DVS In combination with In-line Raman measurements

– White Paper 24-04

Scope

This application note shows water vapor sorption measurements in combination with inline Raman measurements as a powerful tool for investigating product changes triggered by the interaction with moisture.

1. Introduction

The sorption behavior and the interaction of a substance with water vapor is of great importance for the shelf life, physical and (bio)chemical stability of the product. In addition, product properties such as flow behavior, compatibility, solubility and bioavailability can be significantly influenced by the interaction with water vapor. [1,2]

Water vapor sorption measurements therefore offer a well-suited method for estimating product properties and changes during the manufacturing and distribution process of a product and controlling them with the help of suitable measures.

The combination of the proUmid's SPS devices with Raman spectroscopy is an excellent way not only to precisely analyze the moisture sorption behavior of materials, but also to understand moisture-related changes of a product in detail and to monitor them directly with the help of Raman spectra. [3,4]

The advantage of the combination of Raman and DVS is that water has a very low Raman activity and therefore the influence of the water vapor atmosphere on the Raman signal of the sample is almost negligible. In addition, it is a non-destructive measurement technique, so Raman spectra can be recorded in parallel with water vapor adsorption, making material changes directly visible [5]. Both Raman spectroscopy and the proUmid SPS devices allow to use small sample quantities, so that the combination of both measurement methods also enables meaningful and reliable results, e.g. in the area of pharmaceutical/API substance development, where typically only small product quantities are available.

2. Theory of Raman spectroscopy

In Raman Spectroscopy, a monochromatic laser light is directed onto a sample. The sample molecules interact with the incident radiation by absorbing, reflecting or scattering.

In particular, the scattering profile of the material is used to collect the Raman spectrum. The energy of the laser beam temporarily raises the electrons to a higher energy level. When they return to the original level, the energy is released as scattered light.

Scattering is caused either by so-called Rayleigh scattering or by Raman scattering. *Rayleigh scattering,* that makes up the largest part, is caused by elastic collisions of the light with the sample molecules. Thus, the scattered light has the same wavelength and frequency as the incident laser beam.

Raman scattering, on the other hand, is caused by inelastic collisions of the light with the sample molecules. As a result, the scattered light exhibits lower frequencies compared to the incoming laser beam. This frequency shift corresponds to the vibrational frequencies of the bonds of the sample molecules and represents an individual fingerprint of a material. Therefore, Raman spectroscopy is often used to identify materials or to verify their purity. In combination with DVS analyses, Raman spectroscopy offers the possibility to monitor moisture induced material changes such as hydrate formation or crystallization processes. [5,6,7,8]

3. Raman Specification and Raman-DVS Integration

The Raman probe is easily attached to the SPS instrument using a heated sensor holder integrated into the glass lid of the SPS instrument. The setup is shown in Fig. 1.

The Raman system is fully integrated into the SPS software, which enables convenient control and operation of both measuring systems. The samples from which Raman spectra are to be recorded are selected from the “Raman” menu (Fig. 2). The time of data acquisition can also be defined, e.g. every time an equilibrium state is reached or at fixed intervals. The Raman spectra can be observed during the sorption measurement and the spectra can be easily assigned to the sorption data during the subsequent data evaluation in Excel.

The detailed technical specification of Raman-System is summarized in Table 1.

Fig. 1: Integration of the Raman probe into the proUmid SPS instrument

Fig. 2: Integration of the Raman spectrometer into the SPS Sorption Control software

Table 1: Technical specification of the Raman-System

Technical data	
Manufacturer model	Wasatch Photonics WP 785
Spectral range	270 … 2000 cm^{-1}
Resolution	7 cm^{-1}
Detector TEC set point	10 ± 0,2 °C
Integration time	3 ms … 60 s
Laser	785 nm, multimode
Laser power	up to 450 mW, adjustable by the software
Working distance	50 mm (variable)
Dimension & weight	width 16.5 cm, depth 16.2 cm, height 8.2 cm, weight 2.2 kg
Environmental conditions	0 °C to 40 °C, non condensing
Software	Synchronization of the SPS with the Raman spectrometer User defined event triggered recording of Raman spectra (e. g. equilibrium condition, time interval) Display of Raman spectra within the SPS Software
Compatibility	SPS11-10 µ, SPSx-1µ-High-Load, SPSx-1µ-Advance

4. Experiments

The following examples show the water vapor sorption behavior of some materials. In addition to gravimetric water vapor sorption, Raman spectra of the samples were recorded over the course of the measurement. By combining both measurement techniques, it was possible to assign the water vapor sorption curves to characteristic changes in the Raman spectra and thus gain deeper insights into the moisture-induced structural changes of the materials.

