

Improving Powder Flow Properties of Citric Acid by Crystal Hydration

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ABSTRACT: A batch of poorly flowing citric acid anhydrate was exposed to 69.9% relative humidity to prepare pure monohydrate with nearly identical particle size and morphology but different surface properties. Flow properties of the powders were tested using a ring shear cell. Results show the hydration can significantly improve flow properties of anhydrous citric acid. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 98:1744–1749, 2009

Keywords: powder flow properties; shear cell; citric acid; hydrate; unconfined yield strength; surface properties

INTRODUCTION

Poor powder flow, among others, is a major challenge to the successful high speed manufacture of tablets especially when very fine drug or excipients are used. Particle size enlargement, for example by granulation, can profoundly improve flow properties of pharmaceutical powders.¹ However, fine particle size of a drug is sometimes required for achieving good uniformity, especially for a low dose drug in a direct compression formulation. Other times, fine particle size is a result of the formulation and process, e.g., milling. Thus size enlargement, although effective, is not always suitable to address flow problems. Under the restriction of retaining fine particle size, flow properties of a powder may possibly be modified by modifying surface chemistry, surface texture, particle density, and morphology.¹ An effective implementation of

any of the strategies rests on the understanding of how each factor works. However, this objective has been difficult to achieve largely because it is extremely difficult to maintain comparable particle size when the above-mentioned particulate properties are modified.

Conceptually, any bulk property, for example, surface energy, that has its origin from crystal surfaces are also affected by modification of surfaces.² Because each surface on a crystal is related to a specific crystallographic plane, identified by the Miller index (*h k l*), modifications of chemical nature on a crystal surface could be achieved by changing crystal structure (polymorphs, salts, co-crystals). In fact, chemical nature can be different on different crystal faces of the same crystal because of the anisotropic nature of organic crystals.³ However, reproducible modifications only to crystal surfaces by the means of true polymorphism or salt formation are difficult because processes, such as crystallization and mechanical treatment, invariably change particle size and morphology. Some hydrate systems present advantages in this regard. The conversion between a hydrate and a corresponding anhydrate can be achieved by a vapor mediated process. A hydrate can be obtained by exposing anhydrate to an environment with sufficiently high relative

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humidity (exceeding critical water activity) while keeping particle size and morphology constant. In this way, it is possible to obtain bulk powders with essentially identical particle size and morphology but different surface properties. This strategy was successfully implemented in an earlier study to eliminate effect of different particle size and shape on powder compaction.⁴ In this study, we explore effects of crystal hydration, through the vapor mediated process, on flow properties of a batch of commercial citric acid anhydrate that exhibits poor flow properties.

MATERIALS AND METHODS

Material

Anhydrous citric acid was purchased from Mallinckrodt Inc. (Phillipsburg NJ).

Preparation of Bulk Citric Acid Monohydrate

Citric acid monohydrate was prepared by exposing anhydrous citric acid to an atmosphere of 69.9% relative humidity (RH) over the saturated aqueous solution of KI at 21°C over a period of approximately 3 months. Preliminary studies showed that citric acid deliquesced at 75% RH when the temperature was either 23°C or 40°C. Thus, the RH needed to be below 75% to avoid deliquescing. When the anhydrous citric acid was exposed to 65% RH at 30°C over a period of 130 days, no weight was gained. A suitable RH to induce hydration of citric acid should lie between 65% and 75%. The saturated aqueous solution of KI, exhibiting a RH of 69.9% at 20°C,⁵ was used to prepare bulk monohydrate. A total of 30.5 g of anhydrous citric acid in a 250 mL plastic beaker was placed in a closed chamber containing a saturated KI solution at 20°C. Weight of the bulk powder was monitored periodically to monitor the extent of the hydration reaction. After each weighing, the powder bed was gently agitated with a spatula before being put back to the chamber.

Both the anhydrate and monohydrate were equilibrated at 60% RH overnight prior to flow properties characterization using a shear cell.

