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Griseofulvin: Thermodynamic insight to solubility, solvation and partition processes

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Abstract−The solubility of griseofulvin in buffer solutions (pH 2.0 and 7.4), 1-octanol and hexane was measured in the temperature range 293.15-313.15 K by the shake flask method. It was found that griseofulvin is poorly soluble in aqueous buffer solutions ($x \leq 8.63 \cdot 10^{-7}$), while the best solubility is observed in 1-octanol ($x \leq 6.56 \cdot 10^{-4}$). The solubility evaluation in different solvents with the help of Hansen solubility parameters showed the consistency with the experimental data. The solubility was revealed to significantly depend on the dispersion interactions and polar bonds. The dissolution and solvation thermodynamic functions of the drug were calculated. The Gibbs energy and enthalpy of drug dissolution in aqueous and organic solvents are positive, which characterizes the dissolution process as hindered and endothermic. The van't Hoff and Apelblat equations gave good correlations when used for modeling the experimental solubility results. Based on the data on the solubility and thermophysical parameters of the compound, the temperature dependences of the activity coefficients were determined and the excess thermodynamic functions of dissolution were calculated. Positive deviation from ideality was observed in all the solvent-solute systems studied. The partition coefficients of the drug in the 1-octanol/buffer pH 7.4 system were obtained and the transfer thermodynamic functions were derived. It was established that the drug distribution from the aqueous solution to the octanol phase was thermodynamically favorable and endothermic.

Keywords: Griseofulvin, Solubility, Solvation, Activity Coefficients, Partition, Thermodynamics

INTRODUCTION

Griseofulvin ((2*S*,5′*R*)-7-chloro-3′,4,6-trimethoxy-5′-methylspiro-[1-benzofuran-2,4′-cyclohex-2-ene]-1′,3-dione) is an important bioactive compound with a broad spectrum of pharmacological applications due to its antifungal and fungistatic properties (the structural formula is given in Fig. 1). As a low-toxic systemic antibiotic, griseofulvin is used to treat a variety of fungal diseases, including skin and hair conditions [1]. As a fungistatic compound, it is active against dermatophyte fungi with a chitin cell wall [2].

Griseofulvin, one of the first natural antifungal drugs, is an antibiotic produced by molds of *Penicillium nigricans* (*griseofulvum*). First obtained in 1939 it was used to treat fungal infections of plants. It began to be applied in medical practice only in 1958 to treat dermatomycoses in humans [3]. Over 400 griseofulvin analogues have been synthesized since then. In the last few years, compounds of this class have come into the focus of scientific attention again due to the discovery of griseofulvin anticancer activity. Griseofulvin was found to increase the antitumor effect of the nocodazole preparation causing apoptosis in several cancer cell lines when introduced in concentrations up to 1 mM [4].

In accordance with the BCS classification, griseofulvin is a II class preparation with low solubility and high permeability. Because of the poor solubility in the gastro-intestinal tract, the bioavailability of griseofulvin is only 30-70%. It means that increasing the GF solubility is the first critical aspect of the drug adsorption and bioavailability improvement.

Solubility, solvation and distribution drugs in studied solvents simulating physiological fluids are the most important physicochemical properties needed to improve existing formulations and develop new ones. A large amount of data have been accumulated on the griseofulvin solubility by now. However, the solubility experiments were largely carried out in water of an indefinite pH value, so the data varied from 8.64 mg/L [5,6], 15.6 mg/L [7] to 29.9 mg/L [8]. Only a few works focused on the GF solubility in buffer solutions. Hamdy et al. [9] reported that the solubility of GF at pH 1.2 and pH 6.8 was 12.32 and 12.37±0.26 μg/ml, respectively, and Alvarez-Lorenzo et al. [10] indicated solubility of GF at pH 1.2, 5.8 and 7.4 as 4.0, 7.8, 7.5 mg/100 ml, respectively. At the same time, there is a limited amount of data on the griseofulvin solubility and its thermodynamic aspects in different organic solvents. For example, in the works of Guoqin Hu et al. [11] and Shaolei Zhao et al. [12] the GF solubility was measured in alcohols, esters and nitriles. However, there are no data on the GF solubility in solvents, such as 1-octanol and hexane used to model drug partition between biological tissues and permeability through lipophilic membranes. Thermodynamic parameters are useful not only for determining the driving forces of the dissolution, solvation and partition processes, but also for selecting the optimal solubility improvement approaches. Of special interest for determining solvent effects on substance dissolution are the thermodynamic characteristics of solvation. Solvation largely influences solubility, partitioning behavior, absorption properties, active and passive transport properties, and biodegradation. Besides, thermodynamic ideal solubility of a dissolved substance can be used as the

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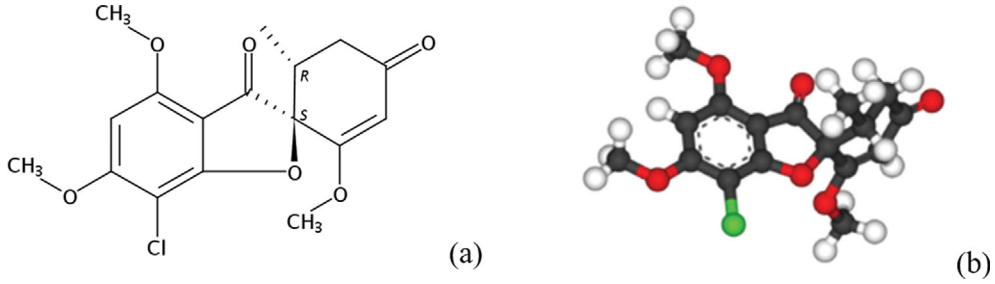

Fig. 1. Chemical structure: (a) and three-dimensional presentation (b) of griseofulvin (GF).

Table 1. Detailed information of the chemicals used in the experiments

Chemical name	CAS register No.	Formula	M/g mol^{-1}	Source	Mass fraction purity[a]
Griseofulvin	**126-07-8**	C_{17} H_{17} Cl O_6	352.77	TCI Co., Ltd	≥0.98
1-Octanol	111-87-5	$C_8H_{18}O$	130.2	Sigma-Aldrich	≥0.99
Hexane	110-54-3	C_6H_{14}	86.18	Sigma-Aldrich	≥0.97
Potassium dihydrogen phosphate	7778-77-0	KH_2PO_4	136.08	Merck	≥0.99
Disodium hydrogen phosphate dodecahydrate	10039-32-4	$Na_2HPO_4{\cdot}12H_2O$	358.14	Merck	≥0.99
Potassium chloride	7447-40-7	KCl	74.55	Sigma-Aldrich	≥0.99
Hydrochloric acid mol/dm^3 fixanal	7647-01-0	HCl	-	Sigma-Aldrich	None

[a]As stated by the supplier

first approximation of solubility, which is equal for all solvents [13].

In this work, we obtained temperature dependence of griseofulvin solubility in buffer solutions (pH 2.0 and 7.4) imitating various physiological media of the gastro-intestinal tract. Moreover, for the first time, temperature dependence was measured of griseofulvin solubility in 1-octanol that is often used in pharmaceutical chemistry to model the amphipathic properties of biological membrane lipids and in the inert solvent hexane as a component of the blood-brain barrier medium and also partition coefficients in 1-octanol/buffer pH 7.4 system widely applied in pharmaceutics to evaluate the transport properties of drug compound.

In our work, we used the classic shake flask method, which is considered the "gold standard" for determining the thermodynamic solubility of biopharmaceutically relevant drugs. The experimental solubility data were also correlated by two thermodynamic models including the modified Apelblat and the van't Hoff equations. In addition, thermodynamic functions (enthalpy, entropy and Gibbs free energy) of dissolution, solvation and partition of GF were calculated and discussed for the first time.

The physicochemical and thermodynamic properties of griseofulvin solutions obtained in this work will be useful for pharmaceutically important processes, formulation development and further theoretical studies.