4.1 Amorphous-Crystalline-Transition

The crystallization of amorphous materials releases water, which leads to undesired product changes. These include caking and reduced flowability, as well as reduced microbial and chemical stability. In addition, the appearance of the product may be altered, resulting in color changes and loss of transparency. The amorphous state is caused by rapid solidification of a product, e.g. during spray drying, and therefore resembles a solidified liquid. In contrast to the crystalline state, such materials have no spatial order and no long-range translational symmetry. Therefore, Raman analysis can be used to distinguish between these two states of a substance. [9]

Fig. 3 shows the crystallization of amorphous α-Lactose. Both the sorption isotherm and the Raman spectra clearly show the onset of crystallization when a relative humidity of 40 % is exceeded. [10]

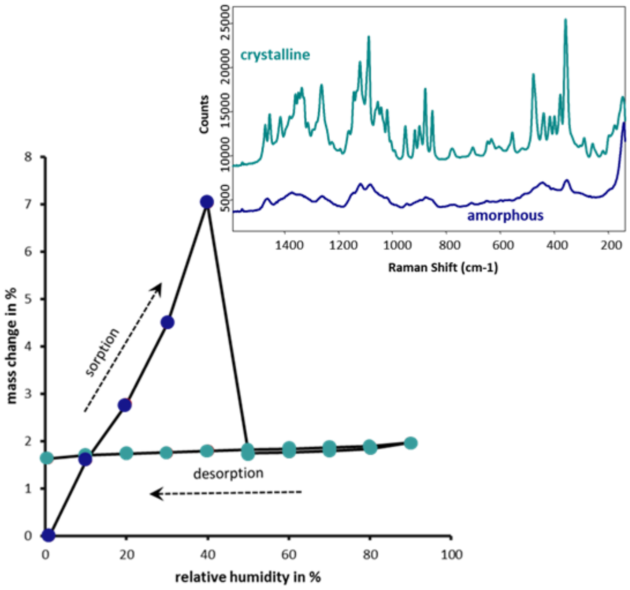

Fig. 3: Crystallization of amorphous α-Lactose

Fig. 4 shows the sorption of moisture and the corresponding Raman spectra of a hard candy. The sorption isotherm shows a first increase in moisture at a relative humidity of 34 % RH and a second increase at 50 % RH. Looking more closely at the Raman profiles at these characteristic points, a first change in the spectrum was observed at 34 % relative humidity. With a further increase in relative humidity, these changes progressed continuously. These material changes can be attributed to the crystallization of sucrose. The absence of a crystallization peak can be explained by the addition of stabilizers such as glucose-fructose syrup to the formulation. The results show that a combined DVS and Raman analysis is suitable for investigating observations from the sorption analysis in more detail and thus providing valuable insights into the moisture-dependent behavior of a product.

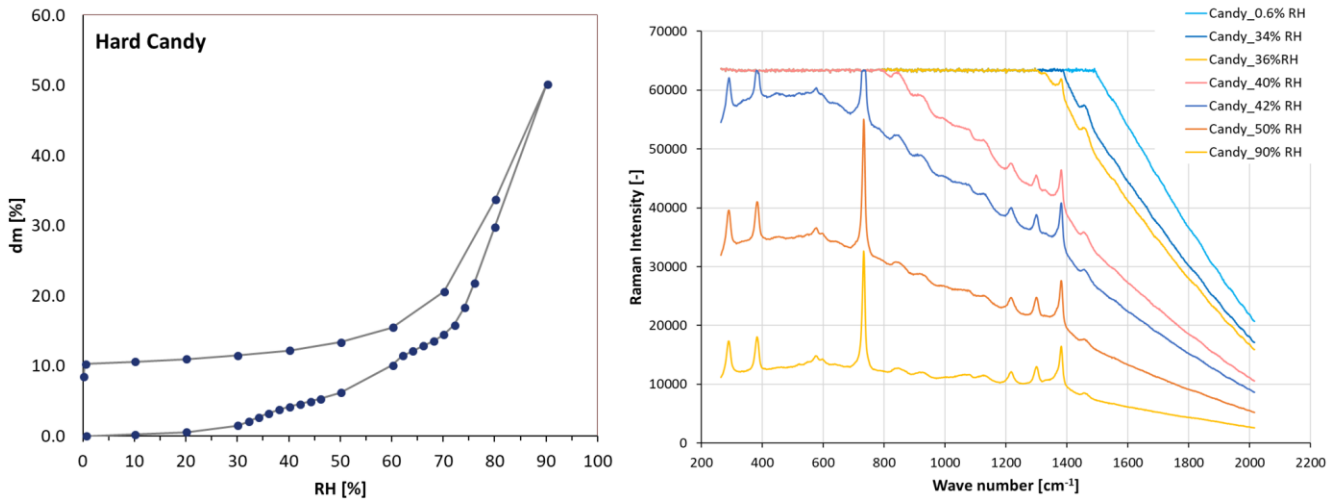

Fig. 4: Moisture sorption isotherm and effect on moisture adsorption on the molecular structure of hard candy.

