Study on Dissolution Thermodynamics and Cooling Crystallization of Rifamycin S

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ABSTRACT: The solubility data of rifamycin S were measured in isopropanol, butyl acetate, and their mixed solvents across the temperature range of 283.15–323.15 K by the gravimetric method. The results demonstrate that the solubility of rifamycin S increases with the increasing temperature in the two pure solvents, and in the mixed solvents, it increases first and then decreases with increasing butyl acetate content. The experimental data of rifamycin S in the mixed solvents were better correlated using the modified Apelblat equation and ideal model equation. Furthermore, the relevant thermodynamic parameters of the dissolution process were determined based on the van’t Hoff equation. The obtained dissolution enthalpy and Gibbs free energy are positive in all cases, which indicate that the dissolving process of rifamycin S is endothermic and nonspontaneous. The supersolubility data of rifamycin S were measured by the laser and thermal analytic method. The results demonstrate that the width of the metastable zone of rifamycin S becomes larger with decreasing cooling rate and increasing butyl acetate content. Furthermore, the crystallization process of rifamycin S was optimized on the basis of thermodynamic research. The results showed that when $V_{\text{butyl acetate}}:V_{\text{mixed solvent}}$ was 0.04, the cooling rate was 0.1 K/min, the stirring rate was 150 rpm, the final crystallization temperature was 283.15 K, and the aging time was 8 h, the purity of rifamycin S crystals could reach 98.5%, and the crystalline yield was 89.6%. After crystallization optimization, the size of rifamycin S crystals increased, and the dissolution in water was improved.

1. INTRODUCTION

Rifamycin antibiotics are a class of antibiotics produced by Streptomyces Mediterranean, which have a wide range of antibacterial effects. They have a strong influence on Gram-positive bacteria such as Mycobacterium tuberculosis, leprosy-causing bacteria, Streptococcus, and Pneumococcus, especially, drug-resistant Staphylococcus aureus. Rifamycin S (C37H45NO12, CAS registry no. 13553-79-2) is an important precursor for the synthesis of other rifamycin families. Figure 1 shows the molecular structure of rifamycin S.

Figure 1. Molecular structure of rifamycin S.
method of rifamycin S with high purity. The steps were as follows. At first, rifamycin S was added into the solvent of tetrahydrofuran for dissolution, and then, the acid alumina into the reactor was added with agitation. With the agitation process, cyclohexane was slowly added into the solution until the solid precipitates out. The suspension was agitated for 5 h until a large amount of solid precipitates out. The filtered solid was washed with cyclohexane and then dried to obtain bright red rifamycin S crystals with a purity of 99%.

At present, most of the reports related to rifamycin S are about its synthesis process, but there are few studies on the thermodynamics, kinetics, and purification crystallization process of rifamycin S. As an important precursor for the synthesis of rifampicin and other rifamycin families, the purity, particle size, and crystal form of rifamycin S directly affect the production of subsequent drugs. However, in traditional industrial production, in order to obtain high-purity rifamycin S, it usually converts the rifamycin S obtained by oxidation of the fermentation broth rifamycin SV into rifamycin S-Na first and then acidifies rifamycin S-Na to rifamycin S. The innovation of this study is that through the crystallization process, high-purity rifamycin S can be directly obtained, instead of the intermediate rifamycin S-Na. All the purity data of rifamycin S in the paper were measured by high-performance liquid chromatography. After the crystallization process, the purity reached 98.5%, and our research group successfully synthesized qualified rifampicin with high-purity rifamycin S. In addition, our research team has developed an effective oxidation separation method from rifamycin SV to rifamycin S, which improve the purity of rifamycin S used as a raw material in subsequent crystallization. In the process of rifamycin S preparation, butyl acetate is used as the extractant and isopropanol is used as the crystallization solvent.

Therefore, in the purification crystallization system of this study, isopropanol–butyl acetate was selected as the solvent, and the solubility of rifamycin S was measured in nine different ratios of isopropanol–butyl acetate mixed solvents.

