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Influence of Solvent Systems on the Thermodynamic Properties and Energy Changes in Traditional Chinese Medicine Extraction

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ABSTRACT

The extraction of traditional Chinese medicine (TCM) is a crucial step in the modernization of TCM, where the efficiency and energy consumption are significantly affected by the microscopic properties of the solvent system, such as polarity and hydrogen bonding capacity. Current optimization of extraction processes largely relies on empirical trial-and-error approaches, lacking a systematic understanding of the intrinsic relationships between solvent systems and the thermodynamic behavior and energy dynamics of the extraction process. Although existing studies have applied models like Apelblat and Jouyban-Acree to fit solubility data, they face limitations in accurately characterizing interactions in multicomponent solvent systems, clarifying the separation of thermodynamic parameters, and linking energy changes with underlying molecular mechanisms. To address these challenges, this study investigates the mechanistic influence of solvent systems on the thermodynamics and energy transformations during TCM extraction from two perspectives: (1) constructing thermodynamic models by quantifying the temperature-solubility relationship via the Apelblat model, analyzing synergistic effects of mixed solvents using the Jouyban-Acree model, and fitting solubility behavior in complex solvent systems through an integrated modeling approach; and (2) introducing the KAT-LSER model, which employs Kamlet-Taft solvent parameters to establish linear correlations between solvent molecular characteristics and changes in enthalpy and entropy, thereby isolating the contributions of hydrogen bonding, dipolar interactions, and other forces to the thermodynamic driving forces of dissolution. This research reveals how the microscopic properties of solvents regulate the enthalpy-entropy balance of dissolution, affecting the spontaneity and energy requirements of the extraction process. A quantitative framework linking "solvent composition–thermodynamic parameters–energy changes" is thus established. The results provide theoretical support for a "thermodynamics-guided" optimization of TCM extraction, offering new insights into improving extraction efficiency, reducing energy consumption, and advancing green extraction technologies.

1. INTRODUCTION

TCM extraction is the core step in the modernization of TCM production [1, 2], and its efficiency and quality directly affect the material basis of pharmacological efficacy and the industrialization prospects of Chinese patent medicines [3]. As the "core medium" of TCM extraction, the solvent system determines the dissolution rate and equilibrium concentration of target components through processes such as dissolution, diffusion, and distribution. Differences in solvent polarity, hydrogen bonding capacity, and dielectric constant [4-7] not only lead to significant changes in solute solubility, but also cause complex fluctuations in the thermodynamic properties and energy consumption during the extraction process. However, the current optimization of TCM extraction processes mostly relies on empirical trial-and-error [8], lacking systematic understanding of the intrinsic relationship between solvent systems and the thermodynamic properties and energy changes of the extraction process. It is urgent to reveal the influence mechanism of solvent systems from the perspective of intermolecular interactions and thermodynamic essence.

In-depth analysis of the influence of solvent systems on the thermodynamic properties and energy changes of TCM extraction is the key to overcoming the bottlenecks of traditional extraction processes such as "high energy consumption, low efficiency, and poor predictability". From a scientific perspective, how the microscopic molecular properties of solvents affect the spontaneity and energy demand of the extraction process by changing the enthalpy-entropy balance of solute dissolution [9, 10] remains a core issue that has not been fully elucidated; from an application perspective, if a quantitative relationship between solvent composition, thermodynamic parameters, and energy consumption can be established, it can accurately guide solvent screening and process parameter optimization, and promote the transformation of TCM extraction towards "greening, intelligence, and energy-saving".

Although existing studies have attempted to describe the influence of temperature on solute dissolution through solubility models [11-14], or analyze the synergistic effects of mixed solvents using the Jouyban-Acree model [15, 16], there are still three limitations: First, most studies focus on single solvents or simple binary systems, lacking systematic thermodynamic parameter characterization for the commonly used multicomponent mixed solvents in TCM extraction, making it difficult to reflect the interactions in complex solvent systems; second, most existing models remain at the level of solubility fitting and lack separated analysis of enthalpy change, entropy change, and Gibbs free energy change of the dissolution process, leading to unclear contributions of intermolecular forces to thermodynamic driving forces [17, 18]; third, studies on energy changes in the extraction process are mostly limited to macroscopic energy consumption statistics, without establishing a quantitative relationship with the microscopic thermodynamic properties of solvent systems, making it difficult to reveal the essential reasons for energy consumption at the molecular level.

This study explores how solvent systems influence the thermodynamics and energy changes in TCM extraction, focusing on two key aspects: 1) Using the Apelblat model, it quantifies how solute solubility varies with temperature in different solvents. Combined with the Jouyban-Acree model, it examines the synergistic effects of mixed solvent components on solubility, and further develops an integrated model to describe dissolution behavior in complex solvent systems. This provides theoretical support for optimizing extraction temperature and solvent composition. 2) By introducing Kamlet-Taft solvent parameters, the study establishes linear relationships between solvent molecular properties and changes in dissolution enthalpy and entropy. This allows decomposition of the contributions from hydrogen bonding, dipole interactions, and others, revealing the molecular mechanisms by which solvent systems affect extraction thermodynamics.

This research moves beyond traditional single-factor analysis by integrating microscopic solvent properties, thermodynamic parameters, and energy changes into a unified framework. It offers a comprehensive theoretical basis for understanding TCM extraction and proposes a technical pathway for developing "thermodynamics-guided" green extraction processes. The findings are expected to greatly enhance the predictability and control of extraction, shift the industry from empirical methods to theory-driven practices, and provide significant scientific and practical value for the high-quality development of the TCM industry.

2. THERMODYNAMIC MODEL CONSTRUCTION

2.1 Solubility–temperature relation via Apelblat model

The Apelblat model can be used to correlate the relationship between the solubility of TCM components in different solvent systems and temperature. Through this model, the influence of temperature on solubility can be quantitatively described, providing theoretical support for studying temperature as a key factor in the extraction process. For example, if the solubility of a TCM component in a certain solvent change with temperature in accordance with the Apelblat model, it is possible to predict the solubility at different temperatures based on the model parameters, thereby optimizing the extraction temperature condition and improving extraction efficiency. Based on the Apelblat model, thermodynamic parameters such as enthalpy change and entropy change in the dissolution process can be further calculated. These parameters are crucial for understanding the dissolution mechanism of TCM components in solvents and the thermodynamic characteristics of the extraction process. For instance, the enthalpy change value calculated by the model can be used to determine whether the dissolution process is endothermic or exothermic, thereby providing a basis for controlling energy input during extraction.

