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Solubility of Forms I and II of Clopidogrel Hydrogen Sulfate in Formic Acid, *N*-Methylpyrrolidone, and *N*,*N*-Dimethylformamide

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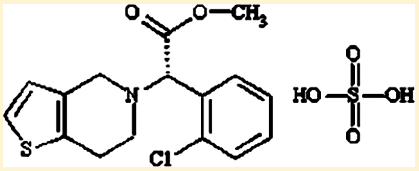
ABSTRACT: The solubilities of forms I and II of clopidogrel hydrogen sulfate (CHS) were measured in solvents such as formic acid (FA), *N*-methylpyrrolidone (NMP), and *N*,*N*-dimethylformamide (DMFA) at a temperature range of (283.15 to 353.15) K. The solubilities of forms I and II of CHS in FA + propan-2-ol, NMP + propan-2-ol, and DMFA + propan-2-ol were measured at a temperature of 308.15 K and various propan-2-ol mass fractions. The enthalpy and entropy of dissolution of CHS forms I and II of CHS in pure solvents were determined by using the van't Hoff equation.



INTRODUCTION

Clopidogrel hydrogen sulfate (CHS) is a common antithrombotic material and is widely used in the treatment of vascular disease. It has two polymorphic forms. Two patents for its preparation have been published.[1,2] Our recent work investigated the effect of solvent on the polymorph screening of CHS during crystallization in solution.

Crystallization in solution is one of the useful methods for polymorph screening. 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. To understand polymorphic transformation during crystallization in solution, operating parameters such as solvent, temperature, supersaturation, and so forth should be considered. The drowning-out crystallization using antisolvent induces that the polymorphic form with the higher solubility is primarily crystallized and then transformed into the form with the lower solubility. Thus, solubility offers the basic information for polymorph screening and transformation. Antisolvent has been widely used to generate the supersaturation in the drowning-out crystallization. It plays a key role in reducing the solubility. It is not able to dissolve CHS but to be miscible with solvent.

In this work, propan-2-ol was chosen as an antisolvent for CHS crystallization with the various solvents investigated in this study.

Our previous works reported the formation and transformation behaviors of CHS in methanol + propan-2-ol using an ultrasonic velocity measuring technique.[3,4] It was shown that the polymorphic form was dependent on the temperature and the composition of the mixed solvent. The time required for transformation of forms I into II in methanol + propan-2-ol depended on the supersaturation conditions such as temperature, solvent composition, and agitation speed. Thus, obtaining the saturation concentration is necessary for the understanding of polymorphic transformation.

The first step to determine the crystallization mode is to measure the solubility of CHS in solvents. Propan-2-ol, as an antisolvent, plays an important role in generating the supersaturation desired. Previous works indicated that the solubilities of CHS were measured in ethanol, propanol, isopropanol, butanol, and acetone.[5,6] However, data on the solubility of CHS in strong solvents such as formic acid (FA), *N*-methylpyrrolidone (NMP), and *N*,*N*-methylformamide (DMFA) have not been presented. Strong solvents are required for generating the high supersaturation. Thus, this study focused on solubility of CHS in strong polar and nonpolar solvents.

The aim of the present work is to quantify and investigate the solubility of CHS in various mixed solvents as functions of temperature and composition of antisolvent. The data obtained were correlated by the empirical equation. The solubilities of forms I and II were determined in FA, NMP, DMFA, FA + propan-2-ol, NMP + propan-2-ol, and DMFA + propan-2-ol mixtures. The enthalpy and entropy of dissolution of the two forms were estimated from the solubility data at different temperatures by using the van't Hoff equation.

EXPERIMENTAL SECTION

Materials. Forms I and 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. Its chemical structure is shown in Figure 1. FA, NMP, DMFA, and propan-2-ol purchased from Aldrich were of analytical reagent grade with a mass fraction purity >0.995.

Preparation of Forms I and II of CHS. The screening of forms I and II was successfully completed by our previous works.[7] From these results, CHS was crystallized at a solvent mass fraction of 0.1 and saturation temperatures of (298.15 and 308.15) K. After recrystallization was carried out, it was observed that form II was prepared in FA + propan-2-ol, NMP

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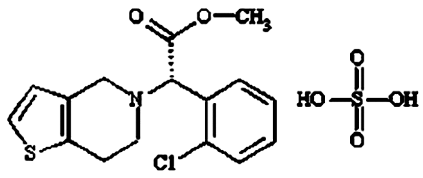

Figure 1. Chemical structure of CHS.