Therefore, this work first studied the solubility of rifamycin S in isopropanol, butyl acetate, and their mixed solvents across the temperature range of 283.15–323.15 K by the gravimetric method. The experimental data were correlated with the modified Apelblat equation and ideal model equation. According to the van’t Hoff equation, relevant thermodynamic data of dissolution were obtained. According to the obtained thermodynamic data, the crystallization process of rifamycin S was optimized by cooling crystallization. The effects of final crystallization temperature, cooling rate, stirring rate, aging time, seed crystal, and butyl acetate content on the crystallization of rifamycin S were investigated. The results showed that the crystalline form of rifamycin S was improved, the particle size and distribution of the crystals were optimized, and the purity of the crystals was improved, which provided strong support for the subsequent synthesis of rifampicin quality drugs.

### 2. RESULTS AND DISCUSSION

#### 2.1. Thermodynamic Properties of Rifamycin S

##### 2.1.1. Solubility of Rifamycin S

The solubility data of rifamycin S in butyl acetate, isopropanol, and their mixed solvents were determined in the temperature range of 283.15–323.15 K. The mole fraction of rifamycin S in organic solvents can be calculated using the following eq 1

\[
x_1 = \frac{m_1/M_1}{(m_1/M_1) + (m_2/M_2)}
\]

wherein \(x_1\) is the mole fraction of rifamycin S; \(m_1\) and \(m_2\) is the mass of rifamycin S and the solvent; \(M_1\) and \(M_2\) is the molar mass of rifamycin S and solvent, respectively.

Figure 2 shows the solubility curve of rifamycin S in mixed solvents with different butyl acetate volume fractions.

The temperature range was selected according to the operable range of the production process. In this paper, five points were selected for measurement with a temperature difference of 10 °C. Each measurement point was carried out for more than three sets of experiments, and it was found that it was enough to get a good pattern. The solubility of rifamycin S in isopropanol and butyl acetate solvents increases with the increasing temperature. At the same temperature, the solubility of rifamycin S in butyl acetate is much greater than that in isopropanol. The mixed solvent has a solubilizing effect in this case. Considering the dissolution performance alone, choosing the right solvent ratio and proper dissolution temperature can not only reduce heating energy consumption but also save solvents.

#### 2.1.2. Rifamycin S Solubility Correlation

The modified Apelblat equation is a semiempirical model, which has widely been used to correlate the mole fraction solubility against temperature.

\[
\ln x = A + \frac{B}{T} + C \ln T
\]

The ideal model equation is a commonly used equation describing the solid–liquid equilibrium state based on the principle of thermodynamics.

\[
\ln x = a + b/T
\]
here A, B, C, a, and b are parameters of this equation. T is the absolute temperature. x is the mole fraction solubility of the solute.

The relative deviation (RD) between the calculated value of the solubility model and the experimental data can be calculated by eq 4

\[
RD = \frac{x_{cal} - x}{x}
\]  
(4)

The root-mean-square deviation (RMSD) can be obtained from eq 5

\[
RMSD = \left[ \frac{1}{N} \sum_{i=1}^{N} (x_i - x_{cal})^2 \right]^{1/2}
\]

wherein N is the number of experimental data points; x is the experimental solubility value; x_{cal} is the calculated solubility value.

The obtained RD is shown in Table 1, and the relevant parameters and RMSD are shown in Table 2. It can be seen from Table 2 that the R^2 obtained by the Apelblat equation was greater than 0.994, and the RMSD values were less than 10^{-4} under different solvent ratios. From the overall results, the...
fitting effects of the Apelblat equation were better than the ideal model equation.

