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Polymorph Screening Technology by Controlling Crystallization

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Polymorphic transformation among the Form I, Form II and amorphous of clopidogrel hydrogen sulfate was carried out experimentally. In this study, the effect of solution composition, temperature and supersaturation was investigated. Supersaturation < 2.3 is acceptable for stable form, Form II formation. Supersaturation > 8.9 is required for unstable form, amorphous form. Higher supersaturation can be obtained by evaporation coupled with higher vacuum. It is concluded that the screening of polymorphs can be done by control of supersaturation level.

1. Introduction

Compounds that exist in various solid-state forms, crystalline or amorphous, offer unique challenges in product development and manufacturing (Morris et al., 2001). Pharmaceutical development of thermodynamically metastable forms is often desired because of their enhanced biopharmaceutical properties as a result of higher solubilities and faster dissolution rates (Byrn et al., 1995). In other cases, metastable forms are unacceptable because of crystallization and transformation to a more thermodynamically stable form during processing, storage, or dissolution (Rodríguez-Hornedo, et al., 1999).
The solution-mediated mechanism only allows the transition from a metastable phase to the stable phase (Llinas et al., 2008). This type of transformation is driven by the difference in solubility between the two phases. In contrast to the solution mechanism where transformation occurs during drying, the solution mediated mechanism operates when the metastable phase is in contact with the saturated solution. In this study, polymorphic transformation among the Form I, Form II and amorphous of clopidogrel hydrogen sulfate was carried out experimentally. The screening of polymorphs was grasped.

2. Experimental Methods

2.1 Materials and Identification of polymorphs

Form I and II crystals of CHS ($C_{16}H_{16}ClNO_2S.H_2SO_4$, MW 419.2, 99.0% pure was used without purification. Formic acid and isopropyl alcohol were purchased from Duksan pure chemicals Co., Ltd South Korea. Polymorphs obtained were identified using XRPD (X-ray powder diffractometer). XRPD patterns were taken with 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^o–40^o (2θ); step size, 0.02^o; scanning speed, 1^o/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.

2.2 Experimental Method

The experimental setup used in this study is shown below in Figure 1. It consists of a double-jacket crystallizer, mechanical stirrer, an ultrasonic measurement system, thermostatic bath, vacuum filter and

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drying equipment. The experiments were conducted in batch crystallization mode. In every batch operation; ultrasonic velocity, concentration and temperature were recorded in 2 seconds interval.

The crystallizer was a 300 mL-jacketed cylindrical glass vessel equipped with a 5 cm marine type propeller with a stirring speed of 400 rpm and an ultrasonic sensor immersed in it. The CHS Form II crystals were dissolved in the solvent at 10 ^{o}C higher than the saturation temperature. The solution was kept at the same temperature until all the crystals were fully dissolved then slowly cooled to the saturation temperature and maintained for an hour. It was then fed to the agitated IPA at constant temperature using a thermostatic bath.

The ratio of solvent to IPA ranged from 0.05 to 2 g/g. The ratio of CHS to solvent ranged from 1 to 8 g/g. Crystallization was carried out at 298.15 K and 328.15 K. The solution was sampled at regular intervals using a solid–liquid separator with a glass filter. The precipitated polymorphic form was identified by XRD and SEM analysis.