+ propan-2-ol, and DMFA + propan-2-ol mixtures. However, form I was clearly crystallized by adding form I seed crystals into the CHS solution with FA + propan-2-ol.[7] Crystallization was carried out at a FA/propan-2-ol mass ratio of 0.05, a CHS/FA mass ratio of 2.84, and 308.15 K. The seeding time was 500 s, and the seed amount was 0.035 mass fraction of the charged CHS. Form I was found from (1600 to 2460) s and then was transformed into form II.

Solids of forms I and II were filtered and washed with propan-2-ol, and the solids were dried in a vacuum oven at 323.15 K overnight. The purity of CHS prepared was above 0.995 mass fraction.

Characterization of Polymorphic Forms. Powder XRD patterns of CHS crystals prepared in this study was determined 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; then the sample weight was accurately measured. They are the same peaks as previously reported (see Figure 2).

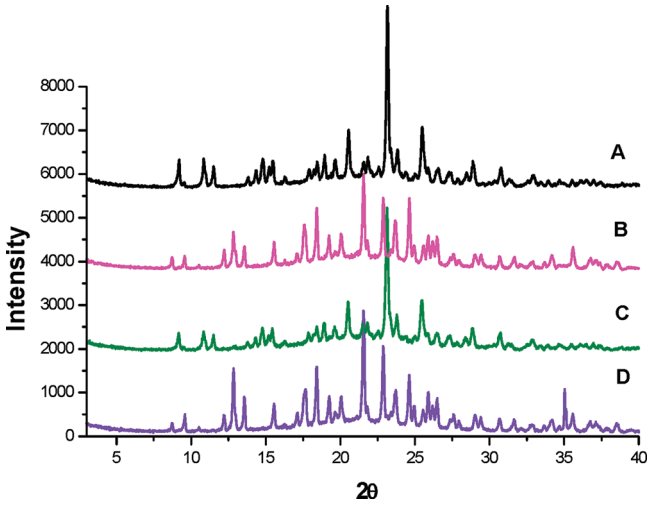

Figure 2. PXRD patterns of forms I and II of CHS: A, B, standard PXRD patterns of forms I and II, respectively;[2] C, D, PXRD patterns of forms I and II recrystallized in this study, respectively.

Measurement of Solubility. The solubility of CHS in the solvent and solvent + propan-2-ol mixtures was measured by the isothermal method. Figure 3 shows a diagram of the experimental apparatus measuring the solubility. We used the vessel equipped with an FBRM (focused beam reflectance method) probe, which can accurately and precisely monitor the particle count and control the temperature in line.[8−11] The apparatus was equipped with a 150 mL jacketed curved-bottom

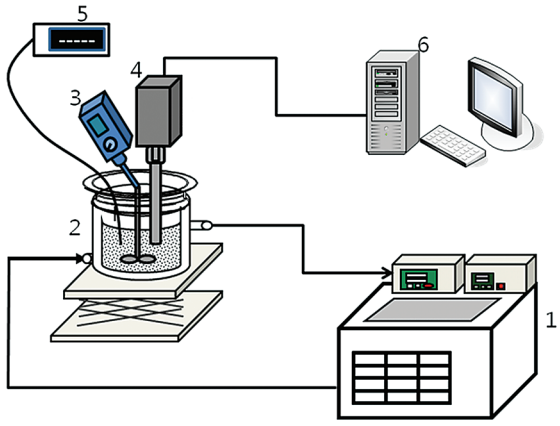

Figure 3. Diagram of experimental setup: 1, thermostatic bath and temperature control system; 2, vessel; 3, mechanical stirrer; 4, FBRM sensor; 5, temperature indicator and recorder; 6, in-line crystal analysis system.

