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DVS Vacuum Application Note 115

Optimising Hydrate Drying - The Influence of Temperature, Vacuum, and Humidity on Drying Kinetics

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Vacuum drying is a widely used technique in the pharmaceutical and food industries for processing materials that are heat-sensitive, hygroscopic, or susceptible to oxidative degradation. This method enables enhanced moisture removal at lower temperatures due to operation under reduced pressure, making it ideal for delicate compounds. However, the effects of specific process variables on the overall drying kinetics remain insufficiently characterized. This study demonstrates the use of Vacuum Dynamic Vapor Sorption Analysis (DVS Vacuum) for exploring the influence of variables such as temperature, pressure, and humidity on cake drying kinetics. We use citric acid monohydrate (CAM) as a model material, as a compound extensively used in pharmaceuticals and food, that transitions between monohydrate and anhydrous forms and is sensitive to heat. It is revealed that the complex interplay of different variables not only impacts the rate of drying but also plays an important role in extent of drying achieved.

Introduction

Drying of different materials is a critical operation in the pharmaceutical, food, and biotechnology industries, where removal of water not only ensures stability and shelf life but also affects the physical form and performance of the final product. For many active ingredients, excipients, and food additives, conventional drying approaches using elevated temperatures are unsuitable due to the heat sensitivity, hygroscopicity, or susceptibility to oxidative degradation of the compounds involved [1]. Vacuum drying has emerged as a widely adopted strategy for such materials because it allows moisture removal at reduced pressures, thereby lowering the boiling point of water and enabling drying at temperatures significantly below those of atmospheric conditions. This makes the method particularly valuable for preserving bioactivity, minimizing chemical degradation, and controlling solid-state transformations during dehydration [2].

Despite its practical importance, the fundamental understanding of drying kinetics under vacuum conditions remains relatively underdeveloped compared with conventional drying methods. Drying is governed not only by temperature and pressure but also by sample morphology, water–solid interactions, and phase transformations occurring during dehydration [3]. For crystalline hydrates, in particular, the situation is further complicated by potential transformations between hydrated and anhydrous forms, which influence both the kinetics and the extent of drying [4]. A systematic investigation of these factors at small

laboratory scales is required to provide the fundamental variables needed for process modelling and to guide industrial process optimization and mechanistic understanding.

Citric acid monohydrate (CAM) is a particularly relevant model system for such investigations. Widely used as an excipient, acidulant, buffering agent, and preservative in both pharmaceutical and food applications [5,6], citric acid exists in both an anhydrous and monohydrate crystalline forms, with solid-state transitions that are sensitive to temperature and humidity [7]. Understanding these transformations and the influence of various process parameters including temperature, humidity and pressure is important because they can influence not only product quality but also processing choices in scale-up manufacturing.

Dynamic Vapor Sorption (DVS) technology, and in particular instruments capable of vacuum operation (DVS Vacuum), offers a powerful platform to probe drying kinetics under precisely controlled conditions of temperature, pressure, and humidity. Unlike traditional drying experiments, which often lack tight control over the vapor-phase environment, the DVS Vacuum allows systematic variation of individual parameters while continuously monitoring minute changes in sample mass with microgram resolution. This combination provides quantitative insight into adsorption/desorption behavior, drying kinetics, phase transitions, hydration and crystallization under varied conditions.

In this study, we utilized the DVS Vacuum to analyze the cake drying kinetics of citric acid monohydrate, with a focus on the interplay between operational parameters of temperature, pressure, and humidity and their impact on drying performance. By capturing both rate and extent of water removal under controlled conditions, the work aims to shed light on critical parameters underlying vacuum drying of crystalline hydrates. Such insights not only provide understanding of drying kinetics of CAM as a model compound but also have broader implications for optimizing vacuum drying protocols of heat-sensitive pharmaceutical and food materials.

Methods

All experiments were carried out using the DVS Vacuum, a high-resolution instrument that precisely controls the pressure of vapours and gases around the sample while recording the continuous mass data. This instrument is equipped with an ultra-sensitive microbalance (resolution 0.01 µg) housed in a temperature-controlled chamber operating between 10 and 70 °C. Gas and vapor dosing are regulated by integrated mass-flow controllers, while the system pressure from high vacuum (<10^{-6} mbar) is maintained using integrated vacuum pumps connected through a butterfly valve, enabling stable operation under dynamic flow conditions. A simplified schematic of the instrument is shown in **Figure 1**.

