



Combining Raman Spectroscopy with Gravimetric Vapour Sorption Analysis for Pharmaceutical Materials

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Raman spectroscopy is a widely used physical characterization technique used in the pharmaceutical industry. The combination of Raman spectroscopy and Dynamic Vapour Sorption (DVS) allows for a more complete understanding of vapour-solid interactions for pharmaceutical materials as it relates to structural properties. This paper overviews the DVS-Raman capabilities and gives several examples

Introduction

The interactions of water vapour with solid materials have impact over a wide range of industries and materials. In particular, in the pharmaceutical industry the physical and chemical performance (i.e. flow, compaction, dissolution, stability, storage, and formulation) of drugs, excipients, and packaging materials are dependent on the presence and interaction of/with water [1]. Dynamic gravimetric vapour sorption instruments have now become the standard method for investigating the vapour sorption properties for pharmaceutical materials. The combination of additional techniques with DVS can further enhance the understanding of how vapour interacts with solid materials. For instance, in-situ optical microscopy can confirm structural changes indicated by the gravimetric data [2,3]. Additionally, vibrational spectroscopic techniques, such as Near-IR [4,5] and Raman spectroscopy [6] have also been combined with gravimetric sorption methods. This paper describes the first 'turn-key' solution for the combination of Raman spectroscopy with gravimetric vapour sorption analysis.

Theory

Raman spectroscopy is a technique used to study vibrational, rotational, and other low-frequency modes in a system [7]. Monochromatic radiation can interact with a material by reflecting, absorbing, or scattering the light. Raman spectroscopy is the measurement and detection of the wavelength and intensity of inelastically scattered light from molecules, i.e. the Raman effect. When electromagnetic radiation passes through matter, most of the radiation continues in its original direction but a small fraction is scattered in other directions, such as: Rayleigh scattering (light that is scattered at the same wavelength as the incoming light) or Raman scattering (light that is scattered at a different wavelength due to vibrations in molecules or optical phonons in solids). Raman spectroscopy can be used to study the crystal lattice and intermolecular vibrations and has proved to be a useful tool to investigate structural properties.

Raman spectroscopy is ideal for use in the DVS for several reasons. First, sampling techniques are relatively straightforward since the only requirement is that the laser irradiates the material and the scattered radiation can be focused on a detector [8]. Also, sample prep is minimal and Raman spectroscopy requires small samples



(typically a few milligrams). Glass and stainless steel are common holders for Raman samples, making DVS pans ideal for Raman spectroscopy. In particular, glass is a very weak Raman scatterer. In particular to DVS experiments, Raman is an ideal spectroscopic choice of technique due to the low Raman activity of water vibrations [9].

Method

A picture of the DVS system with integrated Raman probe is shown in Figure 1a, 1b and 1c. The close up picture in Figure 1a and 1b illustrates how the Raman probe interfaces with the DVS chamber. The laser used has a wavelength of 785nm. The details of the Raman system (detector and spectrometer) are listed in Table 1. The temperature range of the simultaneous DVS-Raman system is 5 °C to 50 °C. The Raman probe is 130mm in length. The above specifications are for the DVS-Raman measurements done in this study. However, it is possible to interface virtually any Raman system, provided the Raman probe is of compatible size with the DVS system.



Figure 1(b.)

