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Crystallization of probucol from solution and the glassy state

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ABSTRACT

Crystallization of probucol (PBL) from both solution and glassy solid state was investigated. In the crystallization study from solution, six solvents and three methods, i.e., evaporation, addition of a poor solvent, and cooling on ice, were used to obtain various crystal forms. In addition to common two crystal forms (forms I and II), two further forms (forms III and cyclohexane-solvate) were found in this study, and their thermodynamic relationships were determined. Forms I and II are likely to be enantiotropically related with thermodynamic transition temperature below 5 °C. Isothermal crystallization studies revealed that PBL glass initially crystallized into form III between 25 and 50 °C, and then transformed to form I. The isothermal crystallization appears to be a powerful option to find uncommon crystal forms. The crystallization of PBL was identified to be pressure controlled, thus the physical stability of PBL glass is higher than that of typical compounds.

1. Introduction

The physical characterization of candidate compounds is an essential step during drug development. If the candidate has low aqueous solubility, the importance of physical characterization increases significantly because the solubility is sensitive to its physical form. Since each crystal form has different energy states, aqueous solubility of the compound depends on the crystal form (Pudipeddi and Serajuddin, 2005; Kawakami, 2012). Although the solubility differences between different crystal forms are generally below 2 (Pudipeddi and Serajuddin, 2005), occasionally the difference in solubility causes serious problems as in the case of ritonavir, where products were withdrawn from the market owing to the appearance of a new crystal form with lower solubility (Chemburkar et al., 2000; Bauer et al., 2001; Morissette et al., 2003). In the present study, the polymorphism of probucol (PBL), a poorly soluble cholesterol-lowering agent, was investigated. Two crystal forms of PBL have been identified and investigated in detail in the literature, where both forms I and II have monoclinic structures with onset melting points of 125 and 116 °C, respectively (Gerber et al., 1993). Form I has been believed to be the stable form because of its higher melting temperature. Also, form II was observed to transform into form I in the suspension at room temperature. Melting enthalpies of forms I and II have been reported to be 64 and 68 J/g, respectively. The smaller enthalpy of the form with higher melting temperature suggests that these forms are enantiotropically related according to Burger and Rumberger's rule (Burger and Ramberger, 1979a,b; Kawakami, 2007). In other words, a transition temperature should exist between forms I and II. In this study, additional crystal forms are also introduced and their physical properties are discussed.

The amorphous form is also a part of polymorphism and has the largest free energy. Since it can provide high solubility and dissolution rates, amorphization is an important formulation technology for drugs with poor solubility (Serajuddin, 1999; Yu, 2001; Kawakami, 2012, 2015a). However despite extensive research in the field, the number of marketed oral amorphous formulations remains limited partially because of its low and unpredictable physical stability (Bhugra and Pikal, 2008; Kawakami, 2012, 2015a, 2016). Thus, many attempts have been made to find a general rule that governs the crystallization tendency of organic compounds. Stable glasses generally have characteristics such as a large molecular weight with a low number of benzene rings, a low level of molecular symmetry, many rotatable bonds, branched carbon skeletons, and electronegative atoms (Miyazaki et al., 2007; Mahlin et al., 2011). In addition, stable glasses often have a large enthalpy/entropy of fusion, a large free-energy difference between crystalline and amorphous states, and high melting temperatures (Baird et al., 2010). Interactions between the molecules and molecular mobility are also important (Aso et al., 2000; Kaminski et al., 2011). Fragility is a measure of the deviation from non-Arrhenius behavior for supercooled liquids and glasses, and is related to glass stability (Baird et al., 2010; Kawakami et al., 2015). However, these conclusions were mostly obtained by

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observing hot crystallization behavior, i.e., crystallization during cooling from the melt. This behavior is completely different from that of isothermal crystallization, which is important from the viewpoint of storage stability because changes in the molecular mobility and free volume do not occur during the isothermal process. A careful investigation of isothermal crystallization revealed that the initiation time of crystallization can be quantitatively explained in a simple manner, where the initiation time was shown to be a function of only the ratio of glass transition to storage temperature (Kawakami et al., 2014; Kawakami, 2015b). Some compounds exhibited an exceptionally higher stability against crystallization, but this exceptionality was eliminated by increasing the surface area (Kawakami, 2015b), as the surface is sometimes responsible for the initiation of the crystallization (Wu and Yu, 2006; Kawakami et al., 2013). In the present study, the isothermal crystallization behavior of PBL from the glassy state is also discussed for strengthen insight on the isothermal crystallization behavior of pharmaceutical glasses.

2. Materials and methods

2.1. Materials

PBL was supplied from Tokyo Kasei (Tokyo, Japan) and used as supplied. All organic solvents used were of reagent grade. All chemicals were used without further purification.

