Solubility of Forms I and II of Clopidogrel Hydrogen Sulfate in Methanol and 2-Propanol Mixture

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The solubilities of forms I and II of clopidogrel hydrogen sulfate (CHS) in methanol + 2-propanol mixture were measured over the temperature range of (−5 to +55) °C and the methanol mass fraction range of (1.0 to 0.1). Enthalpy and entropy of dissolution of forms I and II of CHS in methanol +2-propanol were determined by using the van't Hoff equation. Form II had a lower solubility and a higher enthalpy of dissolution compared to those of form I, which indicated that form II was the stable form and form I was the metastable form at the studied temperature range of (−5 to +55) °C.

Introduction

The crystal form of the active pharmaceutical ingredient is closely connected with the bioavailability, bioactivity, compactibility, dissolution, shelf life, and stability of a drug substance. Due to this point, the change of polymorph is a useful process for the production of pharmaceutical drugs.

Clopidogrel hydrogen sulfate (CHS) is a common antithrombotic material and has two polymorphic forms. Many patents for preparing it have been published.[1,2] Recently our work indicated that polymorphic transformations and screening of CHS were carried out in crystallization with methanol + 2-propanol as solvent.[3,4] It was found that form I was first formed and then transformed into form II during the crystallization in solution.

Crystallization in solution is one of the most widely used methods for polymorph screening.[5] In the crystallization process, a metastable polymorph may often be obtained first during the process, and then a stable polymorph is crystallized through polymorphic transformation.[6] To understand polymorphic transformation during crystallization from solution, operating parameters such as solvent, temperature, supersaturation, etc., should be considered. The solubility was based on these parameters. In drowning-out crystallization using anti solvent, solubility difference between two polymorphs induces that the polymorphic form with higher solubility can be primarily crystallized and then be transformed into the form with lower solubility. Thus, solubility offers the basic information for screening of polymorph and transformation. Anti solvent has been widely used to generate supersaturation in crystallization process. Anti solvent plays a role in reducing solubility in solution as well as change the temperature dependence of solubility. In this work, IPA was chosen as antisolvent for CHS crystallization in methanol.

Our previous works[3,4] reported that the formation and the transformation behaviors of clopidogrel hydrogen sulfate during crystallization with methanol+2-propanol as solvent were measured by an ultrasonic velocity measuring technique. It was shown that the polymorph observed depended on both the temperature and the composition of the methanol+2-propanol solvent mixture. The polymorphic transformation time of Form I to Form II in methanol+2-propanol depended on the supersaturation condition such as temperature and cooling rate. Therefore, the saturation conposition should be found to understand polymorphic transformation.

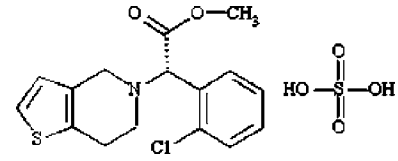

Figure 1. Chemical structure of clopidogrel hydrogen sulfate.

The first step to determine the crystallization mode is to measure the solubility of CHS in solvents. 2-Propanol, as the antisolvent, plays an important role in obtaining the supersaturation. However, the solubility data of CHS in a methanol + 2-propanol mixture required to select the appropriate solvent composition, have not been presented.

The aim of the present work is to quantify the solubility characteristics of CHS in methanol + 2-propanol as functions of temperature and composition of solvent.

Experimental Section

Materials. Form II of CHS (CAS 120202−66−6, $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$, MW 419.2, mass fraction purity >0.99; purchased by JC Chem, South Korea) was used without purification. Its chemical structure is shown in Figure 1. Methanol (mole fraction >0.999) and 2-propanol (mole fraction >0.999) were purchased from Aldrich.

Preparation of Forms I and II of CHS. Screening of forms I and II was successfully enclosed by our works.[3,4] By using these results, CHS was recrystallized at mass ratio of methanol per 2-propanol of 0.14 and mass ratio of CHS per methanol of 1.2 at 298.15 K. After recrystallization was carried out, the form I crystals were obtained at 9500 s and the Form II crystals were at 20000s. Solids of forms I and II were filtered at 9500 and 20000 s, respectively, and the solids were dried in a vacuum oven at 50 °C for 12 h.

