fusion is 153.9 J/g.

Thermogravimetric analysis revealed that the thermal stability of the excipients decreases in the following order: PEG 4000 > PVP K30 > mannitol > HPMC > cetostearyl alcohol. For PEG 4000, the most thermally stable among the studied samples, total mass loss over the entire scanning temperature range was only 0.72%. PVP K30 showed a mass loss of 6.14% in the range of 60.89–99.02 °C (likely due to thermal water loss, as PVP is highly hygroscopic), but by the end of the scan, the total mass loss was 8.48%, i.e., excluding dehydration – only 2.34%. Mannitol showed no signs of mass loss due to dehydration on its thermogravimetric curve, indicating that the substance is non-hygroscopic; the onset of thermal degradation was determined at 314.62 °C, with the degree of decomposition at the final temperature being 7.66%. HPMC exhibited two-step dehydration of 0.97% in the range of 61.56–78.73 °C and 2.59% in the range of 137.97–195.84 °C;

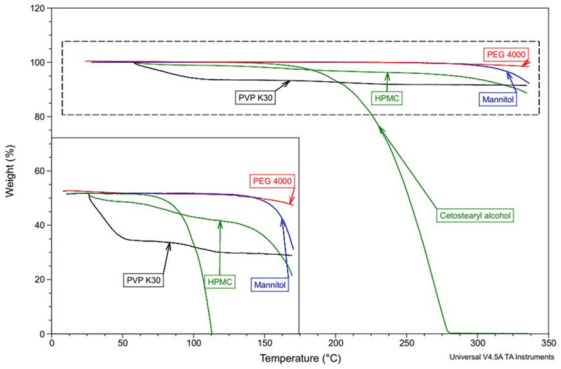

Fig. 5. Thermographic analysis results of quercetin solid dispersions.

the onset of decomposition can be considered to be a temperature of 288.20 °C, with the degree of decomposition at the final temperature being 7.72% (total mass loss in the scanning range is 11.26%). Cetostearyl alcohol undergoes complete thermal degradation, starting at 227.20 °C and ending at 278.72 °C. Therefore, when determining the enthalpy of melting of quercetin in solid dispersions by DSC, the cetostearyl alcohol will decompose before reaching the quercetin melting point.

Thus, all samples, except those based on cetostearyl alcohol, were analyzed by DSC to study the amorphization of quercetin in binary solid dispersions. The results showed that PEG 4000 and cetostearyl alcohol have the highest thermal stability among the studied substances and are recommended as the main carriers

Table 3. Determination of the degree of quercetin amorphization in dispersions with different carriers.

Sample number and composition	Quercetin melting		Amount of API in the amorphous state in the dispersion, %
	Enthalpy, J/g	T_{onset}	
No.1: quercetin (43.10%) + PEG 4000	25.36	252.62	26.63% (or 61.77% recalculated to 100% API)
No. 2: quercetin (53.19%) + HPMC	40.59	254.60	26.82% (or 50.42% recalculated to 100% API)
No. 3: quercetin (50.00%) + mannitol	25.47	247.01	33.45% (or 66.90% recalculated to 100% API)
No. 4: quercetin (50.00%) + PVP K30	5.760	265.61	46.28% (or 92.51% recalculated to 100% API)

for thermal methods (e.g., melting). PVP K30 and HPMC have limited thermal stability but can still be used in technologies that involve controlled or low heat (e.g., dissolution-drying). Mannitol exhibits moderate stability and can be employed under certain conditions, particularly for fast-dissolving formulations.

To assess the effectiveness of different excipients in creating an amorphous state of quercetin, four solid dispersion samples were studied, differing in both composition and the content of the API. The calculation of the amount of crystalline and amorphous forms of the API by the DSC method was based on a comparison of the enthalpy of melting of the sample with the enthalpy of 100% crystalline form. This made it possible to quantitatively assess the degree of crystallinity and, accordingly, the proportion of the amorphous phase (Table 3).

In sample No.1, the melting enthalpy was 25.36 J/g with Tonset =252.62 °C. It was determined that 26.63 % of the API is in the amorphous state, corresponding to 61.77% amorphization when recalculated to 100% API. The use of PEG-4000 provides moderate stabilization of the quercetin amorphous form, likely due to the formation of hydrogen bonds between the components. This result is associated with partial dissolution of quercetin in the carrier, forming a solid solution or molecular dispersion.

