Effect of Experimental and Sample Factors on Dehydration Kinetics of Mildronate Dihydrate: Mechanism of Dehydration and Determination of Kinetic Parameters

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ABSTRACT: The dehydration kinetics of mildronate dihydrate [3-(1,1,1-trimethylhydrazin-1-ium-2-yl)propionate dihydrate] was analyzed in isothermal and nonisothermal modes. The particle size, sample preparation and storage, sample weight, nitrogen flow rate, relative humidity, and sample history were varied in order to evaluate the effect of these factors and to more accurately interpret the data obtained from such analysis. It was determined that comparable kinetic parameters can be obtained in both isothermal and nonisothermal mode. However, dehydration activation energy values obtained in nonisothermal mode showed variation with conversion degree because of different rate-limiting step energy at higher temperature. Moreover, carrying out experiments in this mode required consideration of additional experimental complications. Our study of the different sample and experimental factor effect revealed information about changes of the dehydration rate-limiting step energy, variable contribution from different rate limiting steps, as well as clarified the dehydration mechanism. Procedures for convenient and fast determination of dehydration kinetic parameters were offered. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1747–1755, 2014
Keywords: dehydration; kinetics; thermal analysis; particle size; mathematical model; kinetic model; isoconversional methods

INTRODUCTION

It is known that many organic compounds can exist in hydrated forms[1,2] and a variety of active pharmaceutical ingredients (APIs) are produced as hydrates.[2] The determination of the hydrate stability is thus important both form industrial and scientific point of view. Typically hydrate stability is evaluated by characterizing the dehydration conditions and observed phase changes. The most common techniques for studying dehydration are powder X-ray diffraction (PXRD),[3–7] thermal analysis,[3,5,6,8–14] spectroscopic methods,[8,12,15–17] and particle morphology and particle size characterization of the original and dehydrated products.[18–20] By using these methods, it is possible to determine the dehydration conditions and understand the behavior of hydrate upon dehydration. An additional tool for the better understanding of dehydration mechanisms is the determination of dehydration kinetic parameters: kinetic model and activation energy (E_a).[4,21]

Although it is generally accepted that the crystal structure in most cases determines the dehydration kinetics,[17,22,23] several other factors may contribute significantly.[24] Determination of the dehydration reaction kinetic parameters has been thoroughly explored, and a lot of studies can be found in the literature for organic compound hydrates, especially for API, for example,[3,11,15] because of the practical interest in these compounds.[2] However, determination of the API hydrate dehydration kinetic parameters under various experimental modes and under different conditions has not been sufficiently studied.

As already mentioned, it has been observed that the dehydration kinetic parameters can be strongly affected by various sample and experimental factors.[25–27] Differences of the sample particle size,[28–32] crystal habit,[33] sample history,[25] and crystal defect distribution[24] can result in different dehydration rates, E_a variation, and even change the kinetic model. Besides these factors, all the mentioned kinetic parameters can be affected by the relative humidity,[31,32,34–36] inert gas flow rate,[31,34] and sample weight.[28,37] Thus, for the better understanding of the dehydration process and calculated kinetic parameters, the effects of sample and experimental factors should be evaluated.

Mildronate [3-(1,1,1-trimethylhydrazin-1-ium-2-yl)propionate; Fig. 1] is a γ-butyrobetaine analogue, inhibitor of γ-butyrobetaine hydroxylase, and used as an anti-ischemic drug.[38,39] It is known to exist in a form of dihydrate DH,[40,41] monohydrate MH, and anhydrous phase AP.[42] Water molecules in the DH and MH are situated in structural channels,[40,41,43] whereas in the structure of the AP, empty channels are present.[43] Dehydration of the DH is a single-step process resulting directly in the formation of AP.[44] The effects of some sample and experimental factors on the dehydration kinetic parameters have already been reported. However, only limited number of factors were studied for one sample in isothermal mode.[44]

In this study, (1) the possibilities of determining the dehydration kinetic parameters of mildronate hydrate DH (the form used as API) by both isothermal and nonisothermal methods were explored, (2) the effect of various sample and experimental factors on the dehydration activation energy and kinetic model were studied in depth, (3) variations of kinetic parameters were used for understanding the dehydration mechanism,
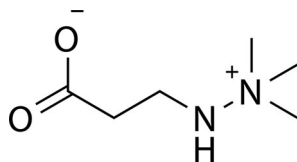
Figure 1.   Molecular structure of mildronate.

and (4) optimal conditions for determining the dehydration kinetic parameters were selected.

Although the effects of various sample and experimental factors on the dehydration process of API hydrates have been investigated in a number of papers,[14,18,28–30,45,46] in this study the effect of multiple factors on a single system was examined, so the magnitude and direction of each effect could be analyzed and explained. Investigation of the sample and experimental factors in both isothermal and nonisothermal modes allowed us to compare the influence of each factor on the results obtained in both modes. Moreover, evaluation of various factors allowed the identification of the most appropriate sample and experimental factors for performing reliable determination of the dehydration kinetic parameters.

