Solid–Liquid Equilibrium Behavior and Solvent Effect of Gliclazide in Mono- and Binary Solvents

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ABSTRACT: The solubility data of gliclazide in 10 mono-solvents (1,2-dichloroethane, 1,4-dioxane, 2-methoxyethanol, n-propyl acetate, isopropyl acetate, n-butyl acetate, pentyl acetate, dimethyl sulfoxide (DMSO), N,N-dimethylacetamide (DMA), and 2-butanone) and one kind of binary solvent (DMA + water) were measured between 278.15 and 323.15 K under atmospheric pressure by the gravimetric method. The Hansen solubility parameters and the KAT-LSER equation were used to investigate the solubility order and the influence of solvent effects on solubility. The experimental data were correlated by six thermodynamic models (the λh model, the Yaws model, the Apelblat model, the Jouyban model, the modified Jouyban–Acree model, and the Sun model). The results show that all of these models can correlate the experimental data well. Among them, the Apelblat model is the most suitable for correlating the solubility data of gliclazide in mono-solvents and binary solvents.

1. INTRODUCTION

Solution crystallization plays a significant role in separating and purifying products in pharmaceutical production, which determines the purity, particle size, and the final yield of products. Crystal properties of drugs will significantly affect the bioavailability, release, metabolism, and excretion of drugs.2,3 The solubility data of drugs are particularly important for the design and optimization of the crystallization process, which can provide the necessary parameters for crystallization process design. Meanwhile, solubility data are also of great significance for the selection of solvents in the crystallization process.4–8

Gliclazide (CAS No. 21187-98-4, molecular formula: C₁₅H₂₁N₃O₃S, Figure 1) is a second-generation sulfonylurea oral hypoglycemic drug, which is a white crystalline powder and widely used in the treatment of type 2 diabetes mellitus.9,10 There is no reported polymorph about gliclazide recently.9,11 The mechanism of action of gliclazide is similar to that of toluene sulfonylurea, which selectively stimulates islet precursor cells to promote insulin secretion and release.12,13 A lot of research has been reported on the synthesis and preparation of gliclazide, but few people pay attention to its crystallization process. Although gliclazide solubility data have been reported in some literature studies,12,14 the solubility of gliclazide in some commonly used solvents is still not available.

In this work, the solubility data of gliclazide in 10 kinds of mono-solvents (1,2-dichloroethane, 1,4-dioxane, 2-methoxyethanol, n-propyl acetate, isopropyl acetate, n-butyl acetate, pentyl acetate, dimethyl sulfoxide (DMSO), N,N-dimethylacetamide (DMA), and 2-butanone) and one kind of binary solvent (DMA + water) were measured between 278.15 and 323.15 K under atmospheric pressure by the gravimetric method. The Hansen solubility parameters and the KAT-LSER equation were used to investigate the solubility order and the influence of solvent effects on solubility. The experimental data were correlated by six thermodynamic models (the λh model, the Yaws model, the Apelblat model, the Jouyban model, the modified Jouyban–Acree model, and the Sun model). The results show that all of these models can correlate the experimental data well. Among them, the Apelblat model is the most suitable for correlating the solubility data of gliclazide in mono-solvents and binary solvents.

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thanol, n-propyl acetate, isopropyl acetate, n-butyl acetate, pentyl acetate, dimethyl sulfoxide (DMSO), N,N-dimethylacetamide (DMA), and 2-butane and one kind of binary solvent (DMA + water) were measured between 278.15 and 323.15 K under atmospheric pressure by the gravimetric method. The solvents selected in this study are common solvents, which can be used to optimize the crystallization process of glitazide and improve the product quality of glitazide, such as crystal size distribution, yield, and whiteness. Six thermodynamic models, including the $\lambda h$ model, the Yaws model, the Apelblat model, the Jouyban model, the modified Jouyban–Acree model, and the Sun model, were used to correlate the experimental data. Hansen solubility parameters were employed to study the solubility order of glitazide in mono-solvents and binary solvents. Furthermore, the KAT-LSER equation was used to study the influence of the solvent effects on the solubility of glitazide.

2. THEORETICAL BASIS

In this research, the solubility data of glitazide in 10 mono-solvents were correlated by the $\lambda h$ model, Apelblat model, and Yaws model. The solubility data of glitazide in DMA + water binary mixed solvents were correlated by the Apelblat model, the modified Jouyban–Acree model, and the Sun model. An open-source fitting software named 1stOpt (Professional Version 1.5, 7D-Soft High Technology Inc., China) was used in this investigation.

