Characterization of Polymorphs in Tolbutamide

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ABSTRACT

Crystalline pharmaceutical drugs often exist in polymorphic forms that have the same chemical composition but differ in crystalline structure and physical properties such as solubility, bioavailability and storage stability. Also, the most stable form may not be the one desired for a particular application. For these reasons, plus others associated with the development and manufacture of efficient and effective drug delivery systems, it is important to know if a specific compound can exist in different polymorphic forms. DSC is shown to be a valuable tool to this end.

INTRODUCTION

DSC is the most widely used analytical technique for measuring crystallinity and crystalline polymorphs. However, inexperienced users can misinterpret results if they fail to realize that the sample may be changing as it is heated due to inherent kinetic processes. These include crystallization of amorphous material and conversion of less stable polymorphic forms into more stable versions that melt at higher temperatures.

Tolbutamide is an oral drug used to treat Type 2 diabetes. It is reported to have at least two polymorphic crystalline structures, which are enantiotropic meaning that no one form is the most stable at all temperatures (1). Other results show that there are actually three (3) polymorphs of Tolbutamide, but only one is detected under most test conditions (1). Of the three polymorphs, one pair is monotropic and another pair is enantiotropic based on use of Burger and Ramberger's rules for polymorphic transformation (1):

–Heat of Transition Rule: if an endothermic transition (from one solid form to another) is observed the two forms are enantiotropes

–Heat of Fusion Rule: if the higher melting form has a lower heat of melting, the two forms are enantiotropes

DISCUSSION

Figure 1 shows a comparison of DSC results for a Tolbutamide sample heated at 10 and 200 °C/min respectively. Using significantly different heating rates makes it possible to determine the stability of the material as a function of temperature. If a particular polymorph is not stable, DSC results at lower heating rates will typically show multiple crystallization / melting transitions as seen in Figure 2 for a proprietary anhydrous drug.

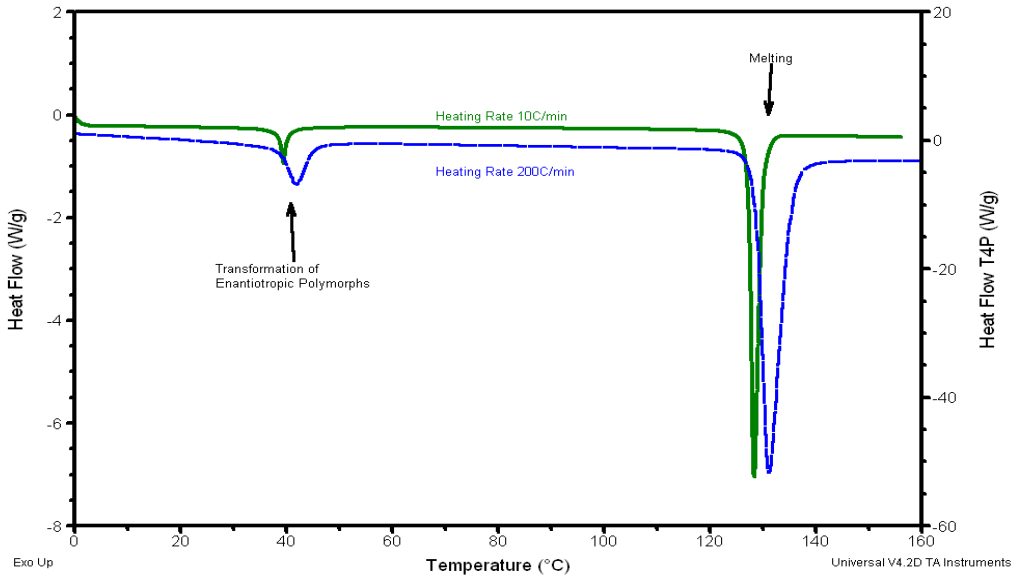

Figure 1. The Measured Structure of Tolbutamide Does Not Change With Heating Rates Between 10 and 200 °C/min.

