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# Measurement and Correlation of Solubility of Clopidogrel Hydrogen Sulfate (Metastable Form) in Lower Alcohols

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**ABSTRACT:** The solubility equilibrium of clopidogrel hydrogen sulfate (Form I) was set up without the nucleation of Form II, as the nucleation rate of Form II is very slow under the low supersaturation. Using the laser monitoring technique, solubilities of clopidogrel hydrogen sulfate (Form I) in ethanol, 1-propanol, 1-butanol, 1-pentanol, and 2-propanol were measured at temperatures ranging from (273.15 to 318.15) K. The experimental data were correlated by the modified Apelblat equation, and the dissolution enthalpy and entropy of Form I were determined with van't Hoff plots. Compared with those of Form II, Form I exhibits a higher solubility and a lower enthalpy of dissolution. Therefore, we can draw the conclusion that Form I was the metastable form under the conditions in this work.

## INTRODUCTION

The importance of polymorphism in crystals is well-appreciated in terms of its impact on the preparation and formulation of pharmaceuticals.[1] Different polymorphs of the same compound may have different melting points, shapes, dissolution rates, and solubilities. As the dissolution rate and solubility of a drug are directly related to its absorption, the effect of polymorphism on solubility or dissolution[2] has become an intense subject in pharmaceutical for over 40 years. Although there are many works[3] reported about the methods of the solubility measurement of the metastable forms, it is still difficult to be determined accurately as the occurrence of polymorphic transformation in the process.

Clopidogrel hydrogen sulfate (CAS Registry No. 120202-66-6), with its chemical name, (*S*)-(+)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydro-4*H*-thieno[3,2-c]pyridin-5-yl)acetate hydrogen sulfate, is an antiplatelet agent,[4] whose chemical structure is shown in Figure 1. Among the several different polymorphs, Form I and Form II were employed in the pharmaceutical industry. The study on Form I is a hot issue now due to its good absorption. Recently the dimer structure of Form I crystal was revealed.[5] However the relationship between its structure and absorption is still puzzled. To solve it, the dissolution process is the key point, so the solubility data is needed. As the difficulty for the measurement of solubility of metastable forms, solubility data of clopidogrel hydrogen sulfate (Form I) in pure solvents have not been reported.

In this work, on the basis of the solubility data of clopidogrel hydrogen sulfate (Form II),[6] the solubility equilibrium of clopidogrel hydrogen sulfate (Form I) was set up without the nucleation of Form II. Using the laser monitoring technique, the solubilities of clopidogrel hydrogen sulfate (Form I) in ethanol, 1-propanol, 1-butanol, 1-pentanol, and 2-propanol were measured at temperatures ranging from (273.15 to 318.15) K by a synthetic method. The experimental data were correlated by the modified Apelblat equation, and the dissolution enthalpy and entropy of clopidogrel hydrogen sulfate (Form I) were estimated by van't Hoff equation.

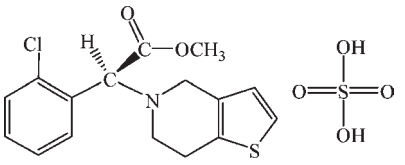


**Figure 1.** Molecular structure of clopidogrel hydrogen sulfate.

## EXPERIMENTAL SECTION

**Materials.** Clopidogrel hydrogen sulfate (mass fraction purity > 99 %, supplied by Zhejiang Huahai Pharmaceutical Co., Ltd., China) was used without purification. Ethanol, 1-propanol, 1-butanol, 1-pentanol, and 2-propanol used in the experiments (from Tianjin Chemical Reagent Co., China) were of analytical reagent grade, whose mass fraction purity is greater than 99.5 %.

**Preparation of Clopidogrel Hydrogen Sulfate (Form I).** To obtain the pure Form I of clopidogrel hydrogen sulfate, the clopidogrel base was first prepared by reacting clopidogrel hydrogen sulfate with sodium bicarbonate and then reacted with concentrated sulfuric acid in the solvent of methyl isobutyl ketone at lower temperature with the seed of Form I. After about 5 h the suspension was filtered, washed, and dried in a vacuum oven at 55 °C for 20 h. The white powder was identified to be Form I using an X-ray diffractometer (Rigaku D/max-2500) and maintained Form I at room temperature at least six months. The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 100 mA; receiving slit, 0.3 mm; scan range, 5° to 50° (2$\theta$); step size, 0.02°; scanning speed, 1 deg/min. The powder X-ray diffraction patterns (shown in Figure 2) are same as previously reported,[7] with the characteristic peaks at 9.1, 10.7, and 11.4.

