Surface Effects on the Crystallization of Ritonavir Glass

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ABSTRACT: In our previous study, initiation time of crystallization was shown to be basically expressed as a function of only the reduced temperature, which was a ratio of storage and glass transition temperatures. This conclusion was obtained using quenched glasses with minimized surface area stored under a dried atmosphere. In this study, the surface effects on the crystallization were investigated using freeze-dried ritonavir (RTV) glass. Although quenched RTV glass exhibited exceptionally long initiation time, the initiation was accelerated by using the freeze-dried glasses. Storage of the samples under humid conditions further accelerated the crystallization. These surface effects eliminated the energetic barrier for nucleation, and the RTV glass exhibited universal initiation time. In contrast, subsequent crystal growth was slower for the freeze-dried glasses relative to the quenched one, presumably because of less condensed and porous structures that would suppress molecular cooperativity. Storage under a humid atmosphere also appeared to inhibit the crystal growth, presumably because of disruption of the molecular network by water. These findings support the existence of the universal initiation time for crystallization and indicated the importance of surface effects in crystallization behavior. Also, the suppression of crystal growth because of the void structure and incorporation of water molecules were indicated. J Pharm Sci 104:276–279, 2015

Keywords: amorphous; crystallization; physical stability; surface effect; glass transition; thermal analysis

INTRODUCTION

Although amorphous solid dispersion is one of the most effective formulation technologies for improving the oral absorption of poorly soluble drugs,[1–4] certain issues, such as manufacturing difficulty and low stability, inhibits its wide use.[3,4] In particular, the development of an accelerated study protocol for predicting the physical stability of the amorphous state has been an important issue for enhancing the use of amorphous technology.[4,5] Thus far, the crystallization behavior of organic glasses has been discussed on a case-by-case basis. In our previous study, the universal initiation time was found for the compounds, for which crystallization was dominated by temperature.[6] This observation was made by eliminating surface effects, for which quenched glasses were used for minimizing the surface area and they were stored under dried atmosphere. Note that the surface molecules usually have high-molecular mobility and may accelerate the crystallization process.[7–9] The adsorption of moisture may enhance the crystallization as well.[10–12] Such surface effects have to be considered also for understanding the crystallization behavior of practical glasses.

Ritonavir (RTV) is used as a model drug, which exhibited pressure-controlled crystallization in our previous study.[6] In other words, the crystallization of RTV was slower than that of the temperature-controlled compounds because of the large energetic barrier for nucleation. In this study, RTV glass with large surface area was fabricated by freeze-drying and subjected to stability studies in either dried or humid conditions.

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MATERIALS AND METHODS

Materials

Ritonavir was obtained from LKT Laboratories (St. Paul, Minnesota). *t*-butyl alcohol was purchased from Nacalai Tesque (Kyoto, Japan). Both chemicals were used as supplied.

Preparation and Storage of RTV Glass

Ritonavir was dissolved in *t*-butyl alcohol at a concentration of 2 wt %, followed by freezing at −20°C. Primary and secondary drying was conducted at ambient temperature for 24 h and 40°C for 30 min, respectively. Samples were stored under dried or humid conditions, which were achieved by storing the samples in desiccators with silica-gel (dried condition), saturated potassium acetate solution (22% RH at 50°C), or saturated magnesium nitrate solution (46%RH at 50°C). The chemical stability during the storage was confirmed to be negligible by using the protocol described in our previous study.[6]

Physical Characterization of RTV Glass

The glass transition temperature (T_g) and crystallinity of the stored samples were determined by differential scanning calorimetry (DSC) (TA Instruments Q2000, New Castle, Delaware) using the procedure described in our previous paper.[6] Briefly, the melting enthalpy was used for the calculation. The instrument was periodically calibrated using indium and sapphire. Dry nitrogen was used as the inert gas at a flow rate of 50 mL/min. Crimped aluminum pans were used for the measurements of T_g, and pinholes were applied to the lids when measuring the crystallinity for removing adsorbed water. All evaluations were at least triplicated. The onset T_g is reported in this paper. X-ray powder diffraction (RINT Ultima; Rigaku Denki, Tokyo, Japan) was also used to confirm crystal form. The morphology of the freeze-dried RTV was observed under a

scanning electron microscope (S8000; Hitachi, Tokyo, Japan) at an accelerating voltage of 1 kV after sputter coating for 30 s with platinum coater (E-1030 ion sputter; Hitachi, Tokyo, Japan).

RESULTS AND DISCUSSION

Figure 1 shows the effect of the preparation procedure and storage conditions on T_g. T_g of the RTV glass stored under humid conditions was evaluated using the samples exposed to moisture for 1 day. T_g of the freeze-dried glass was slightly lower than that of the quenched one even in the case of the dried samples. Note that a slight amount of residual moisture was removed by heating the sample at 100°C in DSC prior to the measurement of T_g. Thus, the lower T_g appear to have been caused by the increase in the proportion of the molecules that have high mobility because of the increase in the surface area. The storage of the sample under humid conditions decreased T_g as a function of relative humidity, as can be expected from the Gordon–Taylor equation.[12,13]

Figure 2 shows crystallization curves of the RTV glasses stored under various conditions. Each dataset was fitted using the Avrami–Erofeev equation shown below.

$$X(\%) = 100[1 - \exp\{-k(t-d)^n\}] \quad (1)$$

where k and d are the crystallization rate constant and induction time, respectively, and n is an Avrami exponent, which is influenced by the dimension of the crystal growth and nucleation mechanism. Freeze-dried samples exhibited faster crystallization compared with the quenched ones. Also, the crystallization was aided by increasing storage humidity. Thus, it is obvious that the lowering of T_g led to faster crystallization.

