Hydrate formation of creatine

– Application Note 20-09

Introduction

Identifying of polymorphic structures, including different hydrate and anhydrous forms, is a major concern in pharmaceutical research and development.

In general, hydrates are formed by the interaction of a substance with water. The subsequent incorporation of the water molecules into the molecular structure is usually achieved by electrostatic dipole-dipole interactions, by hydrogen bonding or by coordinative binding in complexes. In crystalline hydrates, water molecules are bound in a certain stoichiometric ratio.

The different solid states often have a strong influence on the physical properties and efficiency of active pharmaceutical ingredients (API's). For example, properties such as density, solubility, dissolution rate, hardness, melting point, mechanical strength or chemical stability can be influenced. These characteristics are important not only for the processability and handling but also for the stability and bioavailability of the products [1].

Creatine

Creatine occurs naturally in vertebrates, with > 90 % in the skeletal muscles as phosphocreatine. Due to its involvement in the energy metabolism, creatine – mostly as monohydrate – is one of the most used dietary supplements in sports nutrition. Here, a creatine supplementation is assumed to improve the short-term performance, maximum muscle strength and recovery [1,2].

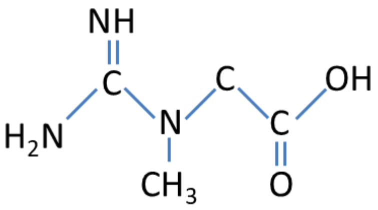

Fig. 1: Molecular structure of creatine

Creatine hydrate forms

In case of creatine, crystallization out of an aqueous solution always results in the formation of monohydrate crystals. By drying and removing the crystallization water, the monohydrate turns into an anhydrous state [3].

Hydrate characterization by DVS analysis

Dynamic vapor sorption measurements are well suited to identify different hydrate states and to characterize the kinetics of hydrate formation as a function of temperature and relative humidity.

For reliable characterization, however, it is important to ensure a sufficiently high RH resolution in the critical range and an adequate equilibration time for each moisture step [4].

Hydrate formation of creatine was measured in a SPS HighLoad device. Measurement settings were adjusted as summarized in Table 1. The relative humidity was varied from 0 – 90 – 0 % in 5 % RH steps. The temperature was kept constant at 25 °C.

Table 1: Measurement settings

Time between weighing cycles:	5.0 min
Min. time per climate cycle:	25.0 min
Max. time per climate cycle:	36.0 h
Default weight limit:	100 %
Equilibrium condition:	0.02 % / 25 min

Results

Fig. 2 shows the water vapor sorption kinetics of creatine, measured with a SPS HighLoad.

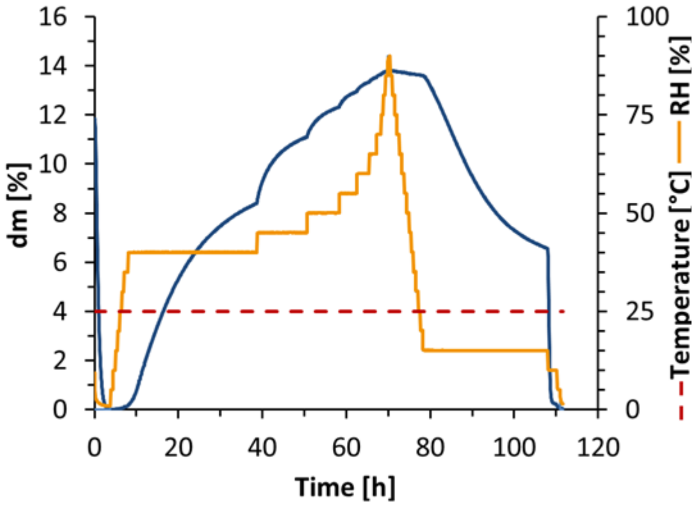

Fig. 2: Kinetics of water vapor sorption behavior of creatine.

The results show that up to a relative humidity of 35 % little moisture is adsorbed by the creatine powder. Only at a relative humidity of 40 % a strong increase in weight is observed, indicating a phase transition to a hydrate state. The further moisture adsorption up to relative humidity of 90 % is again less pronounced.

During desorption an opposite behavior can be observed. Here a stable phase with only slight weight loss was measured for relative humidities ranging from 90 % to 20 %. A first strong moisture desorption takes place at a relative humidity of 15 %, followed by a further sharp weight loss at RH values of 10 %.

In "Equilibrium view" (Fig. 3) the transition from the anhydrous to the hydrate state of creatine can be identified more clearly. In accordance with literature data, the usually present anhydrate state of creatine is stable up to a relative humidity of 35 %. However, two further but less common anhydrate polymorphs with an increased moisture stability up to 60 % could be detected recently [1].

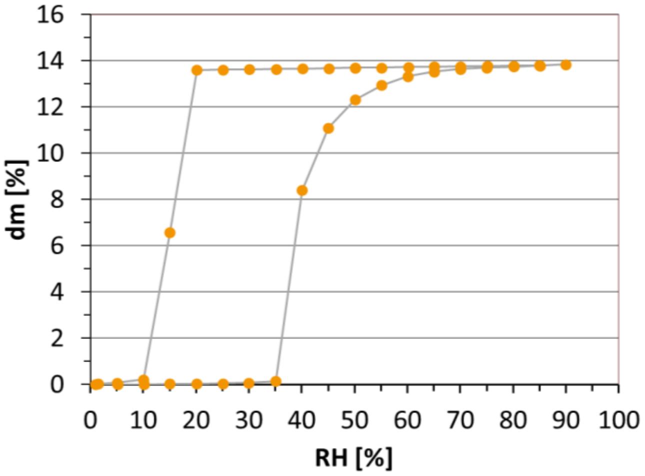

Fig. 3: Sorption isotherm of creatine.

Fig. 3 shows that the hydrate of creatine is stable from 90% down to a relative humidity of 20%. Within this range, an average moisture adsorption of 13.7 %, based on the dry weight of the sample, could be determined. Using equation 1, the stoichiometric ratio of the creatine-water interaction can be calculated and thus the hydrate form of creatine can be determined.

In this way, a stoichiometric ratio of 0.99 was determined, which, in accordance with literature, indicates the formation of a monohydrate.

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

$$\mathrm{SR} = 0.137 \left[{}^{\mathrm{g}}/_{\mathrm{g}}\right] * \frac{131.13 \left[{}^{\mathrm{g}}/_{\mathrm{mol}}\right]}{18.01 \left[{}^{\mathrm{g}}/_{\mathrm{mol}}\right]} = 0.99 \qquad \text{(Eq. 1)}$$

Conclusion

Dynamic vapor sorption analysis was used to investigate the transition from creatine anhydrate to monohydrate.

At a temperature of 25 °C the anhydrate proved to be stable only for relative humidities below 35 %. During desorption, the monohydrate was stable in the range of 90 – 20 % RH. Below this range, the removal of the crystallization water and the transition to the anhydrous state can be observed again.

DVS analyses are a well-suited method to precisely investigate the transition between different hydrate states and their stability as a function of relative humidity and temperature. Since the hydrate state can have a great influence on the properties of the material, this plays an important role in the characterization of new substances and formulations

References

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[2] M. Uzzan, J. Nechrebeki, P. Zhou, T.P. Labuza, Effect of water activity and temperature on the stability of creatine during storage Effect of water activity on creatine stability, Drug Dev. Ind. Pharm. (2009). doi:10.1080/03639040902755197.

[3] 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.

[4] proUmid Application note AN_17-01 Speed-vs-Accuracy