Characterization of Polymorphic Forms. Powder XRD patterns of CHS crystals prepared in this study were determined

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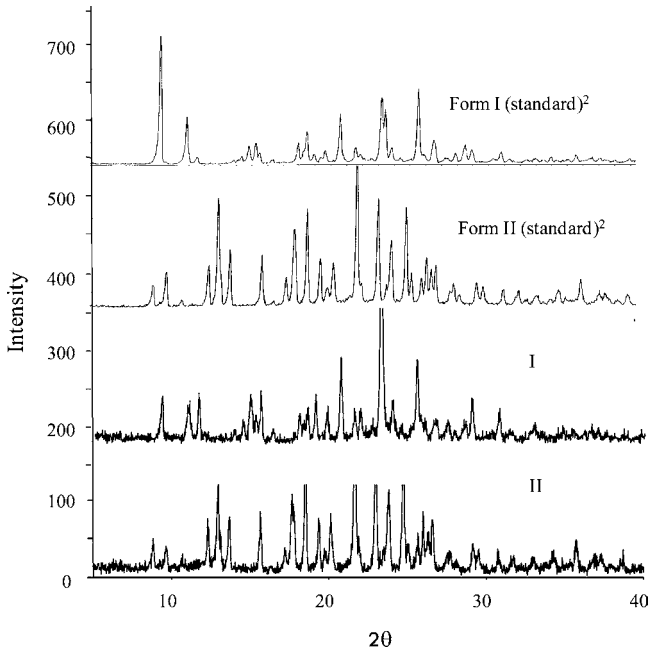

Figure 2. PXRD patterns of the forms I and II of clopidogrel hydrogen sulfate: Forms I (standard) and II(standard), standard PXRD patterns of forms I and II, respectively;[2] I, II, PXRD patterns of forms I and II recrystallized in this study, respectively.

using an X-ray diffractometer (D/MAX 2500H, Rigaku Co., Tokyo, Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 60 kV; current, 300 mA; receiving slit, 0.3 mm; scan range, 1° to 40° (2θ); step size, 0.02°; scanning speed, 1°/min. About 50 mg of the sample powder was carefully loaded into a glass holder, and the sample surface was flattened softly to avoid particle orientation using a spatula and glass plate and then the sample weight was accurately measured. The characteristic peaks were shown at 9.4° and 11.0° for form I, and 8.9°, 9.7°, and 12.5° (2θ) for form II (see Figure 2). They are same to peaks as previously reported.[3]

Measurement of Solubility. The solubilities of CHS in the methanol +2-propanol were measured by the isothermal method. Figure 3 shows diagram of experimental apparatus measuring the solubility. We used the vessel equipped with an FBRM (focused beam reflectance method) probe, which can accurately and precisely monitor and control the temperature on line.[7−9] The apparatus was equipped with a 150 mL jacketed curved-bottom glass vessel, a downward glass propeller stirrer driven by a motor, a temperature sensor, and a thermostatic bath controlled by a PID controller with uncertainty of 0.1 K. It performed temperature control and monitoring in an automated and highly accurate mode. The temperature and the number of particles within the vessel were measured at 2 s intervals during the measurement of solubility.

