Integrated Approach to Study the Dehydration Kinetics of Nitrofurantoin Monohydrate

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ABSTRACT: There is a need for thorough knowledge of solid-state transformations in order to implement quality by design (QbD) methodology in drug development. The present study was aimed at gaining a mechanistic understanding of the dehydration of nitrofurantoin monohydrate II (NF-MH). The dehydration was studied using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), hot-stage microscopy (HSM), and variable temperature X-ray powder diffraction (VT-XRPD). Isothermal TGA data were used to study dehydration kinetics using model-fitting and model-free approaches. Model-fitting analysis indicated a good fit for several models derived from nucleation–growth and/or geometric contraction mechanisms. However, based on visual observations during HSM, Avrami–Erofeyev equations A3 and A4, indicating nucleation–growth phenomenon, were found to be the most suitable kinetic models. HSM showed initiation of dehydration with random nucleation, and nuclei coalesced with the progress of dehydration reaction. VT-XRPD revealed formation of anhydrate β form on dehydration of NF-MH. The phenomenon of random nucleation is justified based on the crystal structure of NF-MH, which showed presence of water molecules in an isolated manner, prohibiting directional dehydration. It was found that supplementary information from HSM and VT-XRPD can be valuable to gain a better understanding of dehydration from formal solid-state kinetics analysis. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:3966–3976, 2010

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INTRODUCTION

Many pharmaceutically relevant substances exist as hydrates, and survey within European Pharmacopoeia indicated that 29% of the compounds are known to form hydrates.[1] The potential impact of changes in the hydrate/anhydrate state of the crystalline drug substances and excipients exists throughout the drug development process.[2] The occurrence and behavior of hydrates has received increasing attention during the last decade, primarily due to the potential impact of hydrates on the development process and dosage form performance.[3,4] Owing to the extensive hydrogen bonding capability of water, it plays an important role in the stability of the crystal structure.[5] In general, breakage of hydrogen bond network due to dehydration can lead to conversion of hydrate to a lower hydrate state, anhydrate or amorphous/melt, which can subsequently crystallize.[6] The hydrate formation/dehydration may occur during various unit operations such as crystallization,[7] wet granulation,[8] pelletization,[9] drying,[10,11] milling,[12] lyophilization,[13] or during normal storage of the finished product.[14,15] Because the phase transition on dehydration is accompanied by a change in the physicochemical properties, it is important to understand the mechanisms of these transitions, the experimental and environmental conditions under which these take place, and their rate constant under various conditions.[16] An understanding of the critical factors involved in the dehydration of hydrate can be of use as a guide both during preformulation and later

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in the development process. A structured approach using formal solid-state kinetics is one way of gaining an understanding of the dehydration reaction, and this approach has attracted pharmaceutical researchers since the 1970s.[17,18] Since then, many other studies have been reported on hydrates and have contributed towards an understanding of the dehydration process.[16,19–23] Moreover, dehydration itself constitutes an important class of reactions which has contributed significantly to the provision of the theoretical foundation for the understanding of solid-state reactions.[24] A classification scheme of dehydration based on structural and kinetic criteria has been proposed by Galwey.[25] Petit and Coquerel[26] have presented another model based on the water release pathways and possible reorganization of the dehydration product. Dehydration of crystalline solids represents an important group of heterogeneous solid-state reactions, and dehydration kinetics analysis can be performed by either model-fitting or model-free methods.[25,27,28] Unlike the rate laws in homogenous kinetics, which usually depend on the reaction order (i.e., first, second, etc.), a rate law for an elementary solid-state reaction like dehydration could depend on factors such as rate of nuclei formation, interface advance, diffusion, and/or geometrical shape of the solid particles. These factors have led to evolution of several kinetic models. These are presented in Table 1.

Model-fitting is carried out in two steps. The first step involves fitting plots of the conversion/dehydrated fraction (α) as a function of time from isothermal measurements to a variety of kinetic models in the following form.

