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Effect of solvent and molecular structure on the crystallization of polymorphs of BPT esters

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ABSTRACT

The polymorphic crystallization behaviors for methylester (Me-est) and isobutyl ester (i-But-est) of BPT in cyclohexane (c-Hxn) and acetonitrile (MeCN) solutions at 298 K were investigated, and the solvent effect was discussed in comparison with the previous results.

In the crystallization of Me-est, only one form with needle-like morphology was obtained in c-Hxn and MeCN solutions at any supersaturation. Two polymorphs of A and B forms appeared in the crystallization of i-But-est in c-Hxn solutions and solution-mediated transformation occurred. The morphology of the stable B form is prismatic and that of the metastable A form is needle-like. From MeCN solutions only, the stable B form with the prismatic morphology crystallized. The polymorphic crystallization behavior of i-But-est is similar to that of Pr-est and different from that of Me-est. The solubility of each ester increases with the dipole moment of the solvents, indicating that solute–solvent interaction increases with dipole moment. In the case of i-But-est and Pro-est, the meta-stable form can crystallize from solvents with weak interaction (EtOH and c-Hxn), but only the stable form crystallizes from solvents with large interaction (MeCN). In the crystallization of Me-est, no polymorphs appear, even in EtOH and c-Hxn. It is presumed that the especially strong hydrogen bonding between two molecules may disturb the formation of the polymorphs.

1. Introduction

The control of the crystallization process of polymorphs and solvated crystals is important in the pharmaceutical industry because this process affects the bioavailability, stability, solubility, and morphology of pharmaceutical products [1–3]. The crystallization process is influenced by various operational factors, such as additives [4,5], solvents [6–8], and interfaces [5,9]. In the pharmaceutical industry, the effect of solvents on polymorphic crystallization is very important because generally, crystallization is performed using various solvents. Furthermore, anti-solvent crystallization is frequently used to increase the efficiency of the yield. In the anti-solvent crystallization of 2-(3-cyano-4-(2-methylpropoxy)-phenyl)-4-methyl-thiazole-5-carboxylic acid (BPT), we observed that the changing rate of the solvent composition greatly influences the polymorphic crystallization behavior [7].

On the other hand, a partial change in molecular structure of solute (e.g. a functional group) affects the polymorphism, and some law may be present governing the relationship between the polymorphism and the molecular structure. For example, the difference between the polymorphism of L-glutamic acid and that of L-histidine was previously correlated with the difference between the molecular structures of these amino acids [3]. Knowing the relationship between molecular structure and polymorphism will shed light on the control of the polymorphism. In previous papers [10,11], we prepared methyl (Me-est), propyl (Pro-est) and isobutylesters (i-But-est) of BPT (Fig. 1), BPT, which is an enzyme inhibitor, and the dependence of the polymorphism on molecular structure was examined in ethanol solutions. It was found that the crystallization behavior of the polymorphs depends on the size of the alkyl group in BPT esters. In this paper, we have investigated further the effect of solvents on the polymorphic crystallization behavior of methyl ester (Me-est) and isobutyl ester (i-But-est) in comparison with the previous results for propyl ester (Pro-est).

2. Experimental procedure

BPT methyl ester (Me-est: Methyl 2-(3-Cyano-4-(2-methylpropoxy)-phenyl)-4-methyl-thiazole-5-carboxylate) and BPT isobutyl ester (i-But-est: 2-methylpropyl 2-(3- Cyano-4-(2-methylpropoxy)-phenyl)-4-methyl-thiazole-5-carboxylate) were used for these crystallization experiments. Crystallization was carried out

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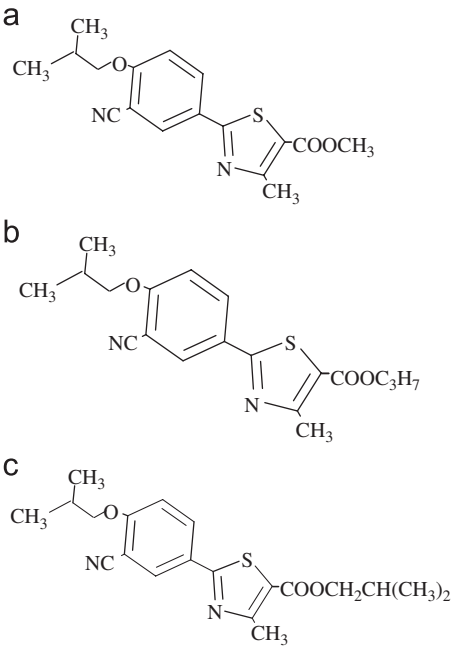

Fig. 1. Molecules of BPT esters: methylester (Me-est)(a), propylester (Pr-est) (b) and isobuthylester (i-But-est) (c).

using the rapid cooling method in cyclohexane (c-Hxn) and acetonitrile (MeCN) solutions. Different amounts of these esters were dissolved in the solvents at 323 K, and the solution was rapidly cooled to 298 K. Therefore, crystallization was performed at a constant temperature (298 K). The slurry was sampled and filtered to separate the crystals from the solution. The concentration of the solution was measured by a UV spectroscopic method at a wavelength of 254 nm. The polymorphic crystal structure was examined by powder X-ray diffraction (XRD) using the RINT2200 (Rigaku).

