Solubility of Clopidogrel Hydrogen Sulfate (Form II) in Different Solvents

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As an urgent need in the design and upscale of the industrial crystallization process, solubilities of clopidogrel hydrogen sulfate (Form II) in ethanol, propanol, isopropanol, butanol, and acetone were measured using a laser-monitoring technique at temperatures ranging from (278.15 to 318.15) K. The experimental data were fitted well by the modified Apelblat equation.

Introduction

Clopidogrel hydrogen sulfate (CAS Registry No. 120202-66-6; (*S*)-(+)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydro-4*H*-thieno[3,2-c]pyridin-5-yl)acetate hydrogen sulfate, shown in Figure 1) is an antiplatelet agent, widely used in the treatment of vascular disease.[1] The existence of several different polymorphs has been reported.[2] Form I was first employed in the pharmaceutical industry, and then Form II was widely used after it was born as its greater thermodynamic stability. A great difference exists between the two forms. Form I is monoclinic, while Form II is orthorhombic; in morphology the Form I crystals are plates, while the Form II crystals are rods. The X-ray diffraction patterns are shown in Figure 2, with the characteristic peaks at 9.1, 10.7, and 11.4 for Form I, and 8.7, 9.6, 12.2, 12.8, and 13.5 for Form II.[3]

Different polymorphs of a drug may have different dissolution rates and bioavailabilities, and that may result in absolutely different therapies.[4] Crystallization is the only unit operation to prepare different drug polymorphs. To optimize the crystallization process for obtaining the required polymorph, thermodynamic data are needed urgently. Clopidogrel hydrogen sulfate is crystallized from pure solvents, while no solubilities of clopidogrel hydrogen sulfate in pure solvents have been reported previously. In this work, the solubilities of clopidogrel hydrogen sulfate (Form II) in ethanol, propanol, isopropanol, butanol, and acetone were measured at temperatures ranging from (278.15 to 318.15) K and atmospheric pressure by a synthetic method.[5,6] A laser beam was used to determine the disappearance of the last solute in the solvent at a fixed temperature.

Experimental Section

Materials. Clopidogrel hydrogen sulfate supplied by Zhejiang Huahai Pharmaceutical Co., Ltd., China, was purified by antisolvent crystallization before use. Ethanol was chosen as the solvent and acetone as the antisolvent. The mass fraction purity of clopidogrel hydrogen sulfate was greater than 0.99 (as determined by high-performance liquid chromatography, HPLC), and its melting temperature found to be 176 °C (Netzsch DSC 204 differential scanning calorimeter), which is the same as that reported in literature.[3] It was characterized to be Form II according to the results of powder X-ray diffraction. The ethanol, propanol, isopropanol, butanol, and acetone used (were obtained from Tianjin Chemical Reagent Co., China) were of analytical reagent grade with a mass fraction purity > 0.995.

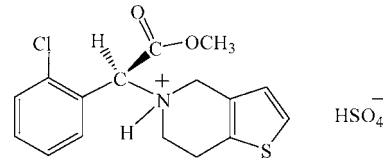

Figure 1. Chemical structure of clopidogrel hydrogen sulfate.

Apparatus and Procedure. The solubilities of clopidogrel hydrogen sulfate (Form II) were measured by a synthetic method. The apparatus is shown in Figure 3. The dissolution of the solute was performed in a jacketed glass vessel, which was maintained at the desired temperature by a constant temperature water bath (Wanda/sida instrument HC2010, China). Temperature was measured by a mercury thermometer with uncertainty of 0.05 K. A magnetic stirrer was used to keep stirring, and a condenser was connected with the vessel to prevent the evaporation of the solvents in experiment.

A predetermined excess amount of clopidogrel hydrogen sulfate (Form II) was added to a certain amount of the experimental solvent (ethanol, propanol, isopropanol, butanol, and acetone) at temperatures ranging from (278.15 to 318.15) K. The undissolved solute was kept suspended for 8 h and then characterized by X-ray diffraction. The results revealed that, under the experimental conditions, the solute maintained Form II.