2.1. $\lambda h$ Model. The $\lambda h$ model is a semiempirical model proposed by Buchowski, which is used for solubility fitting of a solute in individual solvents. The $\lambda h$ model can be expressed as follows:

$$\ln \left[ 1 + \frac{\lambda (1 - x_i)}{x_i} \right] = \lambda \left( \frac{1}{T} - \frac{1}{T_m} \right)$$

where $\lambda$ and $h$ are model parameters of the $\lambda h$ model, $x_i$ is the mole fraction solubility of a solute, $T$ is the absolute temperature, and $T_m$ is the melting temperature of a solute.

2.2. Yaws Model. The Yaws model is also a semiempirical model to correlate the solubility data of a solute at different temperatures in mono-solvents. The equation is shown as follows:

$$\ln x_i = A_1 + \frac{B_1}{T} + C_1 \frac{1}{T}$$

where $A_1$, $B_1$, and $C_1$ are model parameters.

2.3. Jouyban Model. The Jouyban model is based on the van’t Hoff equation and uses the Abraham, Hansen, and Catalan parameters as variables that denote the solute–solvent interactions in the solution. It can be described as follows:

$$\ln x_i = \left( \alpha_0 + \frac{\sum_{i=1}^{4} \alpha_i A_i P_i}{T} + \frac{\sum_{i=1}^{2} \alpha_i H_i P_i}{T} + \frac{\sum_{i=1}^{2} \alpha_i C P_i}{T} \right) + \left( \beta_0 + \frac{\sum_{i=1}^{3} \beta_i A_i A_i P_i}{T} + \frac{\sum_{i=1}^{3} \beta_i H_i H_i P_i}{T} + \frac{\sum_{i=1}^{2} \beta_i C C P_i}{T} \right)$$

where $x_i$ is the mole fraction of a solute, $\alpha$ and $\beta$ terms are the model constants, and Abraham solvation parameters ($A_i$), Hansen solubility parameters ($H_i$), and Catalan parameters ($C P_i$) were used as the solute–solvent interaction terms.

2.4. Apelblat Model. The Apelblat model is widely used to fit the solubility data. It can be described as follows

$$\ln x_i = A_2 + \frac{B_2}{T} + C_2 \ln T$$

where $A_2$, $B_2$, and $C_2$ are model parameters of the Apelblat model and $x_i$ is the mole fraction of a solute.

2.5. Modified Jouyban–Acree Model. The Jouyban–Acree model is used to describe the effects of temperature and the fraction of each component in the binary solvent on solubility. The Jouyban–Acree model can be expressed as eq 5.

$$\ln x_i = x_i^2 \ln(x_i)_2 + x_i^3 \ln(x_i)_3 + x_i^2 \sum_{j=0}^{N} \frac{f(x_i - x_j)}{T}$$

where $x_i$ is the mole fraction of a solute; $x_i^2$ and $x_i^3$ are the mole fractions of each mono-solvent in the binary solvents (without a solute); $f_i$ is the model constant; and $N$ represents the composition of the solvent.

The Jouyban–Acree model can be combined with the Apelblat model to obtain the modified Jouyban–Acree model, which is shown as follows:

$$\ln x_i = a_2 + \frac{b_1}{T} + c_2 \ln T + (a_1 - a_2)x_i^2$$

$$+ \left( b_1 - b_2 + J_0 - J_1 + J_2 \right) \frac{x_i^3}{T}$$

$$+ \left( 3I_0 - I_1 - 5I_2 \right) \frac{x_i^2}{T} + \left( 8J_2 - 2J_1 \right) \frac{x_i^3}{T}$$

$$+ \left( -4J_2 \right) \frac{x_i^4}{T} + (c_1 - c_2)x_i^3 \ln T$$

The above equation can be simplified as

$$\ln x_i = \frac{A_1}{T} + A_2 \ln T + A_3 x_i^2 + A_4 x_i^3 + A_5 \frac{x_i^2}{T} + A_6 \frac{x_i^3}{T}$$

$$A_1 x_i^3 + A_2 x_i^4 + A_3 x_i^5 \ln T$$

where $A_1$ to $A_6$ are model parameters of the modified Jouyban–Acree model.

