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General understanding on physical stability of pharmaceutical glasses

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Although amorphous solid dispersion is one of the most important formulation technologies for poorly soluble drugs [1], the number of marketed oral amorphous formulations is still limited. The lack of an accelerated study protocol for predicting crystallization behavior of amorphous forms has been one of the biggest issues that inhibit their wide use. Isothermal crystallization behavior of pharmaceutical glasses is discussed in this presentation with an eventual aim of predicting physical stability of amorphous dosage forms.

Preparation of glass compounds and determination of crystallinity were done by differential scanning calorimetry (DSC) on a TA Q2000 (TA Instruments, New Castle, USA). Glasses were prepared by quenching at 50 °C/min from above the melting temperature, followed by annealing in temperature-controlled ovens. The samples were stored in desiccator, in which humidity was controlled by silica-gel or saturated salt solutions. Annealing shorter than 48 hours under the dried condition was performed in DSC. Thermal degradation was negligible for all the compounds. As a comparison, freeze-drying using t-butyl alcohol was also applied for preparing glass samples.

Crystallization behavior of glass materials is determined by a balance of thermodynamic and kinetic factors, for which temperature and local pressure are the dominating factors, respectively [2]. Fig. 1 shows the time when the crystallinity reached 10%, t_{10}, as a function of the reduced temperature, T_g/T [2]. The data for the temperature-controlled compounds fell onto the universal line at least above T_g, meaning that their initiation time can be described as a function of only T_g if the crystallization is governed by thermodynamics. The initiation time for the pressure-controlled compounds was significantly longer than that for the thermodynamically-controlled ones because of their large energetic barrier for nucleation. However, if the surface area was increased by employing freeze-drying method, the initiation time of the

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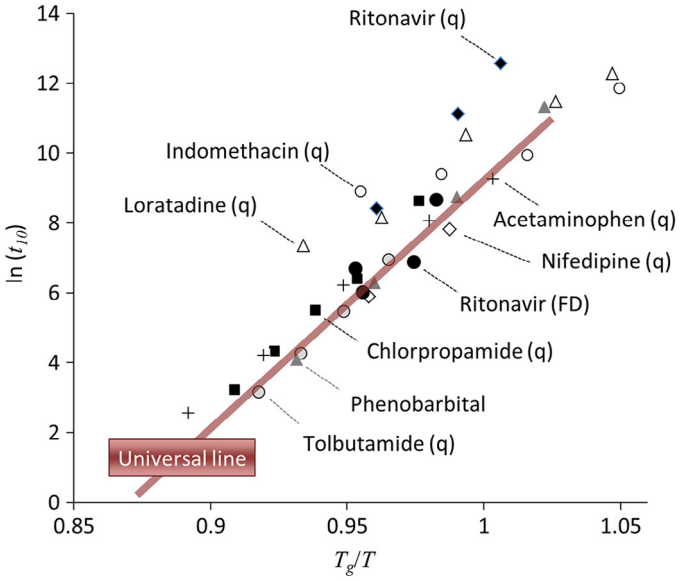

Fig. 1 – 10% crystallization time (in min, t_{10}) of model compounds as a function of T_g/T. q and FD represent quenched and freeze-dried samples, respectively [2,3].

pressure-controlled compounds was shortened to be explained by the universal line as well [3]. It was also the case for the samples stored under humid conditions. Thus, the universal line may be regarded as the worst case of crystallization for the pressure-controlled compounds. Attempts to increase stability of pharmaceutical glasses will also be discussed in the presentation.

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