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Modeling Physical Stability of Amorphous Solids Based on Temperature and Moisture Stresses

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ABSTRACT

Isothermal microcalorimetry was utilized to monitor the crystallization process of amorphous ritonavir (RTV) and its hydroxypropylmethylcellulose acetate succinate–based amorphous solid dispersion under various stressed conditions. An empirical model was developed: $\ln(\tau) = \ln(A) + \frac{E_a}{RT} - b \cdot wc$, where τ is the crystallization induction period, A is *a* pre-exponential factor, E_a is the apparent activation energy, b is the moisture sensitivity parameter, and wc is water content. To minimize the propagation of errors associated with the estimates, a nonlinear approach was used to calculate mean estimates and confidence intervals. The physical stability of neat amorphous RTV and RTV in hydroxypropylmethylcellulose acetate succinate solid dispersions was found to be mainly governed by the nucleation kinetic process. The impact of polymers and moisture on the crystallization process can be quantitatively described by E_a and b in this Arrhenius-type model. The good agreement between the measured values under some less stressful test conditions and those predicted, reflected by the slope and R^2 of the correlation plot of these 2 sets of data on a natural logarithm scale, indicates its predictability of long-term physical stability of amorphous RTV in solid dispersions. To further improve the model, more understanding of the impact of temperature and moisture on the amorphous physical stability and fundamentals regarding nucleation and crystallization is needed.

Introduction

The high-energy state of amorphous materials results in higher apparent aqueous solubility and improved dissolution rates for poorly water-soluble drugs, which in turn can lead to improved oral absorption and bioavailability. However, an amorphous drug in solid dispersions is, intrinsically, physically unstable and tends to re-crystallize to its crystalline counterpart. The rate of crystallization, both nucleation and crystal growth, depends on factors such as the nature of the compound, the composition of amorphous solid, temperature, and relative humidity (RH), and sometimes process. Crystallization of amorphous drug in solid dispersions may occur even at temperatures below their glass transition temperatures, T_g. Thus the risk of crystallization of amorphous solids is always present during manufacture, handling, and storage.

Solid dispersions, in which amorphous drugs are molecularly dispersed in polymer matrices, offer an attractive means of not only increasing the dissolution rate, but also further improving the physical stability of amorphous drugs by inhibiting crystallization through a variety of mechanisms including solvation of the drugs in polymer matrices, an increase in the glass transition temperature (T_g) of the dispersion, and specific interactions between polymer and drug.[1,2] Hydrophilic polymers (e.g., polyvinylpyrrolidone and hydroxypropylmethylcellulose [HPMC]) are often used to prepare solid dispersions. However, because such hydrophilic polymers are usually more water soluble than the drug, and hence more polar, the presence of the polymer could result in increased moisture uptake of solid dispersions compared with the pure amorphous drug. Absorption of water into amorphous dispersions, in most cases, facilitates crystallization. Thus, in addition to the type of polymer and the nature of the drug, the

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physical stability of the solid dispersion is often influenced by the balance between drug loading and moisture absorption under storage conditions.[3,4]

The conventional means of monitoring the crystallization process of amorphous materials is to store samples under various temperature and RH conditions, and then measure the T_g and X-ray diffraction patterns of the samples at various periods of time.[5] This method is not only tedious and labor intensive, but also less sensitive largely due to the detection limit of powder X-ray diffraction which often varies from 2% to 5% of crystalline component in amorphous samples depending on drug loading and crystallinity. As a result, the onset time of crystallization, one of the critical measures of physical stability, is often missed or overestimated. In addition, because of the complexity of crystal growth kinetics, such as the discontinuity of crystal growth rate as a function of temperature across T_g, the conventional methods which often focus only on crystal growth may merely provide a qualitative rank order among various solid dispersions, rather than a quantitative prediction.

It is technically challenging, if not impossible, to quantitatively estimate the long-term physical stability of amorphous drugs and solid dispersions within a reasonable time frame. Although many studies on the physical stability of amorphous materials have been reported,[1,6,7] to the best of our knowledge, a reliable methodology to estimate the long-term physical stability of amorphous solids has yet to be developed. Most of the published literature has been focused on measuring the crystal growth kinetics from the amorphous state, rather than the nucleation process. Attention has been directed toward enthalpy relaxation and fragility parameters which reflect mobility, one of the determining factors of nucleation and crystal growth. Although the correlation between those parameters and physical stability of amorphous solids is reasonably well established,[8] it is still relatively difficult to translate these parameters directly into an estimate of the shelf life of amorphous drugs under regular storage conditions—one of the most critical factors in determining the probability of success for developing an amorphous solid dispersion.