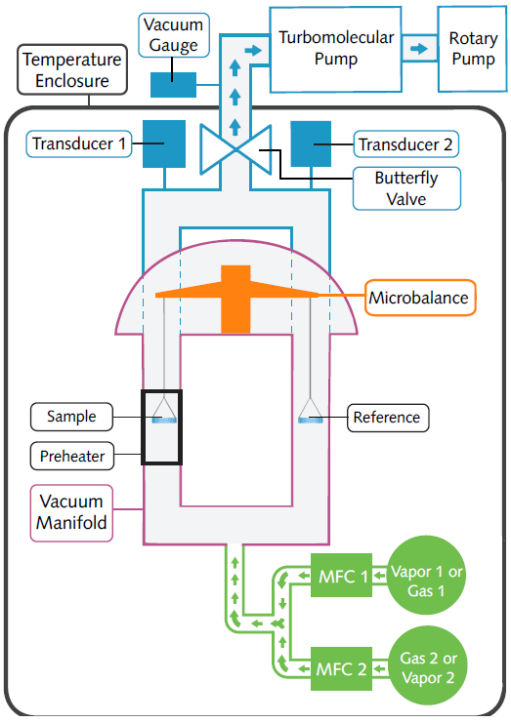

Figure 1. Schematic of DVS Vacuum.

The drying experiments were conducted under different conditions of temperature (25 °C and 40 °C), relative humidity (0% and 50 %) and pressure (1 atm and 0.5 atm). Nitrogen was used as the environment gas in all experiments. 10-20 mg of the sample were loaded in the sample pan of the DVS Vacuum, and the mass change was recorded continuously until the mass of the sample remained

constant. The rate of drying was then obtained by fitting the linear region of mass loss vs time. The percent experimental mass loss of the sample was calculated from the mass difference between the start and end of experiment when no further mass loss occurred. The drying extent (D.E) of CAM was then calculated using the following formula.

$$D.E\ (\%) = \frac{Expt.Mass\ Loss\ (\%)}{8.575\ (\%)} * 100$$

Where 8.575 (%) is the stoichiometric mass loss for complete dehydration of CAM to anhydrous form calculated from the following drying equation:

$C_6H_8O_7.H_2O \rightarrow C_6H_8O_7 + H_2O\ (g)$

Results

Citric acid is known to be deliquescent under sufficiently high humidity and temperature conditions [7]. Therefore, prior to evaluating its drying performance, citric acid monohydrate was exposed to a range of relative humidity (RH) levels at 25 °C to assess the influence of humidity on its phase stability. The resulting kinetic profile shows that at 0 % RH the material undergoes an initial mass loss of approximately 1.56 %, after which the mass remains largely unchanged up to 70 % RH **(Figure 2).** Previous studies have similarly reported the stability of citric acid monohydrate up to approximately 60 % RH at 40 °C, beyond which deliquescence occurs [7]. Given that the aim of this study is to evaluate dehydration rather than crystallisation, drying experiments under humid conditions were restricted to 50 % RH, well below the onset of deliquescence.

The combined drying curves, along with the calculated drying rates and extents, are presented in **Figure 3**. Differences in curve slopes and the total mass loss under varying conditions clearly demonstrate the influence of drying parameters on both the rate and extent of dehydration. The key observations are as follows.

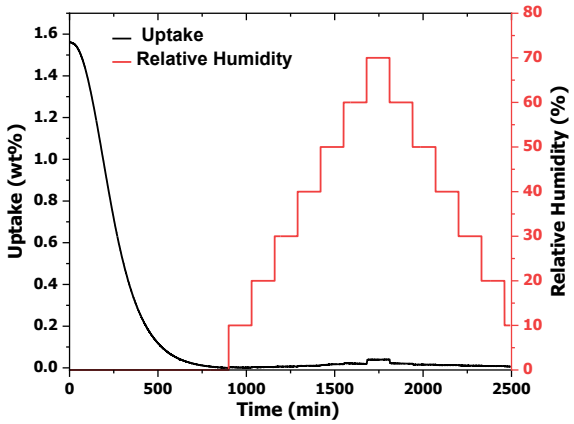

Figure 2. Citric acid monohydrate Kinetic uptake plot of uptake at different humidity levels

Effect of Temperature at Atmospheric Pressure

Temperature had a most pronounced impact on both the rate and extent of drying. When the drying temperature was increased from 25 °C to 40 °C (under dry nitrogen, 1 atm), the drying rate rose by more than an order of magnitude (17.3-fold), from 8.6 × 10-3 %/min to 1.7 × 10^{-1} %/min. At the same time, the extent of dehydration increased from 32% to 91%. This demonstrates that even modest increases in temperature can greatly accelerate dehydration of CAM and achieve a higher degree of drying.

Effect of Reduced Pressure (Vacuum)

The role of pressure was evaluated at both 25 °C and 40 °C. At 25 °C, reducing the pressure from 1 atm to 0.5 atm improved drying, increasing the rate by a factor of 1.97 from 8.6 × 10^{-3} %/min to 1.7 × 10^{-2} %/min and raising dehydration extent from 32% to 92%. This highlights that even the moderate vacuum conditions can effectively compensate for limited thermal energy at lower temperatures by enhancing the driving force for moisture desorption. This could possibly lead to energy efficient dehydration under vacuum conditions. At 40 °C, however, the benefit of reduced pressure was minimal. Once sufficient thermal energy is supplied, pressure reduction no longer contributes significantly, suggesting that temperature becomes the dominant parameter for driving drying under these conditions.