Kinetic Stability of Citric Acid Monohydrate

Phase stability of the monohydrate was studied by monitoring weight change of a monohydrate powder (~3 g) in chambers of 58% RH (saturated

NaBr aqueous solution) and 30% RH (saturated CaCl₂ aqueous solution). Kinetic stability of the monohydrate at 25°C was also assessed by dynamic moisture sorption gravimetry (DMSG) using a moisture balance (SGA-100, VTI Inc., Hialeah, FL). In the DMSG study, a monohydrate sample (~9 mg) was first equilibrated at 70% RH. The RH was then reduced to 5% in multiple steps. The sample was assumed to reach the equilibrium state at a given RH if less than 0.01% weight change was detected in 5 min. Once the equilibrium criteria were met, RH was changed to next target RH.

Particle Size Analysis

The volume-based particle size distribution (PSD) of dry powders was obtained using a Sympatec Helos/Rodos laser diffraction particle size analyzer (Sympatec Inc., Princeton, NJ). The powder dispersing pressure of 3 bar was selected, after a pressure titration step, for all PSD measurements. Three measurements were made on each powder. The mean and standard deviation of each key PSD parameter were calculated.

Powder Density and Compressibility Index

Each sieved powder (0.5 mm sieve opening) was allowed to fall into a 25 mL graduated glass cylinder that rested on a bench top. The weight and the initial volume of filled powder were used to calculate bulk density. Tapping was performed by dropping the cylinder from a ~1 cm height onto the bench. The volume of powder bed after every 100 taps was recorded. When volume change was less than 0.5 mL between two consecutive readings, the last tapped powder volume was used to calculate tap density. The compressibility index was calculated for each powder using the powder bulk and tap density according to Carr.⁶ The smaller cylinder, instead of the 100 mL cylinder specified in the USP, was used to accommodate the limited amount of available citric acid monohydrate powder.

Shear Cell Testing

Flow properties of both powders were measured using a Ring Shear Tester (RST-XS, Dietmar Schulze, Wolfenbüttel, Germany). A powder was first passed through a 0.5 mm sieve. A shear cell with a volume of ~10 mL was then over-filled with

the sieved powder. The powder was slightly compacted using a spatula to eliminate large air pockets before excess powder was scraped off. The filled shear cell was weighed and then placed on the motor-driven base of the tester. The preshear normal stresses 1, 3, 6, 9, and 15 kPa were used in this study to cover a wide stress range despite that stresses higher than 6 kPa do not typically present in pharmaceutical hoppers. Under each preshear normal stress, a yield locus (shear stress vs. normal stress during shear) was obtained at five shear normal stresses using the point-to-point method (instead of linear regression). For all yield loci, the minimum normal stress during shear was kept at 220 Pa. Spacing between neighboring test points on the same yield locus was 1/5 of the corresponding preshear normal stress. From each yield locus, the *unconfined yield strength* (f_c) and the *major principal stress* (σ) were obtained by drawing two Mohr circles. One circle passes the origin, tangent to the yield locus, and intercepts the normal stress axis at f_c . The other circle passes the point of shear stress versus preshear normal stress, tangent to the yield locus, and intercepts the normal stress axis at the σ . A *flow function* describes f_c as a function of σ . At the same σ , the lower is the f_c the easier for a powder to flow. The temperature and relative humidity were 21°C and 60% respectively during the shear cell experiments. Both crystals were kinetically stable under these conditions.