4.2 Hydrate formation

Properties as the dissolution rate, the compressibility, the bioavailability and the hygroscopicity are strongly influenced by the respective hydrate state of a material [2].

Transition from the anhydrous to the hydrate state involves the incorporation in the crystal-lattice of a substance. This is either done in a specific stoichiometric ratio or non-specifically in case of non-stoichiometric hydrates. The binding of water molecules occurs through electrostatic dipole-dipole interactions, hydrogen bonds, or complex formation, which results in a change in the molecular structure [2]. This change in structure leads to a shift in the Raman signal, which can be used to analyze moisture-dependent hydrate formation.

With regards to water vapor sorption studies, the formation of stoichiometric hydrates can easily be observed by the step-like increasing sample weight with exceeding a material specific relative humidity.

The combination of DVS with Raman analysis is therefore an optimal way to gain deeper insights into the moisture-dependent material behavior

Fig. 5 shows the transition from anhydrous to hydrates state of L-Lysin HCL, creatine and citric acid. The corresponding Raman spectra are shown in Fig. 6 A-C.

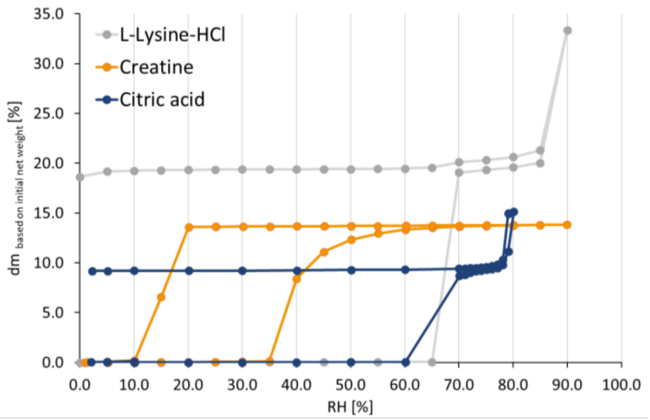

Fig. 5: Sorption isotherm of l-lysin HCL, creatine and citric acid showing hydrate formation