Specifically, assuming that the mole fraction solubility of the solute is represented by a_X and the absolute temperature is represented by *S*, and the adjustable model parameters are represented by *X*, *Y*, and *Z*, the following is the classical expression of the Apelblat model:

$$\ln a_X = X + \frac{Y}{S} + Z\ln(S) \tag{1}$$

The first term *X* on the right side of the equation is a constant related to the characteristics of the solvent and solute, reflecting the influence of the interactions between solvent and solute on solubility under certain conditions. The second term *Y/S* reflects the significant impact of temperature on solubility. As the temperature increases, the value of this term changes, thus causing a corresponding change in solubility. This is mainly because temperature changes affect the thermal motion of solute molecules and the interaction forces between solute and solvent. The third term *Zln(S)* is a further correction to the temperature influence, considering the nonlinear impact of temperature on the dissolution process, enabling the model to more accurately describe the relationship between solubility and temperature. By fitting experimental data and determining the model parameters *X*, *Y*, and *Z*, a quantitative relationship between solubility and temperature under specific solute-solvent systems can be obtained, thereby predicting solubility at different temperatures.

The effect of temperature on solubility is a key factor considered by the model. On the one hand, increasing temperature raises the thermal kinetic energy of solute molecules, making it easier for solute molecules to overcome the interaction force between solvent molecules and enter the solution, thus increasing solubility. On the other hand, temperature changes also alter solvent properties such as density and viscosity, which indirectly affect the dissolution behavior of solutes in solvents. The Apelblat model describes this comprehensive influence of temperature on solubility through a specific functional form, allowing it to accurately capture trends in solubility change with temperature, whether it is a monotonic increase, decrease, or nonlinear variation.

Dissolution enthalpy change is an important thermodynamic parameter that describes the heat change during the dissolution process. The Apelblat model has a certain theoretical relationship with the van't Hoff equation. Assuming the equilibrium constant is represented by *J*, the reaction enthalpy changes by *ΔG*, and the gas constant by *E*, the van't Hoff equation is:

$$\frac{d\ln J}{dS} = \frac{\Delta G}{ES^2} \tag{2}$$

The van't Hoff equation describes the relationship between equilibrium constant and temperature. The dissolution process can to some extent be analogized to an equilibrium process, where solubility T and equilibrium constant K have similar thermodynamic significance. By analyzing and deriving the relationship between solubility and temperature in the Apelblat model, a form similar to the van't Hoff equation can be obtained, thereby establishing a connection between the model parameters and the dissolution enthalpy change:

$$\frac{d\ln T}{dS} = -\frac{Y}{S^2} + \frac{Z}{S} \tag{3}$$

From a physical perspective, the dissolution enthalpy change reflects the energy change during the interaction between solute and solvent molecules in the dissolution process, including the destruction of original solute-solute and solvent-solvent interactions and the energy changes accompanying the formation of new solute-solvent interactions.

Entropy change is a thermodynamic parameter that measures the change in disorder of the system. In the dissolution process, the entropy change mainly arises from the dispersion of solute molecules in the solvent and the rearrangement of solvent molecules. According to the basic thermodynamic relation $\Delta H = \Delta G - S\Delta T$, the Gibbs free energy change ΔH is related to enthalpy change ΔG, entropy change ΔT, and temperature. Meanwhile, the Gibbs free energy change is also related to solubility through a specific thermodynamic formula $\Delta H = -ES \ln(T)$. Utilizing these relationships, the dissolution entropy change ΔT can be calculated from known dissolution enthalpy change, temperature, and solubility data. Specifically, entropy change reflects the variation in the number of microstates in the system during the dissolution process. When a solute dissolves in a solvent, the number of microstates in the system usually increases, leading to an increase in entropy. However, the extent of change depends on the properties of the solute and solvent as well as the dissolution conditions.

2.2 Component effect on solubility via Jouyban-Acree model

Figure 1 is a schematic diagram of the experimental analysis platform for the TCM extraction process. Mixed solvent systems are often used in TCM extraction, and the Jouyban-Acree model can effectively consider the influence of each component in the mixed solvent on solute solubility. It can describe the solubility variation patterns of TCM components under different solvent compositions through model parameters, which helps in deeply studying the synergistic mechanism of mixed solvent systems. For example, when studying the extraction of a certain TCM component using an ethanol-water mixed solvent, the Jouyban-Acree model can accurately analyze the solubility variation of the component under different ethanol contents, providing theoretical guidance for optimizing the composition of mixed solvents. The model can also be used to predict the solubility and related thermodynamic properties of TCM components in multi-component systems. In actual TCM extraction processes, multiple components and complex solvent systems are often involved. The Jouyban-Acree model can comprehensively consider these factors, providing a powerful tool for studying extraction processes under complex systems. For example, for extracts containing multiple TCM components, this model can be used to predict the solubility variation of each component under different solvent compositions and temperature conditions, helping to better understand the competitive dissolution phenomena in the extraction process. Assuming that when solute is not added, the initial mole fractions of the cosolvent and antisolvent are denoted by a_1 and a_2, and the number of curves fitting parameters is denoted by V, the model is expressed as follows:

$$\ln a_X = a_1 \ln\left(a_X\right)_1 + a_2 \ln\left(a_X\right)_2 + a_1 a_2 \sum_{u=0}^{V} T_u \left(a_1 - a_2\right)^u \tag{4}$$

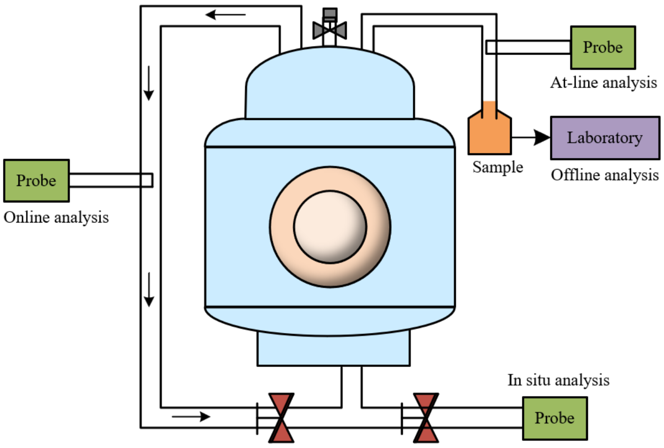


Figure 1. Schematic diagram of experimental analysis platform for TCM extraction process

