Dynamic water vapor sorption to characterize the hydrate formation of L-lysine HCL

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Introduction

Hydrates, in general, are substances which have formed bonds with water molecules. Water binding can take place via electrostatic dipole-dipole interactions, via hydrogen bonds or coordinatively in complexes. In inorganic, crystalline hydrates water molecules are bound in a specific stoichiometric ratio. Usually, hydrates are formed during crystallization from aqueous solutions. By drying and removing the crystallization water, the anhydrous crystal can be formed [1].

The respective hydrate state strongly influences the properties of the material, particularly the dissolution rate, the compressibility and the bioavailability of the product. Furthermore, the high hygroscopicity of the anhydrate influences the storability and handling of the product [2-5].

Therefore, identification and control of hydrate forms is important in the field of quality control, product development and material characterization.

Besides traditional methods like XRD, NMR, NIR, FTIR, Raman spectroscopy and DSC [4], dynamic water vapor sorption analysis is an effective method not only for determining the present hydrate species but also for determining the kinetics of hydrate formation as a function of temperature and relative humidity.

DVS method for hydrate identification

Different hydrate species and corresponding anhydrates vary in their stability depending on temperature and relative humidity [6]. In general, the anhydrous form is more hygroscopic. With exceeding a certain humidity level, a steep moisture increase is usually observed as shown by the schematic draw in Fig. 1. The following plateau as well as the pronounced hysteresis loop indicate the formation of an hydrate [7].

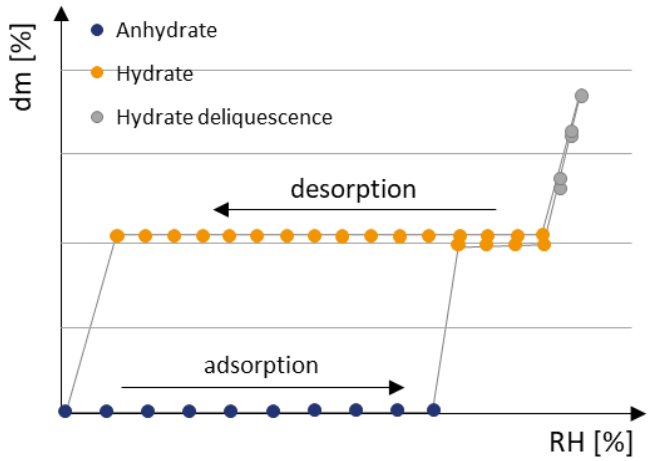

Fig. 1: Schematic draw: Adsorption-desorption cycle with transition from anhydrate to hydrate crystals.

Additionally, for stoichiometric hydrates, DVS analysis enables the determination of the respective hydrate form by balancing the adsorbed moisture at the transition from anhydrate to hydrate. The stoichiometric ratio (SR) can be calculated based on moisture uptake per g sample and the ratio of the molecular weights (MW) of the material and water according to Eq. 1.

$$SR = \text{Moisture uptake} \left[{}^{g}/_{g}\right] * \frac{MW_{Sample}\left[{}^{g}/_{mol}\right]}{MW_{Water}\left[{}^{g}/_{mol}\right]} \qquad \text{Eq. 1}$$

Scope

Hydrate formation was investigated by the example of L-lysine HCl. Phase transition from anhydrate to dihydrate was determined using the moisture sorption analyzer SPSx-1µ HighLoad.

The influence of measurement settings, i.e. equilibration time, humidity step resolution and temperature on hydrate detection and stability is shown.

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Results

Influence of equilibrium time and RH steps resolution

In general, hydrates are thermodynamically favored over anhydrates. If a material-specific critical relative humidity in the environment or rather the critical water activity of the substance is exceeded, hydrate formation is induced [7].

DVS measurements are well suited to investigate the conditions for hydrate formation and stability. However, the kinetics of the process strongly differ depending on the substance. Therefore, the measurement settings are a decisive factor for reliable hydrate identification by means of DVS analysis.

In particular, time for moisture equilibration and resolution of humidity steps are crucial which is demonstrated by the example of L-lysine HCL in Fig. 2.

From A to C the RH resolution was increased from 10 % (A) to 5 % steps (B,C). Additionally, the maximum time for equilibration was increased from 2 h to 20 h. In Fig. 2A the transition as well as the stable phase of the hydrate could not be detected with the settings used. The humidity steps were resolved too low to be able to deduce the processes that take place in the RH range from 60-90 %. Due to the higher RH resolution, at least a stable hydrate phase can be assumed in (B). Further refinement of the measurement in (C) finally allows the precise characterization of the RH-dependent formation and stability range of the L-lysine HCL hydrate.

