EXCIPIENT COMPATIBILITY BY DIFFERENTIAL SCANNING CALORIMETRY (DSC)/ MODULATED DSC (MDSC).

B. Hilker, Ph.D.

Figure 1: Case Study: Lactose Anhydrous Compatibility with API by DSC

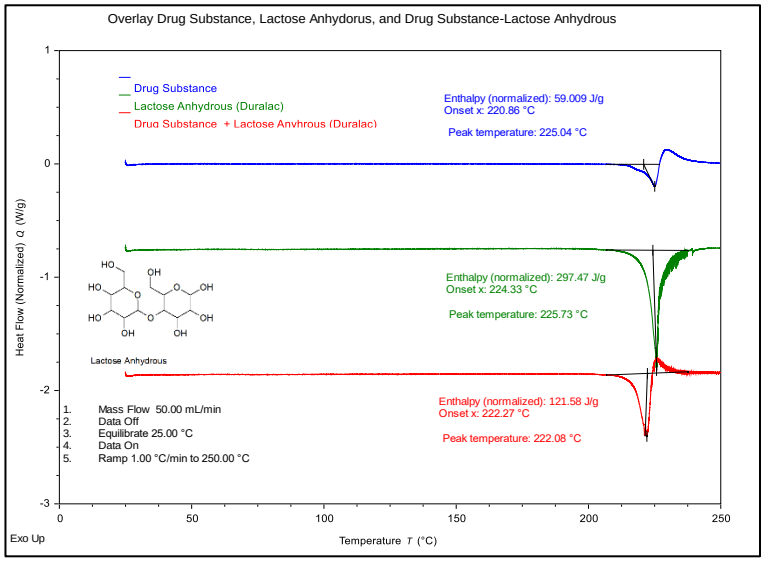


Figure 2: Case Study: Lactose Monohydrate Compatibility with API by MDSC

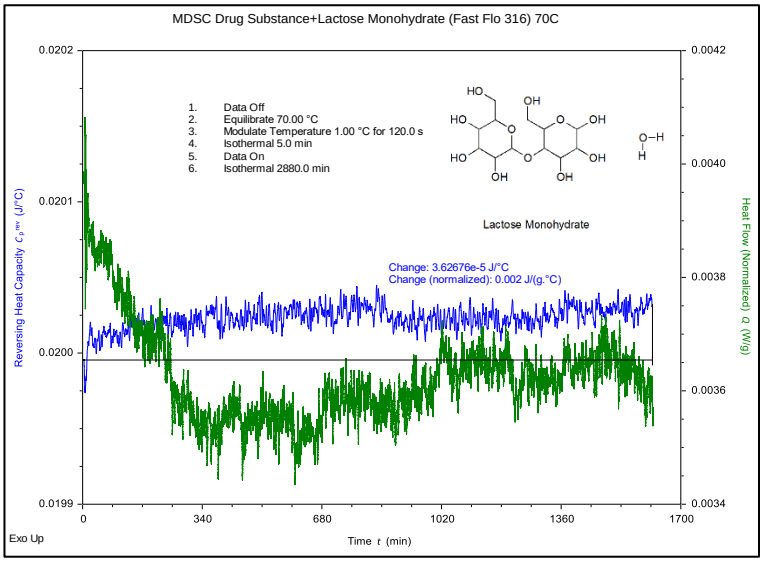
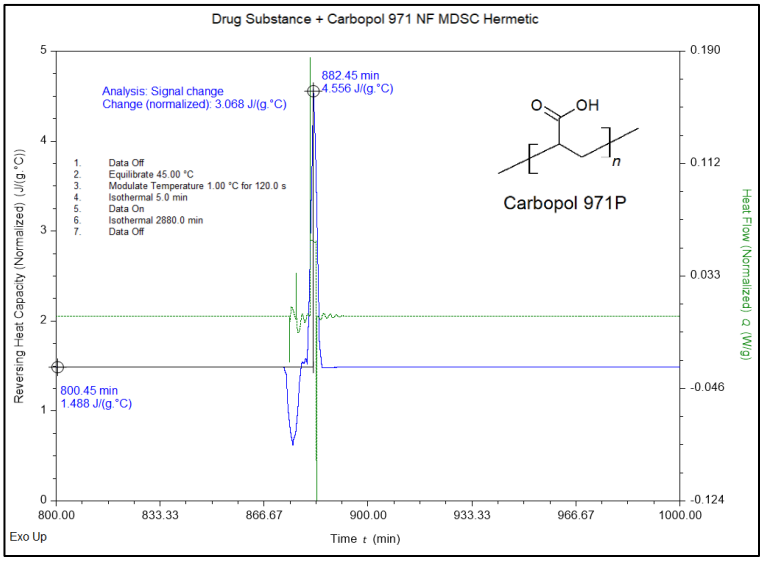