Assuming that the model constant is denoted by K_u, and T_u is calculated by K_u/S. In a binary mixed solvent system under constant temperature S, let V=2, use (1 - a_1) to replace a_2, and Eq. (2) can be transformed into:

$$\begin{aligned}\ln a_X &= \ln\left(a_X\right)_2 + \left[\ln\left(a_X\right)_1 - \ln\left(a_X\right)_2 + T_0 - T_1 + T_2\right] a_2 \\ &+ \left(-T_0 + 3T_1 - 5T_2\right) a_1^2 + \left(-2T_1 + 8T_2\right) a_1^3 + \left(-4T_2\right) a_1^4\end{aligned} \tag{5}$$

Assuming that the model parameters obtained by the nonlinear least squares method are denoted by Y_0, Y_1, Y_2, Y_3, and Y_4. Further simplification gives:

$$\ln a_X = Y_0 + Y_1 a_1 + Y_2 a_1^2 + Y_3 a_1^3 + Y_4 a_1^4 \tag{6}$$

The model assumes that the properties of the mixed solvent are linear combinations of the properties of each pure solvent. For the solubility of the solute in the mixed solvent, the model assumes that it can be approximately described by the weighted average of the solute solubility in each pure solvent. Here, the weights are related to the mole fractions or volume fractions of each component in the mixed solvent. For example, for a mixed solvent composed of solvent X and solvent Y, with mole fractions a_X and a_B (a_X+a_B=1), the influence of the mixed solvent on the solubility of the solute can be expressed as T_{mix}=$a_X T_X$+$a_Y T_Y$, where T_{mix} is the solubility of the solute in the mixed solvent, and T_X and T_Y are the solubilities of the solute in pure solvent X and pure solvent Y, respectively. This additive assumption is the basis for the Jouyban-Acree model to consider the effect of mixed solvents. It simplifies the description of the complex properties of mixed solvents, making it possible to infer the properties of mixed solvents from the properties of pure solvents.

In practice, the interactions between each component in the mixed solvent and the solute are not simply linear relationships. Therefore, the model introduces some correction terms to more accurately describe the mixed solvent effects. These correction terms consider specific interactions between solvent and solute, such as hydrogen bonding, van der Waals forces, electrostatic interactions, etc. For example, when the interactions between solvent X and solvent Y with the solute are different, the solubility of the solute in the mixed solvent depends not only on the content of each solvent but also on the differences in their interactions with the solute. The model introduces parameters related to solvent composition and properties to correct the simple additive relationship, so as to more accurately reflect the influence of complex solvent-solute interactions in mixed solvents on solubility.

For multi-component mixed solvent systems, the Jouyban-Acree model extends the above principles. Assuming that the system contains v types of solvent components, with mole fractions a_1, a_2, ..., a_v ($\Sigma^{v}_{u=1}a_u=1$), then the solubility of the solute in this multi-component mixed solvent can be expressed as $T_{mix}=\Sigma^{v}_{u=1}a_uT_u+\Sigma^{v-1}_{u=1}\Sigma^{v}_{k=u+1}a_ua_k\eta_{uk}$, where T_u is the solubility of the solute in pure solvent u, and η_{uk} is a parameter related to the interaction between solvent u and solvent k. In this way, the model considers the binary interaction effects among each component in the multi-component mixed solvent on the solubility of the solute, and can more comprehensively describe the complex solvent-solute interactions in multi-component systems.

The parameters in the model are usually obtained through experimental data fitting. First, the solubility of the solute in mixed solvents of different compositions is measured, and then nonlinear least squares methods and other methods are used to fit the model to determine the parameters in the model, such as the solubility T_u of the solute in each pure solvent and the interaction parameters η_{uk}. Once these parameters are determined, the model can be used to predict the solubility of the solute in multi-component mixed solvents with different compositions, as well as other properties related to solubility, such as enthalpy of dissolution and entropy of dissolution.

2.3 Comprehensive model construction and model fitting

The Apelblat-Jouyban-Acree model combines the advantages of the Apelblat model and the Jouyban-Acree model, which can not only describe the relationship between solubility and temperature, but also consider the influence of mixed solvents. It can more comprehensively and accurately study the influence of solvent systems on the solubility and thermodynamic properties of TCM components at different temperatures. For example, when studying the effect of temperature and mixed solvent composition on the extraction of complex components in TCM, this model can simultaneously consider the dual effects of temperature and solvent composition, providing a more precise theoretical basis for optimizing the extraction process. The model can be expressed as:

$$\begin{aligned}\ln a_X &= a_1 \ln\left(a_X\right)_1 + a_2 \ln\left(a_X\right)_2 \\ &\quad + a_1 a_2 \sum_{u=0}^{V}\left[K_u\left(a_1-a_2\right)^u / S\right]\end{aligned} \tag{7}$$

where, $(a_X)_1$ and $(a_X)_2$ can be expressed by the Apelblat model respectively as:

$$\ln\left(a_X\right)_1 = X_1 + \frac{Y_1}{S} + Z_1 \ln S \tag{8}$$

$$\ln\left(a_X\right)_2 = X_2 + \frac{Y_2}{S} + Z_2 \ln S \tag{9}$$

By combining the above three equations, we obtain:

$$\begin{aligned}\ln a_X &= a_1\left(X_1 + \frac{Y_1}{S} + Z_1 \ln S\right) \\ &+ a_2 \ln\left(X_2 + \frac{Y_2}{S} + Z_2 \ln S\right) + a_1 a_2 \sum_{u=0}^{V}\left[K_u\left(a_1-a_2\right)^u / S\right]\end{aligned} \tag{10}$$

In the experiment, this paper uses the Average Relative Deviation (ARD) and the Root Mean Square Deviation (RMSD) to evaluate the applicability and accuracy of the three modified models. Assuming the number of experimental points is represented by V, and the model-calculated and experimental values of the solute molar fraction solubility are represented by a_X^{CAL} and a_X^{EXP} respectively, we have:

$$ARD = \frac{1}{v}\sum_{u=1}^{v}\left|\frac{\left(a_X^{EXP}\right)_u - \left(a_X^{CAL}\right)_u}{\left(a_X^{EXP}\right)_u}\right| \tag{11}$$

$$RMSD = \sqrt{\frac{\sum_{u=1}^{v}\left(\left(a_X^{EXP}\right)_u - \left(a_X^{CAL}\right)_u\right)^2}{v}} \tag{12}$$