Sample No.2 is characterized by an enthalpy of 40.59 J/g and Tonset= 524.60 °C. The amorphous fraction of the API in the dispersion is 26.82%, corresponding to 50.42% when recalculated to 100% API. Despite the high enthalpy, the efficiency of amorphization was somewhat lower, which may be due to the more pronounced crystallinity of the polymeric carrier itself.

Sample No.3 shows a melting enthalpy of 25.47 J/g and the lowest Tonset=247.01 °C among all samples. The amorphous fraction is 33.45% (66.90% recalculated to 100% API), indicating the better ability of mannitol to inhibit quercetin crystallization, likely through the creation of a partial mechanical barrier at the molecular level, possibly due to physical freezing of the structure or favorable interactions with the API.

Sample No.4 is characterized by the lowest melting enthalpy – 5.76 J/g, which is an indicator of a significant reduction in the crystalline fraction. Tonset = 265.61 °C is the highest among all samples. The amorphous form of quercetin reaches 46.28% in the sample, corresponding to 92.51% when recalculated to 100% API. These data indicate the high efficiency of PVP K30 as a carrier for forming the amorphous state of quercetin, probably due to the ability of polyvinylpyrrolidone to form strong hydrogen bonds with the hydroxyl groups of the API and its high dispersing capacity.

Thus, the results of the thermal analysis showed that the type of excipient significantly affects the degree of quercetin amorphization in solid dispersions (Fig. 6).

The highest level of quercetin amorphization was achieved in the sample with polyvinylpyrrolidone (No.4), where the amorphous phase reaches 92% when recalculated to 100% API. This indicates a high affinity of PVP K30 for quercetin and the presence of molecular interactions that inhibit crystallization. High enthalpy values and a low percentage of the amorphous phase in the samples with PEG-4000 and HPMC (No.1 and No.2, respectively) indicate less effective amorphization. PEG-4000 occupies an intermediate position and can be recommended when combined properties (solubility + stability) are desired. Mannitol in sample No.3 also demonstrated intermedi-

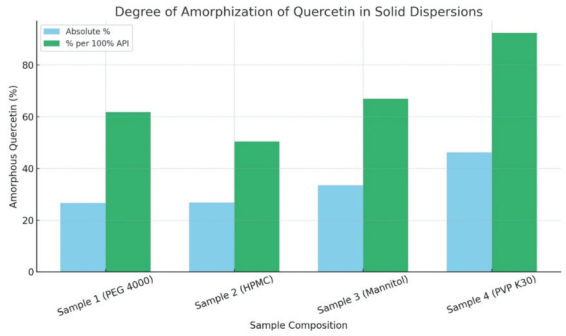

Fig. 6. Degree of quercetin amorphization in solid dispersions.

ate effectiveness but is inferior to PVP K30 in stabilizing the amorphous phase. The obtained data can be used in the development of quercetin solid dispersions with improved bioavailability and stability.

Next, X-ray structural analysis of quercetin and its solid dispersions was performed, the results of which are consistent with the previous thermographic studies (Figs. 7–8).

X-ray structural analysis of quercetin (Fig. 7) showed that the studied samples have an ordered crystalline structure, which is essential for its further use in pharmaceutical formulation technology. The obtained data can also be used for the identification or comparison of quercetin modifications, including nanocrystalline or amorphous forms.

X-ray structural analysis of the quercetin – PEG 4000 mixture (Fig. 8A) showed a decrease in the intensity of characteristic quercetin peaks, especially in the $2\Theta \approx 14–27°$ range, indicating a partial loss of crystalline structure. Instead of sharp, narrow peaks, a broad signal with reduced intensity is observed, suggesting the formation of an amorphous or partially amorphous phase in the presence of PEG-4000. This confirms the ability of the polymer to molecularly disperse the active substance due to possible intermolecular interactions.

In the case of the mixture with HPMC (Fig. 8B), the intensity of the main quercetin peaks is significantly reduced, and the background is leveled over a wide angular range. This indicates a partial transition to the amorphous state, probably caused by the formation of hydrogen bonds between HPMC molecules and quercetin. Such interactions reduce the crystallinity of the substance, which is important for improving its solubility.