2.2. Thermal analysis

Differential scanning calorimetry (DSC) measurements were performed on a DSC Q2000 (TA Instruments, New Castle, DE, USA), which was bimonthly calibrated using indium and sapphire. Dry nitrogen was used as inert gas at a flow rate of 50 mL/min. Crimped aluminum pans were used for the measurements. A heating rate of 10 °C/min was applied unless otherwise mentioned. Thermogravimetric (TG) analysis was made on Thermo Plus TG 8120 (Rigaku Denki, Tokyo, Japan) using open aluminum pans with a heating rate of 10 °C/min. Dry nitrogen was used as inert gas at a flow rate of 300 mL/min.

2.3. X-ray powder diffraction (XRPD)

XRPD patterns were acquired on a Rigaku RINT Ultima X-ray Diffraction System (Rigaku Denki, Tokyo, Japan) using CuKα radiation. The voltage and current were 40 kV and 40 mA, respectively. Data were collected between 2 theta values of 3° and 40° with intervals of 0.02° at a scan speed of 2°/min. The sample was loaded on a glass plate and its surface was carefully smoothed. When the samples in the DSC pans were subjected to the measurement, grinding was required because the samples were in the form of a pellet. However, the grinding was kept to a minimum because its influence on the polymorphic transformation was anticipated as described later.

2.4. Polymorph screening

PBL was precipitated from solutions using three procedures: evaporation, cooling, and the addition of a poor solvent. In all cases, 100 mg of PBL was dissolved in 1 mL of solvent (acetone, chloroform, ethanol, diethyl ether, and cyclohexane) except that 2 mL of methanol was used because of solubility limitations. For the evaporation method, each solution was exposed to air flow inside a fume hood at ambient temperature for 1 day to obtain the powder. For the cooling method, vials containing the solutions were promptly immersed in ice water followed by paper filtration and drying in air flow. A quantity of water equivalent to four times its volume was added to the solutions to obtain precipitates in the poor solvent process. The solvent was removed in the same manner as for the cooling method. In all cases, the powder was finally dried under vacuum and stored in a freezer before evaluation.

2.5. Solvent-mediated transformation

Equal amounts of forms I and II (in weight) were physically mixed and suspended in 25 vol% ethanol aqueous solution followed by storage at 5, 25, 40, and 60 °C. The samples stored at 5 °C were left for 1 month. The other samples were collected after 1 day followed by filtration using filter paper of mesh size of 20–25 μm. The solids were dried in the air flow inside the fume hood for 6 h, and then subjected to the DSC measurements.

2.6. Isothermal crystallization study

Amorphous samples were prepared by quenching crystalline PBL in the DSC apparatus at 50 °C/min starting from above the melting temperature and followed by annealing in temperature-controlled ovens. After storage, DSC measurements were performed to determine the melting enthalpy, which was used for assessing the crystallinity. The chemical stability during the storage was confirmed by the HPLC gradient analysis as described elsewhere (Kawakami et al., 2014) to ensure that no growth of degradation products took place. Thus, degradation products were not likely to influence the crystallization behavior discussed in this paper. A minimum of three samples were evaluated to provide averaged crystallinity values with the standard deviations.

2.7. Solubility measurement

PBL of each crystal form was subjected to solubility measurement (n = 3). Approximately 3 mg of solid was suspended in 5 mL of 50% ethanol aqueous solution, followed by vigorous mixing using a vortex mixer. Then, the suspensions were rotated at 50 rpm for 3 h in screw-capped test tubes under room temperature (23–25 °C). After filtration of the suspensions using syringe filters of 450-nm pore size, the concentrations were measured by HPLC with a YMC-Pack Pro C18 column (150 mm × 2.0 mmID, YMC, Kyoto, Japan) at a flow rate of 0.2 mL/min. The mobile phase was a mixture of acetonitrile and water at a ratio of 96/4 (v/v). Injection volume and the detection wavelength were 2 μL and 245 nm, respectively. The residual solids were dried in the air flow inside the fume hood for 6 h, and then subjected to DSC measurements to confirm whether or not the initial crystal forms were maintained.

3. Results and discussion

3.1. Crystallization of PBL from solutions (polymorph screening)

We employed six solvents to obtain various crystal forms using three crystallization methodologies. XRPD and DSC patterns for the resultant solids are presented in Fig. 1. Note that addition of water to chloroform, diethyl ether, or cyclohexane is inappropriate because those solvents are not miscible with water. The cooling method was applied only for methanol and ethanol. The intact powder exhibited the XRPD and DSC patterns of form I with characteristic diffraction peaks at 2 theta values of 12.6°, 13.4°, 17.8°, 19.0°, and 20.6° as well as the melting peak at 126 °C. The same patterns were observed for the solids obtained from diethyl ether. The melting temperature and enthalpy of form I were 126 °C and 76 J/g, respectively. Although similar patterns were observed for the solids obtained from acetone and chloroform, a slight difference in the XRPD patterns and the trace peak at 116 °C in the