RESULTS AND DISCUSSION

Hydration Kinetics

The conversion from the anhydrous citric acid to monohydrate was relatively slow. Approximately 2 months had lapsed before ~97% of citric acid could be converted (Fig. 1). The phase transformation followed a nearly linear kinetics up to ~97% completion of the reaction. Conversion to

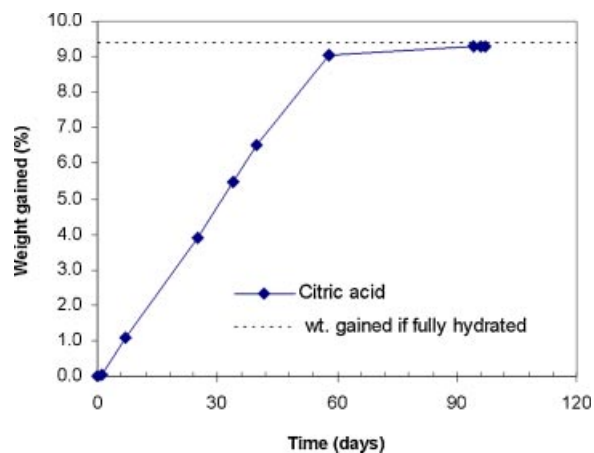


Figure 1. Kinetics of conversion from anhydrous citric acid to monohydrate at 69.9% RH and 20°C.

monohydrate was complete after 100 days. Complete conversion was confirmed by powder X-ray diffractometry (PXRD). Particle size distributions by laser diffraction excluded the possibility of significant enlargement of particle due to hydration (Tab. 1). The particles in both samples were irregular in shape and exhibited qualitatively similar particle size and morphology (Fig. 2). Particles also showed birefringence when examined using a polarized light microscope, suggesting both powders were crystalline.

Kinetic Stability of Citric Acid Monohydrate

In a thermal gravimetric analysis (TGA), upon heating (108°C/min) from ambient temperature under a dry nitrogen flow (40 mL/min), the monohydrate did not lose its water of crystallization until the temperature reached approximately 55°C. The dehydration was complete between 55 and 75°C in one step (data not shown). A monohydrate powder did not undergo detectable weight loss at 21°C for at least 5 and 7 days after being exposed to 58% and 30% RH, respectively.

Table 1. Some Physical Properties of the Citric Acid Anhydrate and Monohydrate Powders (Standard Deviations Are in Parentheses, $n = 3$)

	Particle Size Distribution ^a				Bulk Density (g/mL)	Tap Density (g/mL)	Compressibility Index (%)
	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	$M_{(1,3)}$ (μm)			
Anhydrate	4.2 (0.2)	15.7 (0.8)	43.7 (3.5)	20.5 (1.5)	0.38	0.74	97
Monohydrate	6.7 (0.2)	22.3 (0.2)	48.3 (0.6)	25.5 (0.1)	0.42	0.67	58

^a d_{10} , d_{50} , d_{90} are particle size at 10, 50, and 90 percentiles of the cumulative particle size distribution. $M_{(1,3)}$ is the volume moment mean diameter.

