Investigation of Pharmaceutical Stability Using Dynamic Vapor Sorption Analysis

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INTRODUCTION

A variety of analytical techniques including differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) are commonly used to screen prospective pharmaceutical active ingredients, excipients, and drug formulations. Those techniques provide insights into characteristics such as polymorphism, amorphous / crystalline content, and thermal stability. However, they do not indicate a material's response to changes in relative humidity. Dynamic vapor sorption (DVS) analysis is a technique specifically designed to provide such information.

EXPERIMENTAL

In a typical DVS experiment, the relative humidity (%RH) is stepped from a low initial level (either ambient or 0 %RH) to a high level (90-95 %RH), then back down to a low level, and finally increased again to a higher level. The rate at which the material equilibrates at each humidity level, as well as the overall shape of the resulting adsorption / desorption profile, provides useful information about the material's structure and long-term stability.

RESULTS and DISCUSSION

Figure 1 shows the DVS results for prednisone, which is known to exhibit low moisture absoption (<1 %) over a broad humidity range. In addition, its adsorption / desorption profile is reversible (i.e., the adsorption [increasing %RH] and desorption [decreasing %RH] profiles essentially overlap). This behavior indicates that prednisone is highly crystalline and that the moisture "picked-up" at higher humidities is adsorbed onto the surface of the material and does not affect its internal structure. Hence, prednisone should be a stable active ingredient.

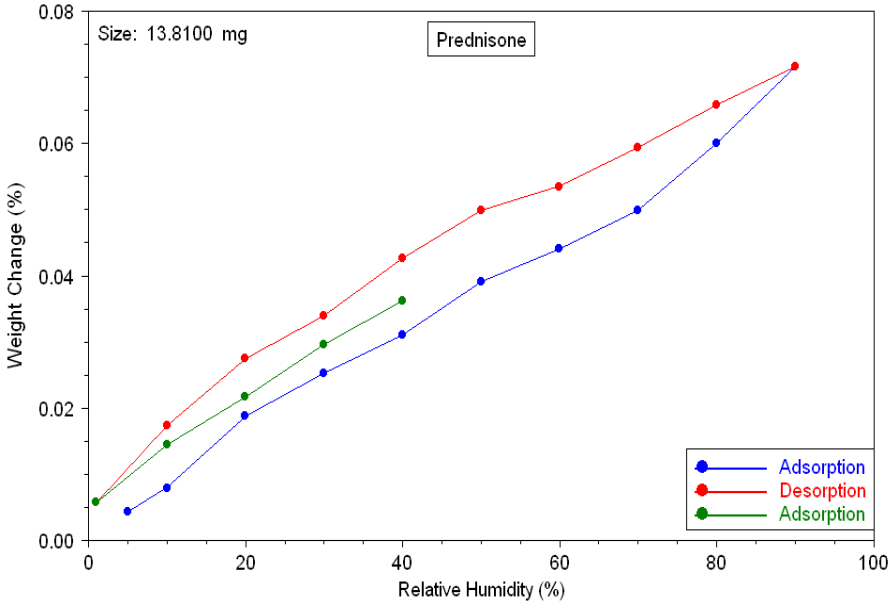

Figure 1. Surface Adsorption Data for Prednisone

Conversely, diphenylhydantoin exhibits significant moisture absorption with increasing humidity and also differences (hysteresis) in its adsorption and desorption profiles (Figure 2). The large moisture gain (~28 %) during the sorption profile, and the sharp weight decrease as humidity is later decreased below 30 %RH, suggests formation of a hydrate. At 5 %RH, the residual weight gain agrees well with that expected for the monohydrate form of the material. Since the hydrated form has a more open structure, its sorption profile shows more rapid uptake of moisture than the original sample. Diphenylhydantoin's DVS behavior does not eliminate it as a potentially useful pharmaceutical, but it indicates that care must be taken during processing and storage.