2.6. Sun Model. The Sun model is shown in 8, which is used to correlate the solubility data at temperature and solvent composition in binary solvents.

$$\ln x_i = D_1 + \frac{D_2}{T} + D_3 x_i^4 + D_4 \frac{x_i}{T} + D_5 \frac{x_i^2}{T} + D_6 \frac{x_i^3}{T} + D_7 \frac{x_i^4}{T}$$

where $D_1$ to $D_7$ represent the model parameters of the Sun model and $x_i$ is the mole fraction of good solvent in binary solvents.

2.7. Hansen Solubility Parameters. HSPs (Hansen solubility parameters) are widely used to predict the solubility order of a solute in solvents, which were proposed by Hansen in 1967. In this research, the effect of the interaction of glitazide with 10 different mono-solvents and one kind of binary solvent was analyzed by Hansen solubility parameters. The HSPs have three basic solubility parameters, namely, dispersion HSP ($\delta_d$), polarity HSP ($\delta_p$), and hydrogen-bonded...
HSP ($\delta_h$). The total Hansen solubility parameter ($\delta_t$) can be expressed by

$$\delta_t = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2}$$  \hspace{1cm} (9)

Values of parameters ($\delta_d$, $\delta_p$, and $\delta_h$) can be calculated by the group contribution method.\textsuperscript{28−30} The equation is as follows

$$\delta_i = \frac{\sum F_{di}}{V_i}$$  \hspace{1cm} (10)

$$\delta_p = \frac{\sum F_{pi}^2}{V_i}$$  \hspace{1cm} (11)

$$\delta_h = \frac{\sum F_{hi}}{V_i}$$  \hspace{1cm} (12)

where $i$ represents the structural group of the substance, $F_{di}$ is the group contribution to the dispersion forces, and $F_{pi}$ and $F_{hi}$ are the contribution of polarity force and hydrogen bonding energy of the structural group $i$, respectively.

The difference in total solubility parameter (Δ$\delta_t$) can be obtained from the following equation

$$\Delta \delta_t = |\delta_{t2} - \delta_{t1}|$$  \hspace{1cm} (13)

where $\delta_{t1}$ and $\delta_{t2}$ are total Hansen solubility parameters of gliclazide and solvents, respectively.

$\Delta \delta$ is used to evaluate the difference in the HSP between them. It can be expressed as follows

$$\Delta \delta = \sqrt{(\delta_{h2} - \delta_{h1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{d2} - \delta_{d1})^2}$$  \hspace{1cm} (14)

There is a concept of a thermodynamic relationship between $\delta_d$ and $\delta_p$, which is used in miscibility investigations. It can be expressed as follows

$$\delta_V = \sqrt{\delta_d^2 + \delta_p^2}$$  \hspace{1cm} (15)

$$Ra_v = 4(\delta_{V2} - \delta_{V1})^2 + (\delta_{h2} - \delta_{h1})^2$$  \hspace{1cm} (16)

The degree of miscibility between the two substances can be calculated by $21$ and $22$. The Hansen solubility parameters ($\delta_d$, $\delta_p$, and $\delta_h$) of each solvent selected in this study can be obtained from the literature.$^{31,32}$

### 2.8. Data Correlation

To evaluate the fitting level of each model, the relative average deviation (RAD) and root mean square deviation (RMSD) were selected to evaluate the fitting degree of each model

$$RAD = \frac{1}{n} \sum_{i=1}^{n} \left| \frac{x_{i}^{\text{exp}} - x_{i}^{\text{calc}}}{x_{i}^{\text{exp}}} \right|$$  \hspace{1cm} (17)

$$RMSD = \sqrt{\frac{1}{n} \sum_{i=1}^{n} \left( x_{i}^{\text{calc}} - x_{i}^{\text{exp}} \right)^2}$$  \hspace{1cm} (18)

where $n$ represents the number of experimental points, and $x_{i}^{\text{exp}}$ and $x_{i}^{\text{calc}}$ are the experimental and calculated solubility data, respectively.
solubility value increases with the increase of the mole fraction of DMA at a fixed temperature and increases with the increase of temperature at a fixed solvent composition. The solubility at the highest temperature and highest DMA content ($T = 323.15$ K and $P = 0.1$ MPa) is the experimental mole fraction solubility of gliclazide in 10 mono-solvents. $x_1$, $x_1^{\exp}$, $x_1^{\text{Jouyban}}$, and $x_1^{\text{Apelblat}}$ represent the calculated mole fraction solubility by the $Jh$ model, Yaws model, Jouyban model, and Apelblat model, respectively. The standard uncertainty of pressure is $u(P) = 0.05$ MPa. The relative standard uncertainty of mole fraction solubility is $u_r(x_1) = 0.04$.

