# A New Approach to the Measurement of Drug-Excipient Incompatibility

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## ABSTRACT

Drug delivery systems or formulations typically consist of several ingredients, one of which is the actual drug or active pharmaceutical ingredient (API). Other components (excipients) in the formulation are added to improve manufacturability, stability or delivery of the drug to the patient. During development of an effective and reliable drug-delivery formulation, it is important to verify that none of the selected excipients has an adverse effect on drug efficacy.

The pharmaceutical industry uses a variety of analytical techniques to evaluate drug-excipient interaction or incompatibility. However, these techniques are often applied after weeks and months of oven aging under varying conditions of temperatures and / or humidity. This delay in detecting drug-excipient incompatibility is expensive and can significantly impact commercialization of a beneficial drug. A new approach, using a combination of DSC and Modulated DSC®, reduces the test time to one day and requires only a few milligrams of sample. Utility of this approach will be illustrated on mixtures of acetylsalicylic acid (aspirin) with magnesium stearate and crystalline sucrose.

## INTRODUCTION

Thermal analysis techniques such as TGA, DSC and Modulated DSC® should be the fastest and most reliable way to detect drug-excipient incompatibility because they have extremely high sensitivity for detecting changes in composition, thermal stability and structure. However, thermal analysis is seldom used for a variety of reasons including:

- Lack of a systematic approach; what time and temperature?
- Difficulty in relating room temperature stability to DSC results that are created at high temperatures, where the form of the drug is often amorphous
- Difficulty in interpreting DSC results

This paper will propose and illustrate an approach that is fast and easy to use. Decisions about compatibility between the drug and excipient can typically be made in a day as compared to traditional oven and humidity aging, which can take months.

## EXPERIMENTAL

Experiments were performed using a TA Instruments Q2000 DSC/MDSC® and Q5000 IR TGA. The sequence and test parameters of experiments are as follows:

- TGA; perform experiments at 1, 3 and 9 ºC/min with approximately 5 mg sample
- DSC; analyze approximately 2 mg of the separate drug and excipient at 1, 3 and 9 ºC/min in hermetic pans
    - The purpose of multiple heating rates is to determine if the crystalline drug and/or excipient undergo true melting or lose crystalline structure as a result of decomposition
- DSC; analyze approximately 5 mg of a 50/50 mixture of the drug and excipient at 1 ºC/min in hermetic pan
    - Compare results of the 50/50 mixture and the pure API (1 ºC/min run)
    - If the melting point or apparent melting temperature are reduced by more than 2-5 ºC/min, this indicates interaction and initiates an MDSC isothermal experiment
- MDSC; Using approximately 10 mg of a 50/50 mixture, perform a twelve-hour isothermal experiment at a temperature which is 10 °C below the first transition observed in the 1 ºC/min DSC experiment on the 50/50 mixture

## RESULTS AND DISCUSSION

TGA Results:

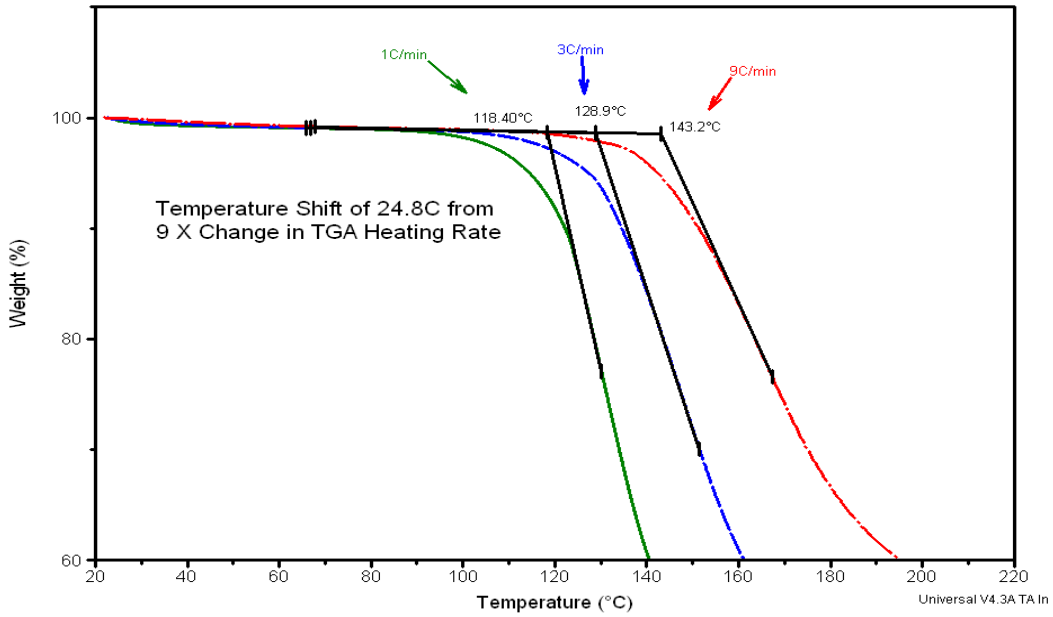


**Figure 1. The effect of heating rate on the temperature of decomposition for an aspirin tablet**

DSC Results

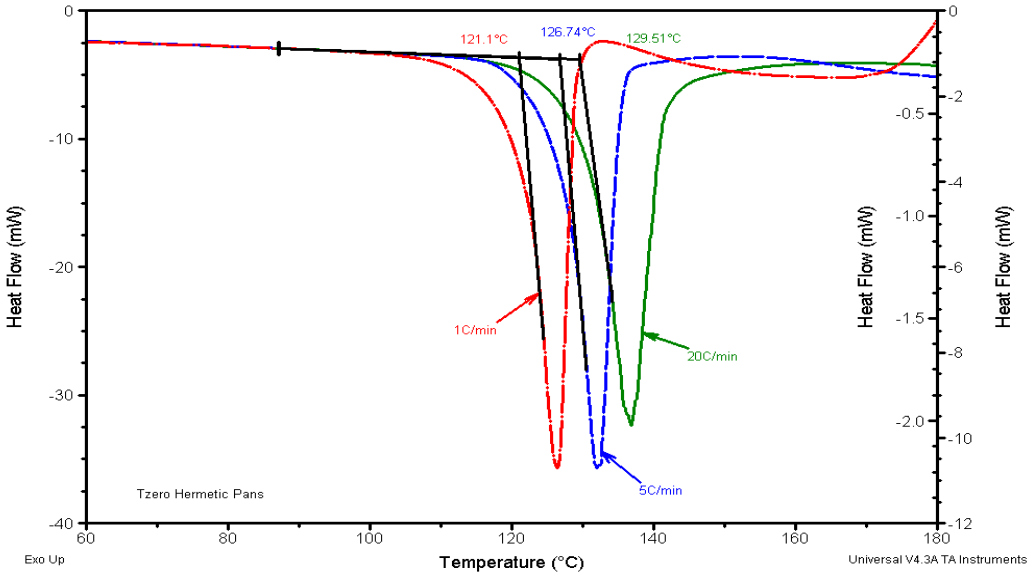


**Figure 2. The effect of heating rate on the apparent melting point of an aspirin tablet (Acetylsalicylic acid with 10% starch). The temperature shift indicates decomposition**