Analysis of the quercetin–mannitol mixture (Fig. 8C) shows that individual crystalline peaks of both components are retained in the

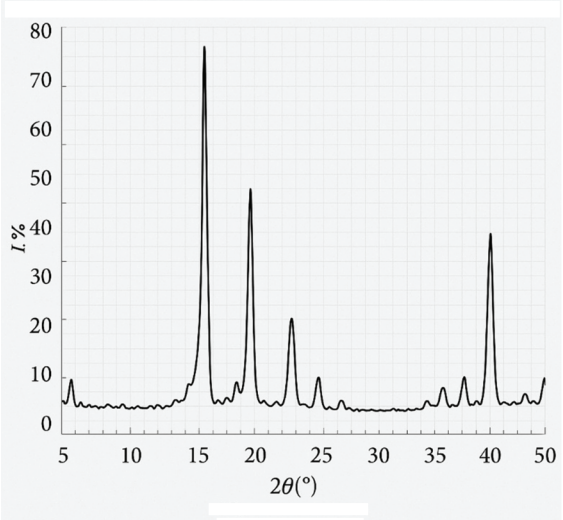

Fig. 7. X-ray structural analysis of quercetin.

range $2\Theta = 14–24°$, although some overlapping of the signals is noted. Despite the presence of characteristic mannitol peaks, the quercetin signal intensity decreases, which may indicate physical interaction or an initial stage of solid dispersion formation. The absence of new peaks indicates no chemical interaction between the components.

In the case of the sample with PVP K30 (Fig. 8D), the crystalline peaks of quercetin almost completely disappear, being replaced by a broad amorphous halo signal characteristic of unstructured systems. This indicates effective amorphization of the substance in the presence of PVP, probably due to the formation of hydrogen bonds between the components. This effect positively influences quercetin bioavailability.

Thus, based on the results of the X-ray structural analysis, it can be concluded that the highest degree of amorphization is achieved using PVP K30, whereas other carriers (PEG-4000, HPMC, mannitol) exhibit moderate or partial effects. These results confirm the effectiveness of solid dispersions in enhancing the bioavailability of poorly soluble substances, including quercetin.

The next stage involved quantitative determination using spectrophotometry with a standard. The solubility of quercetin as a biopharmaceutical substance was assessed by shaking single doses of quercetin (25 mg and 50 mg).

The standard quercetin solution was prepared as follows: a 0.050 g sample of quercetin reference substance (RS) was placed into a 100 ml volumetric flask, 70 ml of 96 % ethanol was added, the mixture was stirred until dis-