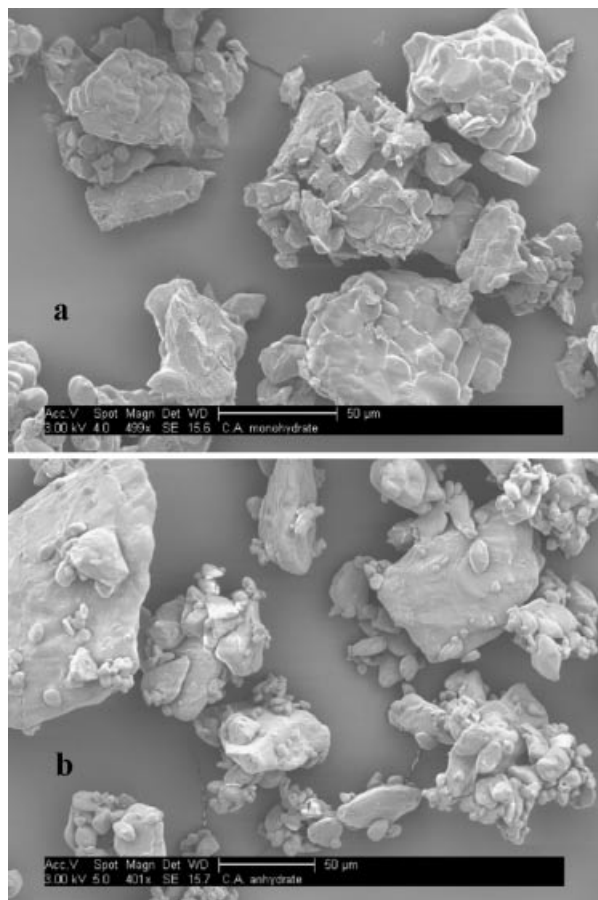


Figure 2. Scanning electron microphotographs of (a) citric acid monohydrate and (b) citric acid anhydrate.

The monohydrate did not undergo dehydration when RH was decreased from 70% RH to 5% RH step-wise in the DMSG study (Fig. 3). The phase purity of the post-DMSG monohydrate was confirmed by PXRD and TGA. These results assured that monohydrate was kinetically stable during the course of this study. The confirmation of kinetic stability is important because citric acid monohydrate is thermodynamically unstable at 25°C when RH is below 65%.⁷

Flow Properties

Flow functions of the anhydrate and monohydrate powders are shown in Figure 4. Under the same major principal stress (σ), unconfined yield strength (f_c) of the anhydrate is 42–104% higher than that of monohydrate (Fig. 4). The higher f_c of the anhydrous citric acid suggests poorer flow properties. Flow properties of the anhydrous citric

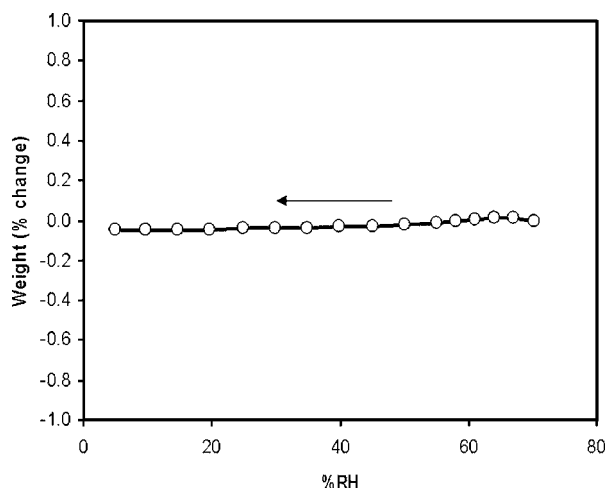


Figure 3. Moisture desorption isotherm of citric acid monohydrate suggests its kinetic stability over a wide range of relative humidity (5–70%) at 25°C.

acid are slightly worse than a fine grade of microcrystalline cellulose, Avicel PH105, which is cohesive and poorly flowing (Fig. 5). Flow properties of the monohydrate powder, despite the improvement, remain poor. It is cohesive and does not flow easily when σ is lower than 11 kPa according to the Jenike flow classification scheme (Fig. 4). The Carr compressibility index of the monohydrate powder is higher than 45% (Tab. 1). Thus, it is considered extremely poorly flowing according to Carr's classification scheme.⁶ The flow function of the monohydrate is similar to that of the Avicel PH101 (Fig. 5), a common pharmaceutical excipient that does not exhibit superior

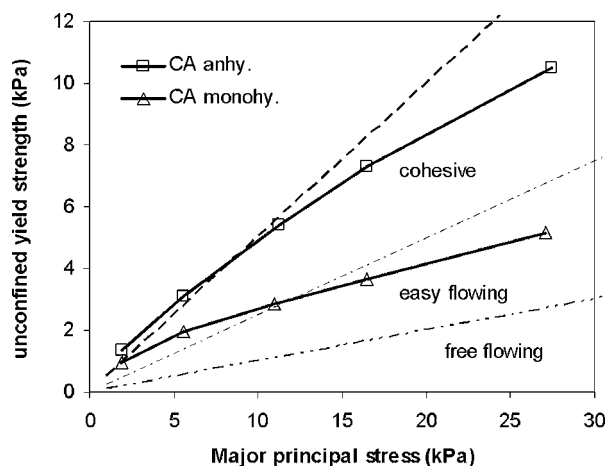


Figure 4. Flow functions of citric acid anhydrate and monohydrate. Flow properties of the monohydrate are significantly better. The Jenike flow classification criteria are shown as broken lines.