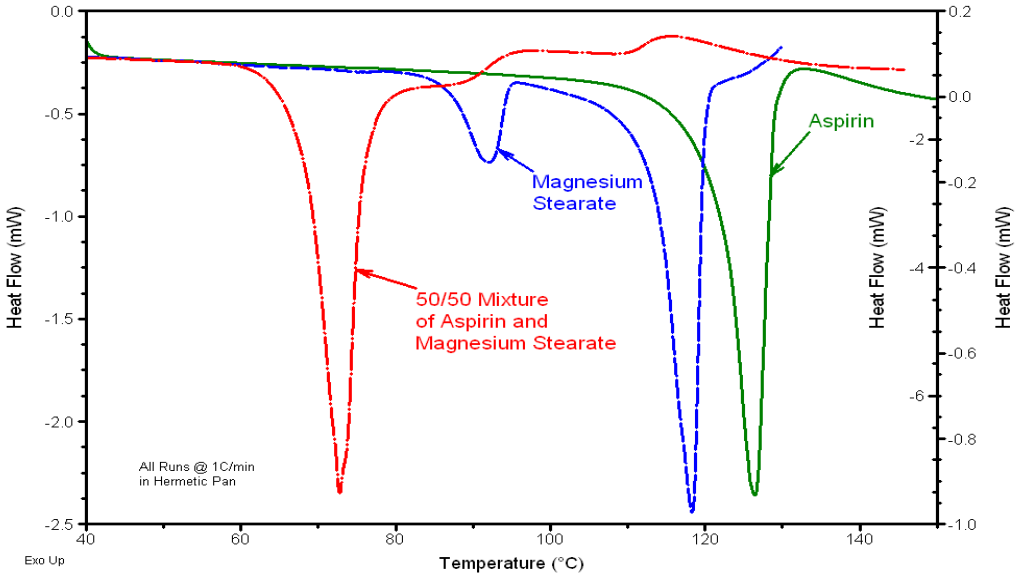


**Figure 3. Comparative DSC results on the drug, excipient and 50/50 mixture at a heating rate of 1 ºC/min. Results indicate strong interaction between aspirin and magnesium stearate**

MDSC® Results

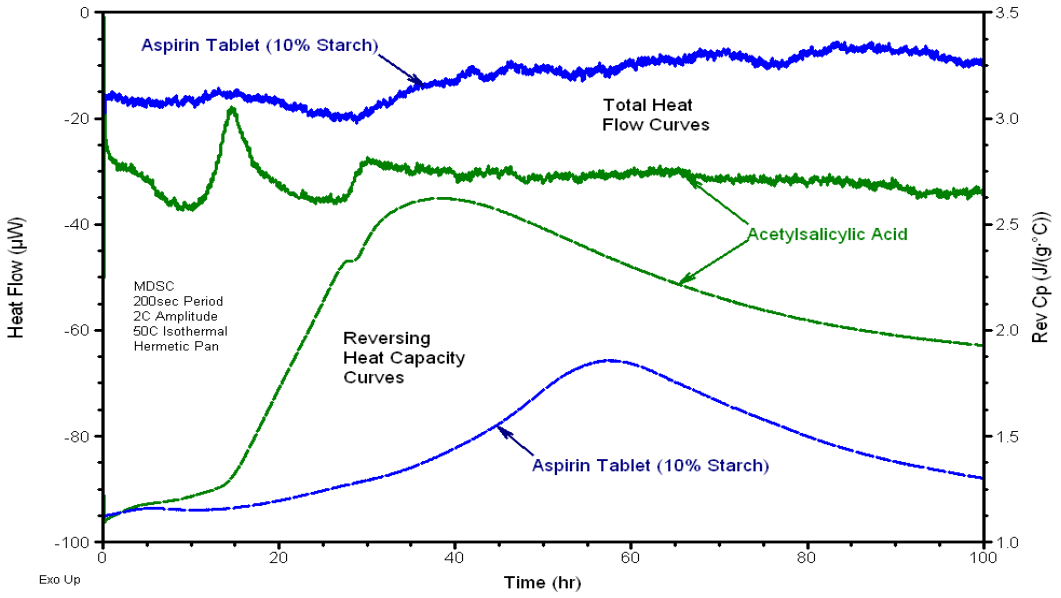


**Figure 4. The Reversing Cp signal shows strong interaction between aspirin and magnesium stearate even at 50 ºC. The rate of reaction is too slow to be measured by the heat flow rate**