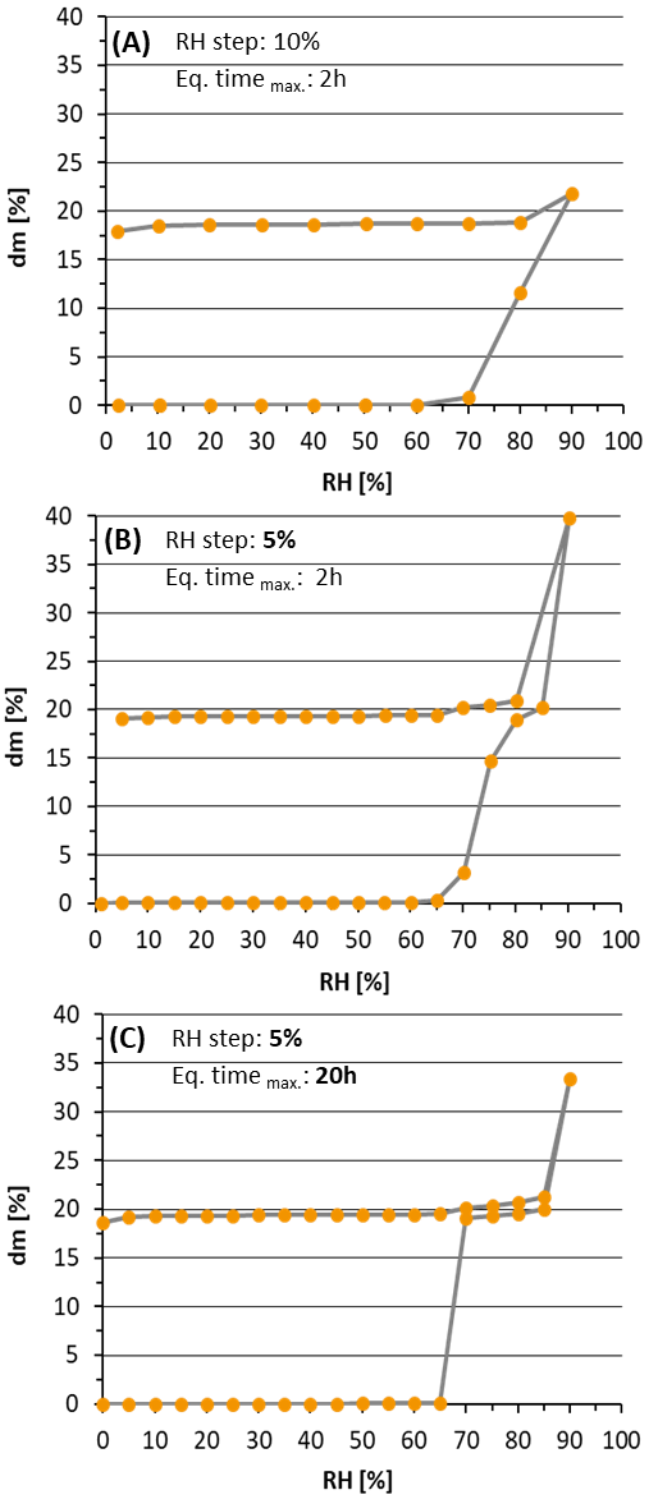

Fig. 2: Influence of the measurement settings on anhydrate-hydrate transition and identification L-lysine HCl dihydrate

Characterization of hydrates species

According to Eq. 1 the hydrate form was determined from the mass difference between anhydrate and hydrate. The hydrate of L-lysine HCl was stable during desorption in the range of 85 % to 0 % RH. Within this range, the average amount of adsorbed moisture was 19.6 %. Based on a sample dry weight of 182.675 mg, the stoichiometric ratio is 1.99 [Eq. 2] which corresponds to the formation of a dihydrate and is consistent with literature data [8].

$$SR = 0.196 \left[{}^{g}/_{g}\right] * \frac{182.65 \left[{}^{g}/_{mol}\right]}{18.01 \left[{}^{g}/_{mol}\right]} = 1.99 \qquad \text{Eq. 2}$$

Influence of temperature on anhydrate-hydrate transition

The phase transition from anhydrate to hydrate as well as their stability depends, beside humidity, strongly on the ambient temperature [1].

According to Tian *et al.* [1], this process can be described by the following equation

$$A_{(solid)} + m_{H_2O} \leftrightarrow A \cdot m_{H_2O\,(solid)}$$

$$K_h = \frac{a\left[A \cdot m_{H_2O\,(solid)}\right]}{a\left[A_{(solid)}\right] a\left[H_2O\right]^m} \qquad \text{Eq. 3}$$

Here, m represents the number of water molecules that react with one mol of the anhydrate and the factors $a\,[x]$ are the thermodynamic activity of the individual components. The temperature dependency of the anhydrate to hydrate transition is expressed by K_h, the equilibrium constant of the reaction.

The influence of temperature on hydrate formation of L-lysine HCL was measured in the range of 20-40 °C. Results are shown in Fig. 3.

$Rh_{critical}$ of anhydrate-hydrate transition was found to increase with increasing temperature from 65 % RH at 20 °C to 75 % RH at 40 °C.

This trend has also been reported in literature for the anhydrate-hydrate transition of lactose [9] and trehalose [4]. However, for citric acid this trend could not be confirmed [6].