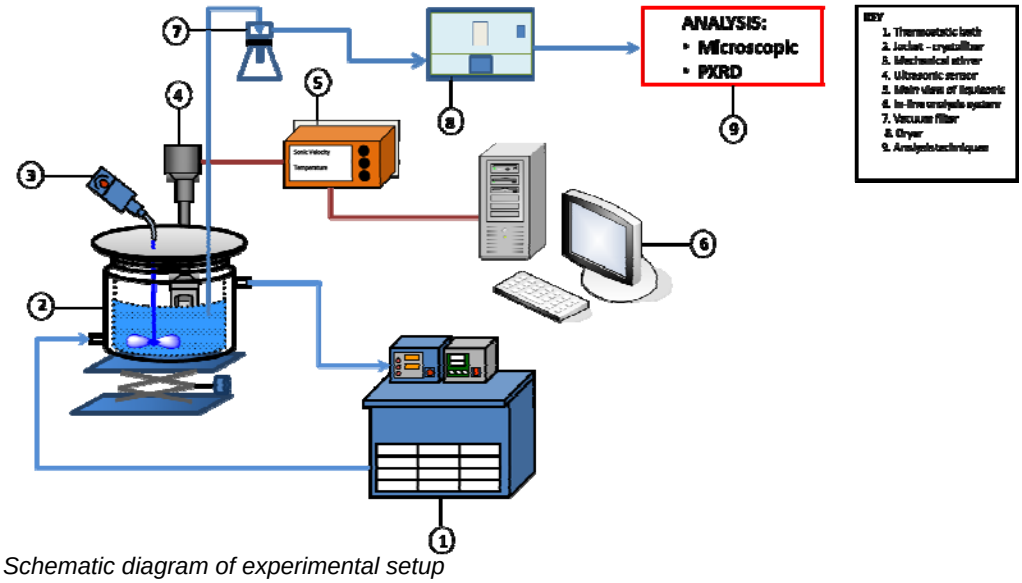

Figure 1: Schematic diagram of experimental setup

3. Solubility

The solubility of CHS Amorphous in formic acid was measured by the isothermal method. CHS Forms I and II, and amorphous form in formic acid were determined in the previous study (Jim et al. 2012).

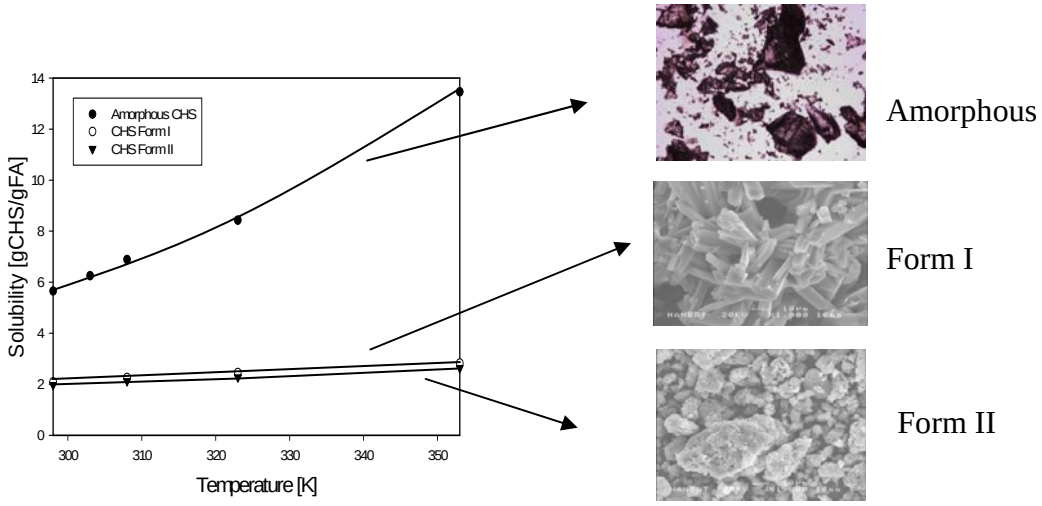

Figure 2: Solubility of amorphous, Form I and II in formic acid at different temperatures

4. Polymorphic crystallization

4.1 CHS Form II polymorph

In-situ crystallization of Form II in FA/IPA was performed using ultrasonic velocity measurements. This measurement of supersaturation levels (Omar et al.,1999) allows for an accurate determination of the concentration and temperature of the crystallization process in real time. Figure 3 shows the temperature and ultrasonic velocity profiles for the crystallization of CHS Form II by drowning out crystallization at FA/IPA ratio of 0.05 g/g.

