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Solubility measurement, thermodynamic modeling, and molecular dynamic simulation of regorafenib in pure and binary solvents

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ABSTRACT

The solubility of regorafenib in six pure solvents (ethanol, acetonitrile, methanol, n-propanol, isopropanol, and acetone) and binary solvent mixtures (acetone + acetonitrile) was determined by the gravimetric method from 298.15 K to 313.15 K. The mole solubility of regorafenib increased monotonously with increased temperature. The solubility data were fitted by four thermodynamic models, namely, the modified Apelblat, λh, non-random two-liquid, and Wilson models. The modified Apelblat model showed the most accurate correlation with solubility data. Molecular dynamics simulation including solvation free energy calculations and radial distribution function were performed to understand the influence mechanism of solute–solvent and solvent–solvent interaction on solubility. The results of solvation free energy calculations well agreed with the solubility order of regorafenib in selected solvents. However, the solvent–solvent interaction had no significant effect on solubility. Moreover, the thermodynamic properties ($\Delta_{dis}H^0, \Delta_{dis}S^0 \ and \ \Delta_{dis}G^0$) of regorafenib were calculated using the van't Hoff equation. The positive value of $\Delta_{dis}H^0 \ and \ \Delta_{dis}S^0$ indicated an entropy-driven and endothermic process of dissolution of regorafenib. These findings can serve as a reference for future synthesis process selection, formulation research, and optimization, as well as for understanding the solid–liquid equilibrium of regorafenib and predict its solubility which is of great significance to production.

Keywords: Regorafenib; Solubility; Thermodynamic properties; Molecular dynamic simulation

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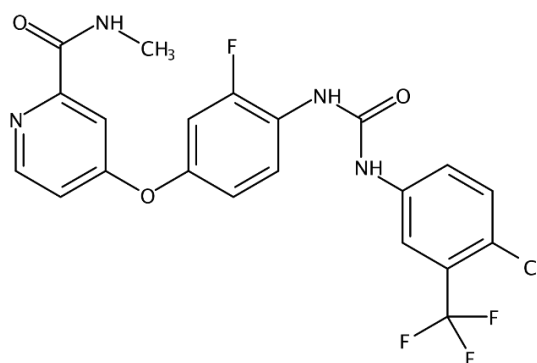
1. Introduction

Figure 1 Chemical structure of regorafenib

Regorafenib (IUPAC: 4-[4-({[4-chloro-3-(trifluoromethyl) phenyl] carbamoyl} amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide; CAS number: 755037-03-7) is a multikinase inhibitor with activity toward angiogenesis and stromal and oncogenic receptor tyrosine kinases [1]. It is the first oral treatment for metastatic colorectal cancer [2]. Regorafenib is also suitable for the treatment of locally advanced, unresectable or metastatic gastrointestinal stromal tumors [3] and hepatocellular carcinoma patients [4]. The low solubility of regorafenib limits its absorption and leads to low oral bioavailability.

Solubility is a basic physical property of drugs and plays an important role in many aspects, such as biopharmaceutical evaluation, prescription optimization, and manufacturing [5]. In manufacturing, the solubility of drugs in selected solvents is crucial to the design of the crystallization process [6]. This process has many benefits based on solubility, such as high yield, low energy consumption, and low pollution. Solubility data can also serve as a theoretical basis for the design of instrument size and operating conditions, which can lead to lowered economic costs. Numerous studies have been conducted on the solubility of different drugs in various solvents such as clozapine, an antipsychotic drug. By measuring the solubility of clozapine in 12 pure solvents, *Gong* et al. [7] concluded that the solute–solvent interaction is primarily due to the dipolarity/polarizability and self-cohesiveness of the solvent. *Yu* et al. [8] obtained solubility data, thermodynamic parameters, and dissolution properties, which play important guiding roles in the optimization of crystallization. However, the experimental solubility data of regorafenib in pure and binary solvents have not been reported.

Crystallization in suitable solvents can improve product purity and economic efficiency [9]. In addition to using pure solvents, the most common method of increasing the yield of drugs during crystallization is to mix good and bad solvents. In the current work, six pure solvents often used in production were selected. The optimal solvents were selected based on the solubility data.

Gravimetric analysis was used to study the solubility of regorafenib in pure solvents and binary solvent mixtures at 298.15 K to 313.15 K. The pure solvents included ethanol, acetonitrile, methanol, n-propanol, isopropanol, and acetone, and the binary solvent mixture was acetone + acetonitrile. Four thermodynamic models including the modified Apelblat (MA), λh, non-random

two-liquid (NRTL), and Wilson models were used to correlate the experimental data. Molecular dynamics (MD) simulation including solvation free energy calculations and radial distribution function (RDF) were performed to understand the influence mechanism of solute–solvent and solvent–solvent interaction on solubility. Furthermore, the thermodynamic properties ($\Delta_{dis}H^0, \Delta_{dis}S^0 \text{ and } \Delta_{dis}G^0$) of regorafenib were calculated by the van't Hoff equation. This study systematically investigated the solubility of regorafenib in various pure and binary solvents to provide data support for future synthesis process selection, formulation research, and optimization [10].

2. Experimental

2.1 Materials

Regorafenib was supplied by Shanghai Rongtai Pharmatech Co., Ltd. The solvents used in the experiments including ethanol, acetonitrile, methanol, n-propanol, isopropanol, and acetone were analytical-reagent grade and purchased from Chengdu Kelong Chemical Co., Ltd. More detailed information is shown in **Table 1**.

Table 1 Details of the materials used in this work

Chemical name	Molar mass[a] (g·mol^{-1})	Density[b] (g·cm^{-3})	Molar volume[c] (cm^3·mol^{-1})	Source	Mass fraction purity[d]	Analysis method
Regorafenib	482.82	1.491[20]	323.6[20]	Shanghai Rongtai Pharmatech Co., Ltd.	≥0.990	HPLC[e]
Ethanol	46.068	0.7893[20]	58.37[20]	Chengdu Kelong Chemical Co., Ltd.	≥0.997	GC[f]
Acetonitrile	41.052	0.7825[20]	52.46[20]	Chengdu Kelong Chemical Co., Ltd.	≥0.995	GC[f]
Methanol	32.042	0.7914[20]	40.49[20]	Chengdu Kelong Chemical Co., Ltd.	≥0.995	GC[f]
n-Propanol	60.095	0.7997[25]	75.15[25]	Chengdu Kelong Chemical Co., Ltd.	≥0.990	GC[f]
Isopropanol	60.095	0.7809[25]	76.96[25]	Chengdu Kelong Chemical Co., Ltd.	≥0.995	GC[f]
Acetone	58.079	0.7845[25]	74.03[25]	Chengdu Kelong Chemical Co., Ltd.	≥0.995	GC[f]

[a] Molar mass of solvents taken from Ref. [11]. Molar mass of solute taken from Ref. [12].
[b] Density of solvents taken from Ref. [11]. Density of solute taken from Ref. [12]. The superscript of the density indicates the corresponding temperature (℃).

2.2 Characterization method

To ensure whether solvate formation or crystal transformation occurred during the dissolution process, raw material and residual solids collected from equilibrium solution were analyzed by X-ray powder diffraction (X'Pert PRO, PANalytical, Holland). X-ray diffraction (XRD) patterns were obtained under the following conditions: XRD tube voltage and current, 40 kV and 40 mA, respectively, with Cu Kα; slit, 1/4 and 1/8; scanning angle, 5°–50° (2θ); and time per step, 30.40 s.

Differential scanning calorimetry (DSC1, Mettler-Toledo, Switzerland) was used to measure the melting point and melting enthalpy of regorafenib. The instrument was calibrated with indium before testing the raw materials. Then, materials with a mass of about 5.0 mg were loaded into an alumina crucible. Under nitrogen protection, the temperature was increased from 303.15 K to 573.15 K at a heating rate of 10 K/min.