EXPERIMENTAL SECTION

1. Chemicals Information

Detailed information about all the chemicals used in this study is listed in Table 1. Bidistilled water (with electrical conductivity of 2.1 μS cm^{-1}) was used to prepare the buffer solutions. Phosphate buffer pH 7.4 (I=0.15 mol·L^{-1}) was prepared by combining the $KHPO_4$ (9.1 g in 1 L) and $NaH_2PO_4{\cdot}12H_2O$ (23.6 g in 1 L) salts. For the preparation of the buffer solution pH 2.0 (I=0.10 mol·L^{-1}) 6.57 g of KCl were dissolved in water, 119.0 mL of 0.1 mol·L^{-1} hydrochloric acid were added and the volume of the solution was adjusted to 1 L with water. The pH values were measured by using an FG2-Kit pH meter (Mettler Toledo, Switzerland) standardized with pH 1.68, 6.86 and 9.22 solutions. All the other chemicals and reagents were of analytical grade.

2. Equilibrium Solubility Determination

The solubility of the compound was measured using the standard shake flask method at five temperatures from 293.15 to 313.15 K with an uncertainty of ±0.15 K. The essence of this method is to determine the concentration of a compound in a saturated solution. Glass vials with the drug and the selected solvent were placed in an air thermostat and rotated for 20-24 h until equilibrium between the solute and solvent was reached. The equilibrium time was determined from the kinetic dependence of the solubility of GF in all the studied solutions.

The saturated solutions were settled in a thermostat within 6 h and then were centrifuged using a thermostatic centrifuge Biofuge Stratos (Germany) at the appropriate temperature of experiment for 20 min at 8,000 rpm. The solid phase was removed by filtration using a filter MILLEX®HA 0.22 μm (Millipore, Ireland).

The mole fraction concentration was calculated based on molarity (S, mol·L^{-1}) using Eq. (1):

$$x = \frac{M_s S}{S(M_2 - M_1) + 1000\rho}, \quad (1)$$

where M_1 and M_2 are the molar masses of solute and solvent, respectively, and ρ (g·cm^{-3}) is the density of the pure solvents. Densities of buffers solutions (pH 2.0 and 7.4) were measured using densitometer DMA 4500 (Anton Paar, Austria) and published earlier [14]. The values of densities used for conversion are given in Table S1 (Supporting Information).

The temperature dependencies of drug solubilities within the chosen temperature interval can be described by the linear function:

$$\ln x = A - B/T \quad (2)$$

The standard Gibbs energies of the dissolution processes ΔG^0_{sol} were calculated using the following equation:

$$\Delta G^0_{sol} = -RT\ln x \quad (3)$$

where x is the drug molar fraction in the saturated solution. The standard solution enthalpies ΔH^0_{sol} were calculated using the van't Hoff equation:

$$\frac{\partial(\ln x)}{\partial T} = \frac{\Delta H^0_{sol}}{RT^2} \quad (4)$$

The standard solution entropies ΔS^0_{sol} were obtained from the well-known equation:

$$\Delta G^0_{sol} = \Delta H^0_{sol} - T\Delta S^0_{sol} \quad (5)$$

3. UV-VIS Spectroscopy

UV-VIS spectra were recorded on a Cary 50 (Varian) spectrophotometer between 190 and 400 nm by using a 1 cm quartz cell at room temperature. The saturated solution, if necessary, was diluted with an appropriate solvent and examined on a spectrophotometer in the ultraviolet region of the spectrum with an accuracy of 2-4%. The solubility experimental results were reported an average value of three replicated experiments. The absorption maximums for griseofulvin in the selected solvents were determined at 292 nm. The calibration procedure was carried out at room temperature using the solutions with known concentrations of drug in selected solvents.

4. Prediction of Solubility Parameters

The basis of the nonelectrolyte solubility theory is Hildebrand's works [15,16], where the author proposed solubility parameter δ for predicting the solubility of a substance in a given solvent. The substance Hildebrand solubility parameter is equal to:

$$\delta = \left(\frac{\Delta_{vap}E_m}{V_m}\right)^{0.5} \quad (6)$$

where $\Delta_{vap}E_m$ - the molar energy of evaporation at zero pressure, V_m - the molar volume of the substance [17].

Hildebrand's theory is mainly based on the behavior of hydrocarbon solvents and cannot accurately predict the efficiency of other solvents or their mixtures. To increase the prediction capacity, the solubility parameter was complemented with summands describing individual types of solute-solvent interactions. And a solubility parameter taking into account the contributions of the dispersion (δ_d) and polar (δ_p) interactions for polar solvents was also suggested [18]:

$$\delta^2 = \delta_d^2 + \delta_p^2 \quad (7)$$

Hansen [19] introduced the notion of hydrogen bonds into nonelectrolyte solubility studies and defined cohesion energy (E) as a sum of dispersion energies (E_d), polar (E_p) interactions and hydrogen bonding energy (E_h):

$$E = E_d + E_p + E_h \quad (8)$$

This became the basis for the so-called Hansen 3D solubility parameter taking into account the contributions of three types:

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (9)$$

where δ_t - Hansen solubility parameter, δ_h - contribution associated with the formation of hydrogen bonds.

The Hansen parameters are quantitatively determined by the following formulae:

$$\delta_d = \Sigma E_{di}/\Sigma V_i \quad (10)$$

$$\delta_p = (\Sigma E_{pi}^2)^{0.5}/\Sigma V_i \quad (11)$$

$$\delta_h = (\Sigma E_{hi}/\Sigma V_i)^{0.5} \quad (12)$$

According to Hildebrand, the similarity (or difference) between two substances is characterized by one number - difference between their solubility values. According to Hansen, every substance is represented by a point in the 3D space with its coordinates equal to the calculated values δ_d, δ_p, δ_h. Then the substance similarity is characterized by the distance between the points, i.e., by three coordinate differences. The 3D Hansen solubility parameter is more sensitive to the nature of the substances to be compared and better agrees with the experimental data for a broad range of solvents, including alcohols. It can be used to explain and predict solubility in solvent mixtures, where the Hildebrand solubility parameter is the least effective. In practice, pharmaceutical scientists are interested in solubility and drug-polymer, polymer-solvent and drug-solvent interactions. This has led to the development of several approaches based on the solubility parameters otherwise known as "like dissolves like". Thus, van Krevelen-Hoftyzer introduced a new solubility parameter, $\Delta\delta_t$, for explaining the miscibility of two materials based on the difference between their common solubility parameters [20]:

$$\Delta\delta_t = \delta_{t1} - \delta_{t2} \quad (13)$$

where indices 1 and 2 refer to the solute and solvent, respectively.

Two components are considered miscible if $\Delta\delta_t \leq 7.0$ MPa$^{0.5}$ and immiscible if $\Delta\delta_t \geq 10.0$ MPa$^{0.5}$. However, to fully understand the interaction between the two components, it is extremely important to divide $\Delta\delta_t$ into individual terms (δ_d, δ_p and δ_h). Determination of these individual solubility parameters is the main limitation of this approach [21]:

$$\Delta\delta = ((\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{h1} - \delta_{h2})^2)^{0.5} \quad (14)$$

Ideally, miscibility is taken into account for a solution containing a constant amount of a dissolved substance. Besides, Bagley established a new conceptual thermodynamic connection between δ_d and δ_p and introduced a combined solubility parameter δ_v [22]:

$$\delta_v = (\delta_d^2 + \delta_p^2)^{0.5} \quad (15)$$

This equation can be used to project the 3D solubility parameter space onto a 2D space by plotting graphs δ_v and δ_h called Bagley plot. The degree of miscibility or solubility of two substances can be evaluated based on the distance between them on the Bagley plot. Thus, R_a is the solubility indicator calculated by the formula:

$$R_{a(v)} = (4(\delta_{v2} - \delta_{v1})^2 + (\delta_{h2} - \delta_{h1})^2)^{0.5} \quad (16)$$

5. Computational Models for Solubility Correlation

The GF solubility in pure solvents was correlated by the thermodynamic models described below.

