



In-situ Monitoring of a Moisture-Induced Polymorphic Transition using Raman Spectroscopy and Gravimetric Vapor Sorption

Introduction

Raman spectroscopy is a widely used physical characterization technique in the pharmaceutical industry. In particular, Raman spectroscopy is used to identify different polymorphic forms. The physical and chemical performance of drugs, excipients, and packaging materials are dependent on the presence of and interaction with water vapor. The combination of Raman spectroscopy and vapor sorption techniques allows for a more comprehensive understanding of vapor-solid interactions for pharmaceutical materials as it relates to the structural properties. In this study, the unique combination of the i-Raman® from B&W Tek with a Dynamic gravimetric Vapor Sorption (DVS) system from Surface Measurement Systems has been used to monitor the real-time transformation of δ D-mannitol (delta form) to β D-mannitol (beta form). This paper investigates the in-situ monitoring of a moisture-induced polymorphic transformation using a combined Raman-vapor sorption technique.

Method

Mannitol is known to exist in at least three polymorphic forms: alpha, beta, and delta. The beta form is considered to be the most stable [1]. Humidity is known to convert the less stable delta form to the beta form [2]. In this study β D-mannitol was recrystallized under specific controlled conditions to obtain pure α form and δ form of D-mannitol.

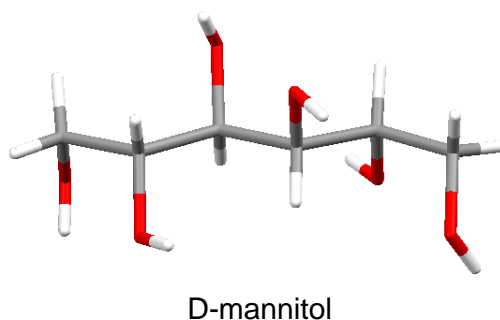
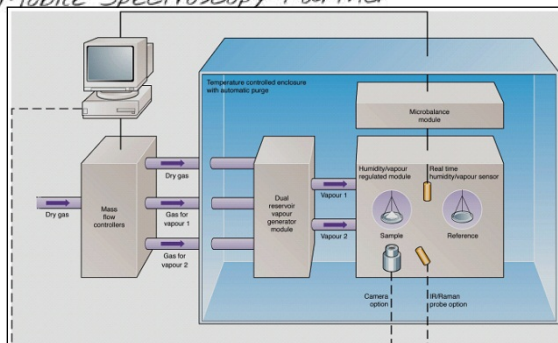


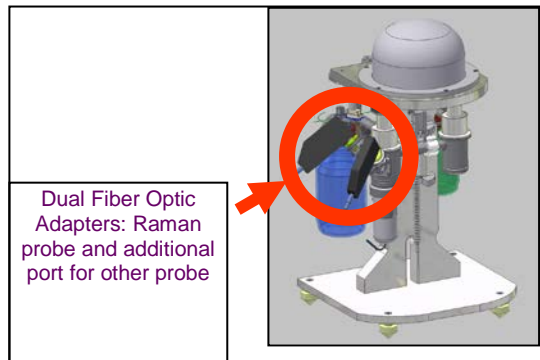
Figure 1. Molecular structure of D-mannitol

Dynamic gravimetric Vapor Sorption (DVS) combined with in-situ Raman Spectroscopy

Figure 2 shows a unique combination of the i-Raman with Dynamic gravimetric Vapor Sorption (DVS), which was used to monitor the real-time transformation of δ D-mannitol to β D-mannitol. Raman-vapor sorption experiments have previously been performed on other systems, but not for monitoring polymorphic transformations.



(a.)



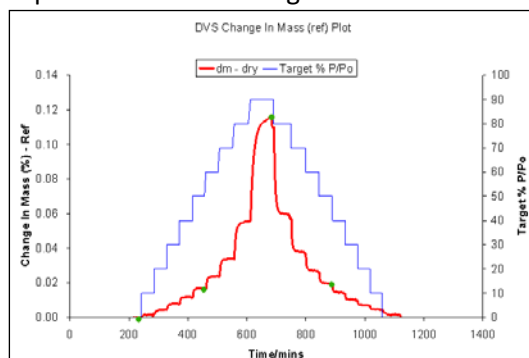
(b.)