High-performance liquid chromatography (HPLC; Agilent 1200, USA) was used with a reversed-phase chromatography C18 column (250 mm × 4.6 mm, 5 µm). The wavelength of the Diode array detector (DAD) detector was 260 nm, and the column temperature was set at 308.15 K. The mobile phase was 0.1 % (w/v) phosphate buffer–acetonitrile (30:70), and the flow rate was 0.5 mL/min. Each experiment was performed at least three times.

2.3 Solubility measurements

In the experiment, a water-bath thermostatic jacketed glass vessel connected with a cooling circulation pump was used. Excessive regorafenib was added to 5 mL of pure solvent or binary solvent mixture in the glass vessel. The temperature was corrected using a mercury thermometer. Continuous magnetic stirring was conducted for 24 h, and the solution was allowed to settle for 3 h before sampling. A preheated/precooled syringe with a filter (0.22 μm) was used to collect 1 mL of the supernatant, which was quickly transferred to a pre-weighed volumetric flask. The flask was weighed again with an electronic analytical balance (BS224S, Sartorius, Beijing; accuracy = 0.0001 g). The sample was diluted with acetonitrile and analyzed by HPLC. Each experiment was performed three times. The mole-fraction solubility x_1 of regorafenib in pure solvents and binary solvent mixture was calculated by Eqs. (1)–(3). [13]:

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \tag{1}$$

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \tag{2}$$

$$\omega_1 = \frac{m_1}{m_1 + m_2} \tag{3}$$

where m_1 is the mass of solute, m_2 is the mass of pure solvent in Eq. (1). In Eq. (2), m_2 is the mass of acetone, m_3 is the mass of acetonitrile, and ω_1 is the mass fraction of acetone in the binary solvent mixtures (the range of ω_1 is 0.1–0.9).

2.4 Molecular dynamic simulation

Molecular dynamic (MD) simulations were used to explore the interactions between solute–solvent and solvent–solvent through RDF and free energy of solvation. MD simulation was calculated on Materials Studio 8.0 using the FORCITE Module [14]. The molecular structure of regorafenib was obtained from the Cambridge Crystallographic Data Centre database. The COMPASS force field, which is suitable for atomistic simulation studies, was used in the process [15]. Before calculation, geometry optimization was performed on regorafenib and all selected solvent molecules, and the steps of iterations were more than 5000 until the molecular energy was minimized. The AC module was used to build a periodic cubic box, and packing was based on the true density of the neat solvent and binary solvent mixtures. Atom-based summation method was adopted to handle dispersion and electrostatic interactions. MD calculations were performed under the ensemble as NVT and thermostat as NHL, and the total simulation time was set at 1 ns. Finally, the RDF and solvation free energy calculations were analyzed with FORCITE Module.

3. Theoretical basis

Four thermodynamic models including the MA equation, λh equation, NRTL equation, and Wilson equation were used to correlate the solubility of regorafenib in pure and binary solvents.

3.1 MA equation

The MA model is a semi-empirical model based on the Clausius–Clapeyron equation [16]. It is used to correlate and predict solubility in pure and mixed solvents due to its simple expression. The expression of MA equation can be presented as Eq. (4) [17]:

$$lnx = A + \frac{B}{T} + ClnT \tag{4}$$

where x represents the mole-fraction solubility of regorafenib, T represents the absolute temperature, A and B reflect the change in activity coefficient, and C shows the effect of temperature on the enthalpy of melting, which are listed in **Table S1**.

3.2 λh equation

The λh model equation, as a classic semi-empirical equation, was first proposed by Buchowski et al. [16]. It is extensively used in solubility correlation because of its simplicity and applicability.

The equation can be expressed as Eq. (5) [14-16]:

$$\ln \ln \left[1 + \frac{\lambda(1-x)}{x}\right] = \lambda h\left(\frac{1}{\frac{T}{K}} - \frac{1}{\frac{T_m}{K}}\right) \qquad (5)$$

where x is the mole-fraction solubility of regorafenib; T is the absolute temperature; T_m is the melting temperature of the solute; and λ and h are the two empirical parameters in the equation calculated by Eq. (5), as shown in **Table S1.**

3.3 NRTL equation

The NRTL [18] and Wilson models [19] are based on solid–liquid equilibrium theory, and both can calculate the solute-activity coefficient [20]:

$$\ln x_1 = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \ln\gamma_1 \qquad (6)$$

where γ_1 is the activity coefficient of the solute, $\Delta_{fus}H$ is the fusion enthalpy, R is the gas constant, and T_m is the melting temperature.

This model is used in partially and completely miscible systems. In this work, the NRTL model was used to correlate the solubility of regorafenib in pure and binary solvents. The NRTL model can be expressed as follows [21]:

$$\ln\gamma_1 = \frac{\sum_j^{NC} \tau_{ji}G_{ji}x_j}{\sum_k^{NC} G_{ki}x_k} + \sum_j^{NC} \frac{G_{ij}x_j}{\sum_k^{NC} G_{kj}x_k}\left(\tau_{ij} - \frac{\sum_l^{NC} \tau_{lj}G_{lj}x_l}{\sum_k^{NC} G_{kj}x_k}\right) \qquad (7)$$

$$G_{ij} = exp\,(-\alpha_{ij}\tau_{ij}) \qquad (8)$$

$$\tau_{ij} = \frac{g_{ij} - g_{jj}}{RT} = \frac{\Delta g_{ij}}{RT} \qquad (9)$$

$$\alpha_{ij} = -\alpha_{ji} = \alpha \qquad (10)$$

where g_{ij} refers to interaction energies, α is an adjustable parameter that indicates the degree of non-randomness of solution (the value of α_{ij} is usually between 0.2–0.47 [22]), τ_{ij} represents the interaction parameter, and G_{ij} refers to the interaction energies between components i and j.

The NRTL model of pure solvents is given in Eq. (11) [23]:

$$\ln\gamma_1 = x_2{}^2\left[\tau_{21}\left(\frac{G_{21}}{x_1 + G_{21}x_2}\right)^2 + \frac{\tau_{12}G_{12}}{(x_2 + G_{12}x_1)^2}\right] \qquad (11)$$

where x_1 represents the mole fraction of regorafenib, and $x_2 = 1 - x_1$ represents the mole fraction of other solvents. The parameters of NRTL in pure solvents are shown in **Table S1**.

In binary solvent mixtures, the NRTL model can be defined as Eq. (12) [23]. The parameters of NRTL in binary solvent mixtures are listed in **Table S2**.

$$\ln\gamma_1 = \frac{(G_{21}x_2 + G_{31}x_3)(\tau_{21}G_{21}x_2 + \tau_{31}G_{31}x_3)}{(x_1 + G_{21}x_2 + G_{31}x_3)^2} + \frac{\tau_{13}G_{13}x_3{}^2 + G_{13}G_{23}x_2x_3(\tau_{13} - \tau_{23})}{(x_3 + G_{13}x_1 + G_{23}x_2)^2} + \frac{\tau_{12}G_{12}x_2{}^2 + G_{12}G_{32}x_2x_3(\tau_{12} - \tau_{32})}{(x_2 + G_{12}x_1 + G_{32}x_3)^2} \qquad (12)$$

where x_2 and x_3 are the mole fractions of acetone and acetonitrile, respectively.