2.1.3. Analysis of Dissolution of Rifamycin S. The Van’t Hoff equation \(23\) can be used to calculate the standard molar enthalpy of solution \(\Delta_{\text{soln}} H_m^\circ\). It can be known from eq 6 that the \(\Delta_{\text{soln}} H_m^\circ\) of the solute can be obtained by calculating the slope of the graph of \(\ln x \sim 1/T\). The standard molar dissolution Gibbs free energy \(\Delta_{\text{soln}} G_m^\circ\) and standard molar dissolution entropy \(\Delta_{\text{soln}} S_m^\circ\) can be obtained from eqs 8 and 9. \(24\) In this study, because the temperature range was small \((283.15–323.15 \text{ K})\), the value of the heat of dissolution can be regarded as a constant. \(24\) These equations are as follows.

\[
\Delta_{\text{soln}} H_m^\circ = -R \left[ \frac{\partial \ln x_i}{\partial (1/T)} \right]_{T_m}
\]  
\(6\)

\[
\ln x_i = -\frac{\Delta_{\text{soln}} H_m^\circ}{R} \left( \frac{1}{T} - \frac{1}{T_m} \right) + \text{intercept}
\]  
\(7\)

\[
\Delta_{\text{soln}} G_m^\circ = -RT_m \times \text{intercept}
\]  
\(8\)

\[
\Delta_{\text{soln}} S_m^\circ = \frac{\Delta_{\text{soln}} H_m^\circ - \Delta_{\text{soln}} G_m^\circ}{T_m}
\]  
\(9\)

where \(T_m\) refers to the average of all test temperatures. \(R\) is the gas constant, for which the value is 8.314 J/(K·mol).

The calculated thermodynamic data of \(\Delta_{\text{soln}} H_m^\circ\), \(\Delta_{\text{soln}} G_m^\circ\) and \(\Delta_{\text{soln}} S_m^\circ\) of rifamycin S are shown in Table 3.

It can be seen from Figure 3 and Table 3 that the values of \(\Delta_{\text{soln}} H_m^\circ\) and \(\Delta_{\text{soln}} G_m^\circ\) of rifamycin S in isopropanol–butyl acetate mixed solvent are positive in all cases, indicating that the dissolution process of rifamycin S is endothermic and nonspontaneous in this experimental study.

Table 3. Relative Solution Thermodynamic Properties of Rifamycin S in Different Solvent Composition (\(V_{\text{Butyl Acetate}}:V_{\text{Mixed Solvents}}\))

| \(V_{\text{Butyl Acetate}}:V_{\text{Mixed Solvents}}\) | \(\Delta_{\text{soln}} H_m^\circ\) | \(\Delta_{\text{soln}} G_m^\circ\) | \(\Delta_{\text{soln}} S_m^\circ\) |
|---|---|---|---|
| 0 | 77.0103 | 18.9944 | 191.3768 |
| 0.1 | 73.8132 | 17.2296 | 186.6523 |
| 0.3 | 67.2754 | 14.1976 | 175.0876 |
| 0.5 | 41.6314 | 11.7965 | 98.4162 |
| 0.7 | 26.3380 | 10.3325 | 52.7312 |
| 0.8 | 6.0740 | 9.2876 | -10.6008 |
| 0.85 | 6.0020 | 9.1622 | -10.4245 |
| 0.9 | 0.0294 | 9.2886 | -10.7448 |
| 1 | 2.7750 | 9.7224 | -22.9175 |

2.1.4. Metastable Region of Rifamycin S in Isopropanol and Butyl Acetate. With isopropanol as the solvent, the metastable zones of rifamycin S at different cooling rates were measured at a stirring rate of 150 rpm, as shown in Figure 4.

When rifamycin S has a lower cooling rate in isopropanol, the width of the metastable region is larger, that is, it has a larger operating range, which is more conducive to the growth of the crystal. When the cooling rate is higher, the width of the metastable region is smaller, which is more conducive to crystal nucleation. Therefore, in order to cultivate large and uniform crystals, the crystallization should take place at a lower cooling rate to maintain a low energy transfer rate and the solution...
should be kept in the metastable zone during the crystallization process and avoid spontaneous nucleation.

The width of the metastable zone of rifamycin S in solvent with $V_{\text{butyl acetate}}:V_{\text{mixed solvents}}$ at 0, 10, and 30% was, respectively, measured at a stirring rate of 150 rpm and a cooling rate of 0.1 K/min, which is shown in Figure 5.

