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DVS Application Note 109

Studying Moisture Induced Transformations and Degradation of Pharmaceutical Ingredients Using Raman Spectroscopy Combined with Dynamic Vapor Sorption

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This study investigates the chemical degradation and dehydration behaviours of pharmaceutical compounds, acetylsalicylic acid (ASA) and citric acid monohydrate, used in drug formulation, stability, and drug delivery systems. The combination of DVS and Raman spectroscopy reveals changes during ASA degradation, influenced by humidity and temperature. Analysing the process of dehydration of citric acid monohydrate is important when understanding drug release mechanisms. This has been shown to be affected by temperature and humidity, with higher humidity necessitating elevated temperatures to produce its anhydrous form. Understanding the changes and kinetics involved in these processes can influence decisions in pharmaceutical design, enhancing drug efficacy and shelf-life.

Introduction

During pharmaceutical development, ensuring the stability and efficacy of drug formulations is of paramount importance. For many materials, chemical and physical transitions can be influenced by the amount of water vapour surrounding the sample. Water vapor can associate with a solid in various ways: adsorption or chemisorption onto the surface, absorbing into the bulk, acting as a plasticizing agent, or chemically reacting with the solid. Measuring temperature dependent stability is important as it impacts physical, chemical, and biological efficacy. Understanding the complex interplay between moisture and temperature in pharmaceutical compounds is essential for mitigating risks caused by transformations and degradation, potentially rendering the pharmaceutical ingredient inactive [1]. Water vapor's multifaceted interactions with pharmaceutical ingredients underscore the need for analytical techniques capable of measuring these processes.

This study uses a combination of water sorption measured using the Dynamic Vapour Sorption technique (DVS) and Raman spectroscopy to detect, monitor, and measure humidity and temperature induced changes in pharmaceutical ingredients. This approach enables researchers to explain chemical changes occurring in drug formulations in response to varying moisture levels. This interdisciplinary approach not only enhances our understanding of the fundamental mechanisms underlying changes, but also facilitates the development of robust strategies for formulation design, storage, and packaging.

Method

Acetylsalicylic acid (ASA) and Citric acid monohydrate (Sigma Aldrich) were used as model pharmaceutical ingredients. A combination of a fibre optic Raman probe (iRaman Plus, B&W Tek) with Dynamic gravimetric Vapor Sorption (DVS,

Surface Measurement Systems) was used to monitor real time degradation and transformations of materials. Raman activity measurements were performed using a TE-cooled back-thinned CCD and a CleanLaze® laser excited at 784.96 nm with a 415-mW max power output, covering the spectral range from 65-3350 cm^{-1}. A long shaft lab grade Raman probe was positioned above the sample surface, at a working distance of ~7 mm such that the laser is focused as a larger spot size over the area of sample. A quartz pan was used to hold the suspended sample for reduced Raman interference. The data was processed using a dark subtract, Relative Intensity Corrected using a SRM2241 ratio file for waveform correction, followed by a Boxcar smoothing window of 2.

Acetylsalicylic acid was exposed to 90% relative humidity (RH) at 25 °C followed by an increase in temperature to 50 °C. Full Raman spectra were acquired at fixed time intervals over a duration of 60 hours, with the sample subsequently undergoing a 24-hour drying period. Citric acid monohydrate was placed in an isobar environment and the temperature was incrementally raised in 5°C steps every 720 minutes from 10°C to 50°C to determine the point of decomposition and transition to its anhydrous citric acid form. This process was repeated at varying relative humidity levels (0%, 20%, 40%, 60%, and 80%) using the DVS. Raman scans were conducted at regular intervals of 360 minutes throughout the experiment.

Result

Chemical Degradation Study

The degradation of ASA at high levels of humidity is primarily due to hydrolysis caused by the presence of water leading to the decomposition into salicylic acid and acetic acid. Moisture content is a major factor in the degradation of nearly 50% of medicinal products, impacting the stability of drugs [2]. Approaches like co-crystallization have shown to increase the stability of moisture-sensitive APIs by reducing hygroscopicity [2]. The use of moisture resistant packaging such as blister packs can also reduce exposure to moisture. Other effective methods involve modifying formulations and incorporating excipients that are more hydrophilic and compete with ASA for the interaction with water molecules [3].