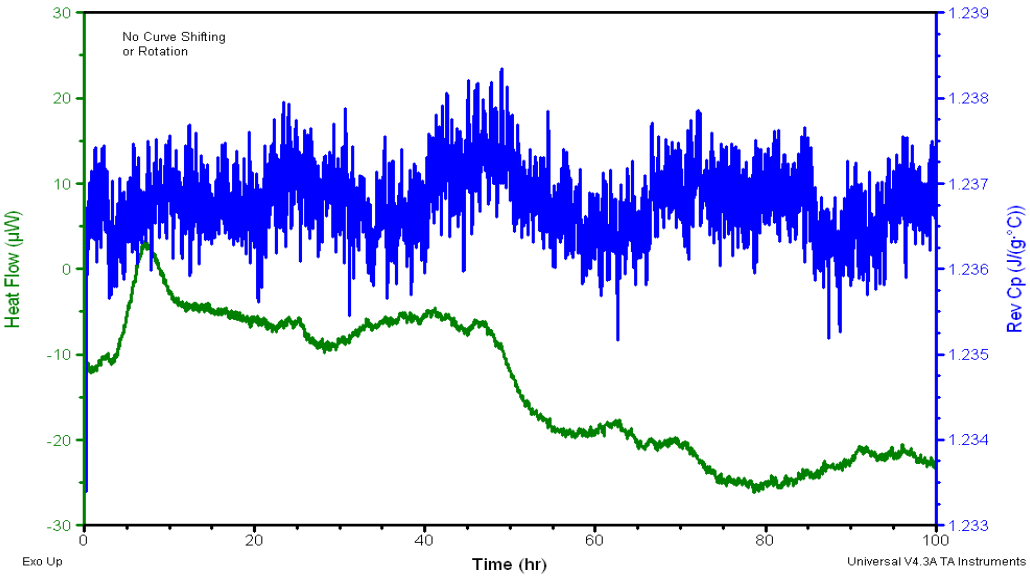


**Figure 5. The sensitivity and stability of MDSC are seen in the 100 –hour isothermal data at 50 ºC on a 50/50 mixture of acetylsalicylic acid (Aspirin) and crystalline sucrose**

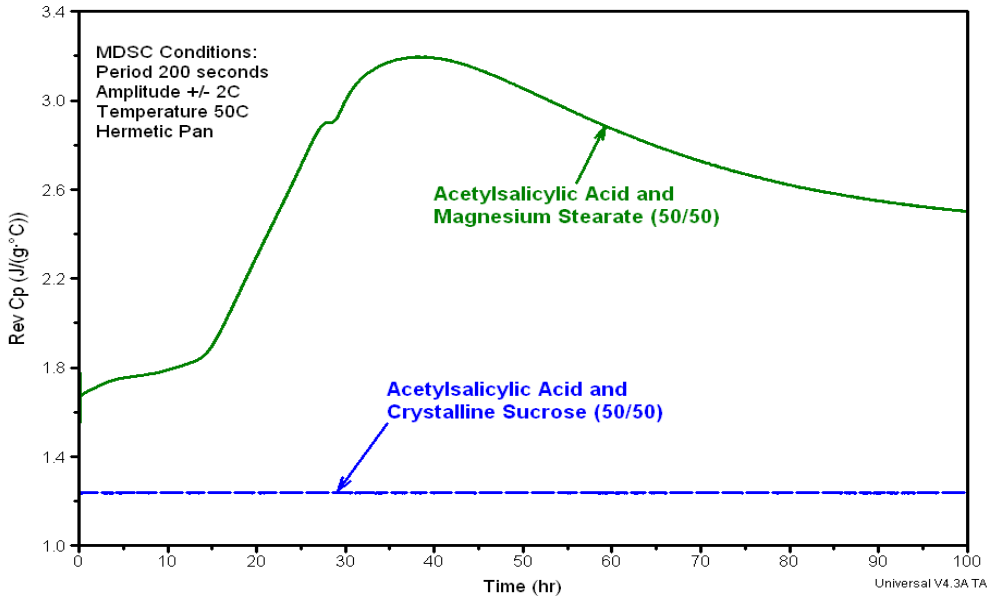


**Figure 6. A comparison of the MDSC® Reversing Cp signals from the 100-hour, 50 ºC isothermal experiments show that acetylsalicylic acid interacts with magnesium stearate but not sucrose**

## CONCLUSIONS

MDSC has much higher sensitivity than DSC for detection of drug-excipient interaction. This is due to the unique ability of MDSC to measure heat capacity under quasi-isothermal conditions. Since heat capacity is an absolute property, and not a rate like the heat flow signal of DSC, interaction can be measured even at low temperatures and low reaction rates

## KEY WORDS

Drug Excipient Incompatibility, DSC, MDSC

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