EXPERIMENTAL

Sample Preparation and Storage

Mildronate DH was provided by JSC Grindeks (Riga, Latvia). The sample was confirmed as pure DH by PXRD. Four samples differing by the preparation procedure and/or storage conditions were used in this study. Samples were prepared by slowly crystallizing mildronate from water at 30°C or by drying a paste obtained by adding a small amount of water to mildronate in mortar. The obtained samples were fractionated by pushing through sieves with mesh size 1300, 700, 350, 150, 67, and 40 µm, yielding a maximum of seven fractions (the obtained particle size distribution for different fractions is given in Fig. S3). Part of the 150–350 and 350–700 µm fractions was slightly ground and then fractionated by pushing through sieves with mesh size 350, 150, 67, and 40 µm, and five fractions were thus obtained. Samples were stored at ambient temperature above saturated solutions of potassium acetate (relative humidity 22.5%) or magnesium chloride [relative humidity 34%, see Supporting Information (SI)]. All of the samples were used for determination of the dehydration kinetic parameters. Inorganic salts for humidity control were purchased from commercial suppliers and used as received. More details of sample preparation procedures are given in the SI.

For studying the effect of mechanical compression on the dehydration kinetics of DH, approximately 30 mg of sample was inserted in a die with 13 mm diameter, and then compressed at 130, 370, and 740 MPa for 1 min. Manual hydraulic press was used for compression of the samples. Right after the compression, the obtained tablet was either gently ground to obtain powder or divided into smaller pieces suitable for analysis with thermogravimetric (TG). Dehydration analyses were started immediately afterwards.

For studying the effect of prior history of dehydration/rehydration, the initial DH sample was dehydrated at 50°C temperature under N_2 flow. Then, the dehydrated sample was stored at the ambient temperature in 22.5% relative humidity.

Powder *X*-Ray Diffraction

Powder X-ray diffraction patterns were measured on a D8 Advance (Bruker AXS GmbH, Karlsruhe, Germany) diffractometer using copper radiation (CuK_α) at a wavelength of 1.54180 Å. The tube voltage and current were set to 40 kV and 40 mA. The divergence slit was set at 0.6 mm, and the antiscattering slit was set at 8.0 mm. The diffraction pattern was recorded using a 0.2 s/0.02° scanning speed from 3° to 30° in 2θ scale and a LynxEye position sensitive detector. To prevent the atmosphere humidity effect, samples were covered with a 10 µm polyethylene film.

Particle Size Analysis

A Mastersizer 2000 (Malvern Instruments Ltd., Malvern, UK) laser diffraction instrument was used for particle size analysis. Integration time was 3000 ms. The measurement range was set to 0.020–2000 µm, and 59 counting channels were used. For sample dispersion, nitrogen with 1.0 bar pressure was used. All measurements were carried out three times and the average particle size distribution was calculated.

Thermal Analysis

For studying the dehydration kinetics of mildronate DH, TG analysis was performed with Exstar6000 TG/DTA6300 (SII Nanotechnology Inc., Chiba, Japan). The samples were heated in nonisothermal mode from 30°C to 120°C temperature with heating rates of 0.5, 1, 2, 3, 4, and 5°C/min. Open aluminum pans were used. The sample weight was 7.0 ± 0.5 mg, and nitrogen flow rate was 80 ± 10 mL/min. The effects of sample size and nitrogen flow rate were determined at additional data points, where the sample weight was 3 or 15 mg and nitrogen flow rate was 30 or 300 mL/min.

Dehydration was also analyzed isothermally at the temperature range from 25°C to 80°C with a step of 5°C. The heater unit was preset to the required temperature before the insertion of the sample. For each sample, dehydration was performed at eight different temperatures selected according to the dehydration rate. The sample weight was 7.0 ± 0.5 mg, and nitrogen flow rate was 80 ± 10 mL/min. The effects of sample weight and nitrogen flow rate were determined at additional data points, where the sample weight was 2, 4, 6, 8, and 10 mg, and nitrogen flow rate was 0, 45, 200, and 300 mL/min.

For studying dehydration at controlled water vapor pressure, a system previously described in the literature[45] was used for providing specific water vapor activity. Dry and moist nitrogen gas was mixed in a gas controller unit (SII) at selected flow rates. The combined flow rate was 300 mL/min. The relative humidity was measured with a TFH 620 (Ebro) humidity meter, which was previously calibrated using saturated solutions of NaCl and $MgCl_2$.

Methods for Kinetic Parameter Determination

For isothermal experiments, both model-free and model-based methods were used, but for nonisothermal experiments only model-free kinetic analysis was performed.[47] For isothermal experiments, data sets of α–time were obtained with $\Delta\alpha = 0.02$ at each temperature. Temperature stability during the reaction was evaluated and further analysis was performed in the conversion degree region where temperature change was smaller than 0.3° for all used temperatures. For nonisothermal experiments, data sets of α–temperature and time were