3.4 Wilson equation

The Wilson model was used to correlate the solubility of regorafenib in pure and binary solvents. The model in pure solvents can be defined as Eq. (13) [24]:

$$ln\gamma_1 = -\ln\ln\left(x_1 + x_2\,\Lambda_{12}\right) + x_2\left(\frac{\Lambda_{12}}{x_1 + x_2\Lambda_{12}} - \frac{\Lambda_{21}}{x_2 + x_1\Lambda_{21}}\right) \tag{13}$$

$$\Lambda_{12} = \frac{V_2}{V_1}\exp\left(-\frac{\lambda_{12} - \lambda_{11}}{RT}\right) = \frac{V_2}{V_1}\exp\left(-\frac{\Delta\lambda_{12}}{RT}\right) \tag{14}$$

$$\Lambda_{21} = \frac{V_1}{V_2}\exp\left(-\frac{\lambda_{21} - \lambda_{22}}{RT}\right) = \frac{V_1}{V_2}\exp\left(-\frac{\Delta\lambda_{21}}{RT}\right) \tag{15}$$

Where $\Delta\lambda_{12}$ and $\Delta\lambda_{21}$ in Eq. (14) and Eq. (15) represent cross-interaction energy parameters; λ_{12} and λ_{21} are the model parameters of the Wilson equation, whose value can be adjusted according to nonlinear least-square fitting [25]; and V_1 and V_2 denote the mole volumes of solute and solvent, respectively [11]. The parameters of the Wilson model in pure solvents are listed in **Table S1**.

For binary solvent mixtures, the Wilson model is shown as Eqs. (16)–(18) [19]:

$$\ln\ln\gamma_i = 1 - \ln\ln\left(\sum_{j=1}^{3} x_j\,\Lambda_{ij}\right) - \sum_{k=1}^{3}\left(\frac{x_k\Lambda_{kj}}{\sum_{j=1}^{3} x_j\Lambda_{kj}}\right) \tag{16}$$

$$\Lambda_{ij} = \frac{V_j}{V_i}\exp\left(-\frac{\lambda_{ij} - \lambda_{ii}}{RT}\right) = \frac{V_j}{V_i}\exp\left(-\frac{\Delta\lambda_{ij}}{RT}\right) \tag{17}$$

$$ln\gamma_1 = 1 - \ln\ln\left(x_1 + x_2\,\Lambda_{12} + x_3\,\Lambda_{13}\right) - \frac{x_1}{x_1 + x_2\Lambda_{12} + x_3\Lambda_{13}} + \frac{x_2\Lambda_{21}}{x_2 + x_1\Lambda_{21} + x_3\Lambda_{23}} - \frac{x_3\Lambda_{31}}{x_1 + x_2\Lambda_{32} + x_3} \tag{18}$$

where V_2 and V_3 denote the mole volumes of acetone and acetonitrile, respectively; and V_1 is the mole volume of regorafenib. The values of the mole volumes of solute and solvents are shown in **Table 1**. The parameters of Wilson model in binary solvent mixtures are listed in **Table S2**.

3.5 Data correlation

The relative average deviation (RAD) and the root-mean-square deviation (RMSD) were selected to evaluate the model fit. The formulas are shown as Eq. (19) and Eq. (20):

$$RAD = \frac{1}{N}\sum_{i}^{N}\left|\frac{x_1^{exp} - x_1^{cal}}{x_1^{exp}}\right| \tag{19}$$

$$RMSD = \left[\frac{1}{N}\sum_{i}^{N}(x_1^{cal} - x_1^{exp})^2\right]^{1/2} \tag{20}$$

where N represents the number of data points. The experimental and calculated solubility data can be expressed as x_1^{exp} and x_1^{cal}, respectively.

4. Results and discussion

4.1 Solid state characterizations

PXRD was adopted to analyze the crystalline transformation. The crystal characteristics of raw material and residual solids obtained from solutions (ethanol, methanol, acetonitrile, n-propanol,

isopropanol, acetone, and acetone + acetonitrile) at 298.15 K are revealed in **Figure 2** The XRD patterns were the same in other temperatures. No obvious characteristic peak change occurred, indicating no crystal transformation during dissolution in selected pure and binary solvents. These results ensured the accuracy of solubility measurement.
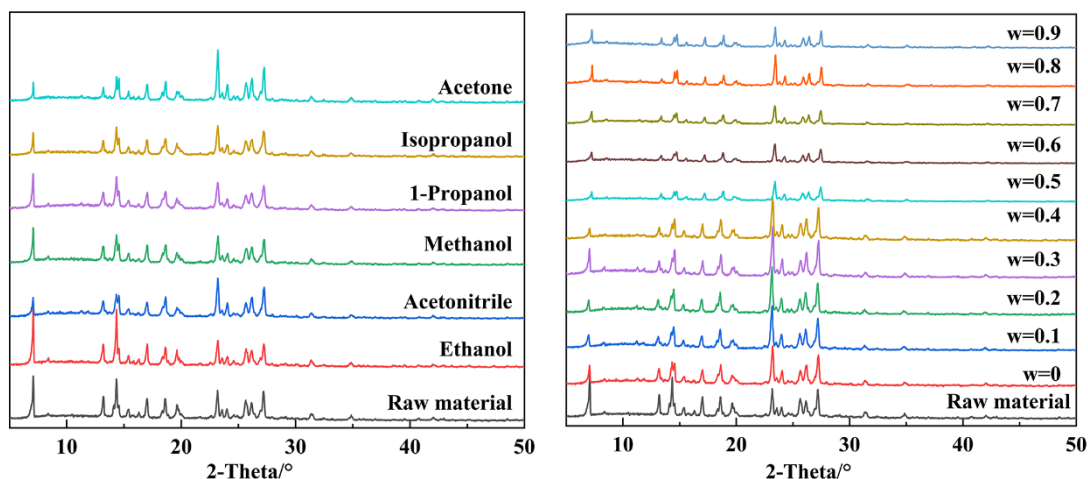

Figure 2 XRD patterns of residual solids and raw material in selected pure solvents and binary (acetone + acetonitrile) solvent mixtures

The DSC result of regorafenib is shown in **Figure 3**. The melting temperature (T_m) of regorafenib were found to be 486.23 K (onset temperature with the combined standard uncertainty of $u_C(T_m)= 0.22$ K) [26]. The peak temperature of melting was 487.13 K. We reported the peak temperature in order to compare our result with published literature. The peak temperature of melting reported in Ref.[27] was 486.85 K. And the value in Ref.[28] was 486.67 K. The melting enthalpy ($\Delta_{fus}H$) of regorafenib was found to be 49.41 kJ/mol (with the relative combined standard uncertainty of $u_{Cr}(\Delta_{fus}H)= 0.06$) which was similar to Ref.[28] in which the value of $\Delta_{fus}H$ was 46.50 kJ/mol. There are few reports on the DSC data of regorafenib. The T_m and $\Delta_{fus}H$ measured in this article were similar to the data currently reported.
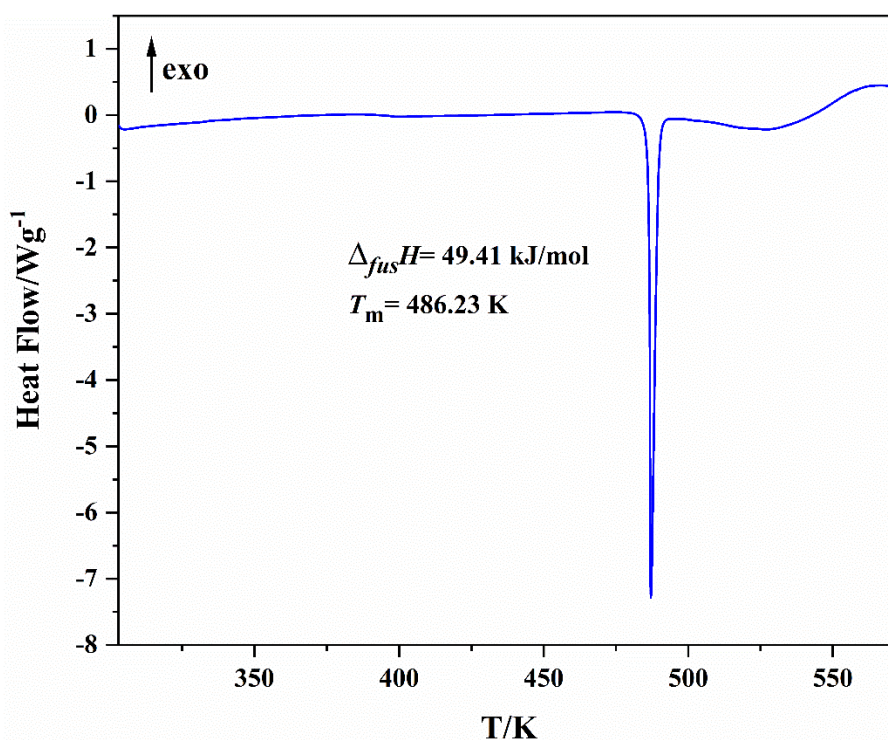
$\Delta_{fus}H$= 49.41 kJ/mol