3. THERMODYNAMIC DRIVING FORCE OF DISSOLUTION VIA KAT-LSER

The KAT-LSER model is based on Kamlet-Taft solvent parameters, transforming complex solvent properties such as polarity and hydrogen bonding ability into quantifiable parameters. In the paper, this model can establish a linear relationship between solute solubility and solvent parameters. Here, solute solubility refers to the solubility of active ingredients in TCM in different solvents. Figure 2 shows the schematic diagram of the online detection system for the dissolution process thermodynamic driving force analysis of TCM extraction. It is assumed that the model coefficients represent the influence of corresponding solvent properties on solubility, denoted by z_0, z_1, z_2, z_3 and z_4x. The hydrogen bond donation ability of the solvent is represented by β, the hydrogen bond acceptance ability by α, the non-specific dipolarity/polarizability by τ^*, the Hildebrand solubility parameter by σ_G, the molar volume of the solute by N_t, and the ideal gas constant by E. The formula usually takes the form:

$$\ln a_X = z_0 + z_1\beta + z_2\alpha + z_3\tau^* + z_4\left(\frac{N_T\sigma_G^2}{100ES}\right) \tag{13}$$

For mixed solvent systems such as ethanol-water and methanol-acetone, the KAT-LSER model can predict solute solubility through the parameters of the mixed solvent, revealing the influence of synergistic effects between solvents on the dissolution process. For example, when the α value of the mixed solvent increases, it may promote the dissolution of

TCM components containing hydroxyl groups, thereby explaining the nonlinear change in solubility through the variation of model parameters.

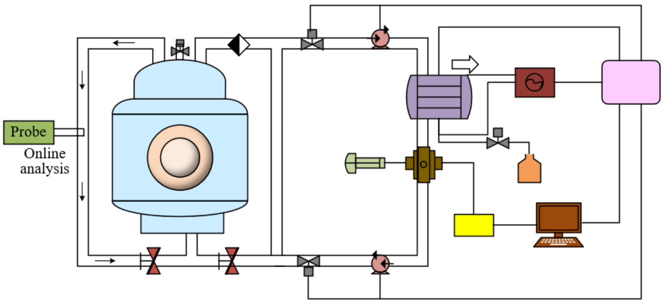


Figure 2. Schematic diagram of the online detection system for the thermodynamic driving force analysis of the dissolution process of TCM extraction

The Gibbs free energy change, enthalpy change, and entropy change of the dissolution process can be calculated through solubility data, and the KAT-LSER model can further associate these thermodynamic parameters with intermolecular interactions of the solvent. For example, enthalpy change reflects the energy change of solute-solvent interactions, such as the enthalpy effect of hydrogen bond formation/breakage, which can be used to analyze the contribution of solvent hydrogen bonding to ΔG through the temperature dependence of α and β parameters in the model. Entropy change is related to the disorder change of solute in the solvent. The change in the τ^* parameter in the model may affect the ordering of the solvent structure, thus explaining the difference in ΔT.

Through the parameters of the KAT-LSER model, the effects of polar interactions, hydrogen bond donors, and hydrogen bond acceptors on the dissolution thermodynamic parameters can be separated. For example, if the dissolution enthalpy change of a certain TCM component shows a significant positive correlation with the β value of the solvent, it indicates that the hydrogen bond acceptor ability of the solvent is the main enthalpic factor driving dissolution, while entropy change may be more related to the molecular arrangement changes caused by solvent polarity.

In TCM extraction, it is often necessary to improve the extraction efficiency of target components through gradient mixed solvents such as water-ethanol. The KAT-LSER model can predict the solubility capacity of different proportioned mixed solvents based on the parameters of pure solvents to screen the optimal solvent composition. For example, for components with large polarity differences such as alkaloids and glycosides, by adjusting the α, β, and τ^* values of the mixed solvent, one can quantitatively analyze the effect of solvent polarity and hydrogen bonding ability on the solubility of target components, thereby optimizing the solvent ratio for extraction.

The extraction process of different solvent systems is accompanied by different energy changes, such as heating energy consumption. The KAT-LSER model can reveal the energy consumption mechanism of high ΔG systems through the correlation between solvent parameters and dissolution enthalpy change, providing a theoretical basis for low-temperature extraction or energy-saving processes. For example, if the dissolution enthalpy change of a certain solvent system is positive and strongly correlated with the α value, it indicates that reducing the hydrogen bond acceptor ability of the solvent may reduce the energy required for dissolution.

The advantage of the KAT-LSER model lies in directly associating macroscopic dissolution behavior with microscopic intermolecular interactions. In this paper, the physical meaning of model parameters can be used in combination with the structural characteristics of TCM components to explain the following scientific problems:

(1) The fundamental reason why polar solvents have higher solubility for polar components lies in the synergistic effect of solvent polarity and hydrogen bond acceptor ability driving the thermodynamic spontaneity of the dissolution process.

Polar solvents have higher τ^* and α parameters, while polar component molecules are rich in polar groups such as hydroxyl and carbonyl. From the perspective of intermolecular interactions, the strong polarity of water enables it to form directional electrostatic attraction with the polar groups of flavonoid glycosides through dipole-dipole interactions, effectively weakening the cohesive force between solute molecules and reducing the energy barrier of the dissolution process; meanwhile, as a strong hydrogen bond acceptor, the oxygen atom in the water molecule can form hydrogen bonds with the hydrogen atom of the hydroxyl group and the oxygen atom of the carbonyl group of the flavonoid glycoside, stabilizing the solvated state of the solute through "solvent-solute" hydrogen bond association. This synergistic effect is thermodynamically manifested as a decrease in dissolution enthalpy change and an increase in dissolution entropy change, ultimately significantly reducing the Gibbs free energy change of the dissolution process and significantly improving the solubility of polar components in polar solvents.

(2) The dissolution-promoting effect of hydrogen bond donor solvents on components containing hydrogen bond acceptor groups originates from the specific interaction between the hydrogen bond donor ability of the solvent and the acceptor groups of the solute.

The hydroxyl group of ethanol acts as a hydrogen bond donor and has a high β parameter, while the carbonyl oxygen in ester groups is a typical hydrogen bond acceptor. When ethanol dissolves components containing ester groups, the hydrogen atom of the hydroxyl group of ethanol can form a hydrogen bond with the carbonyl oxygen of the ester group. This "donor-acceptor" interaction directly disrupts van der Waals aggregation or internal hydrogen bonding between solute molecules, reducing the activation energy required for dissolution and decreasing the enthalpy change of dissolution. At the same time, the hydrogen bonding effect forms a stable solvation layer around the solute, inhibiting the aggregation of solute molecules and increasing their freedom of dispersion in the solvent, thereby leading to an increase in the entropy change of dissolution. In this process, the contribution of the β parameter dominates, reflecting the selective dissolution advantage of the hydrogen bond donor ability of the solvent for components with specific acceptor groups. Especially for ester compounds with relatively weak polarity, hydrogen bonding becomes the key dissolution driving force surpassing dipole interactions, synergistically promoting the spontaneity of the dissolution process from both enthalpy and entropy aspects.