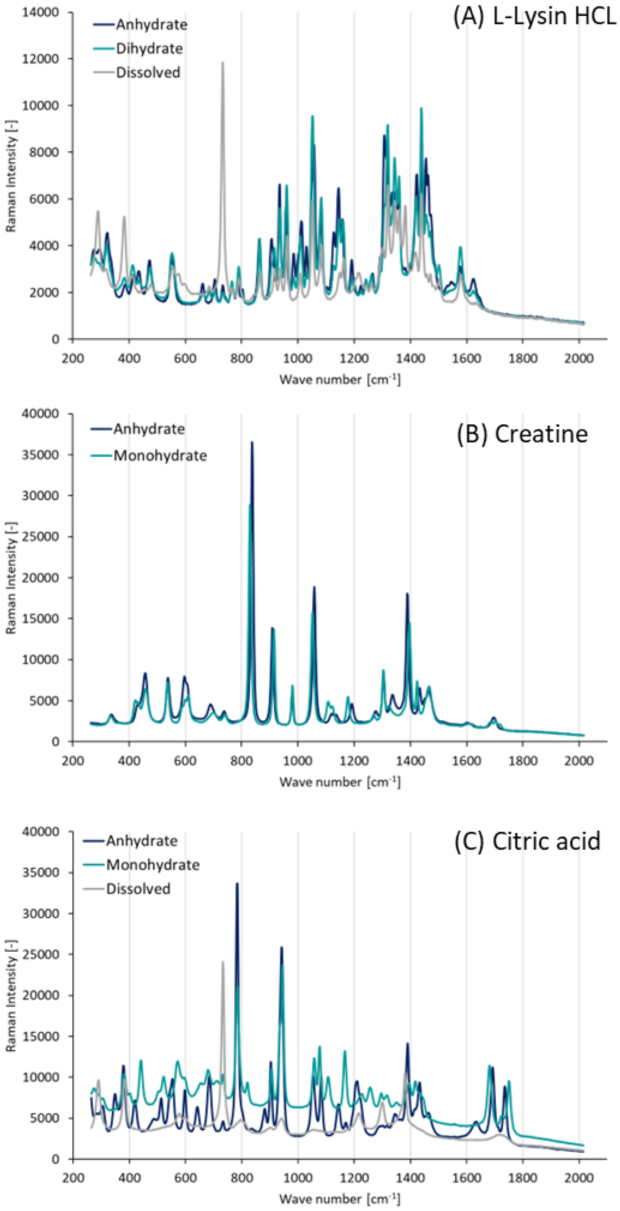

Fig. 6: Raman spectra from L-Lysin HCL (A), Creatine (B) and Citric acid (C), before and after anhydrate-hydrate transition point

Based on the sorption isotherms anhydrate-hydrate transformation could be observed at 65 % RH for l-lysin-HCl, 35 % RH for creatine and 60 % RH for citric acid. In accordance with these transition points, the Raman spectra (Fig. 6 A-C) recorded in-line with the DVS measurements verified the transition from anhydrous to hydrated state of the samples. [11,12]

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In addition, it was found that the hydrates of L-lysine HCl and citric acid began to dissolve when exposed to relative humidity above 85 % RH and 78 % RH, respectively.

This dissolution process was observed both visually and by the sorption isotherms of the samples reflected by a strong increase in weight (Fig. 5).

The associated change in molecular structure due to further water vapor adsorption and subsequent dissolution leads to a further shift in the corresponding Raman spectra as shown in Fig. 6 A and C.

5. Conclusions

Water vapor sorption measurements and Raman spectroscopy are a perfect match. Both methods require only small amounts of sample, are non-destructive, and require minimal sample preparation. Water vapor sorption measurements together with inline Raman spectroscopy is the ideal method for identifying and characterizing characteristic points within the sorption profile and thus gaining deeper insights into moisture-induced phase transitions. Typical applications include the analysis of moisture-dependent material changes such as hydrate formation, crystallization, dissolution, and the identification of polymorphic forms. This is relevant in many industries ranging from food and pharmaceuticals to packaging and construction materials.

References

[1] Eskin, M., & Robinson, D.S. (Eds.). (2000). Food Shelf Life Stability: Chemical, Biochemical, and Microbiological Changes (1st ed.). CRC Press. https://doi.org/10.1201/9781420036657

[2] Khankari, Rajendra K., and David JW Grant. "Pharmaceutical hydrates." *Thermochimica acta* 248 (1995): 61-79.

[3] Martin Philipp Feth, et al. “New technology for the investigation of water vapor sorption–induced crystallographic form transformations of chemical compounds: a water vapor sorption gravimetry–dispersive raman spectroscopy coupling.” *Journal of pharmaceutical sciences* 100, 1080-1092, **2011**). DOI

[4] Godts, Sebastiaan, et al. “Modeled versus Experimental Salt Mixture Behavior under Variable Humidity.” *ACS OMEGA*, vol. 9, no. 18, 2024, pp. 20454–66, doi:10.1021/acsomega.4c01486.

[5] Szymanski, Herman A. *Raman spectroscopy: theory and practice*. Springer Science & Business Media, 2012.

[6] Sheokand, Sneha, Sameer R. Modi, and Arvind K. Bansal. "Dynamic vapor sorption as a tool for characterization and quantification of amorphous content in predominantly crystalline materials." *Journal of pharmaceutical sciences* 103.11 (2014): 3364-3376.

[7] Jurczak, Ewa, et al. "Pharmaceutical hydrates analysis—overview of methods and recent advances." *Pharmaceutics* 12.10 (2020): 959.

[8] Feth MP, Jurascheck J, Spitzenberg M, Dillenz J, Bertele G, Stark H. New technology for the investigation of water vapor sorption-induced crystallographic form transformations of chemical compounds: a water vapor sorption gravimetry- dispersive Raman spectroscopy coupling. J Pharm Sci. 2011 Mar;100(3):1080-92. doi: 10.1002/jps.22317. Epub 2010 Aug 25. PMID: 20740677.

[9] Tuschel, David. "Why are the Raman spectra of crystalline and amorphous solids different?." (2017): 26-33.

[10] proUmid WhitePaper, Dynamic water vapor sorption analysis for the determination of amorphous lactose

[11] proUmid Application note, AN_20-09 Hydrate formation of creatine

[12] proUmid WhitePaper, WP_20-06 Hydrate formation of L-lysine HCl