T_m= 486.23 K

Figure 3 DSC curve of regorafenib

4.2 Solubility data in pure solvents

The solubility of regorafenib in six pure solvents with temperature ranging from 298.15 K to 313.15 K (interval = 5 K) was determined. The mole-fraction solubility (x) of regorafenib obtained from experiment and simulation are listed in **Table 2**. The mole-fraction solubility (x) of regorafenib in selected solvents at different temperatures is shown in **Figure 4**. The parameters of the thermodynamic models for regorafenib in six pure solvents are shown in **Table S1**. **Table 2** and **Figure 4** show that solubility increased monotonically with increased temperature. The order of solubility in six pure solvents was as follows: acetone > n-propanol > isopropanol > ethanol > methanol > acetonitrile. The maximum mole-fraction solubility was 5.40×10^{-3} (acetone, T = 313.15 K) and the minimum was 1.40×10^{-4} (acetonitrile, T = 278.15 K). Moreover, the most obvious change in solubility was that in acetone, and the data change between the maximum and minimum was about 6.82 times, followed by acetonitrile (3.51), methanol (2.53), n-propanol (2.45), isopropanol (2.45), and ethanol (2.26). The theoretical yield of the cooling-crystallization method in ethanol was about 56 % with decreased temperature from 313.15 K to 278.15 K. Considering the actual production, cooling crystallization may not be the best method when ethanol was used as the solvent to purify regorafenib. Similarly, when the solvents were n-propanol and isopropanol, the yield using the cooling-crystallization method was only 59 %. Meanwhile, the yields in methanol, acetonitrile, and acetone were 60 %, 72 %, and 85 %.
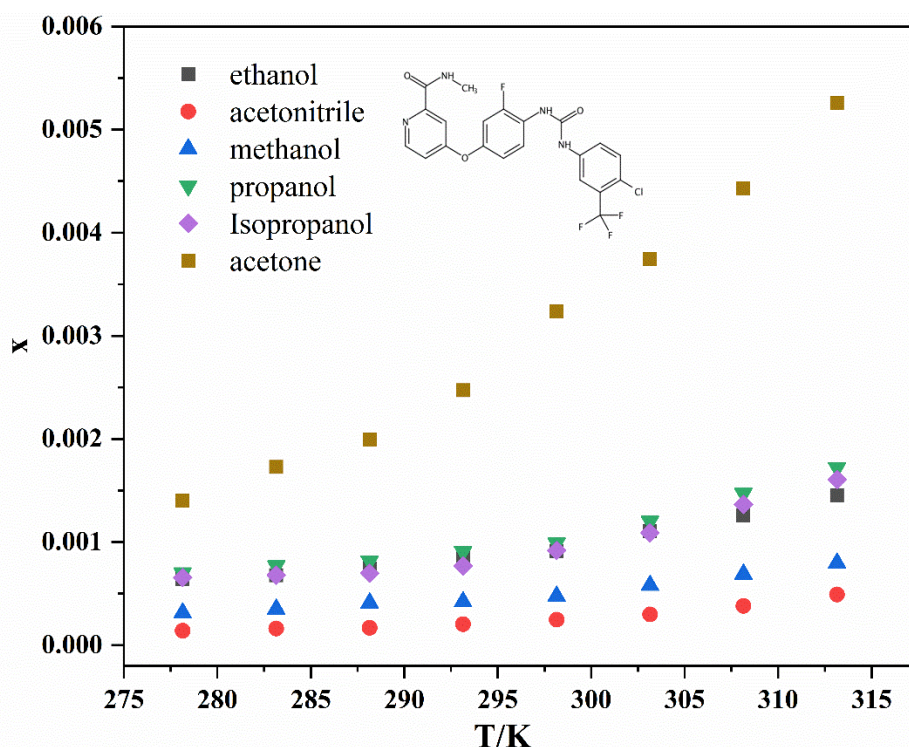
Figure 4 Mole-fraction solubility (*x*) of regorafenib in six solvents at different temperatures.

The six pure solvents investigated in this work can be divided into two groups, including polar protic solvents (methanol, ethanol, n-propanol, and isopropanol) and polar aprotic solvents (acetone and acetonitrile). The polarity value (E_T), dipole moment (μ), dielectric constant (ε), and Hildebrand solubility parameter (δ_H) are listed in **Table 3.** Among the polar protic solvents, the order of solubility was as follows: n-propanol > isopropanol > ethanol > methanol. The solubility order was opposite to the order of E_T, ε, and δ_H except for isopropanol, an i-alkyl alcohol. The three n-alkyl chain alcohols (n-propanol, ethanol, and methanol) had the same dipole moments values. This finding indicated that E_T, μ, and ε were important factors influencing solubility. However, the factors differed between i-alkyl and n-alkyl alcohols.

The physical properties were inconsistent with the solubility value in nonpolar protic solvents. The polarity value of acetone was lower than that of acetonitrile, but the solubility value in acetone was greater than that in acetonitrile. This finding showed that the interaction between molecules (solute–solvent and solvent–solvent) had a certain effect on solubility. Solutes and solvents containing C = O, N – H, and C ≡ N bonds easily formed hydrogen bonds [13]. To better explore the interaction between molecules, molecular simulation was performed and explained in section **4.4**.

Table 2 Experimental and fitted solubility data of regorafenib in six pure solvents (P = 0.1 MPa).ᵃ

T/K	$10^3 x_1^{exp}$	$10^3 x_1^{Apelblat}$	$10^3 x_1^{\lambda h}$	$10^3 x_1^{NRTL}$	$10^3 x_1^{Wilson}$
Ethanol					
278.15	0.641	0.642	0.579	0.574	0.542
283.15	0.677	0.705	0.665	0.661	0.669
288.15	0.739	0.782	0.760	0.758	0.791
293.15	0.865	0.873	0.866	0.865	0.909
298.15	0.911	0.981	0.984	0.984	1.023
303.15	1.102	1.110	1.110	1.115	1.133
308.15	1.260	1.264	1.260	1.259	1.239
313.15	1.453	1.446	1.410	1.418	1.342
Acetonitrile					
278.15	0.140	0.114	0.112	0.145	0.091
283.15	0.162	0.129	0.140	0.172	0.143
288.15	0.168	0.154	0.174	0.203	0.194
293.15	0.203	0.191	0.215	0.238	0.242
298.15	0.248	0.245	0.263	0.279	0.289
303.15	0.299	0.327	0.321	0.325	0.334
308.15	0.381	0.451	0.389	0.377	0.378
313.15	0.492	0.642	0.468	0.437	0.421
Methanol					
278.15	0.315	0.333	0.288	0.292	0.267
283.15	0.351	0.365	0.336	0.337	0.340
288.15	0.410	0.405	0.390	0.389	0.410
293.15	0.422	0.455	0.451	0.447	0.478
298.15	0.475	0.515	0.519	0.514	0.544
303.15	0.581	0.587	0.595	0.591	0.608
308.15	0.689	0.676	0.680	0.679	0.669
313.15	0.797	0.784	0.774	0.784	0.729
n-propanol					
278.15	0.701	0.713	0.607	0.603	0.571
283.15	0.769	0.745	0.709	0.703	0.725