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

where A is the pre-exponential (frequency) factor (min), E_a is the activation energy (kJ/mol), T is the absolute temperature (K), R is the gas constant ($8.314\,JK^{-1}\,mol^{-1}$), $k(T)$ is the rate constant, $f(\alpha)$ is the differential form of the reaction model, t is the time, and α is the conversion fraction. In practice, differential data, $d\alpha/dt$, are often quite noisy so that the integral version of Eq. (1), $g(\alpha)$, is used:

$$g(\alpha) = Ae^{-(E_a/RT)}t \quad (2)$$

where $g(\alpha)$ is the integral form of the reaction model.

For each reaction model, $g(\alpha)$ against time (t) plots are evaluated using various statistical parameters, such as the coefficient of regression line (R^2), the standard deviation of the slope of the regression line (S_b), the standard deviation of the regression line ($S_{y/x}$), and residual plots.[21,29] From these data, the kinetic model that provides the most acceptable fit is identified.

In the second step of model fitting, the natural logarithm of the slope of the regression line from the acceptable fit is plotted against the reciprocal of the absolute temperature, and Arrhenius parameters are calculated.

The model-fitting approach assumes constant E_a values over the entire reaction process. This assumption leads to unambiguous values of Arrhenius parameters that are likely to conceal multi-step kinetics.[30] Thus, use of model-free or isoconversional

Table 1. List of Solid-State Kinetics Models Used in This Study (Modified from Refs.[21,28])

Model	Differential Equation $f(\alpha) = 1/k(d\alpha/dt)$	Integral Equation $g(\alpha) = kt$	Mechanism
Nucleation models			
A2	$2(1-\alpha)[-\ln(1-\alpha)]^{1/2}$	$[-\ln(1-\alpha)]^{1/2}$	1D nuclei growth (Avrami–Erofeyev equation, $n=2$)
A3	$3(1-\alpha)[-\ln(1-\alpha)]^{2/3}$	$[-\ln(1-\alpha)]^{1/3}$	2D nuclei growth (Avrami–Erofeyev equation, $n=3$)
A4	$4(1-\alpha)[-\ln(1-\alpha)]^{3/4}$	$[-\ln(1-\alpha)]^{1/4}$	3D nuclei growth (Avrami–Erofeyev equation, $n=4$)
P1	$\alpha(1-\alpha)$	$\ln[\alpha/(1-\alpha)]+c$[a]	Random nucleation (Prout–Tompkins equation)
P2	$2\alpha^{1/2}$	$\alpha^{1/2}$	Power law ($n=1/2$)
P3	$3\alpha^{2/3}$	$\alpha^{1/3}$	Power law ($n=1/3$)
P4	$4\alpha^{3/4}$	$\alpha^{1/4}$	Power law ($n=1/4$)
Geometrical contraction models			
R2	$2(1-\alpha)^{1/2}$	$1-(1-\alpha)^{1/2}$	2D phase boundary reaction (contracting area)
R3	$3(1-\alpha)^{2/3}$	$1-(1-\alpha)^{1/3}$	3D phase boundary reaction (contracting volume)
Diffusion models			
D1	$1/(2\alpha)$	α^2	1D diffusion
D2	$-[1/\ln(1-\alpha)]$	$((1-\alpha)\ln(1-\alpha))+\alpha$	2D diffusion
D3	$[3(1-\alpha)^{2/3}]/[2(1-(1-\alpha)^{1/3})]$	$(1-(1-\alpha)^{1/3})^2$	3D diffusion (Jander equation)
D4	$3/[2((1-\alpha)^{-1/3}-1)]$	$1-(2/3)\alpha-(1-\alpha)^{2/3}$	3D diffusion (Ginstling–Brounshtein equation)
Reaction-order models			
R1	1	α	Zero-order reaction
F1	$(1-\alpha)$	$-\ln(1-\alpha)$	First-order reaction
F2	$(1-\alpha)^2$	$[1/(1-\alpha)]-1$	Second-order reaction
F3	$(1-\alpha)^3$	$(1/2)[(1-\alpha)^{-2}-1]$	Third-order reaction