**Apparatus and Procedures.** The solubility was measured by a synthetic method. The apparatus was the same as that in the literature.[6] The solubility apparatus consisted of a jacketed glass

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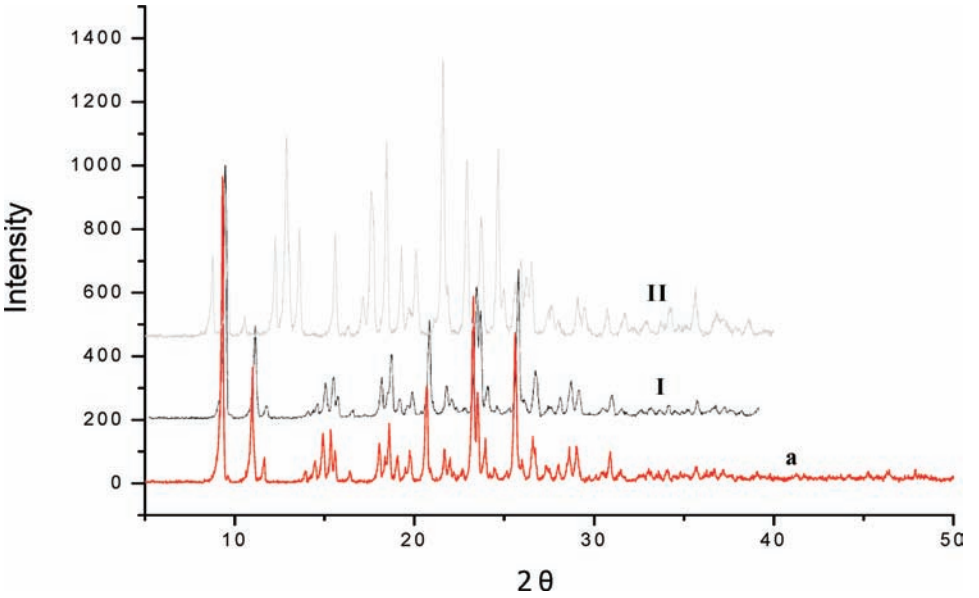


**Figure 2.** X-ray diffraction patterns of clopidogrel hydrogen sulfate: I, II, standard XRD patterns of Form I and II, respectively;[7] a, XRD pattern of the product in this study.

vessel of about 100 $cm^3$, which was maintained at a desired temperature by water circulated from a constant temperature water bath (Wanda/sida instrument HC2010, China). The temperature was accurately measured by a mercury thermometer with uncertainty of 0.05 K inserted into the inner chamber of the vessel. A condenser was connected with the vessel to prevent the evaporation of the solvents in experiment. Continuous stirring was achieved with a magnetic stir bar. A laser beam was used to determine the disappearance of the last solute in the solvent.

During the measurement, the predetermined amounts of clopidogrel hydrogen sulfate (Form I) and solvent were placed in the vessel. When the solute was completely dissolved, the solution is clear, and the intensity of the laser beam penetrating the vessel reached the maximum. Then a certain amount of clopidogrel hydrogen sulfate (Form I) was added into the vessel. When the solute dissolved completely, another addition of solute was added. This procedure was repeated until the last addition could not be dissolved completely and the range of the solubility can be determined. The measurement experiment was repeated, and according to the preceding experiments fewer times of addition was used to reduce the accumulated error and shorten the dissolving time. Finally the solubility was determined when the last addition ((2 to 5) mg) could not be dissolved completely in 30 min. Then the undissolved solute was separated and identified to be Form I by X-ray diffraction (XRD). Through all of the experiments in this work, polymorphic transformation was not found. The total mass of the solute dissolved was recorded. Together with the mass of solvent, the saturated mole fraction solubility ($x_1$) of clopidogrel hydrogen sulfate (Form I) was obtained from eq 1.

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

where $m_1$ and $m_2$ represent the mass of the solute and the solvent, respectively. $M_1$ and $M_2$ are the respective molecular masses. All of the experiments were run at least three times, and the relative uncertainties of the experimental data were within 1 %, obtained from the mass ratio of the additional solute to the dissolved solute.