The width of the metastable region becomes larger while the proportion of butyl acetate in the mixed solvent increases, which is more beneficial to the crystal growth. As the extraction agent in industrial production, a little butyl acetate is left in the crystallization solvent. The investigation of solubility of rifamycin S in different mixed solvents can provide some theoretical reference for the extraction, purification, and production of rifamycin S.

It can be seen from Figures 4 and 5 that the width of the metastable zone is smaller at lower temperatures and larger at higher temperatures. This is because the solubility of rifamycin S does not change significantly with temperature, so the width of the metastable zone becomes larger at higher temperatures.

2.2. Crystallization Process of Rifamycin S. 2.2.1. Effect of Final Crystallization Temperature on the Crystallization of Rifamycin S. From the solubility curve of rifamycin S in isopropanol, it can be seen that its solubility decreases with the decreasing temperature. Therefore, it can be seen from Figure 6 when the final crystallization temperature gradually decreased, the solubility of rifamycin S decreased, and the supersaturation (i.e., the crystallization driving force) was constantly provided during the crystallization process. The small particles formed by stirring and crushing became the nucleus of secondary nucleation, thereby crystallizing to form small crystal grains, causing the average particle size to decrease.

Figure 7 shows that the purity of rifamycin S gradually decreased with the decreasing final crystallization temperature, and it was considered that the solubilities of impurities decreased with the decreasing temperature. The yield of rifamycin S was an increasing trend. When the final crystallization temperature was below 283.15 K, the yield did not

Figure 4. Mesostable zone of rifamycin S in isopropanol at different cooling rates.

Figure 5. Width of the mesostable zone of rifamycin S by temperature difference in different solvent compositions ($V_{\text{butyl acetate}}:V_{\text{mixed solvents}}$).

Figure 6. Particle size distribution at different crystallization final temperatures.

Figure 7. Purity and yield of rifamycin S at different crystallization final temperatures.
not change much because the solubility of rifamycin S in the solvent decreased with the decreasing crystallization temperature. Based on the results, considering the energy and time savings, the final crystal temperature was selected to be 283.15 K.

2.2.2. Effect of the Cooling Rate on Crystallization of Rifamycin S. As can be seen from Figure 4, when the cooling rate was lower, the metastable zone width was larger, and the driving force needed for crystal growth was provided slowly. Saturation took place slowly, which kept the solution in the metastable zone during crystallization, avoiding spontaneous nucleation. Therefore, Figure 8 shows that at a lower cooling rate, larger and uniform crystals can be obtained.

![Figure 8. Particle size distribution of rifamycin S at different cooling rates.](image)

As can be seen from Figure 9, with the decreasing cooling rate, the particle size of rifamycin S gradually increased, and the shape changed from long rods to flakes, the aspect ratio decreased, and the thickness increased. This was because when the cooling rate was large, the driving force needed for crystal growth was provided fast and the nucleation rate was much higher than the growth rate. When the cooling rate was slow, the crystals were fully grown, so the crystalline nature was better.

Considering the crystal size distribution, crystal shape, and purity (Figure 10), the selected cooling rate was 0.1 K/min.

2.2.3. Effect of the Stirring Rate on Rifamycin S Crystallization. Figure 11 shows that without stirring, rifamycin S had a wide particle size range with two higher peaks. When the stirring rate was 100 or 150 rpm, the particle size range of rifamycin S was narrow. This showed that providing appropriate agitation strength was beneficial to obtain a rifamycin S product with uniform particle size.