5-1. Modified Apelblat Equation

The modified Apelblat equation is an effective method of predicting the concentration of an organic compound in saturated solutions. The modified Apelblat equation can be used if the solution enthalpy is assumed to change linearly with temperature [23,24]. The model represents a semiempirical equation that can be expressed as follows:

$$\ln x = A + \frac{B}{T/K} + C\ln(T/K) \quad (17)$$

where x is the GF mole fraction in the solution, the values of coefficients A, B and C are extracted by approximating the experimental solubility data curve by the nonlinear optimization method [25], and T is the temperature in K.

5-2. van't Hoff Equation

The van't Hoff model is also widely applied to simulate the interrelation between the solubility of a compound in mole fraction and temperature. It is expressed as [26]:

$$\ln x = A + \frac{B}{T/K} \quad (18)$$

where x is the solute mole fraction, T is the absolute temperature, A and B are the empirical constants related to the enthalpy and entropy, respectively.

5-3. Data Correlation

The applicability and credibility of the correlation results in these models were assessed using the relative deviation (RD), average relative deviation (RAD) and root mean square deviation (RMSD) between the experimental and calculated solubility values of the compound studied.

The relative deviation (RD) of the predicted values from the experimental ones was calculated by the equation:

$$RD = (x_{exp} - x_{cal})/x_{exp} \quad (19)$$

The relative average deviation (RAD) was employed to assess the accuracy of the developed models:

$$RAD = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{x_{exp} - x_{cal}}{x_{exp}}\right| \quad (20)$$

The root-mean-square deviation (RMSD) are defined as:

$$RMSD = \left|\frac{1}{N}\sum_{i=1}^{N}(x_{exp} - x_{cal})^2\right|^{0.5} \quad (21)$$

where N represents the number of experimental points, x_{exp} and x_{cal} are the experimental and calculated mole fraction solubility values of the compound, respectively.

6. Ideal Solubility

The temperature dependence of solute solubility is described by the thermodynamic relationship [27]:

$$\ln x = \ln x^{id} - \ln\gamma = \frac{\Delta H_{fus}}{RT_{fus}}\left[\frac{T - T_{fus}}{T}\right] + \int_{T_{fus\,m}}^{T}\frac{\int_{T_m}^{T}(C_p^L - C_p^S)dT}{RT^2} - \ln\gamma \quad (22)$$

where x, x^{id}, γ, T_{fus}, ΔH_{fus}, $\Delta C_p = C_p^L - C_p^S$, R, and T represent the solubility mole fraction of the solute in solution, ideal mole fraction solubility of the solute, activity coefficient of the solute in solution, melting temperature of the solute, enthalpy of melting of the pure solute, differential molar heat capacity of the pure solute, gas constant and temperature, respectively. In the above-mentioned formula, C_p^L and C_p^S, represent molar heat capacities of the solute liquid and solid forms, respectively. After transformations, Eq. (22) has the following form:

$$\ln x^{id} = \frac{\Delta H_{fus}}{RT_{fus}}\left(1 - \frac{T_{fus}}{T}\right) + \frac{\Delta C_p}{R}\left[\frac{T_{fus}}{T} - 1 + \ln\left(\frac{T}{T_{fus}}\right)\right] \quad (23)$$

As the solubility or equilibrium mole fraction of compound in the solvents studied is very low, it is assumed that the last term in Eq. (22) denotes the infinite dilution activity coefficient $\ln\gamma^{\infty}$, which can be expressed as:

$$\ln\gamma^{\infty} = \frac{H^E}{RT} - \frac{S^E}{R} \quad (24)$$

where H^E and S^E represent the partial molar excess enthalpy, and the partial molar excess entropy, respectively, and are assumed to be temperature-independent.

7. Measurement of Partition Coefficients in System 1-Octanol/Buffer pH 7.4

The classical shake flask method was used to determine the partition coefficients ($P_{O/B}$) in 1-octanol/buffer pH 7.4 system at five temperatures from 293.15 to 313.15 K. The mutually saturated solvents were prepared by mixing buffer and octanol phases for two days at 25 °C. GF was dissolved in from 1-octanol saturated with a buffer in a glass flask. The solute concentration in the initial octanol phase was $1.62 \cdot 10^{-3}$ mol/L. Then saturated octanol with GF and saturated buffer pH 7.4 in a ratio by volume of 1 : 1 were placed in a glass tube and stirred for 24 hours. Compound concentrations were determined spectrophotometrically (Cary-50, USA) in the UV region of the spectrum (at λ=292 nm) with an accuracy of 2-4%. The reported experimental values are the average of at least three repeated experiments. Partition coefficients using the molar concentrations of the substance in both phases were calculated using the following equation:

$$P_{O/B} = s_O/s_B \quad (25)$$

where s_O and s_B are the molar concentrations of the compound in the 1-octanol and buffer phases, respectively.

The 1-octanol/buffer partition coefficients $P^*_{O/B}$ were calculated as the ratio of the equilibrium concentrations in the organic and aqueous phases expressed in mole fraction:

$$P^*_{O/B}=x_O/x_B \quad (26)$$

The standard Gibbs energy of transfer, $\Delta_{tr}G^o$, from the buffer to organic systems was calculated thus:

$$\Delta_{tr}G^o=-RT\ln P^*_{O/B} \quad (27)$$

The temperature dependence of distribution (van't Hoff method) was employed to obtain the enthalpy of transfer $\Delta_{tr}H^o$:

$$\frac{d(\ln P^*_{O/B})}{dT}=\frac{\Delta_{tr}H^o}{RT^2} \quad (28)$$

The entropy of transfer, $\Delta_{tr}S^o$, can be calculated from:

$$\Delta_{tr}S^o=(\Delta_{tr}H^o-\Delta_{tr}G^o)/T \quad (29)$$

The $\Delta_{tr}H^o$ and $\Delta_{tr}S^o$ quantities represent, respectively, the change in the enthalpy and entropy when one solute mole is transferred from the aqueous phase to the 1-octanol phase.

RESULTS AND DISCUSSION

1. Equilibrium Solubility Determination of GF

An analysis of the compound UV-spectrum in the considered solvents (Fig. 2) showed that griseofulvin has an absorption maximum at 292 nm, which indicates that the compound molecule has conjugated bonds. The spectrum also shows two shoulders at 235 and 332 nm associated with the π-π* and n-π* transitions in the GF aromatic part. The shoulder at 235 nm in the 1-octanol spectrum turns into a peak. Molecules of most drugs become ionized in aqueous solutions as they contain at least one acidic or basic functional group. That is why such molecules can exist in their neutral (uncharged) or ionized (charged) form, depending on the solution pH [28]. Although the molecule of the compound studied contains six acceptor groups, it is not ionized in aqueous solutions and exists in its neutral form, i.e., is pH-independent. This fact is confirmed by the same appearance of the GF UV spectra in aqueous buffer solutions of different pH values.

The griseofulvin solubility data obtained by the isothermal saturation method in buffer solutions of various acidity and organic solvents, expressed in molarity and mole fractions within the temperature range of 293.15-313.15 K are given in Table 2.

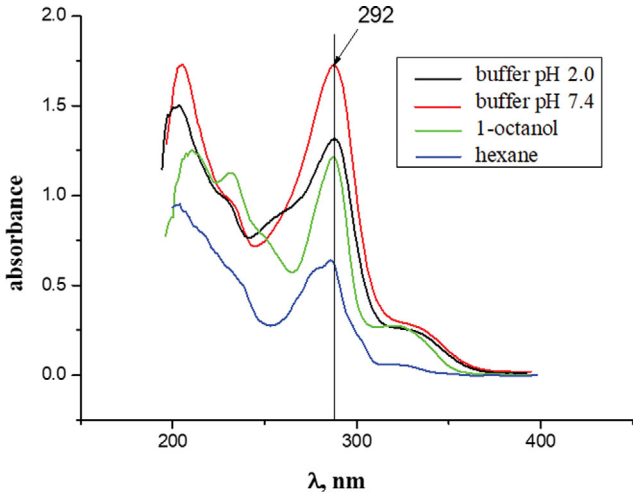

Fig. 2. UV-visible absorption spectra of GF in studied solvents.