In the experiments, predetermined amounts of solvent and solute (weighed by Mettler Toledo AB204-N, Switzerland) were placed in the jacketed vessel, and the solution was stirred continuously at the desired temperature. The intensity of the laser penetrating the vessel reached the maximum when the solute was dissolved completely. Then a certain amount of solute was weighed by the balance with the weighing bottle and added to the vessel through. This procedure was repeated until the last addition of solute could not be dissolved completely. Thus, the range of the solubility can be determined. The measurement experiment was repeated independently a few times at the temperature, and each time the initial concentration was chosen consequently closer to the solubility limit according to the preceding experiments. Finally when only one addition ((2 to 5) mg) to the initial solution could not be dissolved completely, the solubility was determined. The total mass of the solute (including the addition) was used to calculate the mole fraction solubility of clopidogrel hydrogen sulfate. All of the experiments

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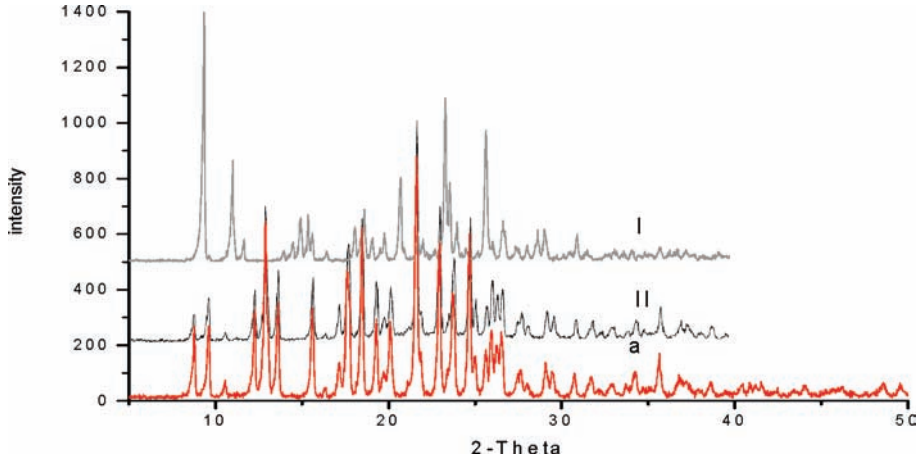

Figure 2. X-ray diffraction patterns of clopidogrel hydrogen sulfate: I, II, standard XRD patterns of Forms I and II, respectively;[3] a, recrystallized product.

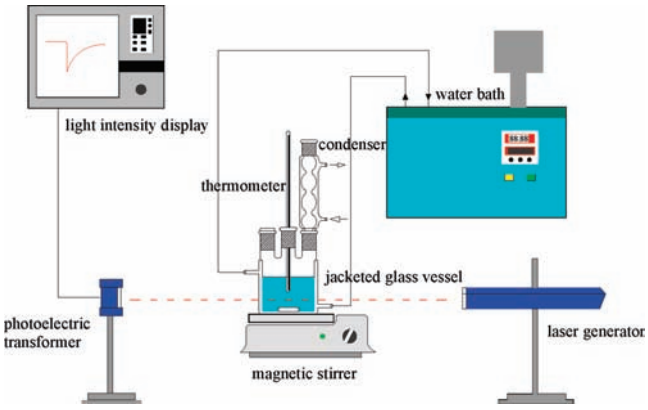

Figure 3. Experimental setup for the solubility determination.

were run at least three times, and the relative uncertainties of the experimental data, which can be obtained by the mass ratio of the additional solute to the dissolved solute, were within 1 %.

Results and Discussion

The solubility data of clopidogrel hydrogen sulfate (Form II) in ethanol, propanol, isopropanol, butanol, and acetone at temperatures ranging from (278.15 to 318.15) K are listed in Table 1 and plotted in Figure 4. The solubility data were fitted by the modified Apelblat equation,[7] eq 1

$$\ln x_1 = a + \frac{b}{T} + c \ln T \qquad (1)$$

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 rmsd defined as eq 2

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

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.

Conclusions

From Tables 1 and 2 and Figure 4, the following conclusions can be drawn:

(1) The solubility of clopidogrel hydrogen sulfate in all of the solvents increases with an increase in temperature.