(3) Hydrogen bond association between solvent molecules in mixed solvents reconstructs the solvation environment around the solute, mainly having a significant impact on the entropy change of dissolution, and its mechanism is closely related to the structural ordering change of the solvent.

In pure water systems, water molecules form a highly ordered network structure through strong hydrogen bonds, while the addition of ethanol disrupts this ordered network, increasing the molecular freedom of the mixed solvent. When the solute dissolves, the formation of the solvation layer no longer depends on strict orientational arrangement of water molecules, and the disorder of solvent molecules around the solute increases significantly, leading to an increase in the entropy change of dissolution, which is conducive to the spontaneity of the dissolution process. In addition, in ethanol-water mixed solvents, the hydrogen bond donor ability of ethanol and the hydrogen bond acceptor ability of water form "cross hydrogen bonds", making the mixed solvent simultaneously possess donor and acceptor characteristics, which can form multiple hydrogen bonds with the multifunctional groups of solute molecules, enhancing the stability of the solvation layer. Although local multiple hydrogen bonds may increase the ordering of the solvation layer, the disordering effect of the bulk solvent structure dominates, ultimately showing an overall entropy-increasing effect. This modulation of entropy change by solvent intermolecular interactions is especially crucial for TCM components containing multiple hydrogen bond groups and may make the entropy effect the key dissolution driving force surpassing the enthalpy effect, revealing the essential rule that the mixed solvent system affects the thermodynamic characteristics of the extraction process by changing the microstructure of the solvation environment.

4. RESULTS AND ANALYSIS

In this study, the solubility of TCM extraction in single and mixed solvent systems under different temperatures was determined using the static gravimetric method. The solubility data from the extraction process were fitted to the modified Apelblat, Jouyban-Acree, and Apelblat-Jouyban-Acree models using OriginPro 9.0 software, in order to validate the effectiveness of the three models.

Table 1. Solubility and fitting parameters, ARDs, and RMSDs of the Apelblat model in single and mixed solvents under low temperature conditions

Solvent	X	Y	Z	ARD/%	10^4RMSD
Water-Ethanol	-115.2365	3251.2136	15.2351	0.674	2.154
Water-Propylene glycol	-187.2315	6548.2315	28.2658	0.962	0.562
Ethanol-Ethyl acetate	-278.2351	11256.3256	42.1023	2.215	0.658
Ethanol-Acetone	-312.1026	12524.3258	47.2658	2.236	0.478
n-Butanol-Water	-11.2356	-2635.3217	2.3256	1.789	0.345
Supercritical CO_2-Ethanol	-61.2015	-356.3215	11.2035	2.201	0.289
Deep eutectic solvent (ChCl-Gly)	-118.3269	2564.5895	18.2574	1.256	0.125
Water	-287.3215	12154.2365	43.2652	0.348	0.056
Propanol	115.3268	-9125.6258	-15.2365	0.889	0.018
Ethyl acetate	-378.2365	12568.3252	57.2365	3.562	0.044

Table 2. Solubility and fitting parameters, ARDs, and RMSDs of the Apelblat model in single and mixed solvents under high temperature conditions

Solvent	X	Y	Z	ARD/%	10^4RMSD
Water-Ethanol	11.2356	-6625.3256	754126.2356	0.668	2.125
Water-Propylene glycol	15.2356	-11256.3259	1252685.3215	1.125	0.625
Ethanol-Ethyl acetate	23.2354	-14158.2365	1895215.2354	2.123	0.648
Ethanol-Acetone	26.3258	-14826.3251	2265821.2352	2.152	0.523
n-Butanol-Water	5.5412	-16598.2352	94521.2356	1.785	0.348
Supercritical CO_2-Ethanol	9.1254	-4126.3256	412548.3265	2.124	0.316
Deep eutectic solvent (ChCl-Gly)	13.2658	-6125.3269	912548.2368	1.268	0.128
Water	22.2154	-9326.3215	2152568.3215	0.446	0.072
Propanol	-1.6859	-16526.2315	-663251.1245	0.912	0.021
Ethyl acetate	36.2359	-22562.3215	2895415.2365	3.489	0.045

From the data in Table 1 and Table 2, it can be observed that the fitting performance of the Apelblat model for solute solubility in different solvent systems varies significantly. Under low temperature conditions, the ARD and RMSD values of single solvents are generally low. For example, the 10^4RMSD of propanol is only 0.018, indicating very high fitting accuracy. In contrast, the ARD range for mixed solvents is 0.674%~2.236%, and the deep eutectic solvent (ChCl-Gly) shows the lowest RMSD of 0.125×10^4, suggesting that the solubility variation with temperature is more easily described by the model. Under high temperature conditions, most solvents show a slight increase in ARD and RMSD. For instance, the ARD of water-ethanol slightly decreased from 0.674% to 0.668%, and ethyl acetate's ARD slightly decreased from 3.562% to 3.489%, but still maintained a high deviation, indicating the complexity of its temperature-dependent solubility. In addition, the signs and numerical values of the model parameters *X*, *Y*, and *Z* vary significantly. At low temperatures, the *X* values of mixed solvents are mostly negative, while at high temperatures, the *X* values of some solvents become positive, reflecting the change in the mechanism of temperature's influence on solubility. In line with the research content, the above data indicate that the Apelblat model can effectively quantify the temperature dependence of solute solubility in different solvent systems. Moreover, the high-accuracy fitting in single solvents at high temperature may be related to their simple intermolecular interactions and regular solubility-temperature relationships. 2) The microscopic properties of the solvent systems are reflected by the signs and magnitudes of the parameters *X*, *Y*, and *Z*, which contribute to the change in dissolution enthalpy and entropy. For example, the negative *X* values under low temperature may correspond to increasing solubility with rising temperature, while the positive *X* values at high temperature may be related to changes in solute-solvent interactions caused by the increase in solvent molecular kinetic energy.