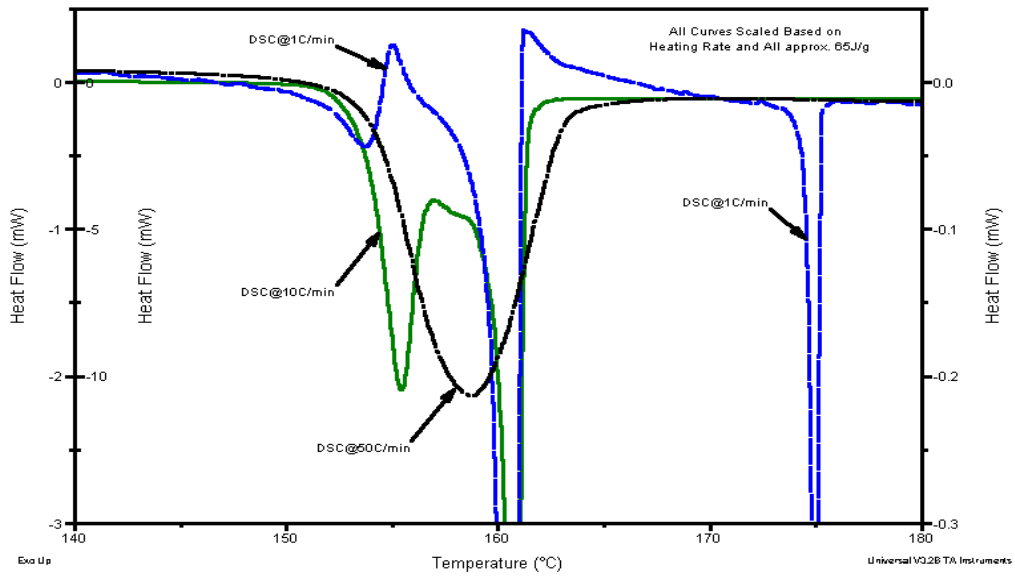

Figure 2. Effect of Heating Rate on Transitions in a Pharmaceutical Drug

Since the Tolbutamide results show no change with heating rate, reliable interpretation of structure or changes in structure can be made. The data in Figure 1 confirm a previous report that Tolbutamide has two enantiotropic crystalline forms. A single melting peak appears at 125 °C with a second endothermic peak near 40 °C for the polymorphic transformation. Based on Berger and Ramberger's heat of transition rule, if an endothermic interconversion occurs then the two forms are enantiotropic. The theoretical basis for this is seen in the relative Gibbs Free Energy plot and Enthalpy plot shown in Figure 3. The crossing of the free energy values of the two forms indicate that the most stable form at a lower temperature becomes the less stable form at a higher temperature. When this occurs, the enthalpy of the system increases, which means that energy, is absorbed (endothermic).