Table 1. Experimental and Fitted Solubility Data of Crystalline Gliclazide in 10 Mono-Solvents at Temperatures from 278.15 to 323.15 K ($P = 0.1$ MPa)

| T/K  | $10^3 x_1^{\exp}$ | $10^3 x_1^{\text{Jouyban}}$ | $10^3 x_1^{\text{Apelblat}}$ | $10^3 x_1^{\text{Yaws}}$ |
|------|--------------------|-----------------------------|-----------------------------|-----------------------------|
| 278.15 | 5.450              | 5.387                        | 5.172                        | 5.496                        |
| 283.15 | 6.847              | 6.743                        | 6.540                        | 6.777                        |
| 288.15 | 8.334              | 8.379                        | 8.323                        | 8.336                        |
| 293.15 | 10.37              | 10.34                        | 10.21                        | 10.23                        |
| 298.15 | 12.39              | 12.69                        | 12.52                        | 12.52                        |
| 303.15 | 15.16              | 15.47                        | 15.29                        | 15.47                        |
| 308.15 | 18.45              | 18.77                        | 18.63                        | 18.62                        |
| 313.15 | 22.67              | 22.65                        | 22.64                        | 22.64                        |
| 318.15 | 27.21              | 27.21                        | 27.24                        | 27.44                        |
| 323.15 | 32.57              | 32.57                        | 32.91                        | 33.20                        |

| T/K  | $10^3 x_1^{\text{Jouyban}}$ | $10^3 x_1^{\text{Apelblat}}$ |
|------|-----------------------------|-------------------------------|
| 278.15 | 1.152                       | 1.172                         |
| 293.15 | 1.416                       | 1.408                         |
| 298.15 | 1.680                       | 1.688                         |
| 303.15 | 2.060                       | 2.006                         |
| 308.15 | 2.522                       | 2.594                         |
| 313.15 | 3.111                       | 3.131                         |
| 318.15 | 3.732                       | 3.714                         |
| 323.15 | 4.389                       | 4.385                         |

Table 2. Temperature and Pressure Range for the Calculations of总有12个温度点和压力点的范围用于计算

| T/K  | $10^3 x_1^{\text{Jouyban}}$ | $10^3 x_1^{\text{Apelblat}}$ |
|------|-----------------------------|-------------------------------|
| 278.15 | 0.8000                      | 0.7979                        |
| 283.15 | 0.9533                      | 0.9696                        |
and $x'_1 = 0.9$) is about 380 times greater than that at the lowest temperature and lowest DMA content ($T = 278.15$ K and $x'_2 = 0.3$). The solvent system involved in this study is an important solvent for gliclazide crystallization purification, especially the DMA + water system. This information would be meaningful in the process of purification and recrystallization of gliclazide.

The Hansen solubility parameters were used to analyze the solubility capable of gliclazide in this investigation. HSPs of gliclazide were calculated by the group contribution method, and the results are shown in Table 3. The HSP values are listed in Table 4. The results of $\delta_d$, $\delta_p$, and $\delta_h$ of gliclazide are 20.81, 18.87, and 7.48 MPa$^{1/2}$, respectively. As shown in Table 4, the solubility data of gliclazide were basically negatively correlated with the values of $R_s(v)$ except for the solvents of 2-butanone and pentyl acetate. For each mono-solvent, solubility data were basically negatively correlated with the values of $\Delta \delta_t$ and $\Delta \delta$. For DMA + water binary solvents, as the DMA mole ratio increases, the value of $\Delta \delta_t$ decreases, which is consistent with the tendency of gliclazide solubility to increase with an increasing positive solvent mole ratio except $x'_2 = 0.3$. Meanwhile, as the DMA mole ratio increases, the value of $\Delta \delta$ decreases, which is basically negatively correlated with the solubility data.