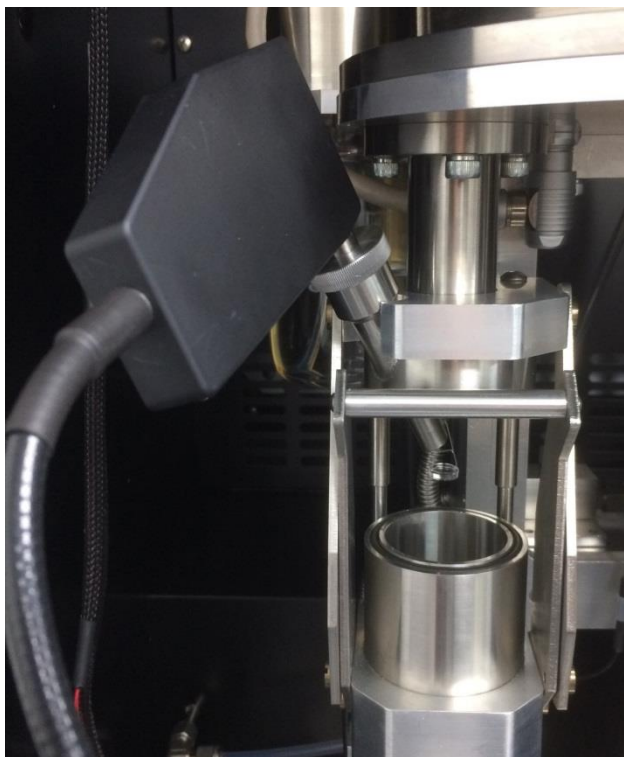


Figure 1(a.)



Figure 1(c.)

Table 1. Raman detector and spectrometer specifications

Laser		
532nm Excitation	< 50mW	
785nm Excitation	< 300mW	
830nm Excitation	< 300mW	
Laser Power Control	532nm [†] , 785nm, 830nm	
Spectrometer	Range	Resolution*
i-Raman-532S	175cm ⁻¹ - 4000cm ⁻¹	~ 4.0cm ⁻¹ @ 614nm
i-Raman-532H	175cm ⁻¹ - 3300cm ⁻¹	~ 3.0cm ⁻¹ @ 614nm
i-Raman-785S	175cm ⁻¹ - 3200cm ⁻¹	~ 4.5cm ⁻¹ @ 912nm
i-Raman-785H	175cm ⁻¹ - 2700cm ⁻¹	~ 3.5cm ⁻¹ @ 912nm
i-Raman-830	200cm ⁻¹ - 2300cm ⁻¹	~ 4.0cm ⁻¹ @ 912nm
Detector		
Detector Type	Back-thinned CCD Array	
Pixel Number	2048 Effective Detector Elements	
Effective Pixel Size	14µm x ~ 0.9 mm	
CCD Cooling Temperature	-2 °C	
Dynamic Range	50,000:1 (Typical)	
Digitization Resolution	16-bit or 65,535:1	
Integration Time	6ms - 30 mins	
Electronics		
Computer Interface	USB 3.0 / 2.0 / 1.1	
Trigger Mode	5V TTL	
Power Options		
DC (Standard)	5V DC @ 5.5 Amps	
AC (Optional)	100 - 240V AC, 50 - 60Hz	
Battery	Optional w/ DC only	
Physical		
Dimensions	6.7x13.4x9.2inc (17x34x23.4cm)	
Weight	~6.6lbs (~3kg)	
Operating Temperature	0 °C - 35 °C	
Storage Temperature	-10 °C - 60 °C	
Humidity	10% - 85%	

Results

Polymorphic Forms

Raman spectroscopy can probe the lattice vibrations that are associated with the solid, crystalline state. The lattice vibrations for different polymorphs will result in unique, characteristic spectra for each polymorph [8,10]. Therefore, Raman spectroscopy has long been used in the pharmaceutical industry to identify different polymorphic forms. In addition, Raman

spectroscopy has been used to quantitatively determine different polymorphic mixtures of cortisone acetate [11].

Hydrates

Raman spectroscopy can be especially sensitive to spectra shifts due to changes in hydrogen bonding. Therefore, Raman spectroscopy is an ideal complement with DVS data to confirm hydration/dehydration phenomena. To illustrate, the Raman results for anhydrate and monohydrate forms of baclofen produced unique spectra for each species [12]. Additionally, Raman spectra confirmed the transformation of sulfaguanidine anhydrate to the monohydrate species as the humidity was increased from 60% RH to 75% RH (at 25 °C) [6]. Differences in Raman spectra between hydrate and anhydrate forms has even been detectable in the presence of excipients [13].