Table 2. Temperature dependences of solubility (x, mol. frac. and S, mol·L^{-1}) of the GF studied in the selected solvents at pressure p=0.1 MPa

T/K	Buffer pH 2.0	Buffer pH 7.4	Hexane	1-Octanol
	x·10^7 (S·10^5)	x·10^7 (S·10^5)	x·10^6 (S·10^5)	x·10^4 (S·10^3)
293.15	5.33 (2.96)	6.27 (3.50)	3.16 (2.42)	2.69 (1.70)
298.15	6.20 (3.44)	6.99 (3.90)	4.16 (3.16)	3.34 (2.11)
303.15	7.17 (3.97)	7.81 (4.35)	5.59 (4.23)	4.15 (2.61)
308.15	8.34 (4.61)	8.63 (4.79)	7.30 (5.48)	5.20 (3.26)
313.15	9.58 (5.28)	9.62 (5.34)	9.42 (7.02)	6.36 (3.97)
A[a]	−5.25±0.05	−7.01±0.06	4.53±0.15	5.35±0.04
B[a]	2696±16	1959±19	5042±46	3981±38
R[b]	0.9999	0.9999	0.9999	0.9999
σ[c]	0.3·10^{-2}	0.2·10^{-2}	0.81·10^{-2}	0.6·10^{-2}

[a]Parameters of the correlation equation: lnx=A+B/T
[b]R - correlation coefficient
[c]σ - standard deviation
The standard uncertainties are u(m)=0.01 mg, u(T)=0.15 K and u(p)=3 kPa.

The experimental values show that the griseofulvin solubility in all the solvents becomes higher with temperature growth. The maximum temperature gradient of the GF solubility is observed in hexane. The griseofulvin solubility in the studied solvents increases over the whole temperature range as follows: buffer pH 2.0, buffer pH 7.4, hexane, 1-octanol.

Solubility is largely dependent on mutual competition between the solute-solvent and solvent-solvent interactions [29]. The strength of a solvent-solvent interaction is determined by cohesion energy density [30]. Higher cohesion energy density usually indicates a stronger interaction between the solvent molecules. In our case, the high cohesion energy density in water (2,096 J·mol·ml^{-1}) weakens the solute-solvent interaction and, as a result, reduces the solubility. Considerably lower values of the cohesion energy density for 1-octanol (282 J·mol·ml^{-1}) strengthens the interaction between the solvent and griseofulvin and improves the solubility. This fact indicates that the strength of the solvent-solvent interaction is the main factor determining the solubility.

The GF solubility in the buffer solutions at 298.15 K is almost the same and is equal to 3.44·10^{-5} mol·L^{-1} in buffer pH 2.0 and to 3.90·10^{-5} mol·L^{-1} in buffer pH 7.4 due to the absence of ionized molecules in the solutions of different acidity values. The GF solubility values obtained by us in buffer solutions are close to those from work [9]: 3.5·10^{-5} mol·L^{-1} in buffer pH 1.2 and 3.52·10^{-5} mol·L^{-1} in buffer pH 6.8. At the same time, the drug solubility values

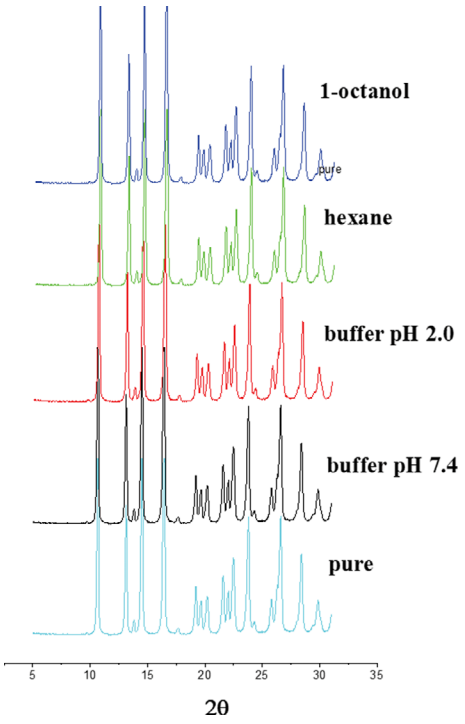

Fig. 3. PXRD patterns of pure and equilibrate GF from the studied solvents.

presented here are a little higher than those obtained by authors [5]: $2.45 \cdot 10^{-5}$ mol·L^{-1}, but lower than those in study [10]: $1.36 \cdot 10^{-4}$ mol·L^{-1} in buffer pH 1.2 and $1.54 \cdot 10^{-4}$ mol·L^{-1} in buffer pH 7.4. The differences between the GF solubility values in these works may result from applying different experimental methods and using buffer solutions of various compositions.

The GF solubility in hexane at 298.15 K was $3.16 \cdot 10^{-5}$ mol·L^{-1}, which was in good agreement with the value of $4.25 \cdot 10^{-5}$ mol·L^{-1}, specified in research [31] for heptane. The data on griseofulvin solubility in a series of saturated alcohols from methanol to 1-butanol presented in work [12] correlate well with the drug solubility value in 1-octanol (Fig. S1 (Supporting Information)).

To determine the solid phase equilibrium structure in different solvents, we removed the bottom phases from the saturated solutions after the solubility experiments and analyzed them by the PXRD method. Fig. 3 shows X-ray diffraction patterns both of the initial compound and of the bottom phase samples in the studied solvents. It is evident that the griseofulvin crystals in the studied solutions have the same crystal structure as the initial material. This fact indicates that neither polymorphic transformation nor solvate formation was observed during the experiments aimed to establish the equilibrium between the solid and liquid phases.

2. Theoretical Exploration of GF/Solvent Miscibility

The Hansen solubility parameters for the solvents and griseofulvin calculated by Eqs. (10)-(16) are given in Table 3. The group contribution parameters and associated molar volumes are summarized in Table S2 (Supporting Information).

As Table 3 shows, the dispersion interactions and polar bonds are the main contribution to the GF solubility and the specific interaction contribution is almost 50% lower and, hence, griseofulvin dissolution is mainly driven by the nonspecific interaction.

The solubility of the studied drug correlates well with the solvent polarity, which can be explained by the rule "like dissolves like". The total value of the GF solubility was calculated as δ_t=23.3 MPa$^{0.5}$, which indicates the low polarity of the drug. For example, the maximum experimental GF solubility was observed in the solvent with lower relative polarity [30] - 1-octanol (0.4), with its Hansen parameter (δ_t) equal to 20.6 MPa$^{0.5}$. In aqueous buffer solutions, where the relative polarity was higher (1.09) and the Hansen parameter (δ_t) equaled 47.8 MPa$^{0.5}$; the GF solubility was found to be low, which confirms the miscibility theory.

Two components are considered miscible if $\Delta\delta_t \leq 7.0$ MPa$^{0.5}$ and immiscible if $\Delta\delta_t \geq 10.0$ MPa$^{0.5}$ [21,32], i.e., if griseofulvin and a solvent have similar solubility values, they are assumed to be well miscible. The highest GF solubility value was predicted in 1-octanol ($\Delta\delta_t$=2.7), a medium value was expected to be in hexane ($\Delta\delta_t$=8.4) and the lowest - in the buffer solutions ($\Delta\delta_t$=24.5), which is explained by the hydrophobic nature of the compound molecule that prevents dissolution in the aqueous medium. So, the predicted solubility value agrees with the experimental results obtained in this work.