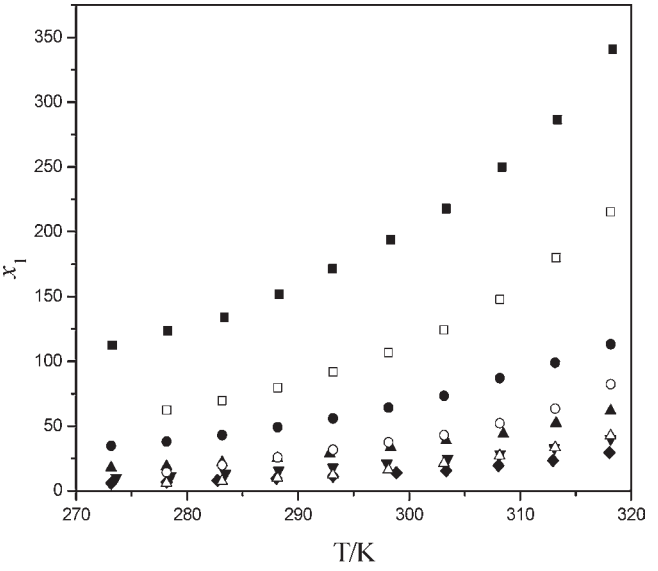


**Figure 3.** Mole fraction solubility ($x_1$) of clopidogrel hydrogen sulfate (Form I) in: ■, ethanol; ●, 1-propanol; ▲, 1-butanol; ▼, 1-pentanol; ♦, 2-propanol; □, ○, and △ solubility of Form II in ethanol, 1-propanol, and 1-butanol in literature.[6]

## RESULTS AND DISCUSSION

The solubility data of clopidogrel hydrogen sulfate (Form I) in ethanol, 1-propanol, 1-butanol, 1-pentanol, and 2-propanol at temperatures ranging from (273.15 to 318.15) K was listed in Table 1 and plotted in Figure 3. The solubility data was fitted by the modified Apelblat equation,[8] eq 2

$$\ln x_1^{cal} = a + \frac{b}{T} + c \ln T \quad (2)$$


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Table 1. Solubility ($x_1$) of Clopidogrel Hydrogen Sulfate (Form I) in Ethanol, 1-Propanol, 1-Butanol, 1-Pentanol, and 2-Propanol

| $T$/K | $10^4\,x_1$ | $10^4\,x_1^{cal}$ | $100(x_1 - x_1^{cal})/x_1$ |
|---|---|---|---|
| | | Ethanol | |
| 273.27 | 112.4 | 116.6 | −3.74 |
| 278.25 | 123.4 | 121.5 | 1.54 |
| 283.35 | 134.2 | 132.2 | 1.49 |
| 288.3 | 151.7 | 147.7 | 2.64 |
| 293.1 | 171.3 | 167.2 | 2.39 |
| 298.32 | 193.7 | 193.1 | 0.31 |
| 303.35 | 217.9 | 222.4 | −2.07 |
| 308.35 | 249.8 | 255.4 | −2.24 |
| 313.35 | 286.6 | 292.0 | −1.88 |
| 318.33 | 340.9 | 331.8 | 2.67 |
| | | 1-Propanol | |
| 273.15 | 34.76 | 34.88 | −0.35 |
| 278.15 | 38.14 | 37.41 | 1.91 |
| 283.15 | 42.92 | 41.71 | 2.82 |
| 288.15 | 49.07 | 47.67 | 2.85 |
| 293.15 | 55.85 | 55.16 | 1.24 |
| 298.15 | 64.33 | 64.09 | 0.37 |
| 303.15 | 73.23 | 74.34 | −1.52 |
| 308.15 | 87.03 | 85.84 | 1.37 |
| 313.15 | 98.89 | 98.49 | 0.40 |
| 318.15 | 113.3 | 112.2 | 0.97 |
| | | 1-Butanol | |
| 273.15 | 18.12 | 18.40 | −1.55 |
| 278.15 | 18.78 | 19.39 | −3.25 |
| 283.15 | 21.99 | 21.46 | 2.41 |
| 288.15 | 24.91 | 24.54 | 1.49 |
| 292.85 | 28.77 | 28.28 | 1.70 |
| 298.35 | 33.34 | 33.63 | −0.87 |
| 303.35 | 38.73 | 39.34 | −1.58 |
| 308.5 | 43.73 | 46.01 | −5.21 |
| 313.25 | 52.23 | 52.82 | −1.13 |
| 318.15 | 61.67 | 60.46 | 1.96 |
| | | 1-Pentanol | |
| 273.61 | 10.16 | 10.3 | −1.38 |
| 278.53 | 11.46 | 11.25 | 1.83 |
| 283.45 | 13.24 | 12.84 | 3.02 |
| 288.25 | 15.77 | 14.96 | 5.14 |
| 293.15 | 18.20 | 17.66 | 2.97 |
| 298.02 | 21.27 | 20.86 | 1.93 |
| 303.49 | 24.93 | 25.01 | −0.32 |
| 308.2 | 28.37 | 29.03 | −2.33 |
| 313.1 | 33.15 | 33.61 | −1.39 |
| 318.15 | 40.05 | 38.74 | 3.27 |
| | | 2-Propanol | |
| 273.15 | 5.995 | 6.776 | −13.03 |
| 278.15 | 6.823 | 6.862 | −0.57 |
| 282.75 | 8.076 | 7.546 | 6.56 |
| 288.05 | 9.620 | 9.002 | 6.42 |
| 293.15 | 11.17 | 11.03 | 1.25 |
| 298.85 | 13.92 | 13.98 | −0.43 |
| 303.35 | 15.66 | 16.78 | −7.15 |
| 308.05 | 19.51 | 20.11 | −3.08 |
| 312.95 | 23.27 | 24.00 | −3.14 |
| 318.05 | 29.50 | 28.48 | 3.46 |