Figure 3 shows the time when crystallinity reached 10% (initiation time), t_{10}, as a function of the reduced temperature, T_g/T. The dataset presented in our previous paper[6] is also

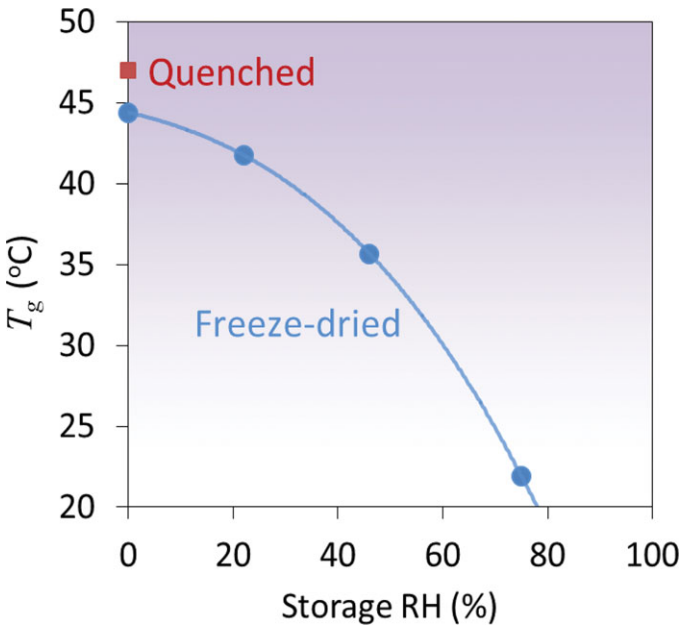

Figure 1. Effect of storage humidity on T_g (onset values) of the freeze-dried RTV. T_g of the quenched RTV is also presented.

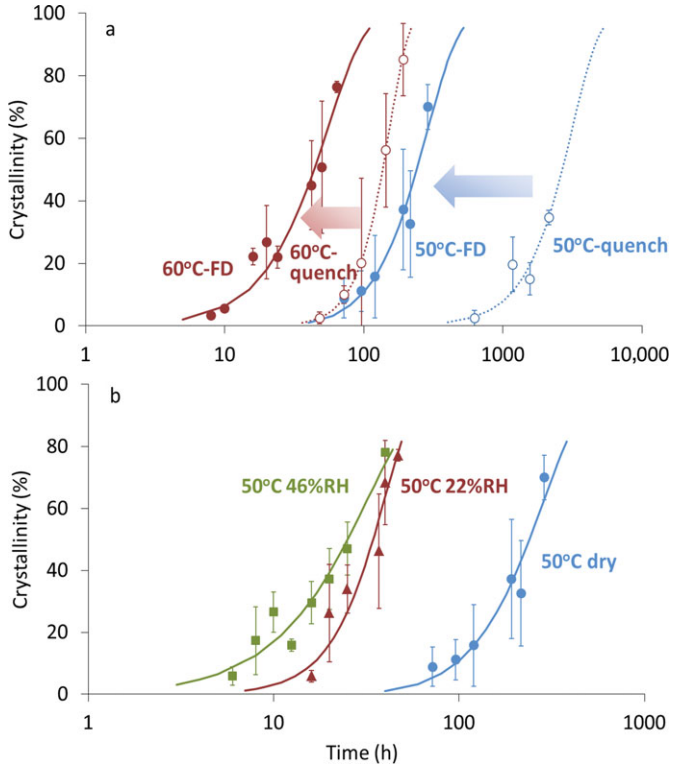

Figure 2. Evolution of crystallinity of (a) quenched and freeze-dried RTV and (b) freeze-dried RTV stored in humid atmospheres as a function of time at the indicated temperature/humidity. Each measurement was at least triplicated, and the error bar represents standard deviations. The fitting lines were drawn using the Avrami–Erofeev equation.

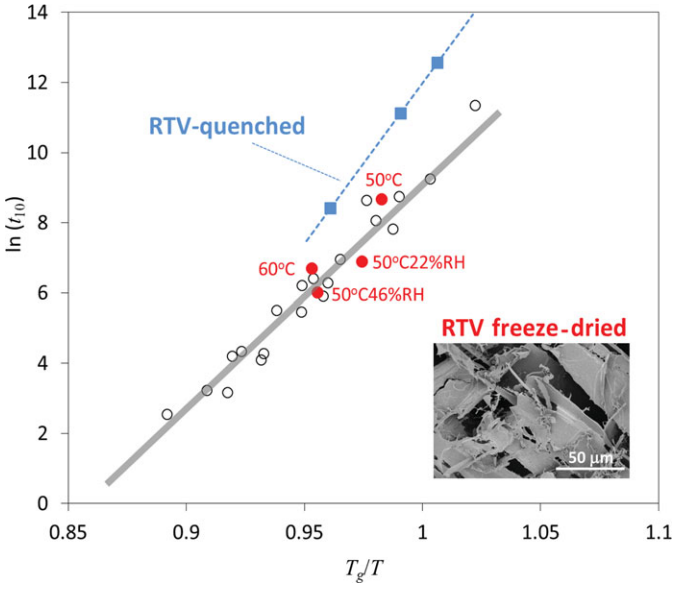

Figure 3. Ten percent crystallization time (initiation time, in the unit of minute) as a function of T_g/T. Open symbols represent the initiation time of the compounds that show temperature-controlled crystallization (tolbutamide, chlorpropamide, acetaminophen, nifedipine, and phenobarbital).[6] The "universal line" was drawn for these data. The initiation time for the quenched and freeze-dried RTV are presented as closed squares and circles, respectively. The storage conditions for the freeze-dried RTV and its scanning electron microscope image in the initial state are shown in the figure.