288.15	0.814	0.805	0.825	0.817	0.873
293.15	0.908	0.896	0.954	0.947	1.016
298.15	0.990	1.026	1.100	1.094	1.154
303.15	1.201	1.207	1.260	1.261	1.288
308.15	1.471	1.456	1.450	1.450	1.416
313.15	1.719	1.796	1.650	1.664	1.541
isopropanol					
278.15	0.657	0.644	0.525	0.522	0.678
283.15	0.679	0.670	0.620	0.613	0.769
288.15	0.698	0.721	0.730	0.718	0.857
293.15	0.769	0.801	0.855	0.839	0.941
298.15	0.918	0.917	0.996	0.980	1.023
303.15	1.090	1.079	1.160	1.146	1.102
308.15	1.366	1.303	1.340	1.341	1.178
313.15	1.606	1.612	1.540	1.574	1.252
Acetone					
278.15	1.400	1.386	1.380	1.577	1.216
283.15	1.727	1.704	1.710	1.852	1.775
288.15	1.995	2.084	2.090	2.176	2.312
293.15	2.471	2.537	2.550	2.560	2.829
298.15	3.233	3.073	3.090	3.021	3.327
303.15	3.745	3.706	3.710	3.588	3.806
308.15	4.432	4.449	4.440	4.317	4.268
313.15	5.258	5.320	5.290	5.354	4.713

[a.] x_1^{exp} is the experimental mole-fraction solubility of regorafenib in six pure solvents. $x_1^{Apelblat}$, $x_1^{\lambda h}$, x_1^{NRTL}, and x_1^{Wilson} represent the mole-fraction solubility calculated by the modified Apelblat, λh, NRTL, and Wilson models, respectively. The standard uncertainty of temperature is u(T) = 0.05 K, and the relative standard uncertainty of pressure is u_r(P) = 0.05. The relative standard uncertainty of mole fraction solubility is u_r(x_1) =0.155.

Table 3 Physical properties of selected pure solvents

Solvents	E_T (30)[a]	μ/D[b]	ε[c]	δ_H /MPa$^{1/2}$ [d]
n-propanol	50.7	1.7	20.1	24.3
isopropanol	48.4	1.66	18.3	23.4

ethanol	51.9	1.7	22.4	26
methanol	55.4	1.7	32.6	29.7
acetonitrile	45.6	3.2	37.5	24.7
acetone	42.2	2.9	20.6	20.5

a Dimroth and Reichardt's polarity parameters, taken from Ref. [29].
b Dipole moment, taken from Ref. [30].
c Dielectric constant, taken from Ref. [30].
d Hildebrand solubility parameter (the unit is $MPa^{1/2}$), taken from Ref. [31].

4.3 Solubility data in binary mixtures

In the field of medicine, mixing a good solvent with a bad one is a common way to increase drug yield. In this work, acetone was used as a good solvent in the binary solvents (acetone + acetonitrile) because solubility in acetone was the largest among the selected pure solvents. The values of the mole-fraction solubility in binary solvents are listed in **Table 4** and shown in **Figure 5**. **Table 4** also lists the solubility values fitted by four thermodynamic models. The parameters of the thermodynamic models, 100 RAD, and 10^4 RMSD in binary solvent mixtures are listed in **Table S2**. **Figure 5** shows that the solubility values were positively correlated with the temperature and mass fraction (w) of good solvents. The solubility at high temperature was four times greater than that at low temperature when w was the same. At a certain temperature, the solubility at a high mass fraction of acetone was 11 times greater than that at a low w. The maximum mole-fraction solubility value (w = 0.9 and T = 313.15 K) was 35 times the minimum value (w = 0.1 and T = 278.15 K).
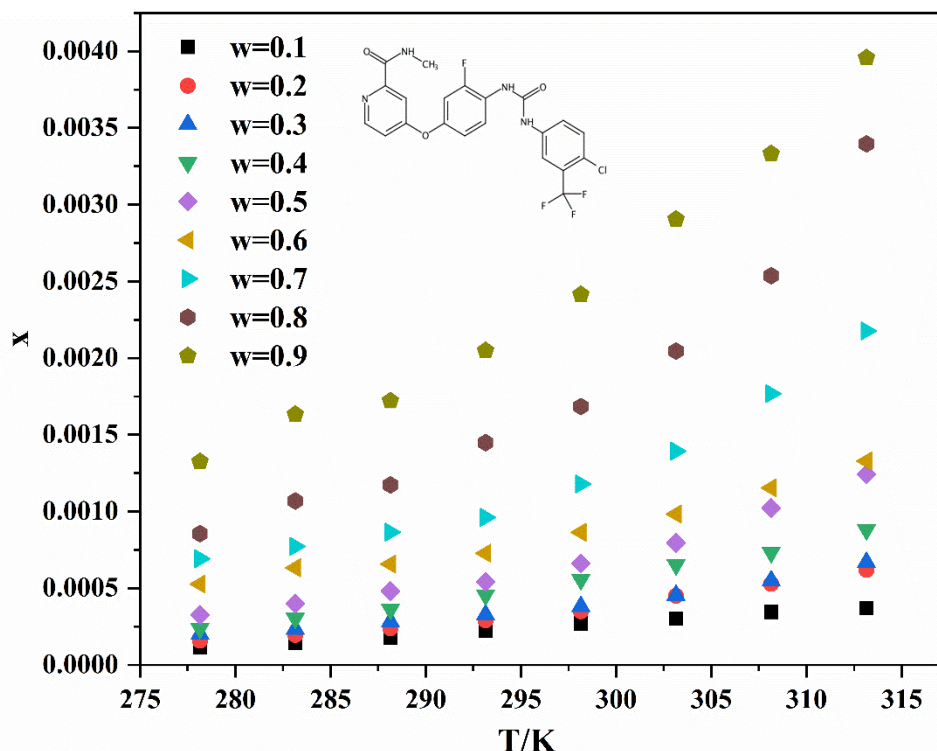

Figure 5 Mole-fraction solubility (x) of regorafenib in (acetone + acetonitrile) binary solvent

Table 4 Experimental and fitted solubility data of regorafenib in (acetone + acetonitrile) binary solvent mixtures (P = 0.1 MPa) [a].