Another approach to the evaluation of miscibility between a solute and a solvent and selection of a suitable system consisting of a solvent and a hydrophobic drug compound is the Bagley plot with a 2D graph of the volume-dependent solubility parameter δ_v versus the δ_h parameter (Fig. 4). To determine the miscibility, we used factor $R_{a(v)}$, calculated by Eq. (16) and shown in Table 3. In work [33], the authors established that the optimal range of the solubility sphere radius values on the Bagley plot was equal to 5.6 MPa$^{0.5}$.

As the Bagley plot shows, griseofulvin can become well soluble only in 1-octanol ($R_{a(v)}$=3.1 MPa$^{0.5}$), which is beyond the solubility sphere with this radius. The other solvents that are beyond the solubility sphere are poorly compatible with GF. The worst solubility of the drug was found in the buffer solution and, as a result, it is located furthest from the solubility sphere on the Bagley plot.

3. Thermodynamic Aspects Dissolution and Solvation of GF

The thermodynamic functions of dissolution in the studied solvents were calculated from the solubility temperature dependences (Fig. 5) by Eqs. (3)-(5) and are given in Table 4.

The positive Gibbs energy of dissolution indicates that the pro-

Table 3. Molar volumes and Hansen solubility parameters for the GF and selected solvents

Compound	V, cm^3·mol^{-1}	δ_d, MPa$^{0.5}$	δ_p, MPa$^{0.5}$	δ_h, MPa$^{0.5}$	δ_t, MPa$^{0.5}$	$\Delta\delta_t$	$\Delta\delta$	δ_v, MPa$^{0.5}$	$R_{a(v)}$, MPa$^{0.5}$
GF	315.6	13.6	16.7	8.8	23.3	-	-	21.5	
Buffer solutions	18.0	15.5	16.0	42.3	47.8	24.5	33.5	22.3	33.5
Hexane	131.6	14.9	0.0	0.0	14.9	8.4	20.9	14.9	15.9
1-Octanol	157.7	17.0	5.0	11.9	20.6	2.7	12.6	17.7	3.1

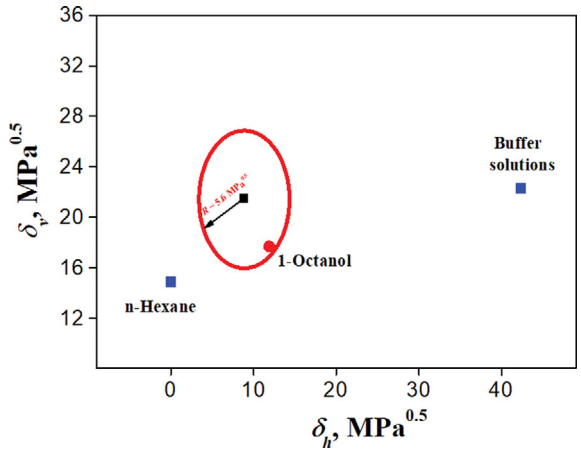

Fig. 4. Bagley diagram of griseofulvin solubility.

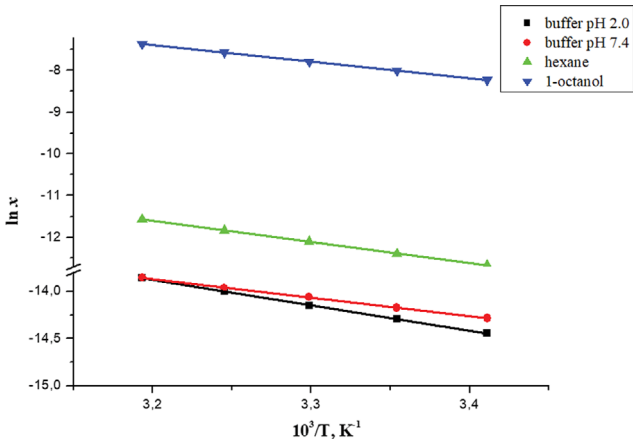

Fig. 5. Temperature dependences of GF solubility in selected solvents.

cess is hindered, which is confirmed by the low solubility values. As a rule, a solvent with higher solubility has a lower Gibbs energy value, which agrees with the general thermodynamic rules. The positive values of the dissolution enthalpy indicate that the solute-solvent interaction is weaker than that of the respective molecules in the solution.

Passing of an ordered solid substance into the liquid state to produce a solution makes the system more disordered, which increases the system entropy ($\Delta S_{sol}>0$) and facilitates dissolution. The positive dissolution entropy values in hexane and 1-octanol indicate higher mobility of the griseofulvin molecules in these solvents. The dissolution entropy in the buffer solutions is negative, which can be explained by the possible hydrophobic hydration around the nonpolar GF groups, namely methyl groups and aromatic ring. This behavior is characteristic of compounds with low solubility in aqueous media. This effect is observed early in the work [34]. As Table 4 shows, the main contribution to the griseofulvin solubility in the studied solvents, except buffer pH 7.4, is the Gibbs energy enthalpy term.

Important information about the nature of a drug compound interaction with membranes can be obtained by analyzing the solvation characteristics of the molecule interaction with solvents modelling various biological media. Solvation is understood as the sum of energy and structure changes that accompany the transfer of gaseous molecules into a liquid medium to form a solution of a certain composition, excluding the changes accompanied by chemical bonds breakage [35]. Quantitative evaluation of the changes in the standard thermodynamic parameters of solvation of a substance requires data on the changes in the solubility and sublimation thermodynamics of this compound in standard conditions. The interrelation between these three parameters is expressed by the following equation:

$$\Delta Y^0_{solv} = \Delta Y^0_{sol} - \Delta Y^0_{sub} \quad (30)$$

where ΔY^0 are the standard thermodynamic functions (G - the Gibbs energy, H - the enthalpy and S - the entropy) of solvation (solv), dissolution (sol) and sublimation (sub) processes.

The sublimation thermodynamic parameters necessary to calculate the griseofulvin solvation characteristics were determined in work [36]. So, the Gibbs energy, enthalpy and entropy of sublimation of the studied compound were 76.0±1.4 kJ·mol^{-1}, 143.8±1.2 kJ·mol^{-1} and 227.4±4.6 J·mol^{-1}·K^{-1}, respectively. The calculated values of the solvation thermodynamic functions are summarized in Table 4.

The negative Gibbs energy values indicate the arbitrary character of griseofulvin solvation in all the studied systems with aqueous and organic solvents. The solvation Gibbs energy values agree with the changes in the griseofulvin solubility, namely, higher solubility values are observed when the solvation Gibbs energy is more negative. The negative griseofulvin solvation enthalpy indicates that the compound crystal lattice energy is higher than the dissolution enthalpy. The data in Table 4 show that the solvents can be arranged in the following series in the ascending order of griseofulvin solvation enthalpy in absolute terms: hexane, 1-octanol, buffer pH 2.0, buf-

Table 4. Thermodynamic solubility and solvation functions of GF in different solvents at 298.15 K and pressure p=0.1 MPa

Solvent	ΔG^0_{sol} kJ·mol^{-1}	ΔH^0_{sol} kJ·mol^{-1}	$T\Delta S^0_{sol}$ kJ·mol^{-1}	ΔS^0_{sol} J·mol^{-1}K^{-1}	ΔG^0_{solv} kJ·mol^{-1}	ΔH^0_{solv} kJ·mol^{-1}	ΔS^0_{solv} J·mol^{-1}K^{-1}	[a]$\Delta H^0_{sol(spec)}$ kJ·mol^{-1}	[b]ε %
Buffer pH 2.0	35.4±0.6	22.4±0.2	−13.0	−43.6±1.2	−38.7	−121.4	−277.4	−19.5	19.4
Buffer pH 7.4	33.7±0.6	16.3±0.1	−17.4	−58.4±2.4	−40.4	−127.5	−292.2	−25.6	25.1
Hexane	30.7±0.6	41.9±0.4	11.2	37.6±1.6	−43.4	−101.9	−196.2	-	-
1-Octanol	19.8±0.3	33.1±0.1	13.3	44.6±1.0	−54.3	−110.7	−189.2	−8.8	8.6