From Figure 12, without stirring, each side of rifamycin S was irregular and the particle size difference was large. When the stirring rate was 225 rpm, the crystals were broken too much. When the stirring speed was 150 rpm, the crystal was complete and the particle size was uniform. This was because when the stirring rate was or was not too low, the solvent and

![Figure 9. Crystal forms of rifamycin S at different cooling rates.](image)

![Figure 10. Purity and yield of rifamycin S at different cooling rates.](image)

![Figure 11. Particle size distribution of rifamycin S at different stirring rates.](image)
the solute could not be fully mixed and allowed to make contact, and local supersaturation levels would be formed, resulting in uneven crystal size and two peaks. When the stirring rate was too high, the crystals would be broken. In addition, the crystal had an obvious curved surface without stirring, but it did not exist when there was stirring, indicating that stirring had changed the crystalline nature.

It can be seen from Figure 13 that when other conditions were constant, the yield of rifamycin S increased with the increasing stirring rate, but it increased slowly when the stirring speed exceeds 100 rpm. It was considered that when the stirring rate was low, the metastable zone of rifamycin S was wide, which led to the incomplete crystallization of rifamycin S. Considering comprehensively, the stirring rate was selected as 150 rpm.

2.2.4. Effect of Aging Time on Crystallization of Rifamycin S. It can be seen from Figure 14 that when other conditions were constant, the particle size of rifamycin S increased with increasing aging time, indicating that after reaching the final crystallization temperature, the crystallization in the solution made small particles grow into large grains. Proper aging time would facilitate to form larger rifamycin S crystals.

Figure 15 shows that the yield and purity of rifamycin S were basically unchanged with the increase of aging time, indicating that after a period of aging, the system had reached crystallization equilibrium. Considering comprehensively, the aging time of 8 h was more appropriate.

2.2.5. Effects of Different Solvent Composition \( \frac{v_{\text{Butyl Acetate}}}{v_{\text{Mixed Solvent}}} \) on Crystallization of Rifamycin S. Figure 16 shows that with the decreasing proportion of the butyl acetate in the mixed solvent, the volume particle diameter of rifamycin S gradually decreased, the particle size was more uniform. It can be seen from Figure 5 that when the content of butyl acetate was relatively low in the mixed solvent, with the butyl acetate content increasing, the metastable zone width became larger. Therefore, rifamycin S was not completely crystallized, resulting in a smaller particle size.

As can be seen from Table 4, with the increasing proportion of butyl acetate in the mixed solvent, the purity of rifamycin S increased slightly, but the yield decreased. From the solubility of rifamycin S obtained in the isopropanol—butyl acetate mixed solvent obtained from the foregoing, it can be known that when the proportion of butyl acetate in the mixed solvent
was small, the solubility of rifamycin S increased rapidly with the increasing butyl acetate content, so the yield of rifamycin S decreased. Considering comprehensively, it was better when $\frac{V_{\text{butyl acetate}}}{V_{\text{mixed solvent}}}$ was 4%.

2.2.6. Effect of Seeds on Crystallization of Rifamycin S. Figure 17 shows that when other conditions were the same, the addition of rifamycin S seeds could increase the particle size of the rifamycin S crystal. With the amount of rifamycin S seeds increasing, the particle size of the rifamycin S crystal did not increase much. When adding seed crystals in the metastable zone, the seeds were equivalent to the nucleus of rifamycin S, which changed the width of the metastable zone and made the crystallization orderly, which was beneficial to the crystallization of large particle size. Because the total amount of rifamycin S in the solution was constant, the particle size would not increase continuously with the increasing amount of seed.

Table 5 shows that when the other conditions were the same, with the increasing amount of rifamycin S seeds, the purity of rifamycin S did not change much, and the yield increased, but the change of yield was small when the amount of seeds reached 0.5%.

2.3. Optimization Results of Rifamycin S. The optimized experimental method is as follows. First, 3.72 g of crude rifamycin S was added into butyl acetate solvent. Then, the solution was transferred to a rotary evaporator to evaporate 42.3 mL of butyl acetate. Second, isopropanol was added to 191 mL and transferred to the double-jacketed glass vessel and then crystallized to 283.15 K (adding 1% seeds at 315.15 K) at a cooling rate of 0.1 K/min and a stirring rate of 150 rpm. Finally, the crystal system was kept static for 8, and then, the crystalline product was analyzed and detected.