The shift of $RH_{critical}$ can be explained by the fact that for a given relative ambient humidity, less moisture is adsorbed by the material with increasing temperature. As a result, less water is available for hydrate formation.

This assumption is confirmed by Raijada *et al.* [10], who investigated the temperature dependency of the hydrate formation of sodium naproxen. With the help of DVS measurements it could be shown that higher temperatures led to a lower moisture adsorption and thus to lower hydrate forms of the material.

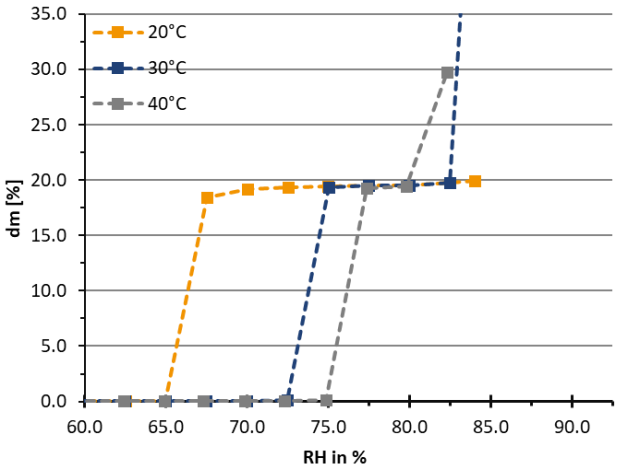

Fig. 3: Influence of temperature on hydrate formation and stability of L-Lysine HCl

Beside the influence on critical humidity for hydrate formation, the temperature also influences the stability of the hydrate. As shown in Fig. 3, at 20 °C the dihydrate is stable up to a relative humidity of 85 %. For 30 °C and40 °C deliquescence is initiated at 82.5 % RH and 80.0 % RH. Furthermore, the RH range in which the dihydrate is stable decreases with increasing temperature. For endothermic materials this temperature impact on deliquescence is in accordance with literature data [4,9].

Conclusion

DVS analysis was used to investigate the formation and stability of L-lysine HCl dihydrate. Measurement settings, such as maximum time for equilibration and resolution of humidity steps, proved to be essential criteria for a precise determination of the boundary conditions for the anhydrate-hydrate transition.

The influence of temperature was investigated in the range of 20-40 °C. Here, increasing temperatures led to a shift of the $RH_{critical}$ for hydrate formation to higher values. Furthermore, the RH of the deliquescence point and the RH range in which the hydrate was stable, decreased with higher temperature.

Based on these results it was shown that DVS analyses are well suited to characterize hydrate formation and stability as a function of RH and temperature conditions.

References

[1] F. Tian, H. Qu, A. Zimmermann, T. Munk, A.C. Jørgensen, J. Rantanen, Factors affecting crystallization of hydrates, J. Pharm. Pharmacol. (2010). doi:10.1111/j.2042-7158.2010.01186.x.

[2] R.K. Khankari, D.J.W. Grant, Pharmaceutical hydrates, Thermochim. Acta. (1995). doi:10.1016/0040-6031(94)01952-D.

[3] S. Debnath, R. Suryanarayanan, Influence of processing-induced phase transformations on the dissolution of theophylline tablets, AAPS PharmSciTech. (2004). doi:10.1208/pt050108.

[4] M. Allan, M.C. Chamberlain, L.J. Mauer, RH-Temperature Stability Diagram of the Dihydrate, β-Anhydrate, and α-Anhydrate Forms of Crystalline Trehalose, J. Food Sci. 84 (2019) 1465–1476. doi:10.1111/1750-3841.14591.

[5] H. Wikström, J. Rantanen, A.D. Gift, L.S. Taylor, Toward an understanding of the factors influencing anhydrate-to-hydrate transformation kinetics in aqueous environments, Cryst. Growth Des. (2008). doi:10.1021/cg070629e.

[6] M.C. Allan, E. Grush, L.J. Mauer, RH-temperature stability diagram of α- and β-anhydrous and monohydrate lactose crystalline forms, Food Res. Int. (2020). doi:10.1016/j.foodres.2019.108717.

[7] Y. Cui, E. Yao, Evaluation of hydrate-screening methods, J. Pharm. Sci. (2008). doi:10.1002/jps.21187.

[8] A.M. Petrosyan, V. V. Ghazaryan, Vibrational spectra of l-lysine monohydrochloride dihydrate and its two anhydrous forms, J. Mol. Struct. (2009). doi:10.1016/j.molstruc.2008.06.026.

[9] A. Lafontaine, M. Sanselme, Y. Cartigny, P. Cardinael, G. Coquerel, Characterization of the transition between the monohydrate and the anhydrous citric acid, in: J. Therm. Anal. Calorim., 2013. doi:10.1007/s10973-012-2798-0.

[10] D. Raijada, A.D. Bond, F.H. Larsen, C. Cornett, H. Qu, J. Rantanen, Exploring the solid-form landscape of pharmaceutical hydrates: transformation pathways of the sodium naproxen anhydrate-hydrate system., Pharm. Res. (2013). doi:10.1007/s11095-012-0872-8.