### 3.3. Effect of Solvents

The KAT-LSER model$^{35,36}$ was employed to study the solvent effects on the solubility of gliclazide, and the equation is expressed as follows

$$\ln(x) = c_0 + c_1 \pi^* + c_2 \alpha + c_3 \beta + c_4 \left( \frac{V_H^2}{100RT} \right)$$

where $\pi^*$ is the dipolarity/polarizability of the solvent; $\alpha$ and $\beta$ represent the acidity and basicity of hydrogen bonding of the solvent, respectively; and $V_H$ and $\delta_H$ are the molar volume of gliclazide and solubility parameter of Hildebrand of the solvent, respectively. The constant $c_0$ is the intercept value at $\pi^* = \alpha = \beta = 0$.
\[ n = 10, \quad R^2 = 0.97, \quad \text{RSS} = 2.03 \times 10^{-4} \]

where \( R^2 \) and RSS represent the squared relative coefficient and residual sum of squares, respectively. The values of the regression coefficient of \( \pi^*, \alpha, \beta, \) and \( V_{\delta H}^2/(100RT) \) are positive, indicating that the solubility of gliclazide is positively correlated with dipolarity/polarizability, hydrogen bond basicity, dipolarity/polarizability, and the Hildebrand solubility parameter in the total solvent effect is 14.34, 36.63, 12.61, and 36.42%, respectively, indicating that the hydrogen bond basicity and Hildebrand solubility parameter play an important role in the solubility of gliclazide.
3.4. Data Correlation. The $\lambda h$ model, Yaws model, Jouyban model, and Apelblat model were used to correlate the solubility data of gliclazide in 10 mono-solvents, while the Apelblat model, the modified Jouyban–Acree model, and the Sun model were used to correlate the solubility data of gliclazide in DMA + water binary solvent mixtures. The numerical values of the Abraham, Hansen, and Catalan parameters used in this work are shown in Table 6. The parameters, RAD, and RMSD of all selected models are listed in Table 7–11. The $P$ values of all model parameters are lower than 0.05. The results of the Jouyban model can be shown as follows

$$\ln x_i = (-14.06 - 51.53c - 249.09e - 5.79s - 41.19a - 24.03b + 16.99v + 0.97h + 3.708d_f + 2.503h_h + 19.915SP + 22.62SDP - 324.53SA - 13.97SB)$$

where $c$, $e$, $s$, $a$, $b$, and $v$ are the Abraham solvation parameters; $\delta_d$, $\delta_a$, and $\delta_h$ are Hansen solubility parameters; and SP, SDP, SA, and SB are Catalan parameters.

For mono-solvents, the Apelblat model, Jouyban model, and Yaws model correlate the experimental solubility better than the $\lambda h$ model by comparing the average value of RAD (0.0078). For DMA + water binary solvents, the Apelblat model is better than the other two models in correlating the experimental solubility, with maximum RAD and RMSD values of 0.0112 and 0.0031, respectively. The $R^2$ of all of the models was larger than 0.997.