T/K	$10^3 x_1^{exp}$	$10^3 x_1^{Apelblat}$	$10^3 x_1^{\lambda h}$	$10^3 x_1^{NRTL}$	$10^3 x_1^{Wilson}$
w=0.1					
278.15	0.112	0.109	0.130	0.134	0.104
283.15	0.142	0.143	0.154	0.158	0.146
288.15	0.179	0.180	0.182	0.185	0.187
293.15	0.223	0.221	0.214	0.216	0.227
298.15	0.270	0.263	0.250	0.251	0.265
303.15	0.302	0.304	0.291	0.291	0.302
308.15	0.344	0.342	0.337	0.335	0.338
313.15	0.369	0.376	0.389	0.385	0.372
w =0.2					
278.15	0.158	0.141	0.156	0.173	0.164
283.15	0.195	0.182	0.194	0.207	0.207
288.15	0.238	0.231	0.240	0.247	0.255
293.15	0.290	0.289	0.294	0.295	0.309
298.15	0.349	0.356	0.359	0.352	0.371
303.15	0.449	0.434	0.434	0.421	0.439
308.15	0.528	0.522	0.523	0.508	0.515
313.15	0.619	0.621	0.626	0.620	0.599
w =0.3					
278.15	0.201	0.183	0.187	0.188	0.157
283.15	0.233	0.212	0.228	0.226	0.226
288.15	0.281	0.250	0.275	0.271	0.293
293.15	0.327	0.299	0.330	0.323	0.359
298.15	0.381	0.362	0.395	0.384	0.423
303.15	0.455	0.444	0.469	0.456	0.485
308.15	0.549	0.551	0.554	0.541	0.547
313.15	0.668	0.691	0.652	0.641	0.607
w =0.4					

278.15	0.237	0.222	0.253	0.265	0.195
283.15	0.303	0.281	0.308	0.316	0.295
288.15	0.362	0.352	0.372	0.376	0.392
293.15	0.455	0.436	0.447	0.446	0.485
298.15	0.556	0.535	0.534	0.529	0.575
303.15	0.652	0.650	0.635	0.627	0.662
308.15	0.731	0.781	0.750	0.745	0.746
313.15	0.880	0.931	0.883	0.887	0.827
$w = 0.5$					
278.15	0.326	0.316	0.298	0.326	0.231
283.15	0.401	0.381	0.372	0.401	0.370
288.15	0.481	0.459	0.460	0.481	0.504
293.15	0.541	0.555	0.566	0.541	0.633
298.15	0.660	0.673	0.691	0.660	0.757
303.15	0.795	0.816	0.839	0.795	0.877
308.15	1.023	0.992	1.010	1.023	0.993
313.15	1.242	1.208	1.220	1.242	1.105
$w = 0.6$					
278.15	0.527	0.621	0.502	0.482	0.461
283.15	0.633	0.654	0.582	0.561	0.582
288.15	0.657	0.704	0.672	0.651	0.700
293.15	0.727	0.774	0.772	0.753	0.813
298.15	0.864	0.868	0.884	0.869	0.923
303.15	0.983	0.990	1.010	1.000	1.030
308.15	1.153	1.149	1.150	1.148	1.133
313.15	1.329	1.355	1.300	1.316	1.233
$w = 0.7$					
278.15	0.691	0.697	0.576	0.613	0.503
283.15	0.772	0.761	0.705	0.726	0.718
288.15	0.864	0.855	0.857	0.860	0.929
293.15	0.961	0.986	1.040	1.019	1.135

298.15	1.178	1.165	1.240	1.212	1.337
303.15	1.393	1.409	1.490	1.451	1.535
308.15	1.768	1.739	1.770	1.762	1.729
313.15	2.177	2.190	2.090	2.218	1.919
w =0.8					
278.15	0.855	0.869	0.743	0.851	0.591
283.15	1.069	1.030	0.936	1.012	0.948
288.15	1.172	1.229	1.170	1.204	1.296
293.15	1.449	1.475	1.450	1.436	1.634
298.15	1.684	1.781	1.790	1.722	1.963
303.15	2.046	2.161	2.180	2.084	2.283
308.15	2.537	2.634	2.660	2.575	2.595
313.15	3.396	3.225	3.210	3.397	2.900
w =0.9					
278.15	1.324	1.173	1.270	1.277	1.131
283.15	1.632	1.413	1.510	1.498	1.502
288.15	1.722	1.692	1.790	1.755	1.871
293.15	2.049	2.017	2.110	2.056	2.239
298.15	2.414	2.392	2.480	2.411	2.604
303.15	2.905	2.824	2.890	2.835	2.968
308.15	3.332	3.320	3.360	3.352	3.329
313.15	3.956	3.886	3.900	4.006	3.689

a. x_1^{exp} is the experimental mole-fraction solubility of regorafenib in binary solvents. $x_1^{Apelblat}$, $x_1^{\lambda h}$, x_1^{NRTL}, and x_1^{Wilson} represent the mole-fraction solubility calculated by the modified Apelblat, λh, NRTL, and Wilson models, respectively. The standard uncertainty of temperature is u(T) = 0.05 K, and the relative standard uncertainty of pressure is u_r(P) = 0.05. The relative standard uncertainty of mole fraction solubility is $u_r(x_1)$ =0.156. w is the mass fraction of acetone in the acetone + acetonitrile binary solvent mixtures. The relative standard uncertainty of the solvent composition is $u_r(w)$ = 0.01.

4.4 MD simulation

4.4.1 Solvent–solvent interaction

RDF analysis was performed by MD simulation to explore the interaction between solvents and solvents [32]. For pure solvents, the hydroxyl oxygen atom of ethanol, methanol, n-propanol, and isopropanol were investigated. Simultaneously, the oxygen atom of acetone and the nitrogen atom of acetonitrile were assigned to investigate the solvent–solvent

interaction respectively. **Figure 6** shows the RDF analysis of six pure solvents. The RDF between the oxygen atom of acetone and the nitrogen atom of acetonitrile was defined to probe the molecular interactions in binary solvents (**Figure 7**).

The value of the RDF peak between 0–5 Å indicates the formation of chemical bonds. An RDF distance between 2.6–3.5 Å represents hydrogen bonds, and that between 3.5–5 Å corresponds to van der Waals force. Ma et al. [33] pointed that the first RDF peak can be regarded as an intuitive standard for the comparison of interaction force, with the higher and sharper peaks representing the stronger interactions between molecules.

Figure 6 shows that the first and strongest RDF peaks of the four alcohol solvents were all at 2.65 Å, meaning that hydrogen bonds formed between the O–O of the four alcohol solvents. By comparing the strongest peak intensities, we observed that the order of the four alcohols was as follows: n-propanol > isopropanol > ethanol > methanol. This finding was consistent with the order of solubility and indicated that the aggregation of solvents had no significant effect on solubility to some extent. Meanwhile, the first peak of acetone and acetonitrile appeared between 3.5–5 Å. The peak was short and smooth, and the order of the first peak distance was inconsistent with the solubility order. Thus, the RDF analysis result proved that solvent–solvent interaction did not play a role in the solubility behavior of compounds in pure solvents.
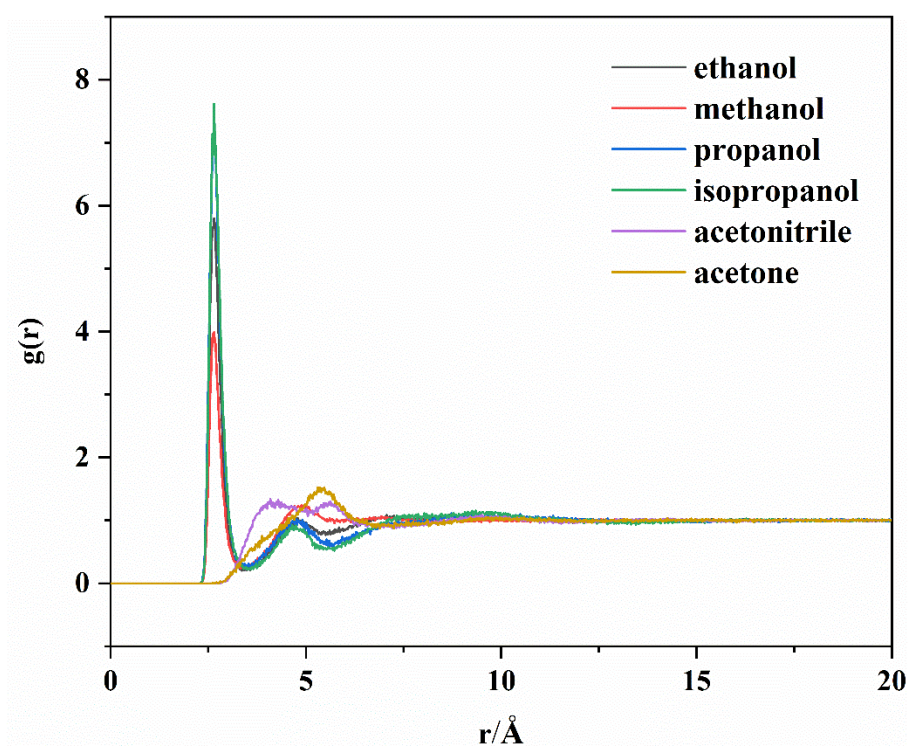
Figure 6 RDF analysis of molecular interactions in six pure solvents at 298.15 K.