This method is based on sequentially adding a known mass of solute to a stirred solution kept at a fixed temperature. Predetermined amounts of CHS and solvent mixture of 100.0 g were added into the jacketed vessel. The amount of solvent was in small excess. After stirring at a fixed temperature for 1 h, an additional solute of known mass of about (0.008 to 0.01) g was added with continuous stirring. This procedure was repeated until the last addition of solute could not dissolve completely within the interval of addition of 30 min. Then, the total amount of the solute added (including the last addition) was used to compute the solubility. To prevent the evaporation of the solvent, a condenser was used. The masses of the samples

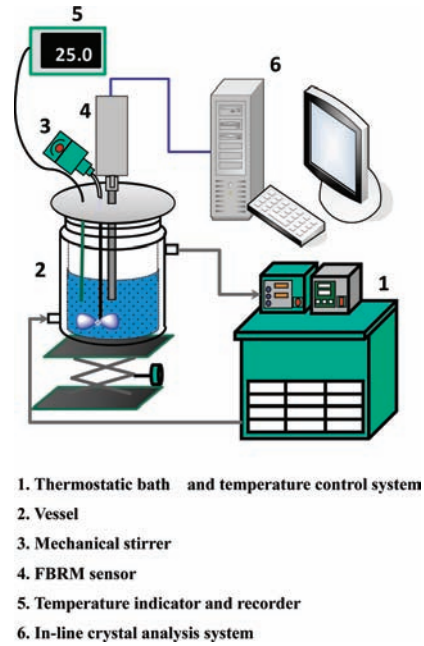

Figure 3. Diagram of experimental apparatus.

and solvents were determined using an analytical balance (Metler Toledo) with an uncertainty of 0.00001 g. The dissolution of the solute was monitored by the FBRM (Lasentec S400A).

When the solute was dissolved completely, the solution was clear, and the particle was not detected. Some of the experiments were conducted in triplicate to check the reproducibility. The solubility for a given mixture was reproducible within uncertainties obtained by the mass ratio of additional CHS to the solution of 0.001.

Results and Discussion

The solubilities of forms I and II of CHS in methanol + 2-propanol were measured over the temperature range from (−5 to +55) °C and methanol mass fraction range from 1.0 to 0.1, and plotted in Figure 4. Table 1 listed the solubility of the two polymorphs of CHS in methanol + 2-propanol at different temperatures and solvent compositions.

Solubility of CHS in methanol + 2-propanol was correlated with the absolute temperature T and methanol mass fraction y_1 by the following equation:

$$w = a + by_1 + cT + dy_1^2 + eT^2 + fy_1T + gy_1^2T + hy_1T^2 + iy_1^2T^2 \quad (1)$$

where w is the mass solubility, which is defined as mass solute per mass of solvent. T is the absolute temperature K, and a, b, c, d, e, f, g, h, and i are the parameters. This equation was obtained by trial-error method using regression software(Sigmaplot version 10).

Table 2 presents parameters of a, b, c, d, e, f, g, h, and i for two forms in binary solvent and the average relative error, σ, of the correlation for each mixture. σ is defined as

$$\sigma = \frac{\sum_{i=1}^{N} \left| \frac{w - w_{cal}}{w} \right|}{N} \quad (2)$$