Figure 2 displays the DVS moisture sorption/desorption isotherms for anhydrous theophylline (Figure 2a) and corresponding Raman spectra (Figure 2b) taken at the end of each humidity step. Theophylline remains anhydrous until the 70% RH sorption step. The sharp mass increase is indicative of hydrate formation [14]. On the desorption side, the sample remains hydrated until the humidity decreases below 30% RH. As Figure 2b indicates, the spectra for the anhydrous material (0% RH adsorption, 50% RH adsorption, and 0% RH desorption steps) are clearly different than the spectra for the hydrated species (90% RH adsorption and 80% desorption steps). Similar differences in Raman spectra were observed previously for anhydrous and hydrated materials [6,12].

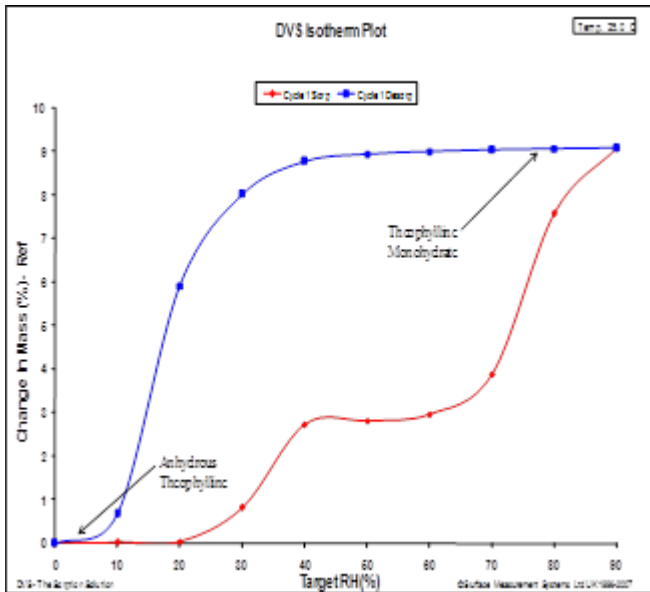


Figure 2(a.)

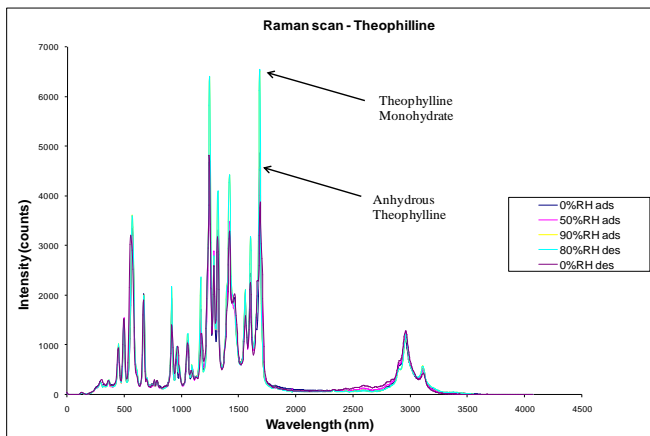


Figure 2(b.)

Figure 2. DVS water sorption/desorption isotherm (a.) and in-situ Raman spectra (b.) for theophylline at 25 °C.

Amorphous Materials

Raman spectroscopy has also been used to differentiate between the amorphous and crystalline phases of the same material. This usually manifests in a broadening of the spectra by the amorphous material compared to the crystalline phase [10]. In fact, Raman spectroscopy has been used to quantify varying amorphous contents [15]. However, careful consideration must be used towards obtaining representative Raman spectra for mixtures.

Figure 3 shows the water sorption/desorption profile (a,) and corresponding Raman spectra (b.) for amorphous lactose at 25 °C. The DVS sorption profile clearly shows the humidity-induced crystallization for amorphous lactose at the 60% RH step. This is a well-known and well-characterized phenomenon for amorphous lactose [16]. In essence, the amorphous material has a greater water vapor sorption capacity than the crystalline material, due to increased void space, free energy, and/or surface area. When the material undergoes an amorphous to crystalline transition, the water sorption capacity decreases drastically, resulting in a net mass loss as excess water is desorbed during crystallization. The corresponding Raman results in Figure 3b, shows a dramatic change in the spectra before crystallization versus after crystallization. The crystalline spectra are much lower in intensity and the features are more clearly defined than the amorphous spectra. This is typical for Raman spectra on the amorphous phase.