Results of the RDF analysis of the molecular interactions between acetonitrile and acetone in a different mass ratio of acetone (w) are shown in **Figure 7**. The peak distance between the oxygen atom of acetone and the methyl hydrogen of acetonitrile in different mass ratios of acetone (**Figure 7(c)**) are all 2.77 Å, 4.25 Å, and 7.19 Å. This result suggested that molar interactions in binary solvents did not change with w. The peak distances were 3.13 Å, 4.39 Å, and 6.77 Å between the nitrogen atom of acetonitrile and the methyl hydrogen of acetone (**Figure 7(a)**). By comparing **Figure 7(c) and Figure 7(a),** O(acetone)–H(acetonitrile) was found to be stronger than N(acetonitrile)-H(acetone). **Figure 7(b)** shows an obvious peak at 5.49 Å. Thus, the order of interaction force was as follows: O(acetone)-H(acetonitrile) > N(acetonitrile)-H(acetone) > N(acetonitrile)-O(acetone). However, the peak distances and intensities did not change with acetone's mass ratio, indicating that it had little influence on solvent–solvent interaction.
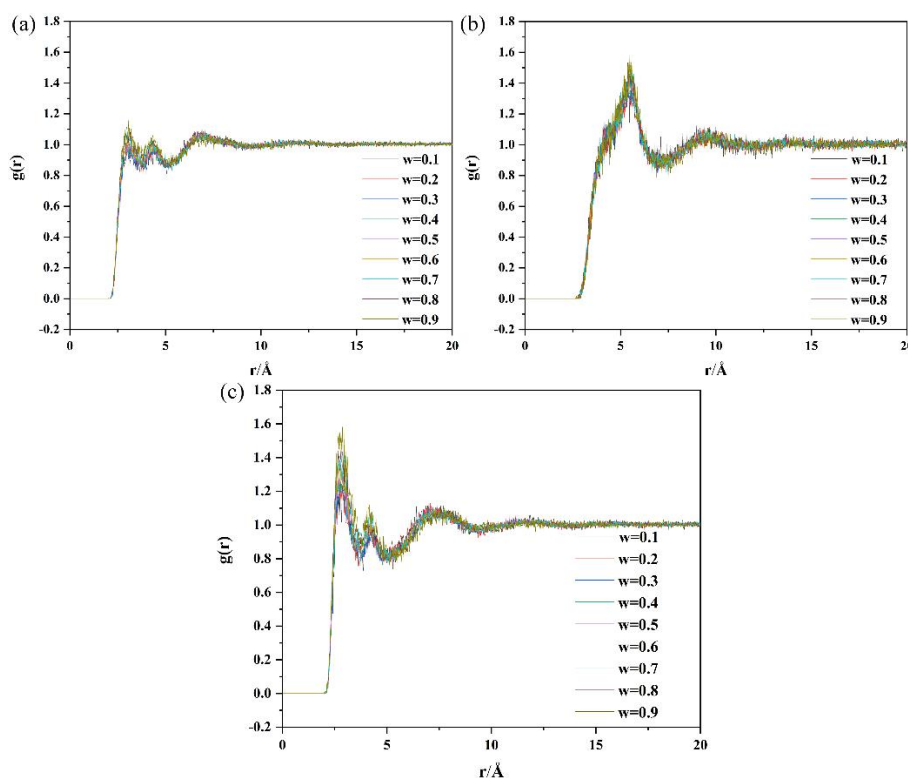

Figure 7 RDF analysis of molecular interactions in binary solvents at 298.15 K: (a) nitrogen atom of acetonitrile and methyl hydrogen of acetone, (b) nitrogen atom of acetonitrile and oxygen atom of acetone, and (c) oxygen atom of acetone and methyl hydrogen of acetonitrile (w represents the mass ratio of acetone).

4.4.2 Solute–solvent interaction

The solvation free energy describes the energy change of the solute from the vapor phase

to the solvent, so it is an indicator of the strength of solute–solvent interactions [34]. A larger absolute value of solvation free energy corresponds to stronger solute–solvent interaction.

Table 5 lists the calculated solvation free energy of regorafenib in six pure solvents. The absolute value of solvation free energy had the following order: acetonitrile < methanol < ethanol < isopropanol < n-propanol < acetone. This finding was consistent with the order of solubility data. Thus, the solute–solvent interaction did have a significant effect on the solubility of regorafenib in pure solvents. The value of solubility was positively correlated with solute–solvent interaction.

Table 5 Calculated solvation free energy of regorafenib in six pure solvents.

Solvent	Solvation free energy $(kJ \cdot mol^{-1})$	Solvent	Solvation free energy $(kJ \cdot mol^{-1})$
Ethanol	-117.035	n-Propanol	-120.763
Acetonitrile	-93.801	Isopropanol	-119.466
Methanol	-114.399	Acetone	-134.064

Table 6 displays the calculated solvation free energy of regorafenib in (acetone + acetonitrile) binary solvent mixtures. When the mass ratio of acetone reached 0.9, the maximum absolute value of solvation free energy was reached, that is, the interaction between solute and solvent became the largest. The order of solubility value was positively correlated with the absolute value of the solvation free energy. With increased initial mass ratio of acetone, the solute–solvent interaction and solubility value increased.

In conclusion, the solvation free energy representing the strength of solute–solvent interaction affected solubility whether in pure or binary solvents. The solvation free energy can well explain the result of the solubility of regorafenib and help predict the solubility of regorafenib, which is important for its production.

Table 6 Calculated solvation free energy of regorafenib in (acetone + acetonitrile) binary solvent mixtures.

w	Solvation free energy $(kJ \cdot mol^{-1})$	w	Solvation free energy $(kJ \cdot mol^{-1})$
0.00	-93.801	0.50	-124.277
0.10	-118.637	0.60	-125.474

0.20	-120.830	0.70	-126.997
0.30	-122.662	0.80	-128.131
0.40	-122.980	0.90	-128.930

4.5 Data correlation

Table S1 and Table S2 list the values of 100 RAD, 10^4 RMSD, and regression parameters obtained from the thermodynamic models MA, λh, NRTL and Wilson. They were utilized to better correlate and analyze the solubility data of regorafenib in pure and binary solvents. RAD and RMSD were used to evaluate the accuracy and applicability of the four models. The mean values of 100 RAD and 10^4 RMSD obtained by the MA, λh, NRTL, and Wilson models in pure solvents were (0.03, 0.27), (0.61, 0.49), (2.10, 0.62), (1.23, 1.19). For binary solvents, the mean values of 100 RAD and 10^4 RMSD obtained by the MA, λh, NRTL, and Wilson models were (0.02, 0.19), (0.85, 0.40), (1.33, 0.38), (0.57, 0.90). The four models showed satisfactory correlation with experimental solubility data in all investigated solvents. Minimum values of 100 RAD and 10^4 RMSD were obtained in the MA model both in pure and binary solvents. In summary, the MA model showed the most accurate correlation with solubility data whether in pure or binary solvents.

