Effect of Heating Rate and Kinetic Model Selection on Activation Energy of Nonisothermal Crystallization of Amorphous Felodipine

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ABSTRACT: The nonisothermal crystallization kinetics of amorphous materials is routinely analyzed by statistically fitting the crystallization data to kinetic models. In this work, we systematically evaluate how the model-dependent crystallization kinetics is impacted by variations in the heating rate and the selection of the kinetic model, two key factors that can lead to significant differences in the crystallization activation energy (E_a) of an amorphous material. Using amorphous felodipine, we show that the E_a decreases with increase in the heating rate, irrespective of the kinetic model evaluated in this work. The model that best describes the crystallization phenomenon cannot be identified readily through the statistical fitting approach because several kinetic models yield comparable R^2. Here, we propose an alternate paired model-fitting model-free (PMFMF) approach for identifying the most suitable kinetic model, where E_a obtained from model-dependent kinetics is compared with those obtained from model-free kinetics. The most suitable kinetic model is identified as the one that yields E_a values comparable with the model-free kinetics. Through this PMFMF approach, nucleation and growth is identified as the main mechanism that controls the crystallization kinetics of felodipine. Using this PMFMF approach, we further demonstrate that crystallization mechanism from amorphous phase varies with heating rate. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: activation energy; nonisothermal; amorphous; crystallization; heating rate; Calorimetry (DSC); Kinetics; Physical Stability; Thermal analysis

INTRODUCTION

Amorphous materials lack long-range molecular order found in crystalline solids. Taking advantage of its higher free energy, the amorphous form may be used to enhance the dissolution kinetics of poorly soluble drug molecules in pharmaceutical development.[1–4] In rare cases, an amorphous solid can additionally improve the chemical stability of materials, for example, by perturbing the proximal packing of reactive functional groups in crystalline phase.[5] Despite these advantages, the development of a commercial pharmaceutical product containing an amorphous drug is often challenged by the lack of physical stability, that is, the tendency to crystallize, which is thermodynamically driven by the higher free energy and kinetically influenced by the molecular mobility.[1,6,7] If the amorphous drug is sufficiently stabilized kinetically, a robust drug product with advantageous drug release rate can be developed. Therefore, a systematic evaluation of crystallization kinetics of amorphous drug is a critical part of the formulation and process design of drug products containing amorphous drugs. Crystallization of amorphous solids can be investigated either under isothermal or nonisothermal conditions.[1,7,8] Nonisothermal crystallization studies are favored mainly because of shorter experimental times allowing the rapid assessment of phase stability,[9] and relevance to real-life thermal variations during amorphous processing, such as melt spinning. Additionally, a true isothermal crystallization study is difficult to achieve because reaching the desired temperatures for carrying out an isothermal study requires nonisothermal sample heat-up or cool-down. Considering these factors, the use of nonisothermal crystallization kinetics to predict amorphous physical instability is of practical interest.

The kinetic approaches for evaluating nonisothermal crystallization kinetics can broadly be classified as model-dependent and model-free approaches.[10] In the model-dependent, or model-fitting approach, the crystallization data are fit to a variety of kinetic models to calculate kinetic parameters that can be used to assess amorphous phase stability, such as the activation energy (E_a) of crystallization. A higher value of E_a indicates a higher kinetic barrier for crystallization to initiate and, thus, lower crystallization tendency. On the contrary, for the model-free methods, the crystallization kinetics is calculated without assuming any particular model.

The model-fitting approach is helpful for studying complex phase transformations, such as crystallization from amorphous phases,[11] because this approach may provide mechanistic insight into how the transformation physically proceeds.[12] For instance, Zhou et al.[11] have showed that the nucleation and growth models, such as the Avrami–Erofeev model (also known as the JMAEK model), are suitable to characterize the crystallization kinetics of amorphous nifedipine, both under the isothermal and nonisothermal conditions. Despite its promise, the model-fitting method incorrectly assumes that the heating

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Table 1. Common Nucleation and Diffusion Models Used in This Study for Analyzing Phase Transformation Kinetics[10]

Model Mechanism	Differential Model Form, $f(\alpha)^a$	Integral Model Form, $g(\alpha)^b$
Nucleation Models		
JMAEK, $n = 2$[22–24]	$2(1-\alpha)[-\ln(1-\alpha)]^{1/2}$	$[-\ln(1-\alpha)]^{1/2}$
JMAEK, $n = 3$[22–24]	$3(1-\alpha)[-\ln(1-\alpha)]^{2/3}$	$[-\ln(1-\alpha)]^{1/3}$
JMAEK, $n = 4$[22–24]	$4(1-\alpha)[-\ln(1-\alpha)]^{3/4}$	$[-\ln(1-\alpha)]^{1/4}$
Power law, $n = 1/2$	$2\,\alpha^{1/2}$	$\alpha^{1/2}$
Power law, $n = 1/3$	$3\,\alpha^{2/3}$	$\alpha^{1/3}$
Power law, $n = 1/4$	$4\,\alpha^{3/4}$	$\alpha^{1/4}$
Diffusion Models		
1D diffusion	$1/2\alpha$	α^2
2D diffusion	$[-\ln(1-\alpha)]^{-1}$	$[(1-\alpha)\ln(1-\alpha)]+\alpha$
3D diffusion (Jander model)[25]	$3(1-\alpha)^{2/3}/2[1-(1-\alpha)^{1/3}]$	$[1-(1-\alpha)^{1/3}]^2$