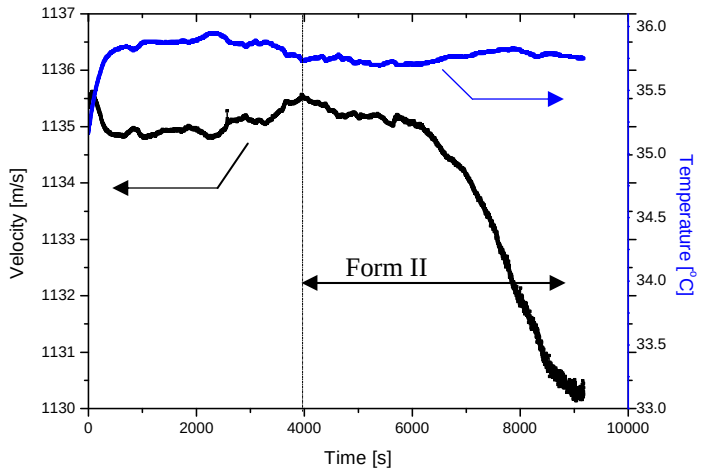

Figure 3.: Ultrasonic velocity profile of FA/IPA in the crystallization of CHS Form II

Form II polymorphs were obtained for all unseeded crystallizations in FA/IPA. The induction time for the crystallizations was decreased with increasing the supersaturation. The supersaturation could be varied by considering the FA/IPA ratio for the crystallization process. Lower supersaturation for seeded crystallization over 24 hours without agitation resulted in the crystallization of Form II with an advantage of larger crystal size. This experimentation leads to the successful growth of CHS Form II in FA/IPA(see Figure 4).

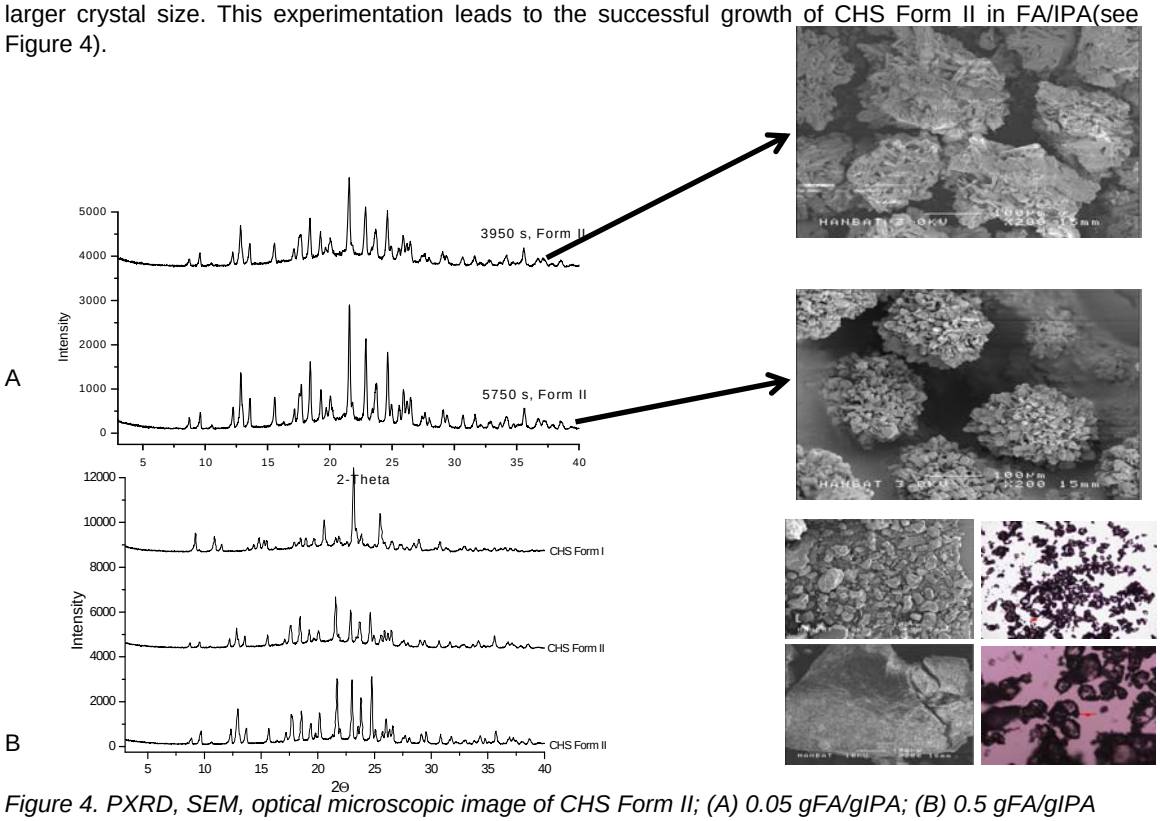

Figure 4. PXRD, SEM, optical microscopic image of CHS Form II; (A) 0.05 gFA/gIPA; (B) 0.5 gFA/gIPA