Figure 3: Case Study: Carbopol 971P Compatibility with API by MDSC



INTRODUCTION

DSC/MDSC analysis can detect **both** chemical and physical interactions between drug substances and excipients. The physical interactions between the API and excipients do not involve formation or breakage of chemical bonds in the drug's molecular structure. Physical interactions can lead to changes in the organoleptic properties (changes in perception to organs of sense: macroscopic appearance, odor, taste, feel), as well as chemical change such as polymorphic forms, crystallization behavior (onset melt, enthalpy of fusion), or drug-release and stability profiles. For these reasons excipient compatibility by DSC/MDSC is superior to traditional HPLC methodology, which detects only chemical reactions. And DSC/MDSC **does not require** a stability indication (HPLC) method or extended storage at 40°C/75%RH.

METHODS

Compatibility is determined by using TGA and DSC/MDSC. TGA determines the thermal degradation profile for API and selected excipients. DSC is performed on excipients, API, and binary samples (API: Excipient). Compatibility assessment is based upon changes to the onset (apparent) melting point of the API between neat and binary samples. If the binary mixture fails acceptance criteria, the material is forwarded to MDSC for quasi-isothermal hold experimentation for confirmation. MDSC Quasi-isothermal hold testing allows for the indirect measurement of heat capacity (Cp) though the separation of the total heat flow (∂H/∂T) into components, **Equation 1**. Binary samples are run at selected temperature with modulation for NLT 12 hours while monitoring reversing heat Cp (RevCp).

Equation 1: $$\frac{dH}{dt} = Cp\frac{dT}{dt} + f(T,t)$$

$\frac{dH}{dt}$ = Total Heat Flow
Cp = Sample Heat Capacity
$\frac{dT}{dt}$ = Heating Rate (°C/min)
$f(T,t)$ = Heat flow fn of time and temperature (kinetic)

CASE STUDY RESULTS

Figure 1, DSC compatibility analysis between API and Lactose Anhydrous. Three scans were performed at (1°C/min) API, excipient, and binary. The binary sample results met the acceptance criteria for compatibility with NMT 5°C change in onset of the melting point for the API.

Figure 2, MDSC compatibility analysis between the API and Lactose Monohydrate modulated 1°C for 120s at 70°C for 48 hrs. RevCp also met the acceptance criteria for compatibility with NMT 0.02 (J/°C) change.

Figure 3, MDSC compatibility analysis between the API and Carbopol 971 NF modulated 1°C for 120s at 45°C for 48 hrs. RevCp **failed** the acceptance criteria for compatibility with greater than 0.02 (J/g°C) change observed. A major reaction was observed between the API and excipient having 4.556 (J/g°C) energy released.

CONCLUSION

TESTING BY DSC/MDSC WAS ABLE TO RAPIDLY SCREEN SELECTED COMPONENTS FOR COMPATIBILITY WITH THE API WITHOUT THE NEED FOR EXTENDED (4-8 WEEKS) OF STORAGE AT 40°C/75% RH, OR THE TIME REQUIRED PRIOR DEVELOPMENT OF A STABILITY INDICATING HPLC METHOD. EXCIPIENT COMPATIBILITY SCREENING BY DSC/MDSC HAS DEMONSTRATED THE POTENTIAL TO STREAMLINE EARLY FORMULATION SELECTION DECISIONS AND DECREASE THE TIME FOR EARLY FORMULATION DEVELOPMENT.

PRESENTOR BIOGRAPHY

Brent Hilker is the Manager of Preformulation CoreRx and has a PhD in Polymer Chemistry from the University of South Florida with over 15 years of thermal analysis characterization experience.

Brent.Hilker@corerxpharma.com
727-259-6950