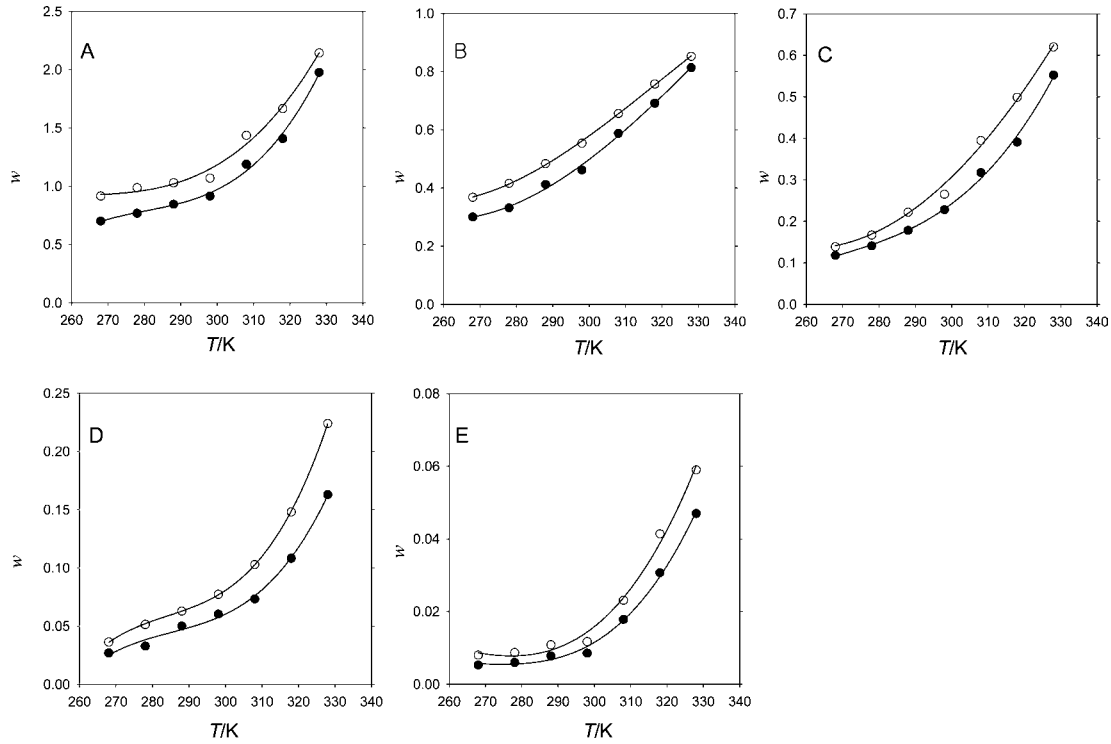

Figure 4. Solubility, w of forms I and II of clopidogrel hydrogen sulfate as functions of temperature and solvent composition. (A) $y_1 = 1.0$; ○, form I; ●, form II. (B) $y_1 = 0.7$; ○, form I; ●, form II. (C) $y_1 = 0.5$; ○, form I; ●, form II. (D) $y_1 = 0.3$; ○, form I; ●, form II. (E) $y_1 = 0.1$; ○, form I; ●, form II.

Table 1. Experimental Solubility of the Forms I (w_I) and II (w_{II}) of Clopidogrel Hydrogen Sulfate in Methanol (1) + 2-Propanol (2)

T/K	$10^2 w_I$	$10^2 w_{II}$
	$y_1 = 1.0$	
268.15	91.6027	70.1257
278.15	98.7158	76.7326
288.15	102.9530	84.5342
298.15	106.8932	91.5530
308.15	143.6254	118.9229
318.15	166.6197	140.9032
328.15	214.4376	197.7488
	$y_1 = 0.7$	
268.15	36.8416	30.0521
278.15	41.5761	33.1784
288.15	48.3332	41.2143
298.15	55.3959	46.1990
308.15	65.6194	58.8053
318.15	75.7350	69.1393
328.15	85.2353	81.3467
	$y_1 = 0.5$	
268.15	13.9217	11.8266
278.15	16.6931	14.1010
288.15	22.1936	17.8320
298.15	26.5328	22.7992
308.15	39.4697	31.7401
318.15	49.8798	39.1215
328.15	62.1177	55.2361
	$y_1 = 0.3$	
268.15	3.6343	2.7319
278.15	5.1450	3.2907
288.15	6.2950	5.0231
298.15	7.7275	6.0320
308.15	10.2899	7.3333
318.15	14.8050	10.8333
328.15	22.4012	16.2573
	$y_1 = 0.1$	
268.15	0.8003	0.5311
278.15	0.8660	0.5963
288.15	1.0851	0.7754
298.15	1.1665	0.8549
308.15	2.3065	1.7833
318.15	4.1375	3.0658
328.15	5.8844	4.6579

where N is number of experimental points. The subscripts cal stands for the calculated values. Figure 5 shows the correlation between experimental data and calculated data for forms I and II. The overall average relative errors are 4.5% and 5.2% for forms I and II, respectively. Thus, despite a little scattering, it can be seen that eq 1 satisfied to correlate the experimental data.