Table 2. Parameters of eq 2 for Clopidogrel Hydrogen Sulfate (Form I) in Different Solvents

| solvent | $a$ | $b$ | $c$ | $10^4$ rmsd |
|---|---|---|---|---|
| ethanol | −11.908 | 490.22 | 1.8047 | 4.71 |
| 1-propanol | −3.8737 | 158.20 | 0.58788 | 0.82 |
| 1-butanol | −2.3115 | 95.051 | 0.35033 | 0.95 |
| 1-pentanol | −1.4396 | 58.820 | 0.21841 | 0.61 |
| 2-propanol | −1.4295 | 59.445 | 0.21614 | 0.67 |

where $T$ is absolute temperature (K) and $a$, $b$, and $c$ are the model parameters. Values of $a$, $b$, and $c$ of different solvents are listed in Table 2 together with the root-mean-square deviation (rmsd) defined as eq 3

$$\text{rmsd} = \left\{\frac{1}{N}\sum_{i=1}^{N}(x_i^{cal} - x_i)^2\right\}^{1/2} \quad (3)$$

where $x_i^{cal}$ is the mole fraction solubility calculated from eq 1, $x_i$ is the experimental value, and $N$ is the number of experimental points.

From the data of Table 2, we can see the correlation equation fitted the experimental data well. Figure 3 shows that the solubility of clopidogrel hydrogen sulfate in all of the solvents increases with an increase in temperature, and the solubility of clopidogrel hydrogen sulfate (Form I) in alcohols is ranked as ethanol > 1-propanol > 1-butanol > 1-pentanol > 2-propanol, along with the increase of the polarity of the solvents [polarity: ethanol (65.4) > 1-propanol (61.7) > 1-butanol (60.2) > 1-pentanol (56.8) > 2-propanol (54.6)].[9] As all of the alcohols have the same hydroxyl functional group, the result can be due to the hydrogen bond formed between the solvent molecules and the solute, which gets stronger as the polarity of the solvent gets larger.

The van't Hoff equation relates the logarithm of mole fraction of a solute in an ideal solution as a linear function of the reciprocal of the absolute temperature.[10]

$$\ln x = -\frac{\Delta H_{fus}}{RT} + \frac{\Delta S_{fus}}{R} \quad (4)$$

where $x$ is the mole fraction of solute in the solvent, $\Delta H_{fus}$ is the molal enthalpy of fusion of the solute, and $\Delta S_{fus}$ is the molal entropy of fusion, $T$ is the corresponding absolute temperature, and $R$ is the gas constant.