Table 4. Values of Solvent Polarity and HSPs of Gliclazide and Selected Solvents

| solvent       | $\delta_d$ (MPa$^{1/2}$) | $\delta_a$ (MPa$^{1/2}$) | $\delta_h$ (MPa$^{1/2}$) | $\delta_f$ (MPa$^{1/2}$) | $\delta_s$ (MPa$^{1/2}$) | $\Delta\delta_d$ (MPa$^{1/2}$) | $\Delta\delta_a$ (MPa$^{1/2}$) | $\Delta\delta_h$ (MPa$^{1/2}$) |
|---------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-------------------------------|-------------------------------|-------------------------------|
| gliclazide    | 20.81                    | 18.87                    | 7.48                     | 29.07                    | 28.09                    | -1.94                         | -1.85                         | -0.98                         |
| 1,2-dichloroethane | 19.02                  | 7.36                     | 4.09                     | 20.80                    | 20.39                    | 15.77                         | 8.27                          | 12.13                         |
| 1,4-dioxide   | 19.00                    | 1.80                     | 7.40                     | 20.50                    | 19.09                    | 18.00                         | 8.57                          | 17.17                         |
| 2-methoxyethanol | 16.20                  | 9.20                     | 16.40                    | 24.80                    | 18.63                    | 20.92                         | 4.27                          | 13.94                         |
| n-propyl acetate | 15.30                  | 4.30                     | 7.60                     | 17.60                    | 15.89                    | 24.40                         | 11.47                         | 15.58                         |
| isopropyl acetate | 14.90                  | 4.50                     | 8.20                     | 17.59                    | 15.56                    | 25.07                         | 11.48                         | 15.55                         |
| n-butyl acetate | 15.30                  | 3.70                     | 6.30                     | 17.40                    | 15.74                    | 24.73                         | 11.67                         | 16.18                         |
| pentyl acetate | 15.80                   | 3.30                     | 6.10                     | 17.26                    | 16.14                    | 23.94                         | 11.81                         | 16.41                         |
| DMSO          | 18.41                   | 16.36                    | 10.23                    | 26.67                    | 24.63                    | 7.45                          | 2.40                          | 4.43                          |
| 2-butane      | 16.00                   | 9.00                     | 5.10                     | 19.00                    | 18.36                    | 19.60                         | 10.07                         | 11.23                         |
| DMA           | 16.80                   | 11.50                    | 10.20                    | 22.77                    | 20.36                    | 15.70                         | 6.30                          | 8.82                          |
| water         | 15.60                   | 16.00                    | 42.30                    | 47.80                    | 42.35                    | 36.66                         | 18.73                         | 35.32                         |
| DMA–water ($x'_w = 0.3$) | 16.43                  | 12.90                    | 20.2                     | 30.56                    | 20.98                    | 19.08                         | 1.49                          | 14.72                         |
| DMA–water ($x'_w = 0.4$) | 16.53                  | 12.51                    | 17.43                    | 28.41                    | 20.81                    | 17.64                         | 0.66                          | 12.56                         |
| DMA–water ($x'_w = 0.5$) | 16.61                  | 12.23                    | 15.41                    | 26.83                    | 20.68                    | 16.80                         | 2.23                          | 11.17                         |
| DMA–water ($x'_w = 0.6$) | 16.66                  | 12.01                    | 13.87                    | 25.63                    | 20.59                    | 16.31                         | 3.44                          | 10.25                         |
| DMA–water ($x'_w = 0.7$) | 16.71                  | 11.85                    | 12.66                    | 24.69                    | 20.51                    | 16.02                         | 4.38                          | 9.65                          |
| DMA–water ($x'_w = 0.8$) | 16.74                  | 11.71                    | 11.68                    | 23.93                    | 20.45                    | 15.84                         | 5.14                          | 9.25                          |
| DMA–water ($x'_w = 0.9$) | 16.77                  | 11.59                    | 10.88                    | 23.3                     | 20.4                     | 15.75                         | 5.77                          | 8.99                          |
Table 6. Numerical Values of the Abraham, Hansen, and Catalan Parameters Used in This Work

| solvent                  | λ   | 10^2λh | 10^2RAD | 10^4RMSD | R²   |
|-------------------------|-----|--------|---------|---------|------|
| 1,2-dichloroethane      | 0.3474 | 1.0600 | 1.36    | 2.78    | 0.9991 |
| 1,4-dioxane             | 0.3000 | 1.2513 | 1.05    | 1.40    | 0.9993 |
| 2-methoxyethanol        | 0.2731 | 1.3940 | 1.49    | 2.11    | 0.9990 |
| n-propyl acetate        | 0.0416 | 7.6203 | 1.17    | 0.51    | 0.9978 |
| isopropyl acetate       | 0.0267 | 11.0941 | 1.24 | 0.31    | 0.9993 |
| n-buty l acetate        | 0.0228 | 12.0032 | 0.75    | 0.21    | 0.9988 |
| pentyl acetate          | 0.0254 | 11.4236 | 0.79    | 0.19    | 0.9993 |
| DMSO                    | 0.1938 | 0.5664 | 0.45    | 6.48    | 0.9986 |
| 2-butanone              | 0.2519 | 1.3390 | 1.01    | 2.26    | 0.9987 |
| DMA                     | 0.0356 | 0.7907 | 0.63    | 8.06    | 0.9993 |
| average                 |       | 0.99    | 2.40    |         |       |

The maximum values of RAD and RMSD of all selected models are no larger than 0.0591 and 0.000806. In general, all selected models give satisfactory results.