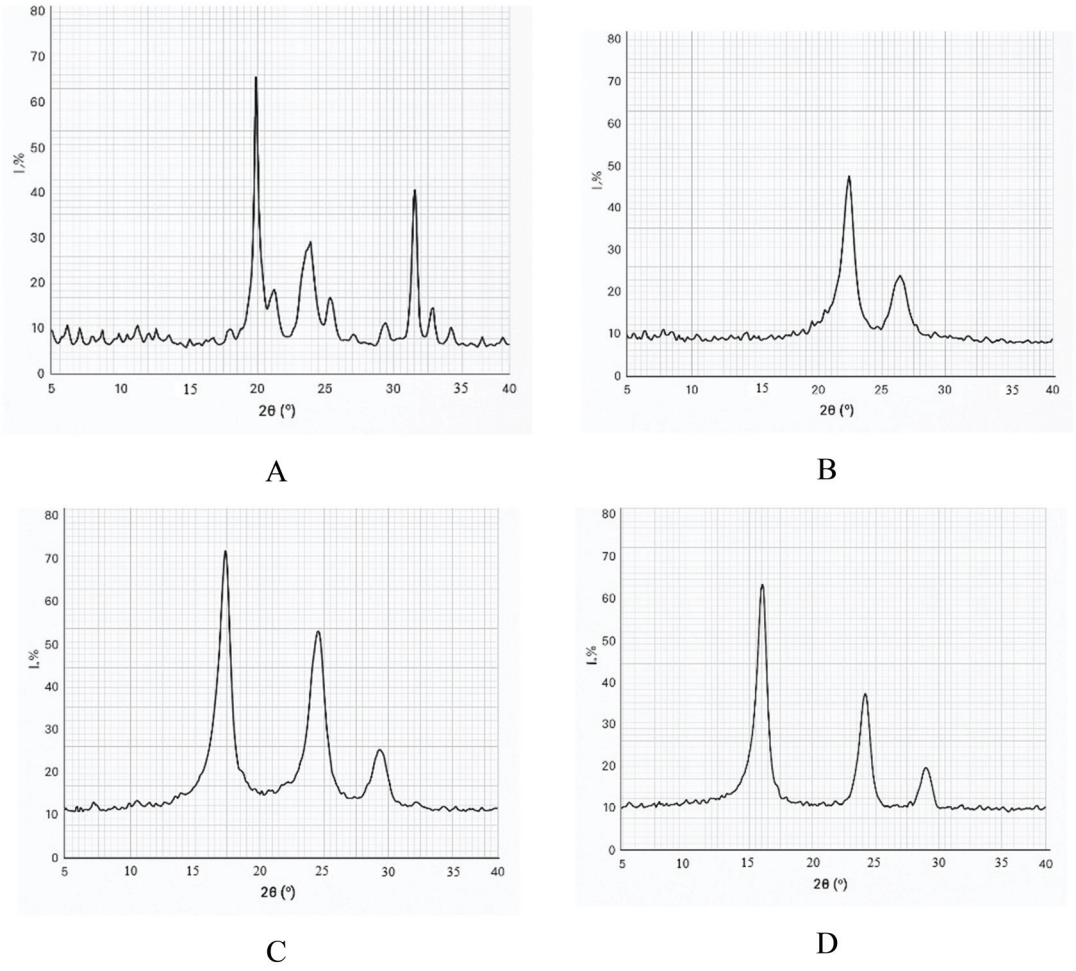

Fig. 8. X-ray structural analysis of quercetin SD with carriers (sample A – No. 1, B – No.2, C – No.3, D – No.4).

solved, and the volume was brought up to the mark with the same solvent (solution A). Then, 1 ml of solution A was transferred to a 50 ml volumetric flask and diluted to the mark with buffer solution at pH 1.2 or 6.8.

The optical density of the obtained solutions was measured using an Evolution 60S spectrophotometer in cuvettes with a path length of 10 mm at the absorption maximum (λ_{max}) of 367 nm. A buffer solution with pH 1.2 or 6.8 was used as the reference solution.

Spectral characteristics of quercetin were initially determined, and its analytical absorption band was established. The absorption spectra of quercetin solutions in the corresponding buffer media were recorded, within the wavelength range of 220 – 440 nm. The obtained results are presented in Fig. 9.

The absorption maximum of the tested quercetin RS solution in a buffer solution at pH 1.2 is observed at a wavelength of 251 nm, which is characteristic of flavonoids. In the range of

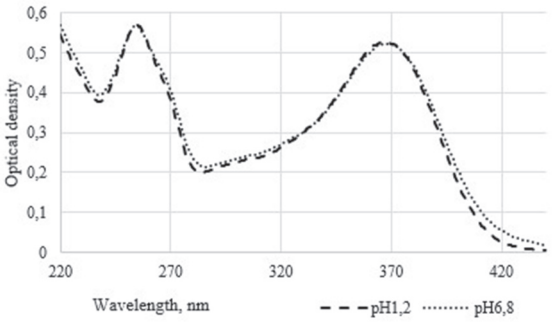

Fig. 9. Absorption spectrum of the tested quercetin solution RS in buffer solutions at pH 1.2 and 6.8.

252 – 280 nm, a decline in the absorption spectrum is noted, with a secondary maximum at 354 nm, typical for aromatic compounds. This band is quite specific and meets all requirements for an analytical absorption band; therefore, it is suitable for further quantitative determination of quercetin in solution in the absence of other components that could interfere with the over-

Table 4. Optical density (A) values as a function of quercetin concentration in a buffer solution with pH 1.2.

Sample number	1	2	3	4	5	6	7	8	9	10
C·10^{-3}, %	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0
A	0.111	0.224	0.331	0.439	0.548	0.659	0.767	0.875	0.987	1.116
$A_{1cm}^{1\%}$	0.555	0.56	0.551	0.548	0.548	0.549	0.547	0.546	0.548	0.558

all result. The absorption spectrum of the tested quercetin RS solution in a buffer solution at pH 6.8 is similar to that in the pH 1.2 buffer, though it is less pronounced. Thus, the spectra of quercetin solutions in buffer solutions at pH 1.2 and 6.8 exhibit a long-wavelength band with a strong maximum at 251 nm, which can be used for further analysis of quercetin concentrationin in these buffer solutions.

A key requirement for the application of spectrophotometric methods for the determination of substances is that the optical absorption of the solution must obey the Beer–Lambert–Bouguer law. To determine this, the optical density of the obtained quercetin solutions was measured at a wavelength of 367 nm. The results are presented in Fig. 10 and Table 4.