From Figure 4, cooling crystallization can be used because of strong dependence between solubility and temperature. Polymorph screening can be made by cooling crystallization. Crystallization using antisolvent like 2-propanol is desirable for polymorph screening because 2-propanol reduces the solubility. Increasing 2-propanol content leads to increase the yield of crystals.

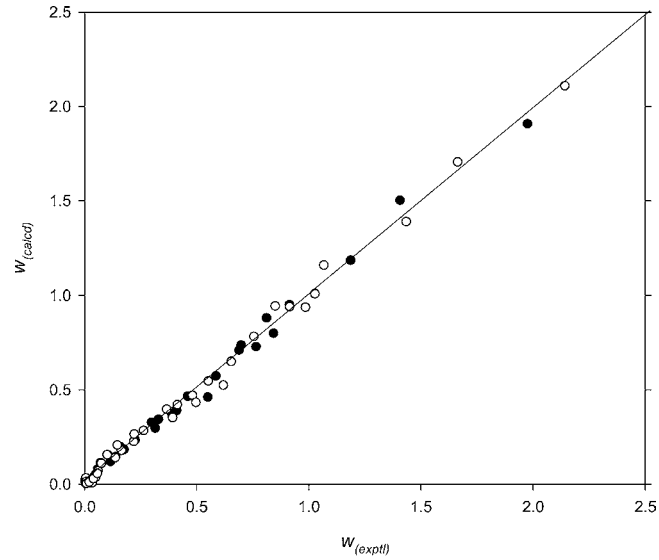

Figure 5. Comparison of experimental solubility $w_{(exptl)}$ and calculated solubility $w_{(calcd)}$. ○, form I; ●, form II.

Table 2. Parameters in eq 2 for Solubility of Forms I and II

form	a	b	10^2c	d	10^5e	$10f$	$10g$	10^4h	10^4i	$10^2\sigma$
I	6.972	−33.208	−4.410	44.312	6.905	1.854	−2.284	−2.446	2.717	3.6
II	5.202	−26.726	−3.330	44.649	5.294	1.562	−2.617	−2.235	3.873	4.3

It can be seen that the solubility of both forms increases with temperature, and Form I has a higher solubility than form II over the entire studied temperature range of (−5 to +55) °C, which indicates that form II is the thermodynamically stable form and form I is the metastable form at ambient temperature. In the temperature range investigated in this study, transition point for polymorph was not found.

From tests in different solvent compositions, solubility of both forms decreases with increasing 2-propanol composition. It means 2-propanol plays a role as an antisolvent of CHS.

Enthalpy and entropy of dissolution of forms I and II of CHS in methanol + 2-propanol were studied. 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]

$$\ln x = -\frac{\Delta_{dis}H}{RT} + \frac{\Delta_{dis}S}{R} \quad (3)$$

where x is the mole fraction of solute in the solvent, $\Delta_{dis}H$ and $\Delta_{dis}S$ are the enthalpy and the entropy of dissolution, T is the corresponding absolute temperature, and R is the gas constant. From the experimentally obtained solubility data, plot of ln x versus $1/T$ gives the values of enthalpy and entropy of dissolution from the slope and the intercept, respectively. The values of $\Delta_{dis}H$ can be regarded as a reflection of the nature of intermolecular interactions.