[a] $\Delta H^0_{solv(spec)} = \Delta H^0_{solv} - \Delta H^0_{solv(nonspec)}$

[b] $\varepsilon = |\Delta H^0_{solv(spec)} / \Delta H^0_{solv(nonspec)}| \cdot 100$

Table 5. Experimental (x_{exp}) and correlated (x_{cal}) mole fractions of GF solubility in the solvents studied at different temperatures and pressure p=0.1 MPa

T/K	x_{exp}	Modified Apelblat equation		van't Hoff equation	
		x_{cal}	10^2RD	x_{cal}	10^2RD
		[a]Buffer pH 7.4			
293.15	$5.329\cdot10^{-7}$	$5.327\cdot10^{-7}$	0.022	$5.318\cdot10^{-7}$	0.190
298.15	$6.204\cdot10^{-7}$	$6.201\cdot10^{-7}$	0.049	$6.205\cdot10^{-7}$	−0.023
303.15	$7.175\cdot10^{-7}$	$7.193\cdot10^{-7}$	−0.241	$7.203\cdot10^{-7}$	−0.388
308.15	$8.341\cdot10^{-7}$	$8.316\cdot10^{-7}$	0.296	$8.321\cdot10^{-7}$	0.235
313.15	$9.576\cdot10^{-7}$	$9.585\cdot10^{-7}$	−0.101	$9.569\cdot10^{-7}$	0.069
		[b]Buffer pH 7.4			
293.15	$6.269\cdot10^{-7}$	$6.273\cdot10^{-7}$	−0.065	$6.260\cdot10^{-7}$	0.148
298.15	$6.996\cdot10^{-7}$	$6.999\cdot10^{-7}$	−0.050	$7.002\cdot10^{-7}$	−0.097
303.15	$7.814\cdot10^{-7}$	$7.794\cdot10^{-7}$	0.257	$7.804\cdot10^{-7}$	0.128
308.15	$8.630\cdot10^{-7}$	$8.664\cdot10^{-7}$	−0.403	$8.667\cdot10^{-7}$	−0.438
313.15	$9.525\cdot10^{-7}$	$9.615\cdot10^{-7}$	0.111	$9.594\cdot10^{-7}$	0.327
		Hexane			
293.15	$3.163\cdot10^{-6}$	$3.148\cdot10^{-6}$	0.470	$3.149\cdot10^{-6}$	0.459
298.15	$4.156\cdot10^{-6}$	$4.201\cdot10^{-6}$	−1.077	$4.201\cdot10^{-6}$	−1.088
303.15	$5.589\cdot10^{-6}$	$5.553\cdot10^{-6}$	0.649	$5.553\cdot10^{-6}$	0.638
308.15	$7.297\cdot10^{-6}$	$7.273\cdot10^{-6}$	0.327	$7.274\cdot10^{-6}$	0.315
313.15	$9.423\cdot10^{-6}$	$9.444\cdot10^{-6}$	−0.229	$9.445\cdot10^{-6}$	−0.240
		1-Octanol			
293.15	$2.687\cdot10^{-4}$	$2.683\cdot10^{-4}$	0.169	$2.674\cdot10^{-4}$	0.508
298.15	$3.347\cdot10^{-4}$	$3.351\cdot10^{-4}$	−0.121	$3.357\cdot10^{-4}$	−0.321
303.15	$4.153\cdot10^{-4}$	$4.169\cdot10^{-4}$	−0.397	$4.184\cdot10^{-4}$	−0.767
308.15	$5.209\cdot10^{-4}$	$5.169\cdot10^{-4}$	0.764	$5.178\cdot10^{-4}$	0.592
313.15	$6.369\cdot10^{-4}$	$6.386\cdot10^{-4}$	−0.276	$6.364\cdot10^{-4}$	0.072

[a]Composition of aqueous buffer pH 2.0: KCl (6.57 g in 1 l) and 0.1 mol/dm^3 hydrochloric acid (119.0 ml in 1 l)
[b]Composition of aqueous buffer pH 7.4: KH_2PO_4 (9.1 g in 1 l) and $Na_2HPO_4\cdot12H_2O$ (23.6 g in 1 l)
Standard uncertainties: u(T)=0.15 K and u(p)=3 kPa.
Relative standard uncertainties for solubility: $u_r(x)$=0.045 for buffer solutions and $u_r(x)$=0.04 for hexane and 1-octanol.

fer pH 7.4. In buffer pH 7.4, the solvation enthalpy is more exothermic than in buffer pH 2.0. The solvation entropy values are negative, with the mutual ordering in the position of the solute and solvent molecules increasing in the following series of solvents: 1-octanol, hexane, buffer pH 2.0, buffer pH 7.4. Solvation enthalpy is a thermodynamic measure of intermolecular solute-solvent interactions. It means that this value can be also represented as a sum of the nonspecific solvation enthalpy (in hexane) and the specific interaction enthalpy. The calculations showed that nonspecific interactions during the griseofulvin dissolution in 1-octanol and buffers were the main contribution to the solvation Gibbs energy enthalpy term (Table 4). The contribution of the nonspecific interaction in case of dissolution in aqueous solutions at pH 2.0 was smaller than at pH 7.4.

4. Correlation of GF Solubility Data

Mathematical correlation of experimental data on the solubility of pharmaceutical compounds is important for practical predictions [37]. Therefore, we correlated the experimental GF solubility values using the modified Apelblat and van't Hoff equations. The experimental GF solubility values in mole fraction and the solubility values calculated by Eqs. (17) and (18) are given in Table 5. The modeling parameters, together with the deviations obtained by Eqs. (20) and (21) are contained in Table S2.

Tables 5 and S2 show that the experimental GF solubility correlates well with the solubility values calculated by the Apelblat and van't Hoff models in all the solvents. Both models can be considered suitable for solubility correlation in the studied solvents. As Table 5 indicates, the mean relative deviations (RD, %) for the employed models increase as follows: buffer pH 2.0 (0.14, 0.18), buffer pH 7.4 (0.17, 0.23), 1-octanol (0.34, 0.45), hexane (0.55, 0.57) for the modified Apelblat model and van't Hoff model, respectively. Table S2 summarizes the RAD and RMSD results using a variety of correlation models. The total average RAD and RMSD values of the proposed models equal 0.21 and $5.33\cdot10^{-5}$% for the Apelblat model and 0.34 and $5.43\cdot10^{-5}$% for the van't Hoff model. Thus, the results obtained using the modified Apelblat model are in better agreement with the experimental GF solubility in pure solvents.

5. Evaluation of GF Excess Thermodynamic Functions Based Thermophysical Data

The x_{id} values and the $\ln\gamma^{\infty}$ activity coefficients of griseofulvin

Table 6. Temperature dependences of ideal solubility ($\ln x_{id}$) and activity coefficients at infinite dilution ($\ln\gamma^{\infty}$) of GF in the studied solvents at p=0.1 MPa

T/K	$\ln x_{id}$	$\ln\gamma^{\infty}$			
		Buffer pH 2.0	Buffer pH 7.4	Hexane	1-Octanol
293.15	−4.57	9.87	9.71	8.09	3.65
298.15	−4.45	9.85	9.72	7.94	3.55
303.15	−4.32	9.83	9.74	7.77	3.47
308.15	−4.19	9.80	9.77	7.63	3.37
313.15	−4.07	9.79	9.78	7.50	3.29
[a]A		8.59±0.1	10.94±0.1	−1.19±0.17	−2.01±0.10
[a]B		373±19	−362±21	2720±52	1658±31
[b]R		0.9961	0.9951	0.9994	0.9995

The standard uncertainties are u(T)=0.15 K, u(p)=3 kPa
The relative standard uncertainty is $u_r(\gamma^{\infty})$=0.04,
[a]Parameters of the correlation equation: $\ln\gamma^{\infty}$=A+B/(T/K),
[b]R is the pair correlation coefficient.

calculated by Eqs. (22), (23) at infinite dilution in the studied solvents are given in Table 6. The griseofulvin thermophysical parameters used in Eq. (23) were obtained by us earlier and were reported in work [36]: the melting enthalpy - 40.92 kJ·mol^{-1}, the melting point - 491.65 K, $\Delta C_{p,m}$ - 114.5 J·mol^{-1}·K^{-1}.