The effect of different carriers on the dissolution of the active pharmaceutical ingredient from solid dispersions was assessed using spectrophotometric analysis. The quercetin content in the solution was measured over 24 hours in model media with pH 1.2 (simulating gastric juice) and pH 6.8 (simulating intestinal conditions) to assess the efficiency of carriers in enhancing solubility and the release rate of the API. Based on the obtained spectrophotometric data, biopharmaceutical parameters such as the dose number and the dose-to-solubility ratio were calculated (Figs. 11, 12), allowing the identification of the most promising quercetin delivery systems for further development of oral dosage forms.

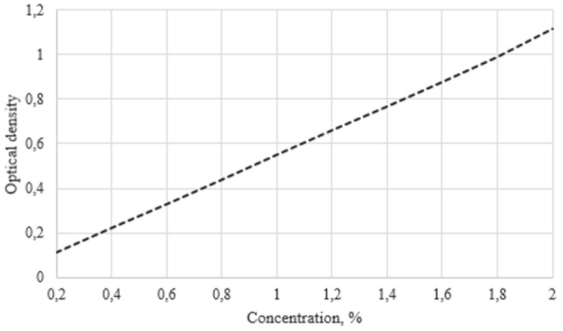

Fig. 10. Calibration curve showing the dependence of the optical density (A) of quercetin solutions on concentration in a buffer solution with pH 1.2.

Table 5 presents the results of the determination of biopharmaceutical parameters of quercetin and its solid dispersions at pH 1.2 and 6.8. For each sample, the dose number (D_0) was determined, reflecting the ratio between the drug dose and its solubility, as well as the equilibrium solubility (S_i), which characterizes the concentration of the substance in solution after establishing dynamic equilibrium.

It was established that at pH 1.2, quercetin exhibits extremely low solubility

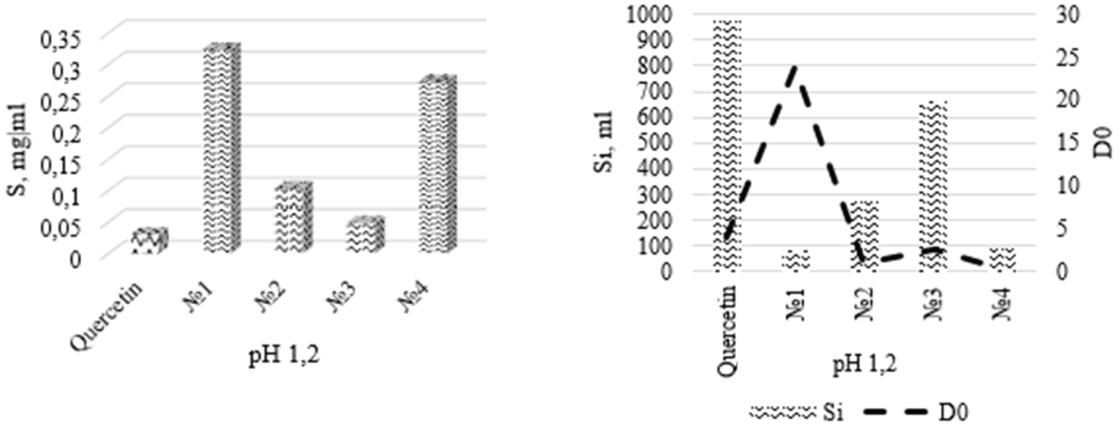

Fig. 11. Solubility parameters, dose-to-solubility ratio, and dose number of quercetin and its SD at pH 1.2.