In searching for a better and more predictive method, isothermal microcalorimetry was identified as a potential alternative for overcoming the shortcomings associated with the existing methods, owing to its high sensitivity, continuity of response over time, and labor-saving sample preparation characteristics. A thermal activity monitor (TAM), the most frequently used isothermal microcalorimeter, has been widely used for studying the kinetics of chemical reactions (e.g., degradation, drug-excipient compatibility) and/or physical processes (e.g., relaxation, crystallization) of sample substances at a constant temperature.[9,10] Herein we describe a methodology mainly using isothermal microcalorimetry and a modified Arrhenius model to estimate the long-term physical stability of amorphous ritonavir (RTV) and its solid dispersions from studies carried out under accelerated test conditions. In addition to the experimental approaches, we will discuss in detail both data interpretation and the scientific rationale for such predictions as a function of temperature and RH. The effects of excipients on the physical stability of amorphous RTV solid dispersions will also be characterized and discussed.

Theory

Crystallization from the amorphous state evolves from a combination of thermodynamic factors, coupled to dynamic factors controlled in large part by molecular mobility. For quantitative understanding of crystallization from the amorphous state, both of these factors must be considered. From the classical theory, the rates of nucleation (I) and growth (U) can be expressed by the following equations[11]:

$$I = Ae^{-\left(\frac{\Delta G_D + \Delta G_K}{RT}\right)} \tag{1}$$

$$U = k/\eta \left[1 - e^{-\left(\frac{\Delta G_v}{RT}\right)}\right] \tag{2}$$

where ΔG_D is the Gibbs free energy change for the formation of a nucleus, a thermodynamic term related to supersaturation or supercooling; ΔG_K is the Gibbs free energy associated with the transport of molecules across an interface, a dynamic term related to mobility. In Equation 2, R is a temperature-independent constant, η is viscosity, $1/\eta$ is a dynamic factor describing the effect of molecular mobility; $1-\exp(-\Delta G_v/RT)$ is the thermodynamic driving force of crystal growth where k is a constant and ΔG_v is the free energy difference between the amorphous and crystalline phases.

In accelerated studies, temperature and RH are commonly the major variables, and the effects of such parameters on thermodynamic and kinetic factors must be taken into consideration. There are many ways to show the dual effects of temperature and RH. Consider an amorphous solid that is undergoing some type of spontaneous transformation at a rate constant k'. We can write an expression that combines the thermodynamic driving force for the transformation and the kinetic barrier primarily controlled by the dynamics in the amorphous solids, that is, molecular mobility. To generalize this latter factor we can express it in terms of free volume—the greater the free volume, the greater the molecular mobility—expressed[12] as Equation 3:

$$k_T' = A' e^{\left[-\frac{E_a}{RT} - \left(\frac{V^*}{V_f}\right)\right]} \tag{3}$$

where V^* is the critical volume for molecular mobility and V_f is the free volume.[11] Here we assume that the thermodynamic part is governed by the Arrhenius equation with the activation energy (E_a) as the major barrier. The second term (V^*/V_f) represents the ratio of the critical volume needed for molecular motion to the free volume of the solid. When V_f is large relative to V^*, as in solution, the term (V^*/V_f) approaches zero, and Equation 3 collapses to the simple Arrhenius equation. Equation 3 can be used to account for factors related to the transformation itself and those determined by the physical state of the solid that influences the rate. Thus Equation 3 may also be considered as a different mathematical expression for Equations 1 and 2 with similar physical meaning.

Genton and Kesserling developed an empirical expression, Equation 4, for the effects of temperature and RH on solid state reactions,[13] which is based on Equation 3:

$$\text{(Arrhenius model with humidity)} \quad \ln(k_{T,h}) = \ln(A) - \frac{E_a}{RT} + bh \tag{4}$$

In Equation 4, b is considered to be a moisture sensitivity term independent of temperature, h is relative humidity, E_a is the apparent activation energy, A is the Arrhenius pre-exponential factor, and $k_{T,h}$ is the rate constant under a given condition. Studies on chemical reactivity, particularly demonstrated by Waterman et al.,[14] show that some "predictions" of long-term chemical stability as a function of absolute temperature T and relative humidity h were quite good. Equation 4 assumes, with