Desolvation Kinetics of Sulfameter Solvates

AMMAR KHAWAM, DOUGLAS R. FLANAGAN

Division of Pharmaceutics, College of Pharmacy, University of Iowa, Iowa City, Iowa 52242

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ABSTRACT: Solvates are often encountered in pharmaceutical solids and knowledge of their physical stability is necessary for their effective formulation. This work investigates the solid-state stability of five structurally related solvates of sulfameter (5-methoxysulfadiazine) by studying the kinetics of their desolvation reaction with thermogravimetric analysis, both isothermally and nonisothermally. Desolvation kinetic analysis was done isothermally by conventional model-fitting and nonisothermally by the complementary method. Calculated kinetic parameters (model, A and E_a) were compared and related to the crystal structure of these solvates. A relationship was established between desolvation activation energy from isothermal results and solvent size; the larger the solvent molecule, the higher its solvate's desolvation activation energy. The best fitting solid-state reaction model correlated to single crystal structural features of sulfameter-solvates where solvent molecules occupied cavities in the unit cell. Finally, it was found that kinetic parameters obtained isothermally and nonisothermally were at variance. Therefore, kinetic results obtained from one method may not be extended to results form the other. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:2160–2175, 2008

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INTRODUCTION

Many drug substances exist in more than one crystal form (i.e., polymorphs); these forms have structures with different unit cells, but, each form has the same chemical composition. Similarly, other substances have structures with different unit cells and chemical composition due to the inclusion of one or more solvent molecules (i.e., solvates; pseudopolymorphs; or solvatomorphs).[1] Therefore, a solvate crystal form involves one or more molecules (guest) occupying specific positions within the crystal structure of a host molecule wherein the guest molecules are normally a liquid as a pure substance under ambient conditions. Solvates or solvatomorphs are often found after crystallization or purifying a drug from a particular solvent. Hydrates are the most common solvates as water is a common solvent or cosolvent in many crystallization systems. Other common solvates are formed with ethanol, methanol, etc.

Desolvation reactions of solvated crystals are characterized by the removal of solvent from the crystalline solvate below its melting point[2] and can be often described by the following scheme:

$$A_{(s)} \rightarrow B_{(s)} + C_{(g)}$$

where A is the solvated crystal form, B the desolvated crystal form, and C the evaporated solvent as a gas.

Physical stability of solvates is a concern to pharmaceutical scientists since it may convert to

Ammar Khawam's present address is Boehringer Ingelheim Pharmaceuticals, 900 Ridgebury Rd., Ridgefield, Connecticut 06877.

Correspondence to: Ammar Khawam (Telephone: 319-335-8819; Fax: 319-335-9349; E-mail: ammar-khawam@uiowa.edu)

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an unsolvated crystal form or an amorphous form upon desolvation. Due to the impact of solvates on the formulation development process and drug performance, it is important to know the stability of such solvates. Solid-state kinetic analysis can be applied to study the thermal stability of such crystals.

Solid-state kinetic studies can be performed isothermally and nonisothermally. The rate of an isothermal solid-state reaction can be generally described by:

$$\frac{d\alpha}{dt} = Ae^{-\frac{E_a}{RT}}f(\alpha) \quad (1)$$

where α is the conversion fraction, A the pre-exponential (frequency) factor, E_a the activation energy, T the absolute temperature, R the gas constant, and $f(\alpha)$ the reaction model.

The general nonisothermal rate law can be derived[3] from Eq. (1) and is described by:

$$\frac{d\alpha}{dT} = \frac{A}{\beta}e^{-\frac{E_a}{RT}}f(\alpha) \quad (2)$$

where β is the linear heating rate.

The frequency factor (A), activation energy (E_a), and model are usually referred to as the "kinetic triplet."

Integrating Eqs. (1) and (2) gives the integral rate laws of isothermal (Eq. 3) and nonisothermal reactions (Eq. 4), respectively,

$$g(\alpha) = Ae^{-\frac{E_a}{RT}}t \quad (3)$$

and

$$g(\alpha) = \frac{A}{\beta}\int_0^T e^{-\frac{E_a}{RT}}dT \quad (4)$$

where $g(\alpha)$ is the integral form of the reaction model, defined by:

$$g(\alpha) = \int_0^\alpha \frac{d\alpha}{f(\alpha)}.$$

Reaction models are functional forms of α that represent a mathematical description of what is observed experimentally. A recent review summarized the theoretical concepts and mathematical derivation of the most commonly reported reaction models (17 models) in solid-state kinetics.[4]

There are several solid-state kinetic analysis methods that are derived from either Eqs. (1) and (3) (isothermal) or Eqs. (2) and (4) (nonisothermal). Kinetic analysis methods are either modelistic or model-free. Modelistic methods evaluate the frequency factor (A) and activation energy (E_a) for each model and the model of choice is selected from among a group of models based on its statistical fit to experimental data (i.e., correlation coefficient).

On the other hand, model-free methods generate activation energies (E_a) at progressive α values without modelistic assumptions. However, these methods are sensitive to experimental errors and can produce artifactual variations in E_a.[5,6] Additionally, these methods cannot directly calculate the frequency factor (A) nor determine the reaction model providing an incomplete kinetic analysis. A review of solid-state kinetic analysis methods and their pharmaceutical applications has been recently presented.[3]

In isothermal experiments, the conventional model-fitting method[3] involves two fits: the first, calculates the reaction rate constant (k) for the model that best fits the data (Eq. 3), while the second fit calculates the activation energy (slope) and frequency factor (intercept) of the Arrhenius plot ($\ln k$ vs. $1/T$).

For nonisothermal experiments, model fitting involves fitting different models to α-temperature ($\alpha - T$) curves and simultaneously determining E_a and A. There are numerous nonisothermal model-fitting methods; one of the most popular being the Coats and Redfern method.[7,8] This method was derived from Eq. (4) and is represented by the following equation,

$$\ln\frac{g(\alpha)}{T^2} = \ln\left(\frac{AR}{\beta E_a}\left[1 - \left(\frac{2RT_{exp}}{E_a}\right)\right]\right) - \frac{E_a}{RT} \quad (5)$$

where T_{exp} is the mean experimental temperature.

According to this method, plotting the left hand side [which includes the model $g(\alpha)$] of Eq. (5) versus $1/T$ gives E_a and A from the slope and intercept, respectively. The model that gives the best linear fit is selected as the model of choice. The use of modelistic methods has been criticized in nonisothermal studies[9–11] because regression methods may lead to indistinguishable fits or mathematical expressions with high correlation for all models. Model-fitting problems are evident with the Coats and Redfern method when used alone but problems can be overcome when combined with isoconversional methods using the complementary kinetic approach[12] to determine the model of choice. The utility of this approach has been

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