The x_{id} values GF at temperatures of 293.15-313.15 K changed from 1.71·10^{-2} to 1.04·10^{-2}, which was much higher than the experimental solubility in mole fraction in all the considered solvents at each of the temperature values. This fact led to a positive deviation from ideality and values γ^{∞}>1 and indicated a weaker molecular interaction of GF with the studied solvents. As the data in Table 6 show, the compound activity coefficients in buffer solution pH 2.0 and organic solvents become lower as the temperature rises, which is caused by a stronger solute-solvent interaction and higher solubility. In buffer pH 7.4, the drug activity coefficients become slightly higher with temperature growth. Depending on the solvent chemical nature, the GF activity coefficients decrease as follows: buffer pH 2.0, buffer pH 7.4, hexane, 1-octanol, which agrees with the compound solubility growth in these solvents.

The GF partial excess thermodynamic functions were calculated based on the $\ln\gamma^{\infty}$ linear dependences on reciprocal temperature by Eq. (24) (Fig. 6). The results are summarized in Table 7.

Molar excess functions are widely used in thermodynamics of solutions to characterize the intermolecular interaction of solution components. As Table 7 shows, there is a positive deviation of the solution properties from ideality (G^E>0), which indicates that the main type of interactions between the solution components is the van der Waals ones. The positive griseofulvin dissolution enthalpy

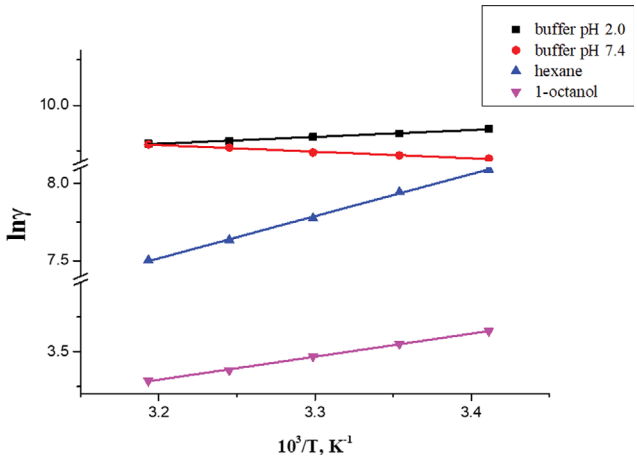

Fig. 6. Temperature dependencies of activity coefficients at infinite dilution of GF in studied solvents.

Table 7. Excess thermodynamic solubility functions of GF in studied solvents at 298.15 K and p=0.1 MPa

Solvent	G^E kJ·mol^{-1}	H^E kJ·mol^{-1}	TS^E kJ·mol^{-1}	S^E J·mol^{-1}·K^{-1}	[a]ζ_H^E, %	[b]ζ_{TS}^E, %
Buffer pH 2.0	24.4±0.4	3.1±0.3	−21.3	−71.4±3.1	12.7	87.3
Buffer pH 7.4	24.1±0.4	−3.0±0.1	−27.1	−90.9±4.4	10.0	90.0
Hexane	19.7±0.3	22.6±0.4	2.9	9.7±0.2	88.6	11.4
1-Octanol	8.8±0.12	13.8±0.3	5.0	16.8±0.1	73.4	26.6

[a]ζ_H=(H^E/(H^E+TS^E))×100%;
[b]ζ_{TS}=(TS^E/(H^E+TS^E))×100%.
Relative standard uncertainties are u(T)=0.05 K, u(p)=3 kPa
Uncertainties for the G^E, H^E and S^E values represent the twice standard deviation.

Table 8. Experimental concentrations and partition coefficient of GF in 1-octanol/buffer pH 7.4 system (x_O - mole fraction in 1-octanol, x_B - mole fraction in buffer) at different temperatures and pressure p=0.1 MPa

T/K	$s_O \cdot 10^5$	$s_B \cdot 10^6$	$P_{O/B}$	$\log P_{O/B}$	$x_O \cdot 10^4$	$x_B \cdot 10^7$	$\log P^*_{O/B}$
293.15	16.03	1.67	96.04	1.98	2.53	2.99	2.93
298.15	16.04	1.58	101.22	2.01	2.54	2.84	2.95
303.15	16.05	1.51	106.22	2.03	2.55	2.71	2.97
308.15	16.06	1.44	111.33	2.05	2.56	2.59	2.99
313.15	16.06	1.38	116.49	2.07	2.57	2.48	3.02
A^a		9.92±0.02					
B^a		932±54			$\Delta G^o_{tr}=-16.8\pm0.3$/kJ·mol^{-1}		
R^b		0.9999			$\Delta H^o_{tr}=7.7\pm0.4$/kJ·mol^{-1}		
σ^c		0.011			$\Delta S^o_{tr}=82.5\pm2.2$/J·mol^{-1}K^{-1}		

[a]Parameters of the correlation equation: $\log P^*_{O/B}=A+B/T$

[b]R - correlation coefficient

[c]σ - standard deviation

The standard uncertainties are u(m)=0.01 mg, u(T)=0.15 K and u(p)=3 kPa.

in buffer pH 2.0 and organic solvents shows that the GF/solvent intermolecular interactions are weaker than the solvent-solvent ones. It was established that the Gibbs energy entropy component exceeded the enthalpy one in absolute terms in the aqueous solutions ($H^E<TS^E$), which indicates the dominant contribution of entropy to the deviation from ideality in these solutions ($\zeta_{TS}^E>73\%$). In the systems with the organic solvents, the deviation from ideality in absolute terms was mainly caused by the Gibbs energy enthalpy term: $H^E>TS^E$ ($\zeta_{TS}^E<13\%$).

6. Partition Process of GF in Biphasic System

Lipophilicity is normally described by distribution between the two phases: the nonpolar (organic medium) and polar (aqueous medium) phases. A quantitative characteristic of lipophilicity is partition coefficient (P) determined as the ratio of neutral molecular species concentrations in the organic and aqueous phases in equilibrium conditions.

As shown earlier (section 3.1), griseofulvin molecules do not get ionized and exist in their neutral form in aqueous solutions. That is why the obtained experimental partition coefficients of the drug compound in the 1-octanol/buffer pH 7.4 represent the ratio of the concentrations of non-ionized molecules. Table 8 contains the experimental equilibrium concentrations of GF in the considered solvents and its partition coefficients in the 1-octanol/buffer pH 7.4 system within the temperature range from 298.15 to 313.15 K.

The partition coefficient values of more than one indicate the compound transferred from the aqueous (hydrophilic medium) to the organic (hydrophobic medium), which reflects the affinity of the bioactive compound under study with the lipid membranes. It was established that the temperature increase led to a larger shift of the equilibrium toward the octanol phase, which indicates a significant temperature effect on distribution. According to the empirical dependences between the partition degree, physicochemical and biological properties of the preparations [38], the compound under study belongs to the most favorable range of partition coefficient values in the 1-octanol/buffer pH 7.4 system: $1<\log P_{O/B}<3$. It means that griseofulvin has high adsorption capacity due to a good balance between the solubility and passive diffusion permeability.

The 1-octanol/buffer pH 7.4 partition coefficient $\log P_{O/B}$ value and the solvation free Gibbs energies ($\Delta G^o_{solv(B)}$, $\Delta G^o_{solv(O)}$) in the buffer and 1-octanol solvents are related by equation:

$$\log P_{O/B}=\frac{\Delta G^o_{solv(B)}-\Delta G^o_{solv(O)}}{2.3RT} \quad (31)$$

where the R is gas constant, and the T is absolute temperature. The $\log P_{O/B}$ value calculated by this equation was equal to 2.43, which was close to the experimental value determined at 298.15 K.