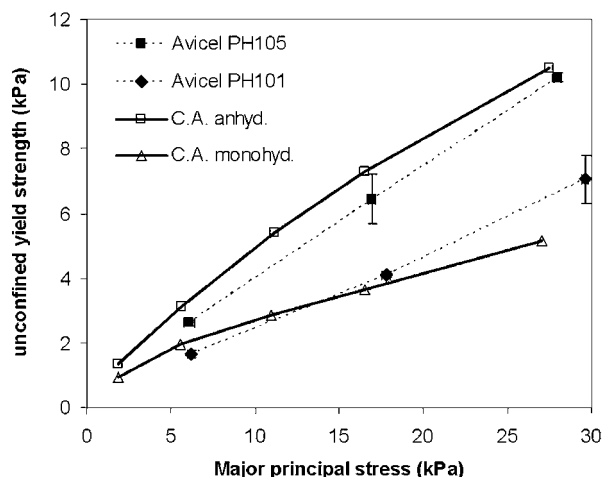


Figure 5. Flow functions of citric acid powders in comparison to Avicel PH105 and PH101.

flow properties. Substantial particle attrition is assumed absent during the shear cell studies because of the low pressure, <0.03 MPa, employed in this study. The assumption is supported by the observation that shear stress during preshear is nearly constant throughout each test (Fig. 6).

Shear cells can also generate data related to flow properties of a powder such as *cohesion*, powder density, and internal friction angle. *Cohesion* describes the strength of a powder under a stress-free state after having been consolidated at a prescribed preshear normal stress. It is the intercept of yield locus on the shear stress axis. Clearly, the anhydrate powder is more cohesive than the monohydrate powder at all stress conditions (Fig. 7). This is consistent with the

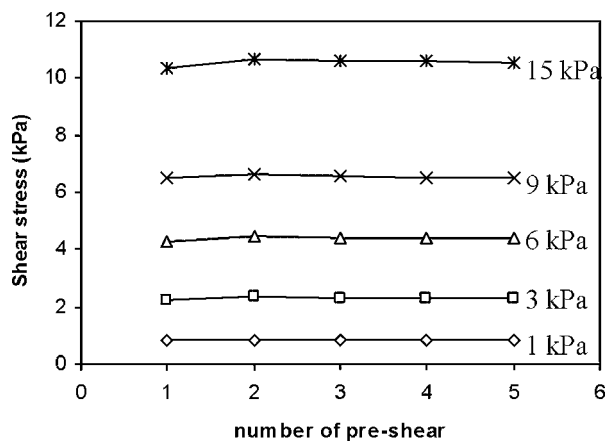


Figure 6. Shear value during preshear are essentially constant, suggesting minimum particle attrition during the measurement. Corresponding preshear normal stresses are indicated.

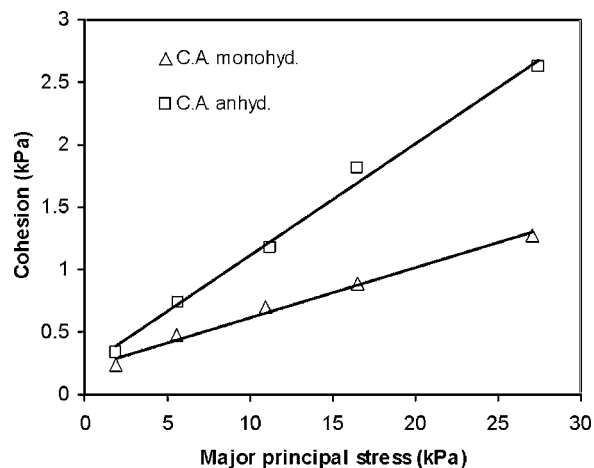


Figure 7. Dependence of powder cohesion on major principal stress for the citric acid monohydrate and anhydrate.