4.6 Solution thermodynamics

The van't Hoff equation is extensively used to estimate standard thermodynamic properties in the dissolution process. The equation is shown as Eq. (21)):

$$lnx_1 = -\frac{\Delta_{dis}H^0}{RT} + \frac{\Delta_{dis}S^0}{R} \tag{21}$$

where $\Delta_{dis}H^0$ and $\Delta_{dis}S^0$ represent standard dissolution enthalpy and entropy, respectively; and $\Delta_{dis}G^0$ indicates the standard Gibbs energy change. Additionally, the values of $\Delta_{dis}H^0$ and $\Delta_{dis}G^0$ calculated by Eqs. (22)–(24) [35] can be determined from the slope and intercept of the curves of $lnx_1 \sim (\frac{1}{T-\frac{1}{T_{mean}}})$. T_{mean} stands for the mean value of temperature, which was investigated in this work. $\Delta_{dis}S^0$ can be calculated by $\Delta_{dis}H^0$ and $\Delta_{dis}G^0$, displayed as Eq. (25) [34].

$$T_{mean} = \frac{n}{\sum_{i=1}^{n}\frac{1}{T_i}} \tag{22}$$

$$\Delta_{dis}H^0 = -R\left[\frac{\partial lnx}{\partial\left(\frac{1}{T}\right)}\right] = -R\left[\frac{\partial lnx}{\partial\left(\frac{1}{T-\frac{1}{T_{mean}}}\right)}\right] = -R \cdot slope \tag{23}$$

$$\Delta_{dis}G^0 = -RT_{mean} \times intercept \tag{24}$$

$$\Delta_{dis}S^0 = (\Delta_{dis}H^0 - \Delta_{dis}G^0)/T_{mean} \tag{25}$$

ζ_H and ζ_{TS} stand for the contribution of enthalpy and entropy to $\Delta_{dis}G^0$, respectively, and they can be expressed as Eq. (26) and (27):

$$\zeta_H = \frac{|\Delta_{dis}H^0|}{|\Delta_{dis}H^0| + |T\Delta_{dis}S^0|} \tag{26}$$

$$\zeta_{TS} = \frac{|T\Delta_{dis}S^0|}{|\Delta_{dis}H^0| + |T\Delta_{dis}S^0|} \tag{27}$$

Table 7 Thermodynamic properties of regorafenib in six pure solvents (P = 0.1 MPa)[a,b].

Solvent	$\Delta_{dis}H^0$ $(kJ \cdot mol^{-1})$	$\Delta_{dis}S^0$ $(J \cdot K^{-1} \cdot mol^{-1})$	$\Delta_{dis}G^0$ $(kJ \cdot mol^{-1})$	ζ_H	ζ_{TS}
Ethanol	17.34	0.59	17.16	0.091	0.909
Acetonitrile	25.72	17.81	20.46	0.005	0.995
Methanol	18.94	0.67	18.75	0.087	0.913
n-propanol	18.45	5.27	16.90	0.012	0.988
isopropanol	19.25	7.12	17.15	0.009	0.991
Acetone	27.84	45.30	14.46	0.002	0.998

[a] The relative standard uncertainty of pressure is $u_r(P) = 0.05$.

[b] The expanding uncertainties are $u(\Delta_{dis}H^0) = 0.05\Delta_{dis}H^0$, $u(\Delta_{dis}S^0) = 0.05\Delta_{dis}S^0$, $u(\Delta_{dis}G^0) = 0.05\Delta_{dis}G^0$ (0.95 level of confidence).

Table 8 Thermodynamic properties of regorafenib in (acetone + acetonitrile) binary solvent mixtures (P = 0.1 MPa)[a,b].

w	$\Delta_{dis}H^0$ $(kJ \cdot mol^{-1})$	$\Delta_{dis}S^0$ $(J \cdot K^{-1} \cdot mol^{-1})$	$\Delta_{dis}G^0$ $(kJ \cdot mol^{-1})$	ζ_H	ζ_{TS}
$w = 0.1$	25.13	15.28	20.61	0.006	0.994
$w = 0.2$	28.74	30.43	19.75	0.003	0.997
$w = 0.3$	24.61	17.41	19.47	0.005	0.995
$w = 0.4$	26.86	27.43	18.76	0.003	0.997
$w = 0.5$	27.13	30.55	18.12	0.003	0.997
$w = 0.6$	18.65	4.11	17.44	0.015	0.985
$w = 0.7$	23.68	23.87	16.64	0.003	0.997
$w = 0.8$	27.15	38.53	15.78	0.002	0.998
$w = 0.9$	22.31	24.97	14.94	0.003	0.997

[a] The relative standard uncertainty of pressure is $u_r(P) = 0.05$.

[b] The expanding uncertainties are $u(\Delta_{dis}H^0) = 0.05\Delta_{dis}H^0$, $u(\Delta_{dis}S^0) = 0.05\Delta_{dis}S^0$, $u(\Delta_{dis}G^0) = 0.05\Delta_{dis}G^0$ (0.95 level of confidence).

The values of $\Delta_{dis}H^0$, $\Delta_{dis}S^0$, $\Delta_{dis}G^0$, ζ_H, and ζ_{TS} are listed in **Table 7** and **Table 8.** The dissolution enthalpy $\Delta_{dis}H^0$ and the dissolution entropy $\Delta_{dis}S^0$ of regorafenib in pure and binary solvents were positive, indicating that the dissolution process of regorafenib was endothermic and entropy driven. The positive $\Delta_{dis}H^0$ also explained the fact that solubility increased with increased temperature. In pure solvents, the $\Delta_{dis}G^0$ order was opposite to the order of solubility value. Similarly, the value of $\Delta_{dis}G^0$ decreased with increased solubility data in binary solvents. Furthermore, the values of ζ_{TS} were larger than ζ_H in pure and binary solvents, illustrating that ζ_{TS} was the major contributor to $\Delta_{dis}G^0$.

5. Conclusions

The equilibrium solubility of regorafenib in pure solvents (ethanol, acetonitrile, methanol, n-propanol, isopropanol, and acetone) and binary solvents (acetone + acetonitrile) was measured by the gravimetric method within the temperature range of 278.15 K to 313.15 K. The solubility data of regorafenib increased with increased temperature in pure and binary solvents. For binary solvents, the data also increased with increased mass fraction of acetone. Four thermodynamic models including the MA, λh, NRTL, and Wilson models were used to correlate the solubility of regorafenib in pure and binary solvents. The MA equation performed better than the other models in pure or binary solvents. Furthermore, the results of molecular dynamic simulation using RDF analysis and solvation free energy indicated that solute–solvent interactions well fitted the solubility order of regorafenib in pure and binary solvents, but solvent–solvent interaction had no significant effect on solubility. The standard thermodynamic properties were calculated by the van't Hoff equation, which indicated that the dissolution process of regorafenib was endothermic and entropy driven. The combination of cooling and antisolvent crystallization method may be optimal for regorafenib purification. Solubility data played an important role in the optimization of regorafenib crystallization.

CRediT authorship contribution statement

Na Yuan: Conceptualization, Methodology, Investigation, Validation, Formal analysis, Data curation, Writing - original draft, Software. **Zhiyuan Chen:** Data curation. **Zili Suo:** Methodology, Investigation. **Qiang Cheng:** Validation, Formal analysis. **Qiaomei Sun:** Writing - review & editing, Supervision. **Yanfang Li:** Writing - review & editing, Supervision. **Hui Li:** Writing - review & editing, Supervision.

Declaration of Competing Interest

We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

The following are the Supplementary data to this article:

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