glass vessel, a downward glass propeller stirrer driven by a motor, a temperature sensor, and a thermostatic bath controlled by a proportional−integral−derivative controller with uncertainty of 0.1 K. It performed temperature control in an automated and highly accurate mode. The temperature and the particle counts 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 a 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 and solvents were determined using an analytical balance (Mettler 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. 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 FA + propan-2-ol, NMP + propan-2-ol, and DMFA + propan-2-ol were measured at a temperature of 308.15 K and various propan-2-ol mass fractions of solvent + propan-2-ol mixtures, as shown in Figure 4. The solubility of the CHS was also measured in FA, NMP, and DMFA at the temperature range of (283.15 to 353.15) K. Table 1 lists the experimental solubilities of forms I (w_I) and II (w_{II}) in pure solvent and mixed solvents. The solubility of CHS tends to FA > DMFA > NMP with respect to the solvent mass fraction of mixed solvent.

The solubility of CHS in the solvent + propan-2-ol mixtures was correlated with the solvent mass fraction y at 308.15 K by the following equation:

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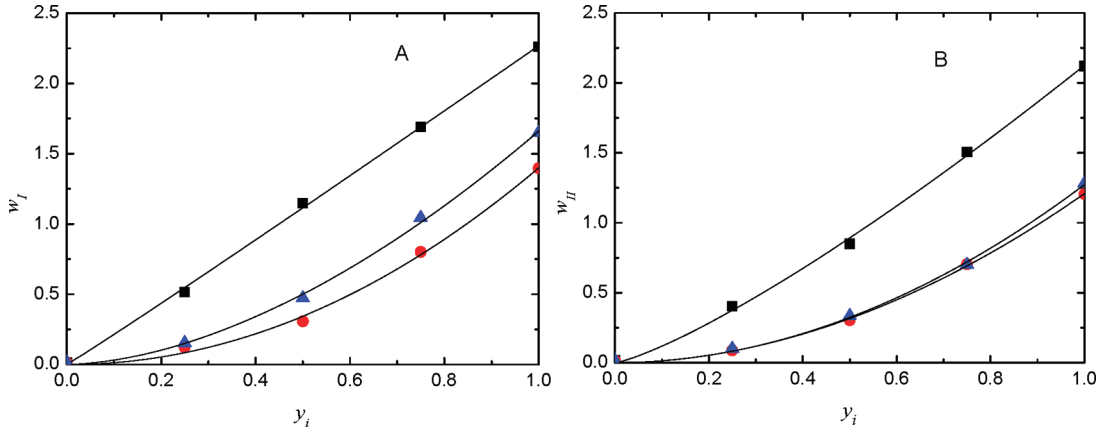

Figure 4. Solubility, w, of forms I and II of CHS as a function of solvent mass fraction y_i. A, form I, ■, FA + propan-2-ol; ▲, DMFA + propan-2-ol; ●, NMP + propan-2-ol. B, form II, ■, FA + propan-2-ol; ▲, DMFA + propan-2-ol; ●, NMP + propan-2-ol.

Table 1. Experimental Solubility of the Forms I (w_I) and II (w_{II}) of CHS in Pure Solvent FA, NMP, DMFA, and Mixed Solvents FA + Propan-2-ol, NMP + Propan-2-ol, and DMFA + Propan-2-ol

solvent	T/K	w_{II}	w_I
FA	283.15	1.811	1.913
	298.15	1.971	2.090
	308.15	2.120	2.261
	323.15	2.271	2.452
	353.15	2.635	2.825
NMP	283.15	0.766	1.133
	298.15	0.930	1.287
	308.15	1.088	1.396
	323.15	1.200	1.543
	353.15	1.615	1.792
DMFA	283.15	1.050	1.417
	298.15	1.200	1.550
	308.15	1.280	1.650
	323.15	1.400	1.833
	353.15	1.667	2.075

mixed solvent	T/K	y_i	w_{II}	w_I
FA + propan-2-ol	308.15	0.000	0.016	0.015
	308.15	0.250	0.403	0.515
	308.15	0.500	0.850	1.147
	308.15	0.750	1.506	1.689
	308.15	1.000	2.120	2.261
NMP + propan-2-ol	308.15	0.000	0.016	0.015
	308.15	0.250	0.088	0.122
	308.15	0.500	0.303	0.307
	308.15	0.750	0.703	0.800
	308.15	1.000	1.088	1.396
DMFA + propan-2-ol	308.15	0.000	0.016	0.015
	308.15	0.250	0.103	0.153
	308.15	0.500	0.334	0.472
	308.15	0.750	0.703	1.043
	308.15	1.000	1.282	1.651

$$w = a + by_i + cy_i^2 + dy_i^3 \quad (1)$$

where w is the mass solubility, which is defined as the mass of CHS per mass of solvent, y_i is the mass fraction of solvent in the solvent + propan-2-ol mixture, and a, b, c, and d are the parameters. This equation was obtained by the trial-error method using regression software (Sigma plot version 10).