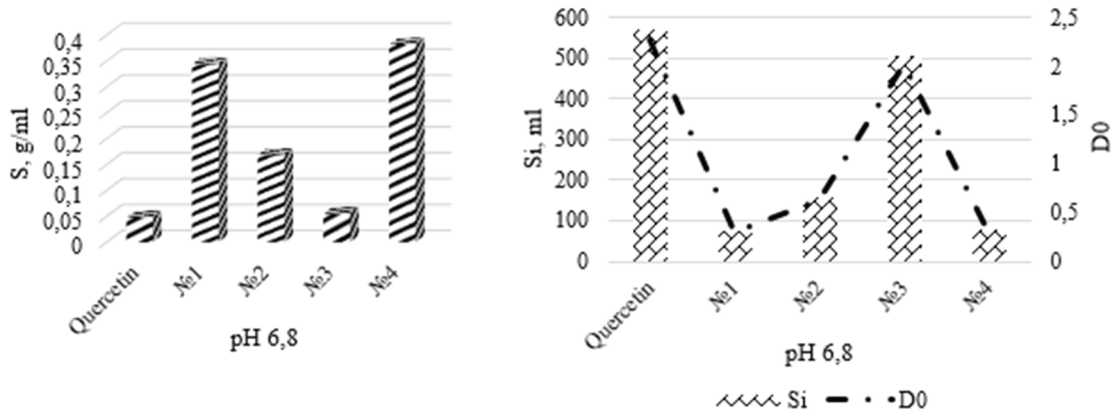

Fig. 12. Solubility parameters, dose-to-solubility ratio, and dose number of quercetin and its solid dispersions at pH 6.8.

Table 5. Biopharmaceutical solubility parameters of quercetin-containing mixtures.

Coefficient	D_0	S_i	S	D_0	S_i	S
pH	1.2			6.8		
Quercetin	3.88	971.08	0.03	2.28	570.017	0.048
Sample No.1	23.82	85.83	0.32	0.30	73.67	0.34
Sample No.2	1.08	270.75	0.10	0.63	157.75	0.17
Sample No.3	2.64	660.33	0.05	0.02	504.17	0.06
Sample No.4	0.37	91.92	0.27	0.31	77.00	0.38

(S = 0.03 mg/ml). Incorporation of quercetin into SD significantly increases this parameter. The highest solubility values were observed for samples No.1 (S = 0.32 mg/ml) and No.4 (S = 0.27 mg/ml), indicating the effectiveness of these carriers. Sample No.2 provides moderate solubility (S = 0.10 mg/ml), while sample No.3 shows only a slight increase in solubility (S = 0.05 mg/ml).

Quercetin demonstrates a high dose-to-solubility ratio (S_i = 971.08 ml) but has a dose number D_0 = 3.88, indicating limited potential for complete dissolution in the stomach. Among the SD samples, samples No.2 and No.4 were more effective (D_0 = 1.08 and D_0 = 0.37 respectively), reflecting an improved dissolution ability under gastric conditions. Sample No. 4 is particularly promising, as it combines moderate solubility with the lowest number of doses in a given environment. Samples No.1 and No.3 have higher dose numbers, limiting their effectiveness in gastric-soluble formulations.

Quercetin at pH 6.8 shows only a slight increase in solubility (S = 0.048 mg/ml). The highest solubility was observed for sample No.4 (S = 0.38 mg/ml), with slightly lower values for sample No.1 (S = 0.34 mg/ml). Samples No.2 and No. 3 exhibited low solubility S = 0.17 mg/ml and 0.06 mg/ml, respectively.

Under these conditions, quercetin has a dose number of 2.28, which is higher than the recommended level for complete dissolution. Among the solid dispersions, the best results were observed for sample No.3 (S_i = 504.17 ml) with an exceptionally low dose number (D_0 = 0.02). Samples No. 1, No.2, and No.4 also showed low dose numbers (D_0 =0.30; 0.63 and 0.31 respectively), indicating a favorable dose-to-solubility ratio and potentially high bioavailability.

Thus, the development of SD represents an effective strategy for enhancing the biopharmaceutical solubility of quercetin. Particularly promising in terms of dose efficiency are samples No.3 (targeted for intestinal conditions) and No.4 (targeted for gastric conditions), which exhibit an optimal balance between solubility and dose number.

The obtained results can be used to justify the selection of carriers for the development of quercetin solid dispersions for oral administration.

4. Conclusions

It has been shown that quercetin in its native form exhibits limited bioavailability due to high crystallinity, particle agglomeration, and

low solubility. To improve its pharmaceutical properties, the use of solid dispersions with polymeric carriers is advisable, as they can promote amorphization of the substance and enhance its solubility.

Microscopic, thermal, X-ray diffraction, and spectrophotometric studies confirmed the formation of an amorphous phase, changes in particle morphology, and improved hygroscopic properties of the SDs. These changes have been shown to result from the formation of intermolecular interactions between the API and the carriers, which contributes to increased bioavailability of quercetin.

Polyvinylpyrrolidone K30 is proposed as the most effective carrier, providing a high degree of amorphization and significant solubility enhancement at pH 1.2.

The use of PEG-4000 and mannitol promotes partial amorphization, but their effects are less pronounced compared to PVP K30. Cetostearyl alcohol was found to be the least suitable carrier due to its thermal instability and tendency to form dense agglomerated complexes, which slow down the release of the API.

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