Table 3 shows that as the initial mole fraction of good and poor solvents increases from 0.1 to 0.9, the signs and values of Apelblat model parameters *X* and *Y* exhibit significant regular changes: when $a_1 \leq 0.2$, both *X* and *Y* are positive, and the ARD and 10^4RMSD are relatively high, indicating lower fitting accuracy. When $a_1 \geq 0.3$, X becomes negative and gradually approaches -92.3257, Y changes from positive to negative and its absolute value decreases, with ARD and RMSD decreasing significantly. Particularly, at a_1=0.4, the ARD drops to 0.145% and 10^4RMSD to only 0.874, achieving the highest fitting accuracy. Notably, at a_1=0.8, 10^4RMSD surges to 31.265, the maximum value across the entire range, indicating that the solubility behavior under this mole fraction deviates significantly from the model prediction. Parameter Z is negative at a_1=0.1~0.2 and becomes positive for $a_1 \geq 0.3$, fluctuating between 21.2015 and 48.2351, reflecting that the mechanism of temperature effect on solubility changes with solvent composition. In line with the research objective, the above data reveal the key influence of the mole fraction of good and poor solvents on solubility behavior: 1) When $a1$ is low, the solvent system is dominated by the poor solvent, where strong repulsive interactions or unstable solvation structures may form between solute and solvent, leading to large fitting deviations; while in the range a_1=0.3~0.7, the ratio of good and poor solvents tends to an optimal synergistic region, where solute molecules may form stable associations with solvents through hydrogen bonding or dipole-dipole interactions. 2) The abnormally high RMSD at a_1=0.8 may be due to the solvent composition approaching a single "good solvent", where intermolecular interactions become more homogeneous but the solute may enter supersaturation or aggregation state, complicating the temperature dependence behavior. The sign change of the parameters implies that the trend of solubility with temperature varies in different solvent compositions. When *X* is negative, solubility may increase with temperature; when *X* is positive, it may correspond to exothermic dissolution or solubility behavior dominated by solvent structural changes.

Table 3. Solubility in single and mixed solvents and fitting parameters, ARDs and RMSDs of Apelblat model under different initial mole fractions of good and poor solvents

a_1	X	Y	Z	ARD/%	10^4RMSD
0.1	778.12565	-37854.23152	-125.23156	6.231	3.875
0.2	678.2365	-32515.23521	-114.23152	8.203	11.235
0.3	-315.32564	11256.32514	48.23512	0.924	4.125
0.4	-135.98562	4658.32512	22.32568	0.145	0.874
0.5	-159.23521	5236.23548	23.21056	0.789	9.126
0.6	-178.23512	6452.32154	27.23568	0.325	4.235
0.7	-138.23521	4897.56825	21.20154	0.374	9.125
0.8	-125.32564	3784.2352	17.23065	1.126	31.265
0.9	-92.32565	2451.32658	13.21458	0.179	5.348

Table 4. Solubility in single and mixed solvents and fitting parameters, ARDs and RMSDs of the Jouyban-Acree model

S	Y_0	Y_1	Y_2	Y_3	Y_4	ARD/%	10^4RMSD
278.23	-9.45214	11.23521	4.52135	-22.32514	12.23015	9.362	6.125
288.32	-8.85213	12.52682	-14.23528	9.52624	-2.51246	0.812	0.685
315.21	-8.32562	11.20325	-5.52612	-2.63215	2.23015	2.154	2.312
326.35	-7.85142	9.45212	-4.20135	-3.45265	2.35689	2.236	1.623
334.36	-7.41256	8.23659	-0.47851	-7.56215	3.84521	1.789	2.789

Table 4 presents the fitting parameters and error indices of the Jouyban-Acree model for solubility in mixed solvents at different temperatures. As the temperature increases from 278.23K to 334.36K, the absolute values of parameters Y_0 and Y_1 gradually decrease, indicating a regular change in the fundamental solubility capacity of the solvent with temperature. Y_2 is positive at 278.23K and turns negative after 288.32K, reflecting the temperature dependence of the synergistic effect between solvent components. The signs and values of Y_3 and Y_4 fluctuate greatly, indicating increasing complexity of molecular interactions between solvent molecules at high temperature. In terms of error, at 278.23K, both ARD and 10^4RMSD are significantly higher than at other temperatures, while at 288.32K, ARD drops sharply to 0.812% and 10^4RMSD to 0.685, achieving the highest fitting accuracy. After 315.21K, the error increases slightly but remains at a relatively low level. In line with the research objective, the above data suggest that the Jouyban-Acree model can effectively analyze the synergistic dissolution effect of mixed solvent components, and the fitting accuracy is significantly affected by temperature. The low error at 288.32K indicates that the hydrogen bonding and dipole interactions among solvent components reach equilibrium at this temperature, forming stable solute-solvent complex structures. This complements the high fitting accuracy of the Apelblat model under low temperature for deep eutectic solvents, verifying the regulatory effect of temperature on the synergistic behavior of solvents.

Table 5 presents the fitting parameters and error indices of the Apelblat-Jouyban-Acree combined model for solubility in complex solvent systems. Among the model parameters, X_1, Y_1, and X_2 are negative, while Z_1, Y_2, and Z_2 are positive, reflecting a dual effect of temperature on solubility: negative parameters may correspond to an endothermic dissolution trend where solubility increases with temperature, while positive parameters may be related to synergistic interactions among solvent components. The interaction term K_0 is significantly larger than K_1 and K_2, indicating that the fundamental contribution of solvent composition to solubility is stronger than the linear or nonlinear interaction between temperature and composition. In terms of error, the ARD is 5.122%, and 10^4RMSD is 2.745, which is between those of the single Apelblat model and complex mixed solvent models, showing that the combined model achieves medium-level fitting accuracy when balancing temperature and solvent composition variables, but can still capture key thermodynamic behaviors. In line with the research objective, the above data indicate: 1) The Apelblat-Jouyban-Acree combined model successfully integrates the temperature dependence of single solvents and the synergistic effect of mixed solvent components. The coexistence of negative temperature-related parameters and positive synergistic parameters confirms the promoting effect of temperature on the kinetic energy of solute molecules and the synergistic mechanism of hydrogen bond/dipole interactions among solvent components during dissolution. For example, the high value of K_0 suggests a significant contribution of solvent composition to solubility, while the negative K_2 may reflect a suppressing effect of competitive interactions among solvent components under high temperature. 2) The model error is within an acceptable range, indicating that it can effectively describe the multivariate relationship of "temperature–composition–solubility" in complex solvent systems and provides a quantitative tool for optimizing extraction processes.