Figure 2. Schematic of dynamic vapor sorption (a.) and the DVS stand with Raman adaptor (b.).

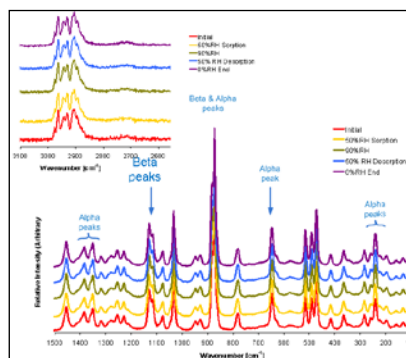
Results

Stable β D-mannitol with Water at 25 °C

As shown in Figure 3, the stable D-mannitol polymorph showed no irreversible change upon moisture sorption. Raman spectra collected during the water vapor sorption and desorption cycle also confirmed that the sample remained unchanged.



(a.)

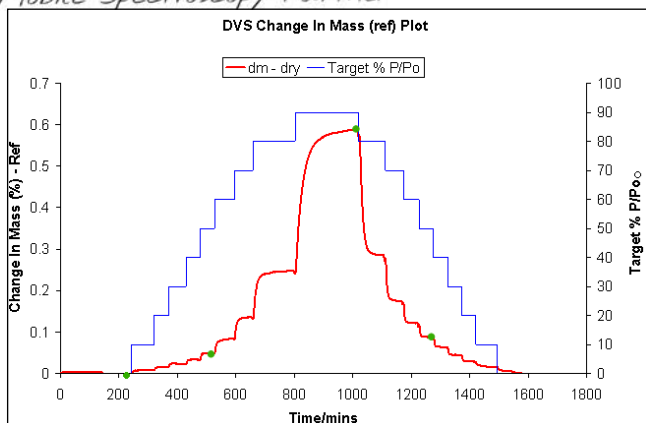


(b.)

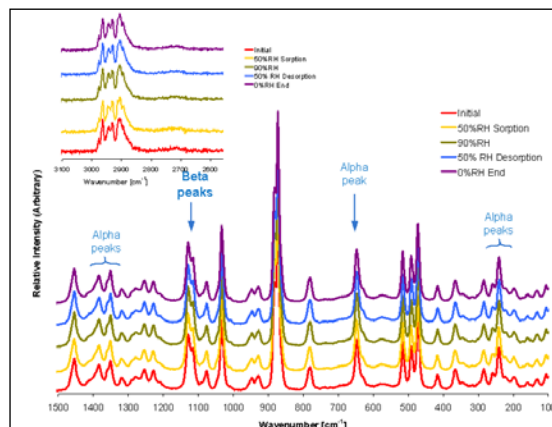
Figure 3. DVS water sorption and desorption cycle (a.) and Raman spectra (b.) for β D-mannitol.

Mixture of α form and β form of D-mannitol showed no irreversible change upon moisture sorption. The Raman spectra collected during the water vapor sorption and desorption cycle also confirmed that the sample remained unchanged (Figure 4).





(a.)

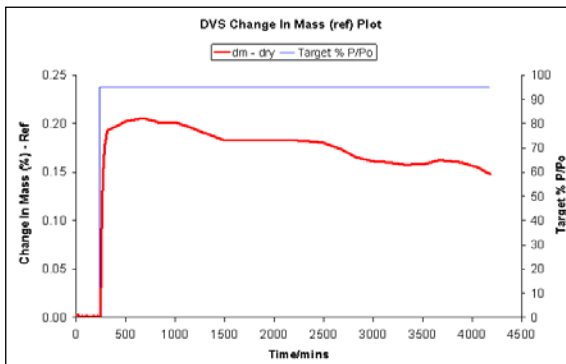


(b.)