The results of the experiment are as follows. The purity of the rifamycin S crystal after optimization was 98.5%, and the yield was 89.6%. The particle size distribution diagram is shown in Figure 18. The SEM images are shown in Figure 19, in which 19a is crude rifamycin S, and 19b,c are the optimized products under different magnifications, respectively. The dissolution rate in water is shown in Figure 20.

It can be seen that after optimization, the crystalline nature of rifamycin S undergoes a great change. The crystalline form of rifamycin S was very broken before crystallization. After crystallization, the particle size of rifamycin S crystals increased significantly, and the aspect ratio decreased. The crystal presented a clear block structure, and the particle size was more uniform. The purity of the optimized rifamycin S could reach 98.5%. At the same dissolution time, the dissolution rate in water was higher than before, which indicates that the optimized rifamycin S has higher solubility in water, and the optimized rifamycin S was more conducive to subsequent experiments.

3. CONCLUSIONS

In this work, the solubility of rifamycin S in pure isopropanol, pure butyl acetate, and their mixed solvents was measured by using the gravimetric method from 283.15 to 323.15 K. The solubility data of rifamycin S increases with the increasing
temperature in the two pure solvents. At the same temperature, the solubility of rifamycin S in pure butyl acetate is much greater than that in pure isopropanol. The solubility of rifamycin S increases first and then decreases with the increasing butyl acetate content. When the volume fraction of butyl acetate reaches 0.80−0.9, the solubility is maximum. When the volume fraction of butyl acetate is greater than 0.80, the solubility of rifamycin S in the mixed solvent is greater than the solubility in either of the pure solvents, indicating that the mixed solvent has a solubilizing effect in this case. The experimental solubility data were correlated by the modified Apelblat equation and ideal model equation, and the relevant thermodynamic parameters of the dissolution process were determined based on the van’t Hoff equation. It was found that the dissolution process of rifamycin S in isopropanol−butyl acetate mixed solvents is endothermic and nonspontaneous. Furthermore, the supersolubility data of rifamycin S at different cooling rates and solvent compositions were measured by the laser and thermal analytic method. The width of the metastable zone of rifamycin S becomes larger with decreasing cooling rate and increasing butyl acetate content.

Based on the thermodynamic research, the crystallization process of rifamycin S was optimized. The results showed that when $V_{\text{butyl acetate}}:V_{\text{mixed solvent}} = 0.04$, the cooling rate was 0.1 K/min, the stirring rate was 150 rpm, the final crystallization temperature was 283.15 K, and the aging time was 8 h; the purity of rifamycin S crystals could reach 98.5%, and the crystallization yield was 89.6%. After crystallization optimization, the particle size of the rifamycin S crystal increased and became more uniform, and its dissolution in water also increased, which improved its solubility in water. This research will facilitate subsequent experimental operations and provide theoretical guidance for the overall optimization of the rifampicin synthesis process.

4. EXPERIMENTAL SECTION

4.1. Materials. Rifamycin S was provided by a pharmaceutical manufacturer and further purified in the laboratory. The organic solvents (isopropanol, butyl acetate) used in the experiment were analytical-grade reagents with the mass fraction purity higher than 99.5%, determined by gas chromatography. All the organic solvents were used in experiments without further purification. All reagents were supplied by Sinopharm Chemical Reagent Co., Ltd.

The low-temperature thermostatic water bath was supplied by Shanghai Shunyu Hengping Scientific Instrument. The stirrer was supplied by Shanghai Shenshun Biological Technology Co., Ltd. The vacuum pump was supplied by Shanghai Dayan Instrument Co., Ltd. The rotary evaporator was supplied by Provided by Shanghai Yarong Biochemical Instrument Factory. The spectrophotometer (SPECORD 210 PLUS) was supplied by Jena Analytical Instrument Company of Germany. The field emission scanning (NOVA Nano-SEM450) electron microscope was supplied by American FEI company.