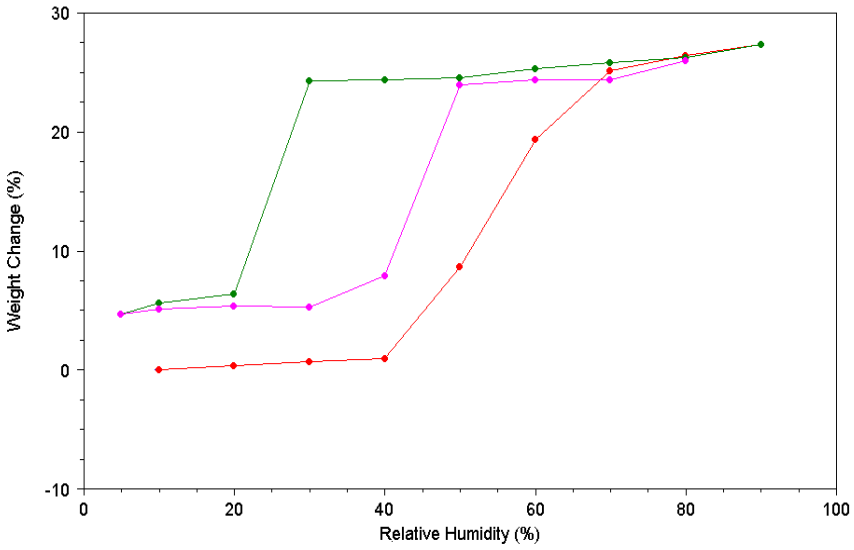

Figure 2. Diphenlhydantoin: Formation of Hydrates

Long-term stability of different formulations of the same active ingredient when exposed to moisture can be assessed by exposing the materials to constant humidity at higher temperature to accelerate the onset of "degradation". Figure 3 compares the behavior of several different salts of the same base compound initially exposed to 50 %RH at 25 °C and then raised to 80 °C while maintaining 50 %RH. All three salts rapidly pick-up about 2 % moisture at 25 °C and 50 %RH. When the temperature is subsequently raised to 80 °C, the phosphate and mesylate salts retain the adsorbed water and the weight remains constant over the next 24 hours. The acetate salt, on the other hand, rapidly gives-up the water adsorbed at 25 °C when the temperature is raised to 80 °C and continues to lose weight with time, indicating that it is the least stable formulation.

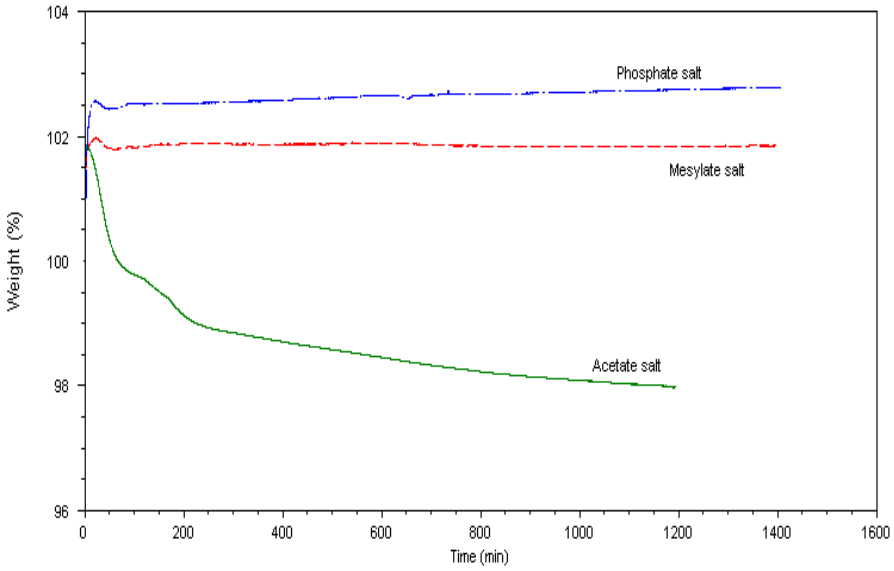

Figure 3. Comparison of Formulations: Stability at 80 °C & 50 %RH

DVS can also be used to evaluate drug stability during processing. In Figure 4, the objective of the experiment is to determine proper drying parameters for a weakly hydrated material. The specific goal is to determine the lowest humidity level, which can be used at a selected drying temperature, without changing the material's structure by removing any of the waters of hydration. These results were obtained by stepping the relative humidity from a high starting level to a lower level (right to left in the figure). The humidity, where a significant weight change (decrease) occurs, indicates loss of waters of hydration. At a 25 °C drying temperature, humidities as low as 10 %RH can be used. At 40 °C and above, the humidity must be at least 15 % to avoid issues. In this material, the impact of sample form (milled versus unmilled) has little effect on the drying properties.

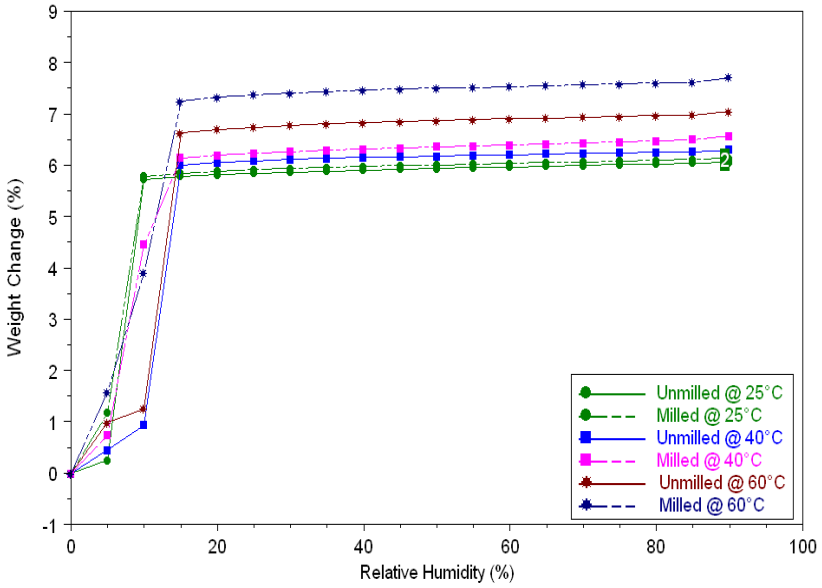

Figure 4. Hydrate Stability on Drying

SUMMARY

Temperature and humidity are important factors in the processing and storage of pharmaceuticals. Dynamic Vapor Sorption provides a versatile and sensitive technique for evaluating the stability of pharmaceutical active ingredients, excipients and formulations under a variety of temperature / humidity combinations.

KEY WORDS

Dynamic vapor sorption, DVS, Pharmaceuticals, Temperature, Humidity

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