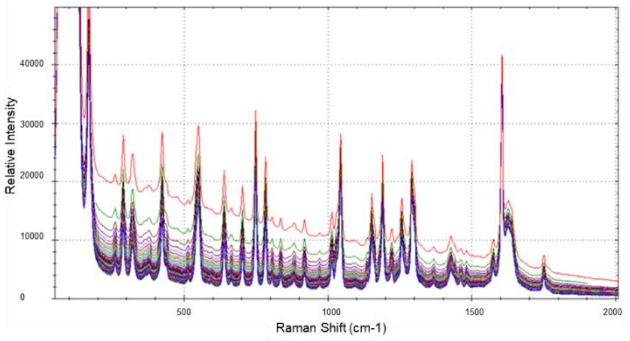

Figure 1. Acetylsalicylic acid Raman spectra at 25 °C with exposure to 90% relative humidity.

Figure 1 displays the full Raman spectra for ASA at 25 °C at 90% RH which shows a decrease in fluorescence over time, with each spectrum having a decreased baseline compared to the spectra before it. This baseline change is likely due to a decrease in static electricity on the sample and sample pan as the experiment was conducted under high humidity. The sample was then heated to 50 °C where only subtle changes were observed shown in Figure 2. The Raman spectra in the 1550 cm^{-1} to 1750 cm^{-1} range indicates a spectral shift at ~1630 cm^{-1} when the sample was heated. The peak shifts from about 1627 cm^{-1} to 1629 cm^{-1} and a peak resolve at 1634 cm^{-1}. Figure 3 compares the sample at 25 °C and 0% RH with the experiment at 50 °C and 90% RH with spectra's taken at the beginning and end of the experiment. This comparison shows that the shift is not simply due to interactions with water because negligible water sorption was observed under these conditions, and this spectral shift remained after humidity was removed and the sample was dried out for 24 hours.

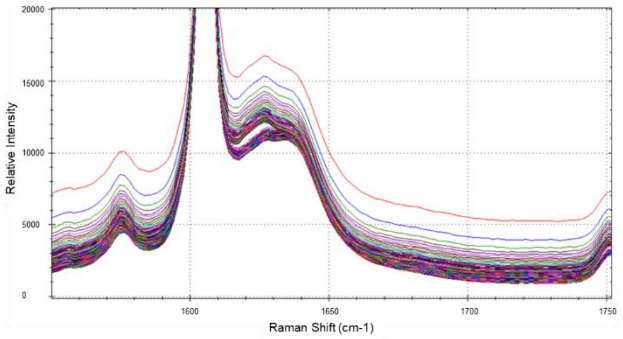

Figure 2. Acetylsalicylic acid Raman spectra at 50 °C with exposure to 90% relative humidity.

Due to the samples hygroscopicity the mechanism of degradation of ASA is dominated by the hydrolysis reaction therefore an increase of temperature alone would not result in its breakdown. At 90% RH the hydrolysis has already taken place and increasing the temperature of the reaction would not affect the extent of hydrolysis but could affect the kinetics of the reaction and increase the rate at which the reaction occurs. This explains why there are only small changes observed when heating the sample to 50 °C.

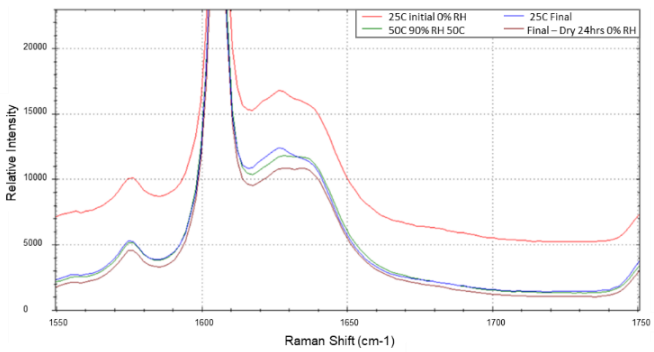

Figure 3. Comparison of ASA showing the initial spectra at the 25 °C experiment (red), the final spectra of the 25 °C experiment (blue) and the initial spectra at 50 °C experiment (green), and the final spectra after drying out the sample at 0% RH for 24 hours.