Figure 21 is a schematic for the solubility and supersolubility measurement apparatus.

4.2. Determination of Thermodynamic Properties. In this work, the gravimetric method was used to measure the
the masses of the samples. At first, excess amounts of rifamycin S were added into the solvent contained in a double-jacketed glass vessel. The temperature of the glass vessel was controlled by a thermostat with an accuracy of ±0.05 K. The suspension was agitated for 8 h to realize the solid–liquid equilibrium. Then, the agitation was stopped. After that, the upper clear saturated solutions were withdrawn and filtered by a sand core funnel and dried in a vacuum oven at 323.15 K until the total weight was constant. At the same time, the undissolved materials were filtered by a weighed sand core funnel and dried in a vacuum oven at 323.15 K until the total weight was constant. An electric balance with an accuracy of ±0.0001 g was used to measure the masses of the samples.

The supersolubility of rifamycin S was studied by laser and indirect thermal analysis. The organic solvents included isopropanol, butyl acetate, and their mixed solvents. First, quantitative amounts of the solvent and rifamycin S were added into the crystallizer. At the same time, the laser recorder was debugged, and the material in the crystallizer was heated to a temperature 5 K higher than the solubility temperature of rifamycin S and maintained for a period of time to ensure that the solute was completely dissolved. Second, the temperature was cooled at a fixed cooling rate, and the supersolubility curve was determined according to the change of the light intensity. To ensure the accuracy of the experimental data, three parallel experiments were conducted in each group, and the average value was taken.

4.3. Optimization of the Crystallization Process. A single variable method was used to investigate the effects of different final crystallization temperature, cooling rate, stirring rate, aging time, solvent system component content, and seed addition amount on the rifamycin S crystals. At first, 3.72 g of rifamycin S and 150 g of the solvent were added into the crystallizer. At the same time, the thermostat and the agitator were opened. When the temperature had risen to 326.15 K, stirring was carried out at a constant temperature for 30 min. Then, the solution was cooled at a certain cooling rate and stirring rate to different final crystallization temperatures. Then, the agitation was stopped, and the system was kept static for different aging times at a constant temperature. Finally, the sample obtained after suction filtration was dried in a vacuum oven for 48 h.