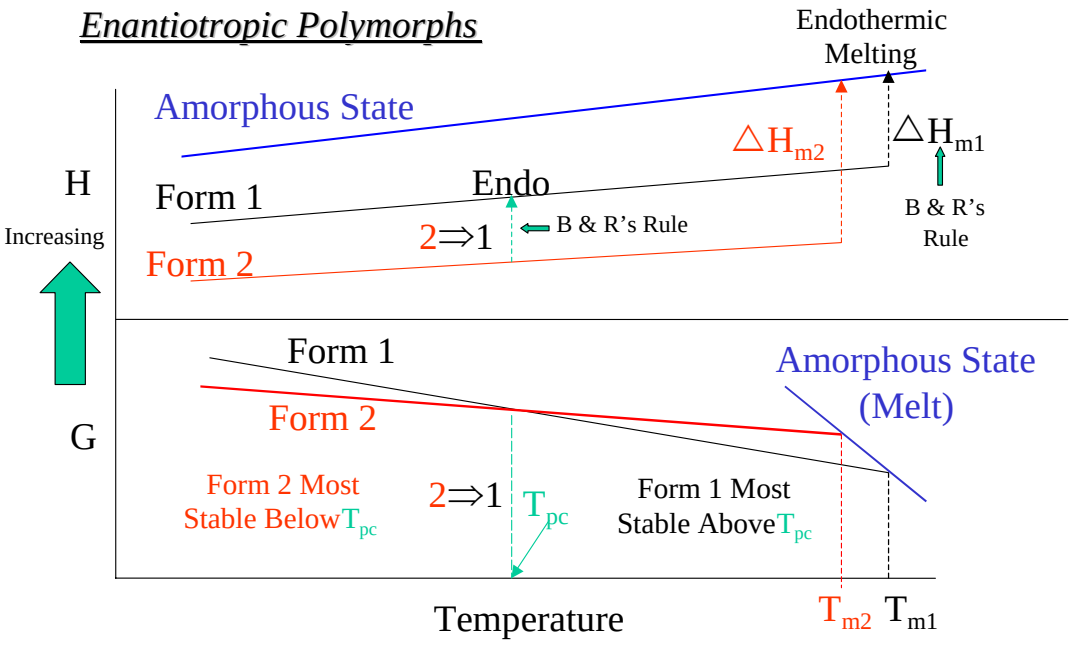

Figure 3. Gibbs Free Energy and Enthlpy Plot

The above results infer that only two polymorphic forms for Tolbutamide exist and they are enantiotropic. However, it is well known that quench-cooling a sample from a temperature above its melting point may create additional forms. This is what occurs in Figure 4, which shows a comparison of results for the original form of the drug, and after quench cooling. The red curve (lowest one) is the result from heating the original drug at

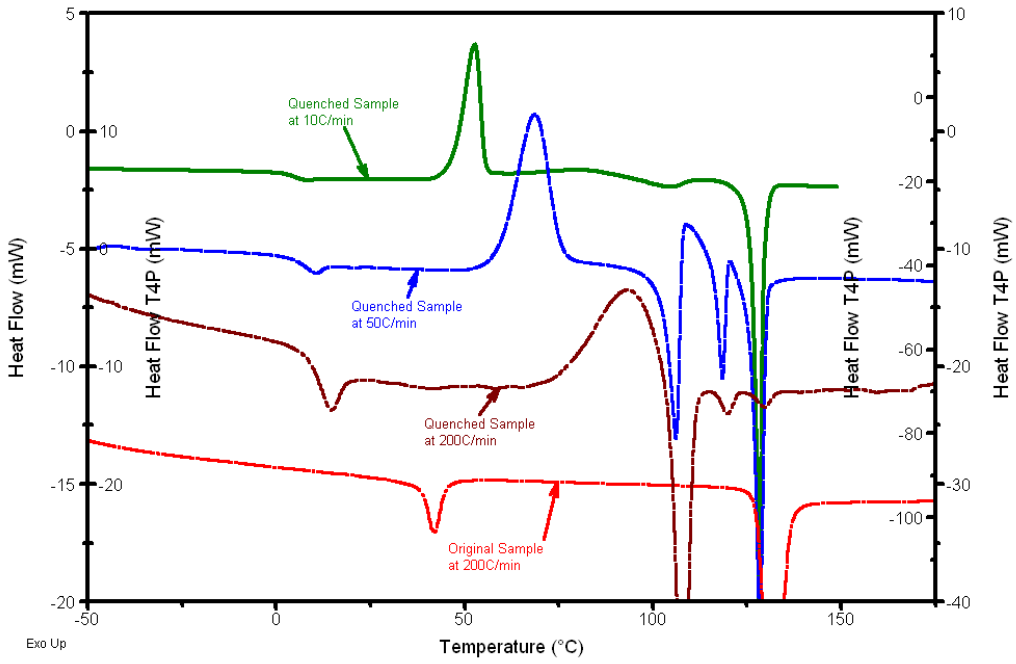

Figure 4. Effect of Quench Cooling and Heating Rate on the Polymorphs of Tolbutamide

200 °C/min. It shows only a single melting point for the form that is stable at higher temperatures. After quench-cooling, a cold crystallization peak is observed just below 100 °C when heated at 200 °C/min, and is followed by three melting peaks (brown curve; second from bottom). The three melting peaks are more clearly seen in the blue curve (second from top), which is the result of heating the quench-cooled sample at 50 °C/min.

SUMMARY

In order to properly characterize polymorphic crystalline structure in many pharmaceutical compounds, it is necessary to vary both thermal history (cooling rate from above the melting point) and heating rate. Use of multiple heating rates can show if the sample is structure is changing as the sample is heated in the DSC.

REFERENCES

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KEY WORDS

Tolbutamide, polymorphs, DSC

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