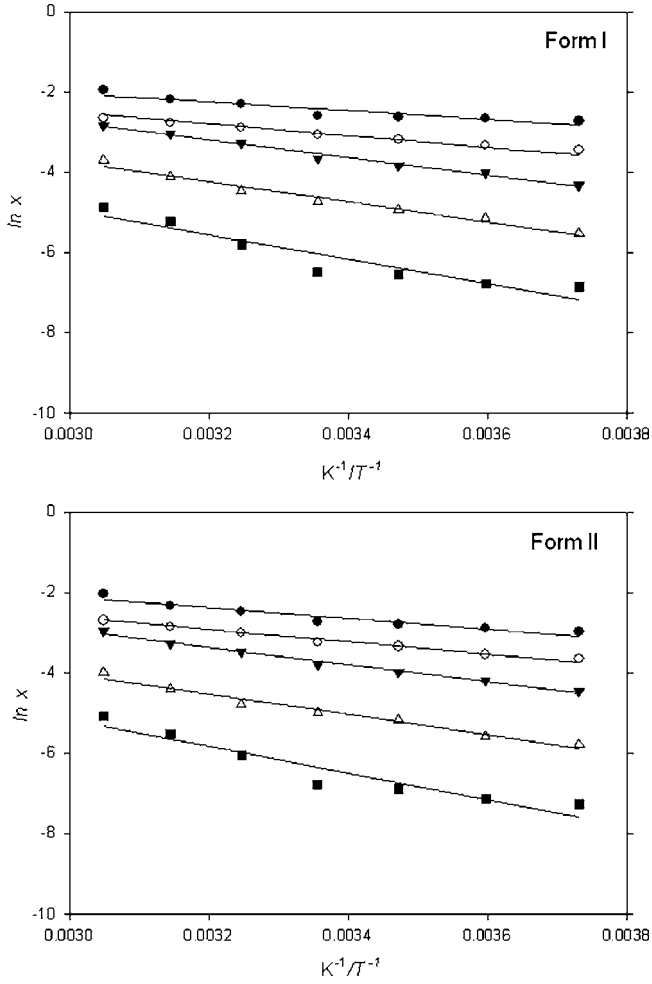

Figure 6. van't Hoff plot of logarithm mole fraction solubility of forms I and II of clopidogrel hydrogen sulfate. ○, $y_1 = 1.0$; ●, $y_1 = 0.7$; ▼, $y_1 = 0.5$; △, $y_1 = 0.3$; ■, $y_1 = 0.1$.

Table 3. Dissolution Enthalpy and Entropy of Forms I and II of Clopidogrel Hydrogen Sulfate

	form I		form II	
	$\Delta_{dis}S$	$\Delta_{dis}H$	$\Delta_{dis}S$	$\Delta_{dis}H$
y_1	J·mol^{-1}·K^{-1}	kJ·mol^{-1}	J·mol^{-1}·K^{-1}	kJ·mol^{-1}
1.0	10.52	9.12	15.51	11.03
0.7	16.02	12.26	16.94	12.89
0.5	28.68	17.62	31.15	18.72
0.3	29.57	20.99	32.00	21.02
0.1	34.66	25.27	39.02	27.34

Figure 6 shows the van't Hoff plot of the logarithm of mole fraction solubility of the two forms versus reciprocal absolute temperature. Table 3 lists the dissolution enthalpy and entropy. The dissolution enthalpies of the Form I and Form II are calculated to be (9.12 to 25.27) and (11.03 to 27.34) kJ·mol^{-1}, respectively, at 1.0 to 0.1 of methanol mass fraction in solvent. The dissolution entropies of the Form I and Form II are determined to be (8.31 to 34.66) and (13.88 to 39.02) J·mol^{-1}·K^{-1}, respectively, at 1.0 to 0.1 of methanol mass fraction in solvent.

Form II shows a lower solubility and a higher energy of dissolution compared to form I, which also supports that form II is the stable form and form I is the metastable form at the studied temperature range of (−5 to +55) °C.

Conclusions

The solubilities of two polymorphs of CHS were measured at various temperatures and with different methanol mass fractions in methanol + 2-propanol mixture. Form II shows a lower solubility and a higher energy of dissolution compared to form I, which indicates that form II is the stable form and form I is the metastable form at the studied temperature range of (−5 to 55) °C. Decrease in the solubilities of both forms with the addition of 2-propanol means that 2-propanol is used as an antisolvent to screen the polymorph of CHS in methanol solution. From the solubilities of two polymorphs of CHS, it is expecting that form I is first crystallized and then second transformed into form II during drowning-out crystallization.

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