4. CONCLUSIONS

The solubility data of gliclazide in 10 mono-solvents (1,2-dichloroethane, 1,4-dioxane, 2-methoxyethanol, n-propyl acetate, isopropyl acetate, n-buty l acetate, pentyl acetate, dimethyl sulfoxide, 2-butanone, N N-dimethylacetamide) and a binary solvent mixture (DMA + water) were measured by the gravimetric method at temperatures ranging from 278.15 to 323.15 K (at intervals of 5 K) under atmospheric pressure. Solubility of gliclazide in all of the selected solvents increases with the increase of temperature. In DMA + water binary solvents, the solubility of gliclazide increased with the increase of the proportion of good solvents at a fixed temperature. For mono-solvents, the maximum solubility (x₁ = 0.1439 mol·mol⁻¹) was obtained in DMSO (T = 323.15 K) and the minimum solubility (x₁ = 0.00008105 mol·mol⁻¹) was obtained in isopropyl acetate (T = 278.15 K). When the temperature is 298.15 K, the solubility order of gliclazide in the selected 10 mono-solvents is DMA > DMSO > 1,2-dichloroethane > 1,4-dioxane > 2-butanone, 2-methoxyethanol > n-propyl acetate > n-buty l acetate > pentyl acetate > isopropyl acetate. The solubility of gliclazide in the selected mono-solvents was affected by many factors, including the polarity of the solvent, viscosity, steric effects, and solute–solvent interaction. Hansen solubility parameters were employed to study the solubility behavior of gliclazide, and the KAT-LSER model was used to study the influence of solvent effects. Six thermodynamic models were used to correlate the experimental data. The Apelblat model and the Yaws model are more appropriate to correlate the solubility data in mono-solvents (with average RAD and RMSD values of 0.0078 and 0.00015), while the Apelblat model can better correlate the experimental data in the binary solvent system (with maximum RAD and RMSD values of 0.0112 and 0.00031).

5. EXPERIMENTAL SECTION

5.1. Materials. The active pharmaceutical ingredient (API) gliclazide (mass percentage 99.5%) was obtained from Shouguang Fukang Pharmaceutical Co., Ltd. Information of all of the materials used in this research are listed in Table 12. All organic solvents selected in this study (i.e., 1,2-dichloroethane, 1,4-dioxane, 2-methoxyethanol, n-propyl acetate, isopropyl acetate, n-buty l acetate, pentyl acetate, DMSO, 2-butanone, and DMA) were of analytical grade obtained from Sinopharm Chemical Reagent Co., Ltd. The deionized water was prepared...
Table 9. Parameters of the Apelblat Model of Gliclazide in 10 Mono-Solvents

| Solvent         | $10^{-3}A_2$  | $10^{-3}B_2$ | $C_2$  | $10^3$ RAD | $10^3$ RMSD | $R^2$  |
|-----------------|---------------|--------------|--------|------------|------------|--------|
| 1,2-dichloroethane | −9.5430      | 1.0150       | 15.8282 | 0.87       | 1.64       | 0.9993 |
| 1,4-dioxane     | −3.4535       | −1.9214      | 6.3559 | 1.03       | 1.39       | 0.9992 |
| 2-methoxyethanol | −11.0984      | 1.4271       | 17.7744 | 0.72       | 0.64       | 0.9996 |
| $n$-propyl acetate | −1.8259      | −2.3049      | 3.4813 | 1.19       | 0.57       | 0.9981 |
| isopropyl acetate | −2.6006      | −1.8115      | 4.5104 | 1.23       | 0.26       | 0.9990 |
| $n$-butyl acetate | −7.7320      | 0.6470       | 12.0803 | 0.73       | 0.16       | 0.9995 |
| pentyl acetate  | −9.0001       | 1.0867       | 14.0354 | 0.45       | 0.13       | 0.9997 |
| DMSO            | −3.1486       | −0.0321      | 5.1318 | 0.41       | 5.75       | 0.9986 |
| 2-butane        | −6.6769       | −0.1897      | 11.0280 | 0.91       | 1.63       | 0.9992 |
| DMA             | −2.1986       | −0.0475      | 3.4902 | 0.23       | 2.83       | 0.9997 |
| average         |               |              |        | 0.78       | 1.50       |        |

Table 10. Parameters of the Modified Jouyban–Acree Model and Sun Model for Gliclazide in DMA + Water Binary Solvent Mixtures

| Solvent          | modified Jouyban–Acree | Sun     |
|------------------|------------------------|---------|
|                  | $A_1$                  | $D_1$   |
| $A_1$            | −12.4840               | 11.2538 |
| $A_2$            | −6586.6697             | −8505.6708 |
| $A_3$            | 3.5266                 | −10.1166 |
| $A_4$            | 1.6097                 | 1920.91303 |
| $A_5$            | 13409.8396             | 26262.2899 |
| $A_6$            | −14191.0975            | 21773.9919 |
| $A_7$            | 9742.8501              | −7280.6598 |
| $A_8$            | −2881.2758             |        |
| $A_9$            | −1.7356                |        |
| $10^3$ RAD       | 5.91                   | 5.10    |
| $10^3$ RMSD      | 7.92                   | 7.60    |
| $R^2$            | 0.9994                 | 0.9994  |

in our laboratory (Advance EDI, Sartorius, Germany). All of the chemicals were used without further purification.