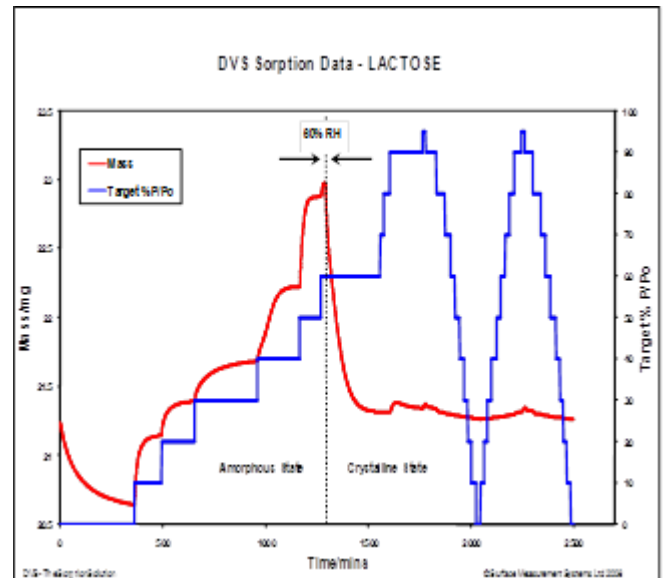


Figure 3(a.)

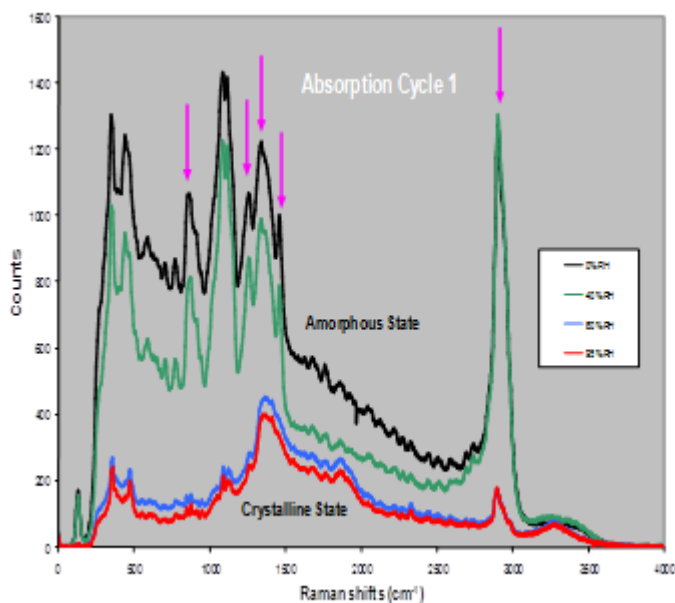


Figure 3(b.)

Figure 3. DVS water sorption/desorption results (a.) and in-situ Raman spectra (b.) for amorphous lactose at 25 °C.

Other

Raman spectroscopy can also be sensitive to changes in hydrogen bonding and other subtle reorientation of the solid material. For instance, Raman spectroscopy has been previously used to determine the changes in strength of hydrogen bonding between water and different pharmaceutical polymers [17]. In the same study, changes in Raman spectra due to water plasticizing the polymers have been observed. Figure 4 displays the water sorption/desorption (a.) and Raman spectra (b.) for microcrystalline cellulose (MCC) at 25 °C. MCC is not expected to form a hydrated species or undergo and polymorphic transformation when exposed to increasing humidity. However, there are clear differences in the Raman spectra as the humidity is increased. MCC does experience a significant amount of bulk water absorption as humidity is increased. Therefore, the changes observed in Figure 4b could be due to increased hydrogen bonding, decrease in void spaces, or other structural rearrangements. Raman spectroscopy has also been previously used to identify sample deliquescence as a sample of ranitidine HCl is

exposed to a relative humidity above the critical deliquescence point [6].