However, the most real solution exhibits nonideal behavior in practice, so the solvent effect should be considered, and the enthalpy and entropy of mixing must be taken into account by replacing $\Delta H_{fus}$ with $\Delta H_d$ (enthalpy of dissolution) and $\Delta S_{fus}$ with $\Delta S_d$ (entropy of dissolution), using:

$$\ln x = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R} \quad (5)$$


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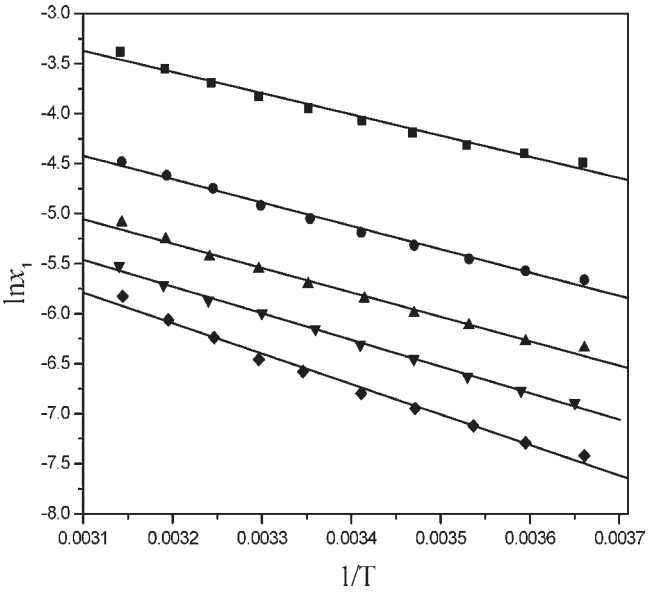


**Figure 4.** van't Hoff plot of logarithm mole fraction solubility of clopidogrel hydrogen sulfate (Form I) in: ■, ethanol; ●, 1-propanol; ▲, 1-butanol; ▼, 1-pentanol; ♦, 2-propanol.

**Table 3. Dissolution Enthalpy and Entropy of Clopidogrel Hydrogen Sulfate (Form I) in Different Solvents**

| | Form I | | Form II | |
|---|---|---|---|---|
| | $\Delta H_d$ | $\Delta S_d$ | $\Delta H_d$ | $\Delta S_d$ |
| solvent | $kJ \cdot mol^{-1}$ | $J \cdot mol^{-1} \cdot K^{-1}$ | $kJ \cdot mol^{-1}$ | $J \cdot mol^{-1} \cdot K^{-1}$ |
| ethanol | 17.61 | 26.56 | 22.81 | 39.18 |
| 1-propanol | 19.38 | 23.31 | 29.96 | 53.90 |
| 1-butanol | 20.30 | 20.92 | 36.85 | 70.33 |
| 1-pentanol | 22.13 | 23.18 | | |
| 2-propanol | 25.30 | 30.31 | | |

The van't Hoff plot of the logarithm of mole fraction solubility of clopidogrel hydrogen sulfate (Form I) versus reciprocal absolute temperature is shown in Figure 4, and the dissolution enthalpy and entropy obtained are shown in Table 3. The enthalpy decreases with the increase of the polarity of the solvents. Compared with that of clopidogrel hydrogen sulfate (Form II) in ethanol, 1-propanol, and 1-butanol from our previous work, the enthalpy of Form I is higher under the same condition.

## CONCLUSIONS

As the polymorphic transformation from the metastable form to the stable form exists in the process of measurement, accurate solubility data of metastable form are difficult to obtain. Clopidogrel hydrogen sulfate is a typical polymorphic drug. Using the characteristic that the dissolution rate of Form I is faster than the nucleation rate of Form II, the solubility equilibrium of clopidogrel hydrogen sulfate (Form I) was set up without polymorphic transformation, and the solubility data were obtained. Generally the nucleation rate is slower under lower supersaturation. As the solubility ratio of each crystal form is typically less than 2,[2,11] this method may be applied in more solubility measurements of metastable form.

The solubility of clopidogrel hydrogen sulfate was measured by a synthetic method. The result illustrates that the solubility of clopidogrel hydrogen sulfate (Form I) in lower alcohols increases with an increase in temperature. In addition, the solubility depends on the polarity of the solvents used to a great degree, and it sharply rises with an increase of the polarity of alcohols. Compared with those of Form II under the same conditions from previous literature,[6] Form I exhibits a higher solubility and a lower dissolution enthalpy. The result is consistent with that in the methanol + 2-propanol mixture,[12] which indicates that Form I is the metastable form in the lower alcohols at the studied temperature ranging from (273.15 to 318.15) K. As the occurrence of polymorphic modifications often follows Ostwald's rule of stages, this work can supply the basic data for the study of the transformation process.

## AUTHOR INFORMATION

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