5.2. X-ray Powder Diffraction Analysis. X-ray powder diffraction (XRPD) was selected to evaluate the gliclazide raw materials and the residual solids obtained from different temperatures in each solvent to ensure that there was no crystal transformation during the equilibrium process. All tests were conducted by an X-ray diffractometer (PANalytical B.V. X’Pert PRO MPD, Netherlands). The experiment was performed by Cu Kα radiation at a scan speed of 10° min⁻¹, and the data were gauged from 5 to 50° (2θ). The tube voltage and the current were 40 kV and 30 mA, respectively. All of the measurements were carried out at room temperature (298.15 K) and atmospheric pressure (0.1 MPa).

5.3. Solubility Determination. The gravimetric method was selected to measure the solubility of gliclazide in both mono-solvents and binary solvents at temperatures ranging from 278.15 to 323.15 K (at intervals of 5 K) under atmospheric pressure. The experimental details and the validation of the system have been mentioned in our previous work.

The experimental process is described as follows. Excess solids of gliclazide were placed in a jacketed reactor, which contains a certain amount of solvent. The specified temperature was maintained through a thermostatic water-circulating bath (CF41, Julabo, Germany). The uncertainty of temperature is ±0.05 K. The solution was stirred for more than 10 h through a magnetic stirrer to ensure that solid–liquid equilibrium was reached, which was confirmed by concentration analysis every 0.5 h. After stopping the stirrer, the solution was allowed to stand for about 6 h. About 5 mL of supernatant was sampled and filtered by a 0.22 μm pore size filter membrane (all syringes and filter membranes used in the experiment were heated to the corresponding temperature in advance) and evaporated in a vacuum drying oven at 40 °C for 12 h to ensure that the weight does not change (the weight was confirmed every 0.5 h in the preliminary experiment to ensure that 12 h was enough for the drying process). The balance (model AL204, Mettler Toledo, Switzerland) with a precision of ±0.0001 g was used to measure the mass of all samples. The test was repeated three times at each temperature, and the average was taken as the final result. The mole fraction solubility of gliclazide in 10 different mono-solvents and a binary solvent mixture (DMA + water) was calculated according to 21 and 22

\[ x_1 = \frac{m_1}{M_1} \]
\[ x_2 = \frac{m_2}{M_2 + m_3/M_3} \]

where $x_1$ represents the mole fraction solubility of gliclazide, $x_2$ is the mole fraction of good solvent (DMA) in the binary solvent (DMA + water); $m_1$, $m_2$, and $m_3$ represent the masses of gliclazide, good solvent, and antisolvent, respectively; and $M_1$,
Table 12. Detailed Information of Materials Used in This Experiment

| chemical name          | CAS No.    | source                                      | mass fraction purity$^a$ | analysis method |
|------------------------|------------|---------------------------------------------|--------------------------|----------------|
| gliclazide             | 21187-98-4 | Shouguang Fukang Pharmaceutical Co., Ltd.   | ≥0.995                   | HPLC$^b$       |
| 1,2-dichloroethane     | 107-06-2   | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.990                   | GC$^c$         |
| 1,4-dioxane            | 123-91-1   | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.997                   | GC$^c$         |
| 2-methoxyethanol       | 109-86-4   | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.995                   | GC$^c$         |
| n-propyl acetate       | 109-60-4   | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.995                   | GC$^c$         |
| isopropyl acetate      | 108-21-4   | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.990                   | GC$^c$         |
| n-butyl acetate        | 123-86-4   | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.995                   | GC$^c$         |
| pentyl acetate         | 628-63-7   | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.985                   | GC$^c$         |
| dimethyl sulfoxide (DMSO) | 67-68-5                        | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.977                   | GC$^c$         |
| 2-butanone             | 78-93-3    | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.977                   | GC$^c$         |
| N,N-dimethylacetamide  | 127-19-5   | Sinopharm Chemical Reagent Co., Ltd.        | ≥0.990                   | GC$^c$         |
| water                  | 7732-18-5  | Ultrapure water machine                     |                          | none           |

$^a$Analytical method and mass fraction purity are sourced from the supplier. $^b$High-performance liquid chromatography. $^c$Gas chromatography.

$M_2$ and $M_3$ represent the molar masses of gliclazide, good solvent, and antisolvent, respectively. For mono-solvents, the values of $m_3$ are equal to 0.

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### Notes

The authors declare no competing financial interest.

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