poorer flow properties of the anhydrate powder based on flow function (Fig. 4). Powder density of the monohydrate powder is lower than that of anhydrate powder at all stress conditions (Fig. 8). The ratio of powder bed density of the monohydrate to that of the anhydrate at 1 kPa normal preshear stresses is 0.933 and is the same as the ratio of crystal density ($1.544/1.655 = 0.933$), suggesting identical packing efficiency in the two powders. This can happen likely because of the nearly identical particle shape and size distribution in the two powders. This observation suggests that the improved flow properties under an external stress are mainly a result of different surface properties rather than different particle packing. In other words, the water of crystal-

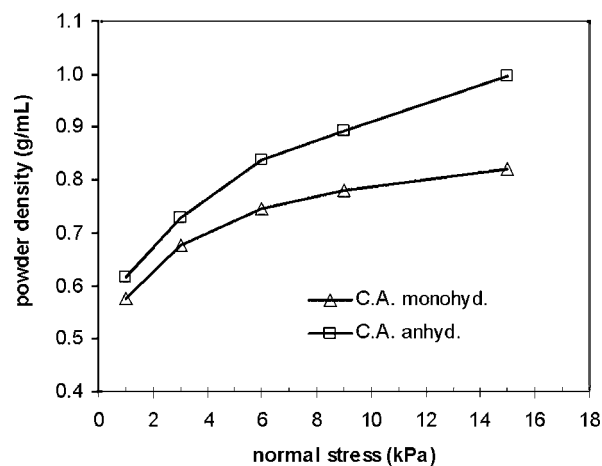


Figure 8. Dependence of powder density on normal stress for the citric acid monohydrate and anhydrate.

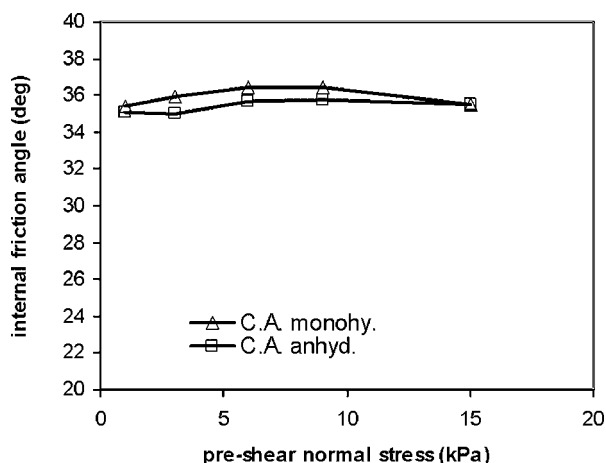


Figure 9. Dependence of powder internal friction angle on major principal stress for the citric acid monohydrate and anhydrous.

lization reduces strength of surface interaction in the citric acid system. When an external stress is absent, such as during the bulk density measurement, the higher surface interactions among anhydrous crystals lead to less efficient particle packing. Consequently, bulk density of the anhydrous was lower than that of the monohydrate despite the higher crystal density of the anhydrous (Tab. 1). This implies that the density curves of the anhydrous and monohydrate will cross at a normal stress below 1 kPa. Despite the different surface interaction strength, internal friction angles of the two powders are very close (Fig. 9). This suggests the particle shape and size, instead of surface interactions, contribute more significantly to inter-particulate friction in the two powders.

CONCLUSIONS

It is shown for the first time that hydration of crystals can significantly reduce strength of interactions among crystal surfaces and improve flow properties of a pharmaceutical powder. This effect is being tested using other model systems to understand its generality and for gaining molecular level understanding of the phenomenon.

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