Table 1. Solubility (x_1) of Clopidogrel Hydrogen Sulfate (Form II) in Ethanol, Propanol, Isopropanol, Butanol, and Acetone

T/K	$10^4\ x_1$	$10^4\ x_1^{\text{cal}}$
	Ethanol	
278.15	62.42	62.45
283.15	69.85	69.97
288.15	79.61	79.47
293.15	91.69	91.41
298.15	106.7	106.4
303.15	124.4	125.1
308.15	147.9	148.7
313.25	179.9	178.9
318.15	215.6	215.6
	Propanol	
278.15	14.36	15.15
283.15	19.80	19.36
288.15	25.84	24.41
293.15	31.79	30.40
298.15	37.43	37.41
303.15	42.95	45.53
308.15	52.32	54.84
313.15	63.56	65.62
318.15	82.23	77.26
	Butanol	
278.15	5.912	5.783
283.15	7.346	7.533
288.15	9.752	9.771
293.15	12.38	12.62
298.15	16.35	16.24
303.15	21.26	20.82
308.15	26.98	26.58
313.15	33.43	33.82
318.15	42.60	42.88
	Isopropanol	
278.15	0.4263	0.3965
283.2	0.7724	0.8256
288.12	1.459	1.561
293.2	2.746	2.795
298.21	4.919	4.627
303.17	7.505	7.146
308.2	10.52	10.44
313.15	13.99	14.33
318.15	18.43	18.69
	Acetone	
278.1	3.802	3.776
283.15	4.355	4.369
288.24	5.032	5.086
293.13	5.903	5.909
298.23	6.925	6.938
303.29	8.278	8.164
308.36	9.687	9.642
313.23	11.26	11.35
318.05	13.34	13.36

(2) The solubility of clopidogrel hydrogen sulfate in alcohols is ranked as ethanol > propanol > butanol > isopropanol. This

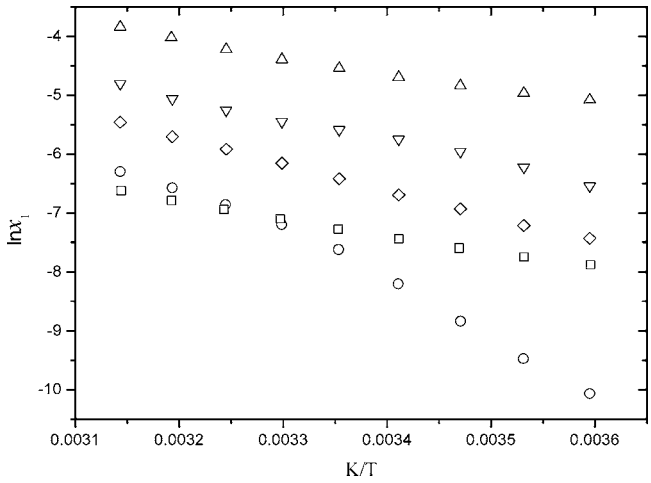

Figure 4. Mole fraction solubilities (x_1) of clopidogrel hydrogen sulfate (Form II) in: △, ethanol; ▽, propanol; ◇, butanol; ○, isopropanol; □, acetone.

Table 2. Parameters of Equation 1 for Solubility of Clopidogrel Hydrogen Sulfate (Form II) in Different Solvents

solvent	*a*	*b*	*c*	10^4 rmsd
ethanol	−377.92	14245	57.146	0.51
propanol	109.26	−8166.7	−15.351	2.28
butanol	−99.872	377.16	16.179	0.28
isopropanol	1196.9	−60738	−175.66	0.22
acetone	−208.46	6549.8	31.454	0.05

can be due to the ion−dipole type interaction between the solvents and the solute, which gets stronger with the increase of the polarity of the solvents [polarity: ethanol (65.4) > propanol (61.7) > butanol (60.2) > isopropanol (54.6)].[8] The curve of solubility in acetone differs from those in alcohols. That could be the result of different functional groups in the solvent molecules.

(3) The correlation equation fitted the experimental data well. This study provided fundamental data for the upscale of industrial preparation of clopidogrel hydrogen sulfate (Form II).

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