Table 2 presents parameters of a, b, c, and d for the two forms in the mixed solvents and the average relative error, σ, of the correlation. σ is defined as

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

where N is the number of experimental points. The subscripts cal stands for the calculated values.

Figure 5 shows the correlation between the experimental data and calculated data for forms I and II. The overall average relative errors are 4.24 % and 2.49 % for forms I and II, respectively. Thus, despite a little scattering, it can be seen that eq 1 is correlated successfully with the experimental data. Crystallization using an antisolvent like propan-2-ol is desirable for polymorph screening because propan-2-ol reduces the solubility. Increasing the propan-2-ol content leads to increase the supersaturation and the yield of the crystals.

It can also be seen from Table 1 that the solubility of both forms increases with temperature. Form I has a higher solubility than form II over the temperature range of (283.15 to 353.15) K. It indicates that form II is the thermodynamically stable form and form I the metastable form. At the temperature range investigated in this study, the transition point for polymorph was not found. Eventually, it supports that form I is formed first and then transformed into form II in the cooling crystallization.

From the tests in different solvent fractions, the solubility of both forms decreases with increasing 2-propanol mass fraction in mixed solvents. It means propan-2-ol plays a role as an antisolvent of CHS.

The enthalpy and entropy of dissolution of forms I and II of CHS in various solvent + propan-2-ol mixtures were studied. The van't Hoff equation relates the logarithm of mole fraction of a solute in an ideal solution as a linear fraction of the reciprocal of the absolute temperature.[12]

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

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, respectively, T is the absolute temperature, and R is the gas constant. From the experimental solubility data, the plot of ln x versus $1/T$ gives the values of enthalpy and entropy of dissolution from the slope and the intercept, respectively. The

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Table 2. Parameters in Equation 1 for the Solubility of Forms I and II

mixed solvent	form	10^2a	$10b$	$10c$	$10d$	σ	T/K
FA + propan-2-ol	I	1.01	19.123	8.777	−5.440	0.0409	308.15
	II	2.17	10.743	15.737	−5.440	0.0478	308.15
NMP + propan-2-ol	I	2.12	−0.220	12.697	1.333	0.0520	308.15
	II	1.78	−1.146	15.223	−2.187	0.0149	308.15
DMFA + propan-2-ol	I	1.91	−1.117	25.200	−7.733	0.0343	308.15
	II	1.46	1.501	7.726	3.413	0.0120	308.15

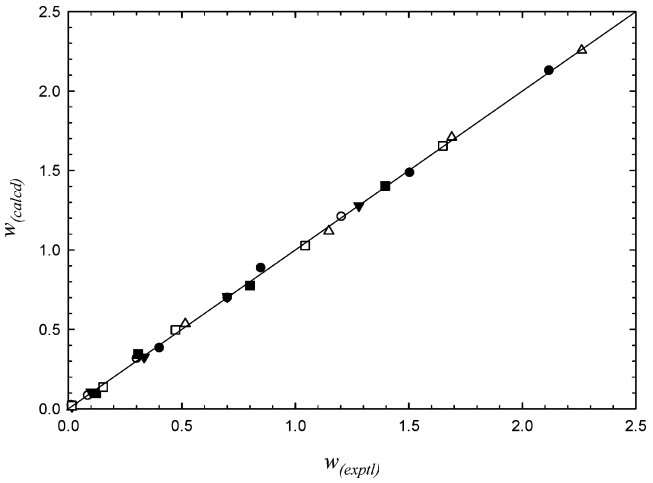

Figure 5. Comparison of experimental solubility $w_{(exptl)}$ and calculated solubility $w_{(calcd)}$ for form I, ●, FA + propan-2-ol; ○, NMP + propan-2-ol; ▼, DMFA + propan-2-ol and for form II, △, FA + propan-2-ol; ■, NMP + propan-2-ol; □, DMFA + propan-2-ol.

values of $\Delta_{dis}H$ can be regarded as a reflection of the nature of intermolecular interactions.