4.2. CHS Form I polymorph

The form I is the metastable form of CHS which was crystallized in MeOH/IPA in previous studies (Kim et al., 2008). However, in FA/IPA systems CHS Form I can only be crystallized at very high supersaturations or by seeding crystallization. Seeding crystallization of Form I proved effective in studying the transformation process for the CHS polymorphs in FA/IPA solvents. Table 1 lists the experimental conditions and results for CHS crystallization for different seed amounts and solvent ratios. The polymorphic outcomes have been shown at different times during the crystallization process with clear morphological characterization to aid in the proper understanding of the time-based transformation process.

Table 1: Effect of seed amount and solvent ratio in crystallization of CHS Form I

Temperature [^{o}C]	C_o [g/g]	Seed amount [%]	Solvent ratio [g/g]
(A) 35	2.0	16	0.2
(B) 25	1.0	10	0.14
(C) 35	2.0	17.5	0.2

Figure 5 shows Form I crystallization at 7,500 s, transformation at 20,520 s and finally the crystallization of stable Form II. At lower supersaturations and temperature, induction time for the crystallization of Form II is higher and vice-versa. Transformation of the Form I to Form II can also be observed at a longer time range which helps in effectively monitoring the transformation process of polymorphs of active pharmaceutical ingredients.

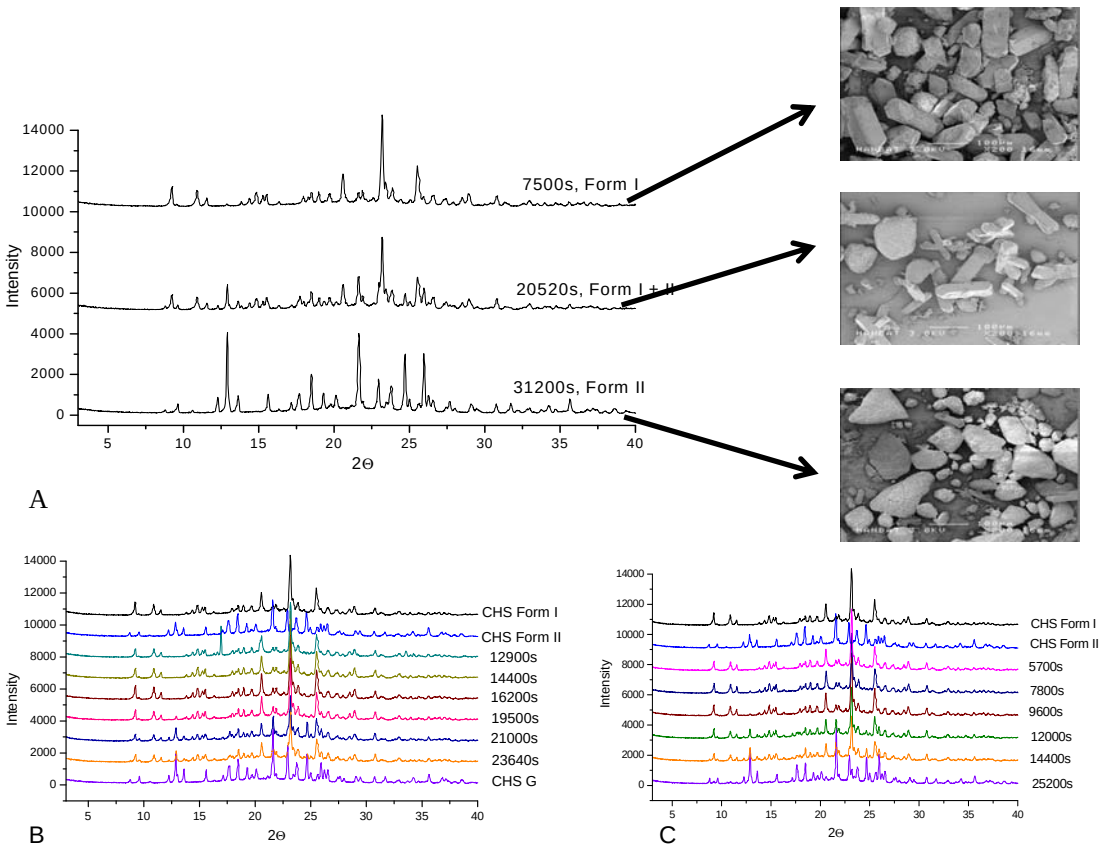