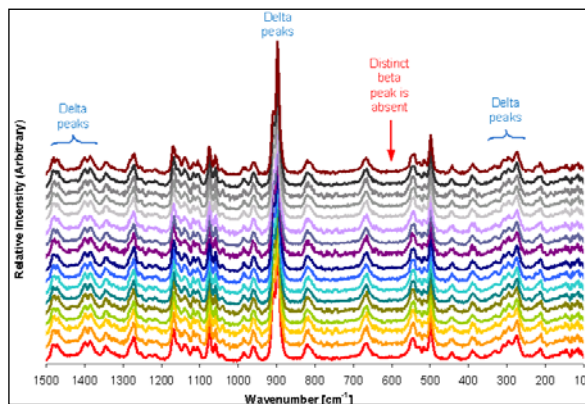
Figure 4. DVS water sorption and desorption cycle (a.) and Raman spectra (b.) for β and α D-mannitol.

Unstable δ D-mannitol with Water at 95% RH at 25 °C

Under 95% RH (Figure 5), the unstable δ D-mannitol polymorph showed very slow change over a 65 hour time period, as shown in the DVS sorption data. This is in contrast to a complete conversion to the β polymorph within one day as reported previously [2]. Raman spectra collected during the period also showed little conversion in the 65 hours.



(a.)



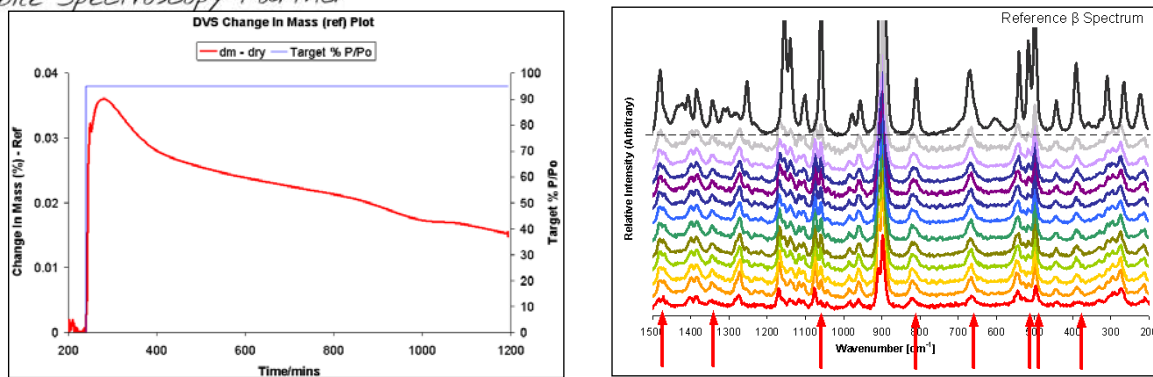
(b.)

Figure 5. DVS water sorption at 95% RH (a.) and Raman spectra (b.) taken at 5-hour intervals for δ D-mannitol.

Unstable δ D-mannitol with Ethanol at 95% P/P0 at 45 °C

Under 95% P/P₀ ethanol at 45°C, the unstable δ D-mannitol polymorph showed faster conversion, as shown in the DVS data and the Raman spectra (Figure 6). Although a complete conversion was not achieved, the intensity of the peaks attributed to the β polymorph increased over 24 hours.





(a.)

(b.)

Figure 6. DVS ethanol at 95% P/P₀ at 45 °C (a.) and Raman spectra (b.) taken at 2-hour intervals for δ D-mannitol.

Conclusions

The combination of gravimetric vapor sorption with Raman spectroscopy allowed for the monitoring of the vapor-induced polymorphic transformation of D-mannitol polymorphs in real-time. The unique combination of these two techniques allows for increased understanding of vapor-induced structural changes of pharmaceutical ingredients.

Acknowledgement:

At B&W Tek we would like to thank Surface Measurements Systems for allowing us to adapt their application note. The original authors would also like to gratefully acknowledge past and present colleagues, especially Dr. Raimundo Ho (Abbott Laboratories, Chicago, USA), for their contributions to this work. For more information please visit www.bwtek.com or call us at 302-368-7824.

References

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