3. Results and discussion

3.1. Crystallization behaviors of Me-est in cyclohexane (c-Hxn) and acetonitrile (MeCN) solutions

The rapid cooling crystallization of Me-est was performed in c-Hxn solutions at initial concentrations (C_o) between 3.6 and 6.0 mM. Fig. 2 shows the change in the concentration of the solution (C) during each run. After a simple decrease in concentration due to crystallization, the concentration reached a constant value. From the XRD measurement (Fig. 3), it is clear that there is only one crystallized form for all supersaturations in the experimental range, which is the same form as that previously obtained in ethanol (EtOH) solutions [10]. From the concentration that was attained in the end, the solubility (C^*) of Me-est in c-Hxn is 2.12 mM. Fig. 4 shows a photo of the crystals obtained in c-Hxn solutions, indicating that the morphology of the crystals is needle-like. In the case of MeCN, crystallization was carried out at much higher initial concentrations than in c-Hxn, i.e. between 47 and 52 mM, because the solubility of Me-est in MeCN is much greater (Fig. 5). From MeCN solutions, needle-like crystals similar to those appearing in c-Hxn were obtained. The decrease in concentration is also simple and similar to that in c-Hxn in Fig. 2. From XRD measurement, it appears that the same form as that obtained in c-Hxn and EtOH at all supersaturations in the experiments crystallized. The solubility (C^*) of Me-est in MeCN was estimated as 36.6 mM, which is higher than those in c-Hxn (2.12 mM) and EtOH (7.87 mM). The initial supersaturations ($S = C_o/C^*$) were calculated from the solubility as 1.71–2.83 for c-Hxn, and 1.29–1.42 for MeCN. These results indicate that polymorphs do not appear at all supersaturations in c-Hxn and MeCN at 298 K, similar to the results obtained in EtOH [11].

3.2. Crystallization behaviors of i-But-est in cyclohexane (c-Hxn)

The rapid cooling crystallization of i-But-est was performed in c-Hxn solutions at initial concentrations (C_o) between 21.0 and 30.0 mM. The initial concentrations are larger than those in the case of Me-est in c-Hxn. This accords to the higher solubility of i-But-est than that of Me-est. It was observed that two steps of concentration change clearly occur at high initial concentrations (29.5, 26.8 mM) in the crystallization from c-Hxn solutions (Fig. 6). The XRD diffraction patterns of the crystals obtained at 100 and 900 min in the crystallization process ($C_o = 29.5$ mM) are shown in Fig. 7(a) and (b). It appears that they are the polymorphs of the A (100 min) and B forms (900 min), which were previously obtained in EtOH solutions [11]. The morphology of both crystals

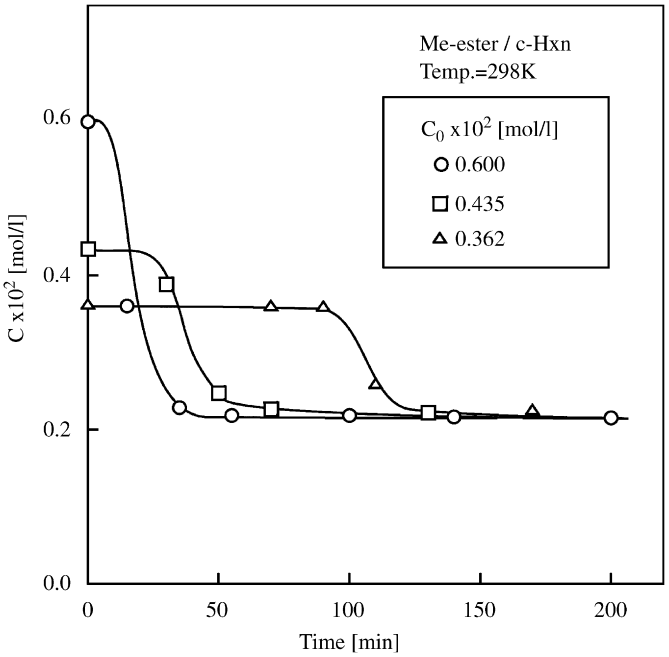

Fig. 2. Concentration change in crystallization of Me-ester in c-Hxn solutions.

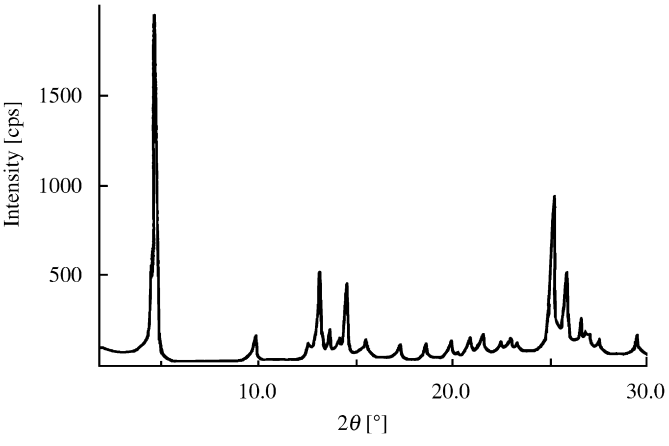

Fig. 3. XRD pattern of Me-est crystal.