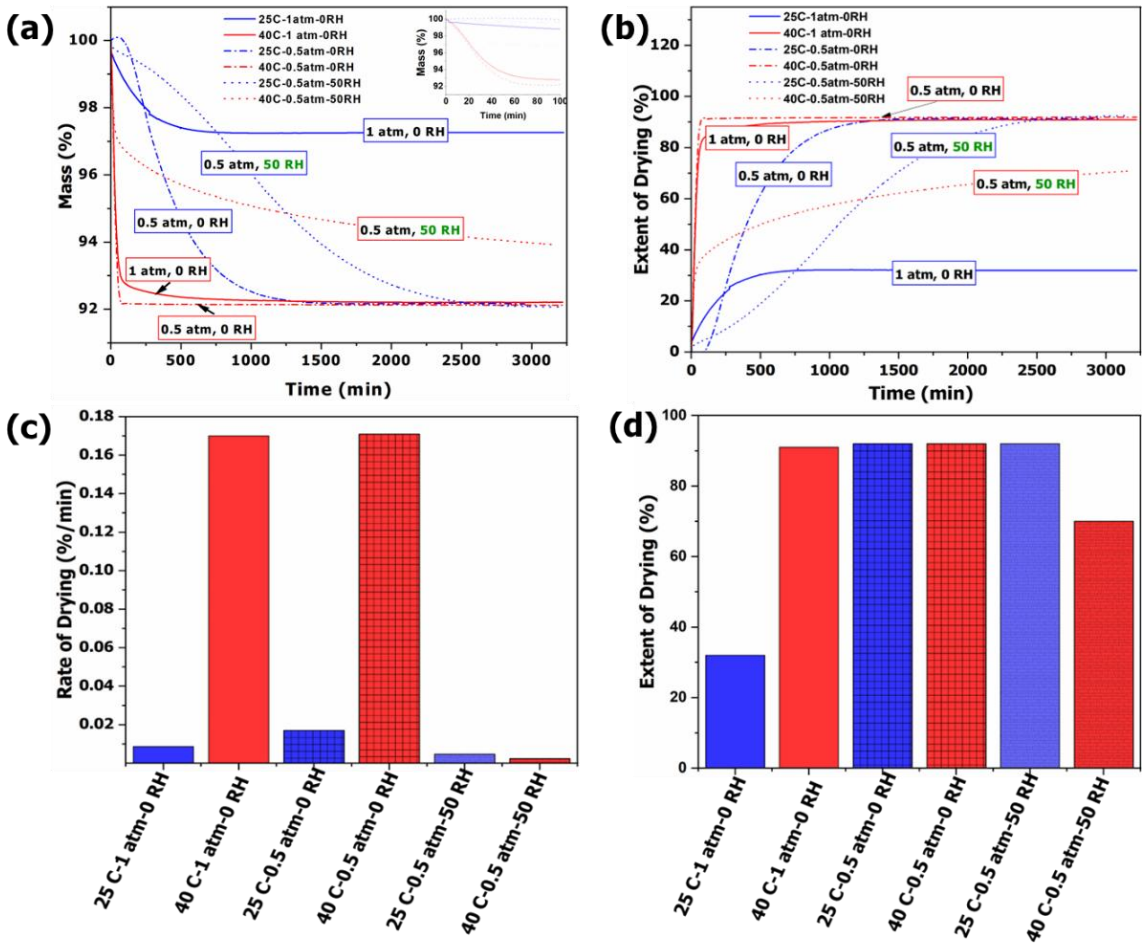

Figure 3. (a) Drying curves showing mass loss under different temperature pressure and humidity conditions (b) Extent of drying curves (c) Rate of drying under different conditions calculated from linear region of the drying curves (d) The net extent of drying obtained under different condition

Effect of Humidity

The surrounding gas humidity was also found to strongly influence drying behaviour at reduced pressure (0.5 atm). As shown in Figure 3, raising the relative humidity (RH) to 50% slowed drying kinetics by 3.5–4-fold at both 25 °C and 40 °C. At 25 °C, the dehydration rate slows down from 1.7×10^{-2} %/min to 4.7×10^{-3} %/min and at 40 °C the value shows a decrease from 1.7×10^{-1} %/min to $2.4*10^{-3}$ %/min. The higher ambient moisture content reduces the capacity of the nitrogen stream to accept additional water vapor, thereby retarding moisture transfer from the sample. This slowdown was accompanied by a decrease in dehydration extent, with the effect being most pronounced at 40 °C.

Conclusions

The drying behaviour of CAM is strongly influenced by environmental conditions. Temperature emerges as the most critical factor, with drying at 40 °C under dry atmospheric pressure achieving rates nearly 17 times higher than those at 25 °C, while also achieving maximum conversion to the anhydrous phase. The use of vacuum at 25 °C also substantially enhances both the rate and extent of drying, although the relative benefit diminishes at elevated temperatures. Conversely, the presence of humidity markedly slows the drying process, reducing rates by approximately fourfold across all tested conditions. These findings highlight the necessity of carefully balancing temperature, vacuum, and humidity to optimize drying efficiency. Using milligram levels of the material, the

instrument DVS Vacuum can provide such information critical to modelling vacuum drying process optimization at higher scales.

References

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