The thermodynamic parameters of partition of compounds from buffer solutions to 1-octanol play an important role in the analysis of their interactions with model solvents and help understand the nature and driving forces of the processes responsible for the transport properties of the drugs. Based on the temperature dependences of the partition coefficients, we calculated the griseofulvin thermodynamic partition parameters at 298.15 K (Table 8). The standard GF Gibbs energy values in the 1-octanol/buffer pH 7.4 system were found to be negative, whereas the enthalpy ones were positive. This fact indicates that the drug distribution from an aqueous solution into the octanol phase was thermodynamically efficient and endothermic. The endothermic nature of the distribution process allowed us to suppose that the interaction between the griseofulvin molecules with the solvate shell was stronger in the aqueous medium than in the organic one. The entropy changes were also positive, which means that the system was disordered and the molecules were more flexible due to the lower energy of the substance molecule interaction with 1-octanol. According to the experimental data, the GF distribution from the aqueous medium to the octanol one was largely determined by entropy ($T\Delta S^0_{tr}>\Delta H^0_{tr}$), which means that this process was entropy-determined.

CONCLUSION

We studied the pharmacologically relevant physicochemical properties of the antifungal drug griseofulvin: solubility, solvation and distribution. The GF experimental solubility values were measured in buffer solutions (pH 2.0 and 7.4), hexane and 1-octanol at tem-

peratures from 293.15 K to 313.15 K. The solubility tended to improve with a temperature increase in all the solvents. Griseofulvin was found to be poorly soluble in aqueous buffer solutions, with the best solubility observed in 1-octanol. The Hansen solubility parameters of drug studied agree with the experimental data and the solubility was revealed to significantly depend on the dispersion interactions and polar bonds. The solubility values obtained experimentally were correlated with the results of application of thermodynamic models, such as the van't Hoff equation and modified Apelblat equation. The modified Apelblat equation gave a more satisfactory correlation with the experimental solubility study results. The thermodynamic functions of griseofulvin dissolution and solvation were determined by the van't Hoff analysis. The results showed that the GF dissolution in the studied solvents was endothermic and not arbitrary, with the main contribution to the dissolution being the Gibbs energy enthalpy term. Positive dissolution enthalpy values were observed in all the solvents, which indicates that the GF/solvent intermolecular interactions were weaker than the solvent/solvent ones. The temperature dependences of the griseofulvin partition coefficients were obtained in the two-phase 1-octanol/buffer pH 7.4 system and the transfer thermodynamic functions were evaluated. It was established that the drug distribution from the aqueous solution to the octanol phase was thermodynamically favorable and endothermic.

The GF solubility, solvation and partition data in the solvents modeling biological media obtained by us, as well as the correlation models used, can be applied to optimize GF synthesis and purification, development of preliminary formulations and different dosage forms of this drug. In addition, the partition coefficient in the 1-octanol/water system (lipophilicity) was used as a key descriptor in the search for the relationship between quantitative structure and activity (QSAR).

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Additional information as noted in the text. This information is available via the Internet at http://www.springer.com/chemistry/journal/11814.

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Supporting Information

Griseofulvin: Thermodynamic insight to solubility, solvation and partition processes

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Table S1. Density of the investigated solvents at different temperatures and pressure p=0.1 MPa[a]

Solvent	ρ/g·cm^{-3}				
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
Buffer pH 2.0[b]	1.0035	1.0023	1.0008	0.9992	0.9973
Buffer pH 7.4[c]	1.0060	1.0048	1.0033	1.0016	0.9998
Hexane	0.6587	0.6543	0.6495	0.6453	0.6432
1-Octanol	0.8251	0.8217	0.8183	0.8148	0.8114

[a]Density data for all solvents were taken from Ref. [S. Blokhina, A. Sharapova, M. Ol'khovich, G. Perlovich, A thermodynamic study of sublimation, dissolution and distribution processes of anti-inflammatory drug Clonixin, J. Chem. Thermodyn. 132 (2019) 281-288.]
[b]Composition of aqueous buffer pH 2.0: KCl (6.57 g in 1 L) and 0.1 mol/dm^3 hydrochloric acid (119.0 mL in 1 L);
[c]Composition of aqueous buffer pH 7.4: KH_2PO4 (9.1 g in 1 L) and $Na_2HPO_4 \cdot 12H_2O$ (23.6 g in 1 L);
Standard uncertainities: u(m)=0.01 mg, u(T)=0.2 K, u(p)=3 kPa and u(ρ)=0.002 g·cm^{-3}.

Table S2. Group contribution parameters and associated molar volume of GF

Individual functional group	Frequency	F_{di}, (J/cm^3)$^{0.5}$·mol^{-1}	F_{pi}, (J/cm^3)$^{0.5}$·mol^{-1}	E_{hi}, J/mol	V_i, cm^3/mol
-Cl	1	397.8	1,477.2	4,706.0	26.0
-CH_2-	1	234.6	0	0	16.1
-O- adjacent	1	30	407	227.8	4.5
-CH-	1	132.6	0	0	−1
>C<	1	−214.2	0	0	−19.2
=C<	8	−56.7	20.0	0	−5.5
-CH_3	4	336.6	0	0	33.5
=CH-	2	255.0	38.0	0	13.5
-O-	4	76.5	1,225.0	101.0	3.8
-CO-	2	105	600	9500	10.8
Phenyl	1	1,515.0	50.0	20.9	71.4
Ring closure 5 or more atoms 3	2	142.8	0	0	16
Total		4300.2	8270.2	24358.7	315.6

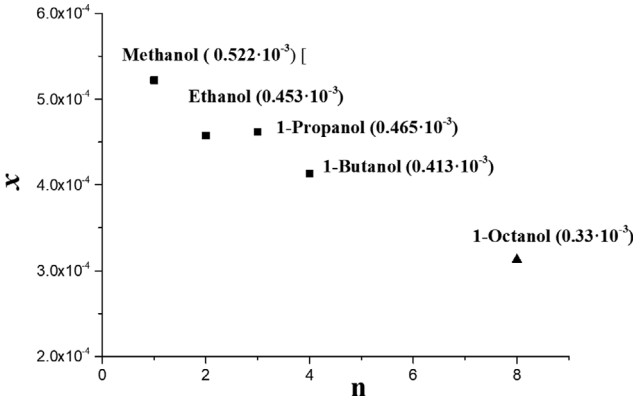

Fig. S1. Dependence mole fraction solubility (x) of griseofulvin in alcohols on the quantity of alkyl groups in alcohol: ▲ - this study; ■ - literature data [S. Zhao, Y. Ma, J. Gong, B. Hou, W. Tang, Solid-liquid phase equilibrium and thermodynamic analysis of griseofulvin in twelve mono-solvents, J. Mol. Liq. 296 (2019) 111861. http://dx.doi.org/10.1016/j.molliq.2019.111861].

Table S3. Parameters of modified Apelblat and van't Hoff equations for of GF in the selected solvents

Solvents	A	B	C	RMSD	10^3 RAD
Modified Apelblat equation					
Buffer pH 2.0	−44.64	−918.6	5.87	$1.42\cdot10^{-9}$	1.4
Buffer pH 7.4	−50.46	−25.9	6.38	$1.87\cdot10^{-9}$	1.8
Hexane	4.51	−5,041.3	0.003	$3.02\cdot10^{-8}$	1.1
1-Octanol	−83.24	16.2	13.2	$2.10\cdot10^{-6}$	4.3
van't Hoff equation					
Buffer pH 2.0	−5.25	−2,695.9		$1.62\cdot10^{-9}$	1.8
Buffer pH 7.4	−7.96	−1,959.8		$2.30\cdot10^{-9}$	2.3
Hexane	4.53	−5,042.3		$3.02\cdot10^{-8}$	5.5
1-Octanol	5.35	−3,980.8		$2.14\cdot10^{-6}$	3.9