$^a f(\alpha) = \{\beta/(Ae^{E_a/RT})\} \times (d\alpha/dT)$
$^b g(\alpha) = (A/\beta) \times \int_0^T e^{-E_a/RT} dT$

rate does not greatly impact E_a.[10,13–18] Practically, there is the difficulty of identifying the most appropriate model because both the correlation coefficients (R^2) and residuals of fit for several models are often comparable for the same dataset used for fitting.[11,19]

The present study examines these deficiencies of applying model-fitting kinetic approach to characterize nonisothermal crystallization kinetics for organic glasses. The objectives of this work are twofold: (1) to systemically assess the dependence of crystallization activation energy on heating rate and kinetic model selection, and (2) to evaluate the strategy of using a paired model-fitting and model-free (PMFMF) approach to identify the most appropriate kinetic model for describing amorphous crystallization.

Mathematical Basis of Model-Fitting Kinetics

The general mathematical form for model-fitting nonisothermal kinetics is given in Eq. (1).

$$g(\alpha) = \frac{A}{\beta}\int_0^T e^{\frac{-E_a}{RT}}\,dT \tag{1}$$

Here, α is the extent of amorphous phase crystallized, A is the pre-exponential frequency factor, β is the heating rate, R is the universal gas constant, and T is the temperature in Kelvin. Equation (1) assumes an Arrhenius temperature dependence of rate constant k. Some of the choices of the reaction models are provided in Table 1. The temperature integral $\int_0^T e^{\frac{-E_a}{RT}}dT$ in Eq. (1) does not have a ready analytical solution,[20,21] but can be solved through the asymptotic series expansion (Eq. (2)).[20]

$$\int_0^T e^{\frac{-E_a}{RT}}\,dT = \frac{E_a}{R}\int_x^\infty \frac{e^{-x}}{x^2}dx = \frac{E_a}{R}\cdot\frac{e^{-x}}{x^2}\left[1-\frac{2!}{x}+\frac{3!}{x^2}-\frac{4!}{x^3}+....\right] \tag{2}$$

where $x = E_a/RT$.

Combining Eqs. (1) and (2) and ignoring higher-order terms lead to Eq. (3).

$$g(\alpha) = \frac{AE_a}{\beta R}\frac{e^{-x}}{x^2}\left[1-\frac{2!}{x}\right] \tag{3}$$

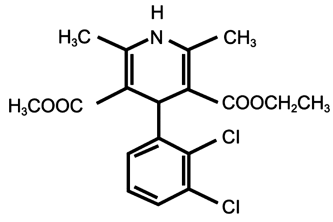

Figure 1. Molecular structure of felodipine.

Replacing $x = E_a/RT$ in Eq. (3) and rearranging the terms yield Eq. (4).

$$\beta.g(\alpha) = e^{-E_a/RT}\left[\frac{AE_a}{R\left(E_a/RT\right)^2}\left(1-\frac{2RT}{E_a}\right)\right] \tag{4}$$

Taking natural logarithm and rearranging the terms yield Eq. (5), which can be employed for analyzing nonisothermal kinetic data with the consideration of heating rate, β.

$$\ln\left[\beta.g(\alpha)\right] = -\frac{E_a}{RT} + \ln\left[\frac{ART^2}{E_a}\left(1-\frac{2RT}{E_a}\right)\right] \tag{5}$$

Activation energy is obtained from the slope of the plot of $\ln\left[\beta.g(\alpha)\right]$ and $1/T$, where T is the crystallization temperature at each α level. Equation (5) differs from the frequently used Coats–Redfern equation[26,27] in that it eliminates the problem in the latter equation where the ordinate, $\ln\frac{g(\alpha)}{T^2}$, is inherently correlated to the abscissa, $1/T$.[19]

EXPERIMENTAL

Material

The model compound, felodipine (Fig. 1) was purchased from Sigma–Aldrich (St. Louis, Missouri; purity >99%) and used without further purification. Felodipine is a small molecular (MW = 384.3 g/mol) calcium channel blocker used for treating hypertension. Amorphous felodipine was prepared by rapidly quenching its melt ($T_m = 139^\circ$C) inside a humidity-controlled glove box (RH < 2%) on a cold metallic block. Faster quenching, such as by immersing into liquid nitrogen, was not employed