The combination of Raman spectroscopy and gravimetric vapor sorption analysis has applications ranging beyond the pharmaceutical industry. For instance, water sorption and Raman studies have been performed on different proton conducting membranes for fuel cell applications [18,19]. Combined water sorption and Raman studies on the hydration of Nafion® membranes confirm that the polymers retain the helical zigzag conformation of the polytetrafluoroethylene [18]. Additionally, Raman spectra were able to differentiate water sorption properties between porous and non-porous proton conducting polymers [19]. Water sorption and Raman spectroscopy studies have also been performed on different polymers, including Nylon 6 [20], Kevlar-49 [21], and poly(vinyl alcohol) [22]. Further, the mechanisms of moisture sorption on different barrier polymers for food packaging applications has been previously investigated [23]. Researchers found that water associates with the packaging materials greatly affects the oxygen barrier properties of the different polymers. Other materials for which Raman spectroscopy has been used to study vapor sorption include silica gels [24], silver [25], carbon nanotubes [26], and starch [6]. In all, the combination of Raman spectroscopy with gravimetric vapor sorption instrumentation has far reaching applications over a range of industries.

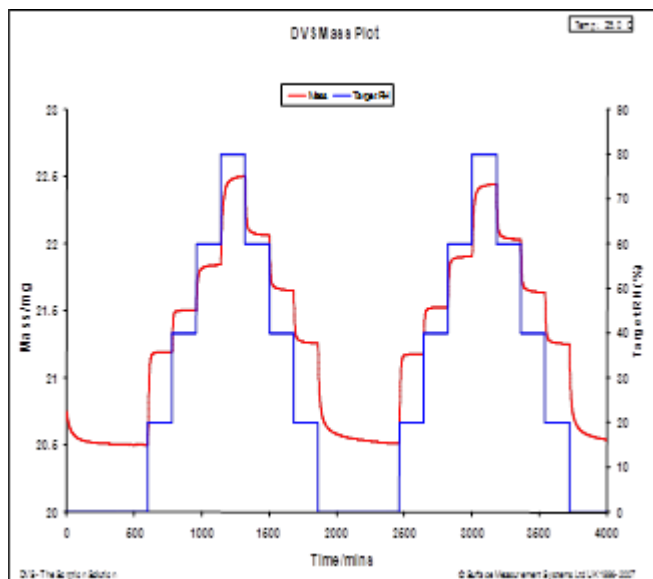


Figure 4(a.)

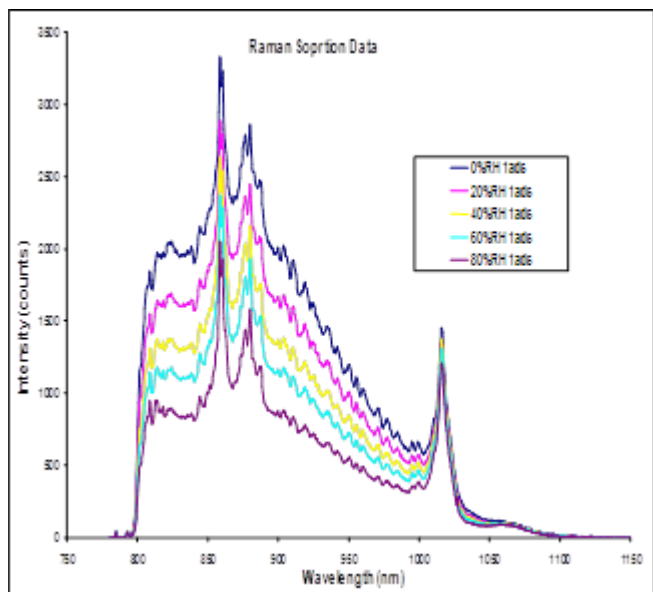


Figure 4(b.)

Figure 4. DVS water sorption/desorption results (a.) and in-situ Raman spectra (b.) for MCC at 25 °C.



Conclusion

The combination of gravimetric vapour sorption and in-situ Raman spectroscopy can be a powerful tool in determining how water interacts with various materials. Raman spectroscopy is an ideal complementary technique to DVS due to its relatively low sample preparation and small sample size requirements and weak interactions with water molecules. These combined techniques can investigate a range of pharmaceutical applications: hydration/dehydration, polymorph identification/transformation, amorphous to crystalline transformation, hydrogen-bonding, and deliquescence. In addition, when used in tandem, these techniques have various applications for different materials and industries.

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