Figure 6 shows the van't Hoff plot of ln x versus $1/T$. Table 3 lists the enthalpy and entropy of dissolution. The dissolution enthalpies of form I are (3.555, 3.722, and 4.066) kJ·mol^{-1} in the solvents FA, NMP, and DMFA, respectively. The dissolution enthalpies of form II are (3.852, 4.382, and 6.882) kJ·mol^{-1} in the solvents FA, NMP, and DMFA, respectively.

Form II shows a lower solubility and a higher energy of dissolution compared to form I. Thus, form II is the stable form and form I the metastable form at the studied temperature range. In all of the solvent systems, form II has higher enthalpy values. It can be evaluated from the specific intermolecular interactions between solute and solvent.

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

	form II		form I	
	$\Delta_{dis}S$	$\Delta_{dis}H$	$\Delta_{dis}S$	$\Delta_{dis}H$
solvent	J·mol^{-1}·K^{-1}	kJ·mol^{-1}	J·mol^{-1}·K^{-1}	kJ·mol^{-1}
FA	−1.514	3.852	−1.403	3.722
NMP	−0.522	4.382	−0.416	3.555
DMFA	8.858	6.882	1.533	4.066

CONCLUSIONS

The solubilities of two polymorphs of CHS were measured in FA, DMFA, and NMP and with various propan-2-ol mass fractions in mixed solvents. Form II shows a lower solubility and a higher energy of dissolution compared to form I. This indicates that form II is the stable form and form I is the metastable form. The results suggest that the supersaturation in drowning-out crystallization and cooling crystallization tends to FA > DMFA > NMP. As the solubility of form I was higher than that of form II with respect to solvent mass fraction and temperature, it is expected that form I crystallizes first and then transforms into form II during the crystallization.

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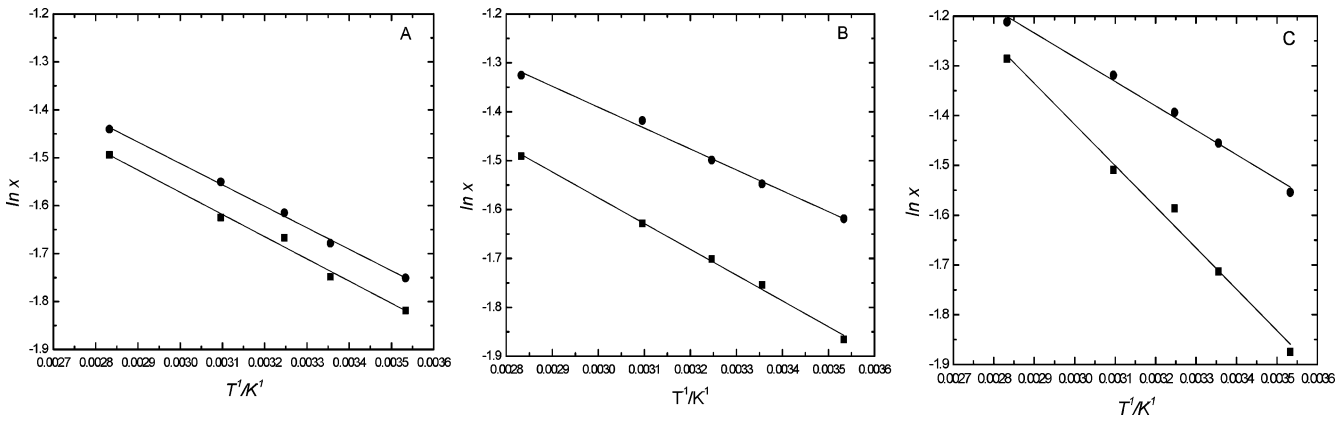

Figure 6. van't Hoff plot of logarithm mole fraction solubility (x) of forms I and II of CHS for solvents. A, FA, ●, form I; ■, form II. B, DMFA, ●, form I; ■, form II. C, NMP, ●, form I; ■, form II.

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