Table 5. Solubility in single and mixed solvents and fitting parameters, ARDs and RMSDs of the Apelblat-Jouyban-Acree model

T/K	A
X_1	-31.2541
Y_1	-645.2811
Z_1	5.3145
X_2	-73.5641
Y_2	947.1245
Z_2	12.3205
K_0	1455.2158
K_1	90.2312
K_2	-512.3214
$ARD/\%$	5.122
10^4RMSD	2.745

Figures 3 and 4 respectively show the fitting of solubility in solvent during the TCM extraction process under low and high temperature conditions with the Apelblat-Jouyban-Acree model. Under both low and high temperature conditions, the model fitting surface is highly consistent with the distribution trend of measured data points, indicating that the comprehensive model can effectively capture the pattern of solubility variation with temperature. The shapes of the fitting surfaces at low and high temperatures are similar, but the distribution density and local trend of data points show slight differences, reflecting that temperature has subtle effects on the dissolution behavior of the solvent system. For example, on the temperature axis, the rate of solubility change with increasing temperature may differ between low and high temperature ranges. The model achieves a unified description of the dissolution behavior under different temperature conditions through the consistency of surface morphology and parameter adjustment. Combined with the research content, the above fitting results show: 1) The Apelblat-Jouyban-Acree comprehensive model successfully integrates the influence of temperature and solvent composition on solubility. The good fitting effect at both high and low temperatures verifies the model's universality in different temperature ranges, providing reliable model support for the synergistic optimization of extraction temperature and solvent composition. 2) The high agreement between the fitting surface and the data points indirectly reflects the effective correlation of solvent microscopic properties and thermodynamic parameters in the model, which is consistent with the research objective of "incorporating solvent microscopic properties, thermodynamic parameters, and energy changes into a unified framework."

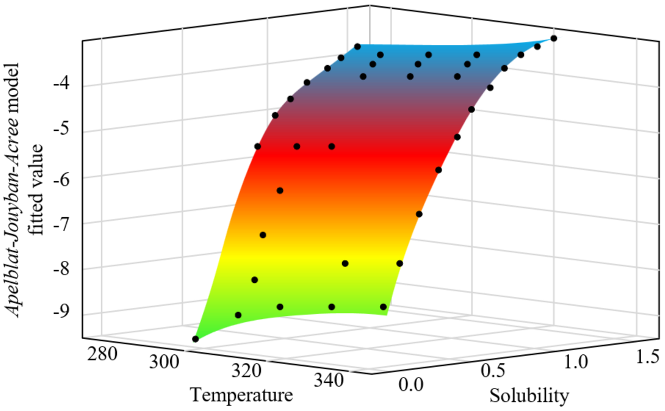


Figure 3. Fitting diagram of solubility in solvent during TCM extraction at low temperature and Apelblat-Jouyban-Acree model

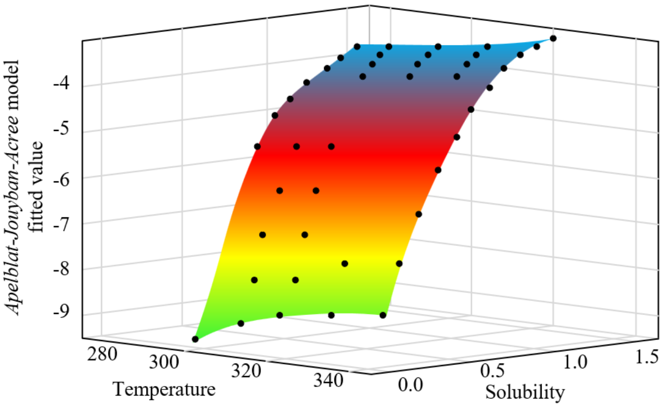
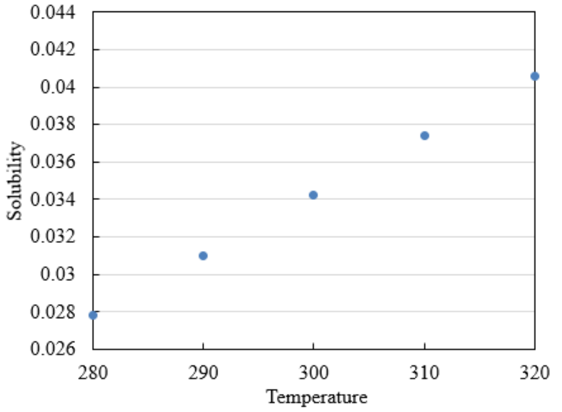


Figure 4. Fitting diagram of solubility in solvent during TCM extraction at high temperature and Apelblat-Jouyban-Acree model



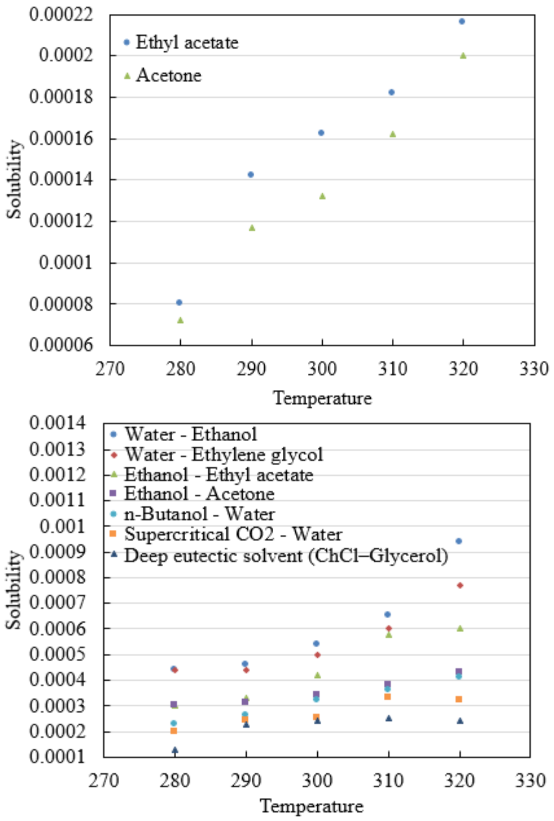
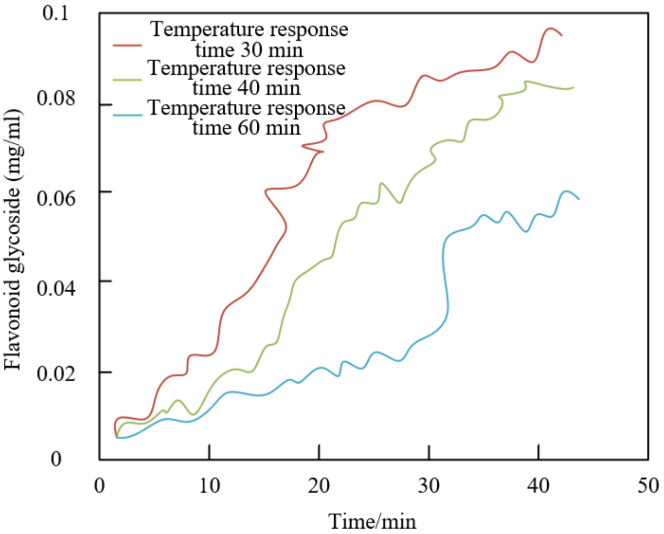