Figure 5: Transformation of CHS Form II; (A) PXRD and SEM analysis, (B) PXRD analysis, (C) PXRD analysis

4.3. Transformation of polymorphic form to amorphous form

The amorphous form of CHS was prepared in solvents by coupling the evaporation and vacuum drying process. Unsuccessful results from drowning out crystallization leads to the formation of Form II stable polymorphs. However, evaporating the solution and vacuum drying it under high vacuum pressure and temperature are required for formation of amorphous. The results were reproducible with various trials.

Table. 2 Experimental conditions for the transformation of CHS Form I to amorphous

T_O [^{o}C]	Raw material	Solvent system	C_o [g/g]	Method	Polymorphic outcome
35	CHS Form I	FA	2.003	Evaporation + Drying	Form I
35	CHS Form I	FA/IPA	2.003	Evaporation+Vacuum drying	Form II
35	CHS Form I	FA	8.400	Evaporation+Vacuum drying	Amorphous

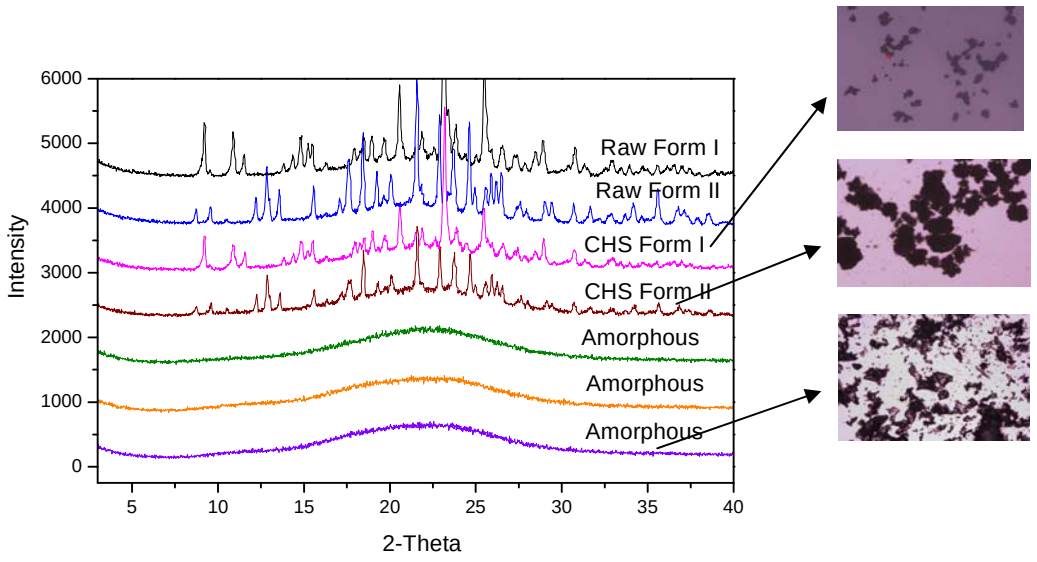

Figure 6. XRD and optical microscopy analysis for; Form II crystallization, Form I and amorphous transformations.

5. Conclusions

A study of the polymorphic transformation among the Form I, Form II and amorphous of clopidogrel hydrogen sulfate was presented in this paper. Supersaturation < 2.3 is acceptable for stable form, Form II formation. Supersaturation > 8.9 is required for unstable form, amorphous form. Higher supersaturation can be obtained by evaporation coupled with higher vacuum.

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