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Wehrli, W.; Staehelin, M. Actions of the Rifamycins. Bacteriol. Rev. 1971, 35, 290–309.
(2) Burman, W. J.; Gallicano, K.; Peloquin, C. Comparative Pharmacokinetics and Pharmacodynamics of the Rifamycin Antibacterials. Clin. Pharmacokinet. 2001, 40, 327–341.
(3) Aristoff, P. A.; Henderson, B.; Lund, P.; Coates, A. Rifamycins — Obstacles and opportunities. Tuberculosis 2010, 90, 94–118.
(4) Bruzzese, T. Process for the preparation of rifampicin. U.S. Patent 4,174,320 A, 1979.
(5) Low, S. A.; Nestl, B. M.; Weissenborn, M. J.; Zepeck, F.; Hauer, B. Process Investigations on the One-Pot Synthesis of Rifamycin S Avoiding Chlorinated Solvents. Org. Process Res. Dev. 2015, 19, 1544–1547.
(6) Marsili, L.; Pasqualucci, C. Process for the preparation of 3-iminomethyl derivatives of rifamycin-SV. U.S. Patent 3,963,705 A, 1976.
(7) Pasqualucci, C.; Bonfanti, G.; Scarpitta, G. A Process for Preparing Rifamycin S by Hydrolysis of Rifamycin O. GB 1431034 A, 1976.
(8) Pasqualucci, C.; Bonfanti, G.; Turolla, C. A Method of Producing Rifamycin O from Fermentation Broths. GB 1381992A, 1975.
(9) Tang, G. Production method for directly extracting rifamycin S from fermentation filtrate. CN 102140102 A, 2011.
(10) Zhao, D.; Li, Z.; Zhang, Y.; Li, Z.; Chen, J.; Zhang, Y.; Hu, Y. Rifamycin S preparing method. CN 105237548 A, 2016.
(11) Li, P. Rifamycin S crystal and preparation method thereof. CN 106749327 A, 2017.
(12) Iio, H.; Nagaoka, H.; Kishi, Y. Total synthesis of rifamycins. 2. Total synthesis of racemic rifamycin S. J. Am. Chem. Soc. 1980, 102, 7965–7967.
(13) Alvarez, A. J.; Myers, A. S. Continuous Plug Flow Crystallization of Pharmaceutical Compounds. Cryst. Growth Des. 2010, 10, 2219–2228.
(14) Lan, G.-C.; Wang, J.-L.; Chen, L.-Z.; Hou, H.; Li, J.; Gao, Y.-P. Measurement and correlation of the solubility of 3,4-bis(3-nitrofurazan-4-ylfuroxan (DNTF) in different solvents. Measurement and correlation of the solubility of 3,4-bis(3-nitrofurazan-4-ylfuroxan (DNTF) in different solvents. J. Chem. Thermodyn. 2015, 89, 264–269.
(15) Li, J.; Wang, Z.; Bao, Y.; Wang, J. Solid–Liquid Phase Equilibrium and Mixing Properties of Cloxacin Benzathine in Pure and Mixed Solvents. Ind. Eng. Chem. Res. 2013, 52, 3019–3026.
(16) Fan, R.; Chen, K.; Zhu, J.; Yu, L. Preparation of rifamycin S by oxidation of rifamycin SV. Chin. J. Chem. Eng. 2018, 46, 51–55.
(17) Yu, L.; Chen, K.; Zhu, J. Preparation of Rifamycin S by Heterogeneous Oxidation. Fine Chem. 2019, 36, 288–294.
(18) Fang, W.; Chen, K.; Ji, L.; Zhu, J.; Wu, B.; Wu, Y. Solubility and thermodynamic properties of N-acyctethylglucosamine in mono-solvents and binary solvents at different temperatures. Phys. Chem. Liq. 2019, 57, 587–599.
(19) Kalam, M. A.; Alshamsan, A.; Alkolieh, M.; Alsarra, I. A.; Ali, R.; Haq, N.; Anwer, M. K.; Shakeel, F. Solubility Measurement and Various Solubility Parameters of Glipizide in Different Near Neat Solvents. ACS Omega 2020, 5, 1708–1716.
(20) Wang, K.; Hu, Y.; Yang, W.; Guo, S.; Shi, Y. Measurement and correlation of the solubility of 2,3,4,5-tetrabromothiophene in different solvents. *J. Chem. Thermodyn.* **2012**, *55*, 50–55.

(21) Sunsandee, N.; Hronec, M.; Stolcová, M.; Leepipatpiboon, N.; Pancharoen, U. Thermodynamics of the solubility of 4-acetylbenzoic acid in different solvents from 303.15 to 473.15 K. *J. Mol. Liq.* **2013**, *180*, 252–259.

(22) Ju, X.; Chen, K.; Zhu, J. Measurement and correlation of solubility of rifampicin form II in two mixed solvents. *J. Chem. Eng. Chin. Univ.* **2020**, *34*, 588–595.

(23) Nam, K.; Ha, E.; Kim, J.; Kuk, D.; Ha, D.; Kim, M.; Cho, C.; Hwang, S. Solubility of oxcarbazepine in eight solvents within the temperature range $T=(288.15–308.15)$K. *J. Chem. Thermodyn.* **2017**, *104*, 45–49.

(24) Krug, R. R.; Hunter, W. G.; Grieger, R. A. Enthalpy-entropy compensation. 2. Separation of the chemical from the statistical effect. *J. Phys. Chem.* **1976**, *80*, 2341–2351.

(25) Ruidiaz, M. A.; Delgado, D. R.; Martínez, F.; Marcus, Y. Solubility and preferential solvation of indomethacin in 1,4-dioxane + water solvent mixtures. *Fluid Phase Equilib.* **2010**, *299*, 259–265.