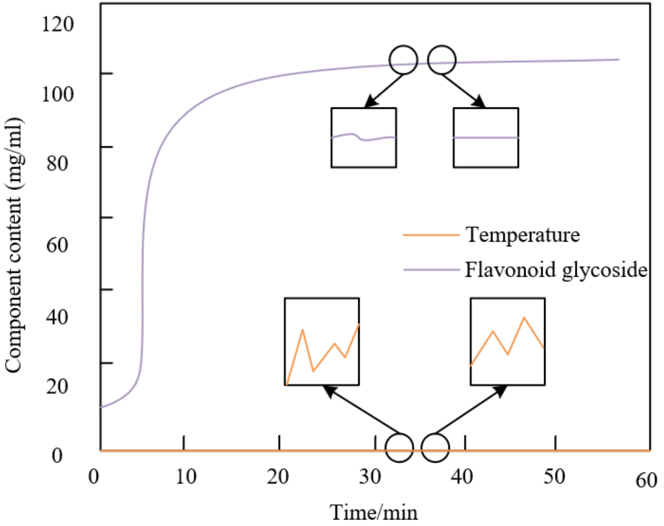
Figure 5. Solubility in single and mixed solvents during TCM extraction process at different temperatures

Figure 5 presents the solubility variation of single and mixed solvents during the TCM extraction process at different temperatures. In single solvents, the solubility of ethyl acetate increases significantly with the rise of temperature, while the solubility change of mixed solvents is more complex. For example, in the 280 K to 320 K range, the solubility variation trends of water-ethanol and deep eutectic solvent (ChCl-gly) differ significantly. The solubilities of ethanol-ethyl acetate and n-butanol-water mixed solvents also differ significantly at the same temperature, highlighting the critical influence of solvent composition on solubility. When the temperature rises, the solubility increase in some single solvents is large, while the solubility change in mixed solvents shows diverse characteristics due to synergistic or competitive effects among components. Combined with the research content, these data confirm the significant influence of the solvent system and temperature on solute solubility, which aligns with the research objective of quantifying solubility's temperature dependence based on the Apelblat model. The complex solubility variation of mixed solvents reflects the synergistic interaction of components analyzed by the Jouyban-Acree model, further indicating the necessity of constructing comprehensive models to fit complex systems. The solubility differences also reflect the contribution of solvent molecular properties to the dissolution process, revealing the intrinsic correlation between solvent microscopic properties and thermodynamic characteristics.

Figure 6(a) shows the change of flavonoid glycoside content with time at different temperature response times. The curve with a response time of 30 min shows the fastest rising rate and the highest final flavonoid glycoside content. The curves of 40 min and 60 min follow, indicating that the difference in response time significantly affects the extraction efficiency and final content of flavonoid glycosides.



(a) Relationship between response time and flavonoid glycoside content



(b) Relationship between steady-state error and flavonoid glycoside content

Figure 6. Correlation analysis chart of medicinal liquid composition and process parameter performance indicators

Figure 6(b) presents the relationship between steady-state error and flavonoid glycoside content. The temperature and flavonoid glycoside content curve shows obvious fluctuations in steady-state error between 30–40 min, and the flavonoid glycoside content also shows irregular changes in this interval, indicating a complex dynamic correlation between process parameters and medicinal liquid component content. Combined with the research content of the paper, the data in Figure 6 indicate: 1) Process parameters affect the extraction efficiency and content of medicinal liquid components by influencing solute solubility and thermodynamic equilibrium, verifying the key role of temperature and time in the dissolution process. 2) The appearance of steady-state error reflects the interaction between thermodynamic equilibrium and dynamic changes of process parameters, suggesting that the contribution of solvent microscopic properties to enthalpy and entropy changes at different time scales differs, further supporting the research idea of "incorporating solvent microscopic properties, thermodynamic parameters, and energy changes into a unified framework." These results provide direct evidence for “thermodynamics-guided” extraction process optimization. By accurately controlling parameters such as response time, it is possible to balance extraction efficiency and component content, promoting the scientific and green development of the TCM extraction process, and demonstrating the guiding significance of multidimensional theoretical interpretation for process development.

5. CONCLUSION

This paper systematically studied the effect of solvent systems on the thermodynamics and energy changes of TCM extraction, focusing mainly on two aspects: solubility model construction and optimization, and the correlation study between solvent molecular properties and thermodynamic parameters. In terms of solubility model construction and optimization, the paper used the Apelblat model to quantify the rule of solute solubility change with temperature in different solvents and combined the Jouyban-Acree model to analyze the synergistic effects of each component in mixed solvents on solute solubility. By constructing a comprehensive model, this paper successfully fitted the dissolution behavior of complex solvent systems, providing model support for the optimization of extraction temperature and solvent composition. In terms of the correlation study between solvent molecular properties and thermodynamic parameters, this paper introduced the Kamlet-Taft solvent parameters, established linear relationships between solvent molecular properties and dissolution enthalpy change and entropy change, and separated the contributions of hydrogen bonding, dipole, and other interactions to the dissolution process, revealing the molecular mechanism by which the solvent system affects the thermodynamic properties of extraction. The research of this paper broke through the traditional model's isolated analysis of single factors and incorporated solvent microscopic properties, thermodynamic parameters, and energy changes into a unified research framework. This innovation not only provides a multidimensional theoretical interpretation for the TCM extraction process but also offers a key technical path for the development of "thermodynamics-guided" green extraction processes. By replacing empirical dependence with theoretical guidance, the research results of this paper are expected to significantly improve the predictability and controllability of the TCM extraction process, promote the transformation of the TCM industry toward high-quality development, and have important scientific value and application prospects.

However, there are also some limitations in this study. Firstly, the universality of the constructed model needs to be validated in a wider range of solvent systems and extracts. Secondly, the influence of factors such as solvent purity and temperature control in the experimental process needs to be further refined and standardized. In addition, due to the complexity and diversity of TCM components, the dissolution behavior of different components varies greatly, and the model may require further optimization when dealing with complex multi-component systems. Future research directions can be expanded from the following aspects: first, further expand and validate the applicability of the model in different solvent systems and various TCM components to improve the model's universality and accuracy. Secondly, optimize experimental design, strictly control influencing factors, and further refine the study of solvent–solute interactions. In addition, for complex multi-component systems in TCM extraction, more refined comprehensive models should be developed to improve the prediction ability of dissolution behavior in complex systems. Finally, combined with thermodynamic models and molecular mechanism studies, more environmentally friendly and efficient TCM extraction processes should be developed to promote the sustainable development of the TCM industry.

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