Dehydration Study

This next study explores the dehydration behaviour of citric acid monohydrate. Citric acid and its hydrates are commonly used as excipients in pharmaceuticals for various purposes, including as a pH adjuster, preservative, antioxidant, and flavouring agents [4]. The dehydration process results in the formation of anhydrous citric acid which can influence drug release profiles, solubility, and shelf-life of pharmaceuticals. Understanding how citric acid monohydrate dehydrates under specific conditions allows for the precise design of drug delivery systems and alter how readily a drug dissolves and is absorbed by the body. For this study citric acid monohydrate was placed in an isobar environment and the temperature was increased in 5 °C steps. Citric acid monohydrate has a molecular weight of 210.14, and anhydrous citric acid has a molecular weight of 192.12. During this experiment, the sample is expected to dry to about 91.4% total mass, or lose 8.6% mass if there is complete drying.

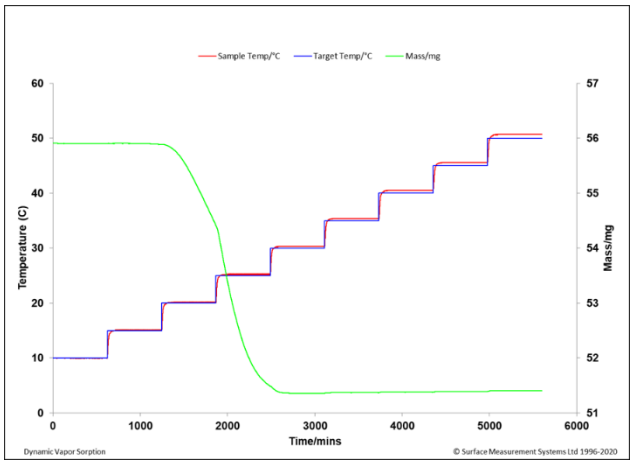

Figure 4. Citric Acid isohume dehydration at 0% relative humidity.

Figure 4 shows that the sample began to dry at 20 °C at 0% RH resulting in a mass loss of 8.2% which is equivalent of one water molecule, consistent with theoretical values. The Raman spectra shown in Figure 5 shows the formation of the anhydrous peak at 1142 cm^{-1} which can be seen above 25 °C. The experiment was repeated at 20%, 40% and 80% RH where dehydration occurred at 25 °C, 30 °C, 40 °C and 45 °C respectively. When citric acid monohydrate is exposed to higher humidity levels, it absorbs water molecules from its surroundings. This hydration process involves the formation of hydrogen bonds between the water molecules and the citric acid molecules. Therefore, the presence of water molecules stabilizes the hydrated form. As a

result, higher temperatures are required to create its anhydrous form.

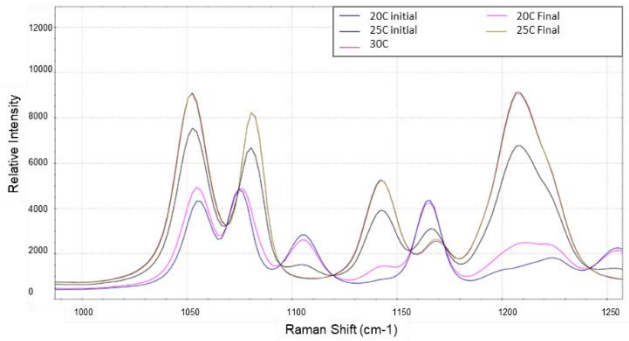

Figure 5. Citric Acid Raman spectra for dehydration at 0% relative humidity.

Conclusion

In situ Raman measurements coupled with DVS water sorption experiments were used to monitor chemical and physical changes of pharmaceutical ingredients. The effects of temperature and relative humidity can be studied directly. This eliminates the need to expose the samples to one set of conditions, then characterize them 'off line' later under different conditions. The ability to study chemical and physical degradation at elevated temperatures and humidity conditions in real time could shorten the time and effort required to study environmental conditions on pharmaceutical ingredient stability.

References

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