Thermal Analysis

Thermal Analysis of Pharmaceuticals

Introduction

Thermal Analysis (TA) is the name given to a group of techniques used to measure the physical or chemical properties of a sample as it is heated, cooled or held at constant (isothermal) temperature.
Differential Scanning Calorimetry (DSC) allows you to determine the amount of energy (heat) absorbed or released by a sample. Thermal effects such as melting, solid-solid transitions or chemical reactions can be studied.
Thermogravimetric Analysis (TGA) measures the change in mass of a sample in a defined atmosphere. This permits processes such as evaporation or decomposition to be investigated. The evolved gases can be analyzed online using hyphenated techniques such as TGA-MS and TGA-FTIR.
Thermo-optical analysis (TOA) measures the changes in optical transmission or reflection of a sample due to thermal effects such as melting, crystallization or other phase transitions. Thermo-microscopy is particularly useful for the investigation of polymorphism.
The various TA techniques are widely used in research and development as well as in routine analysis for quality control purposes.

Application Overview	DSC	TGA	TMA	DMA
Melting point, melting range	●		○	
Melting behavior, fraction melted	●			
Temperature and enthalpy of fusion	●			
Purity, phase diagram	●			
Polymorphism	●		○	
Pseudo-polymorphism	●	●	○	
Evaporation, desorption, vaporization	●	●		
Glass transition	●		○	○
Compositional analysis	●	●		
Thermal stability	●	●		
Interactions, compatibility	●		○	○
Kinetics of decomposition	●	●		

● preferred technique ○ alternative technique

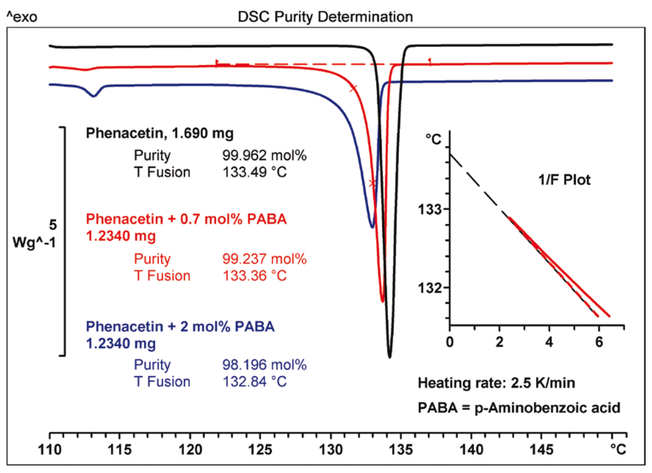
Purity determination by DSC

This method is based on the fact that the presence of impurities in a material depresses its melting point. Evaluation of the DSC melting peak using the van't Hoff equation gives rapid results, and does not require the pure substance to be available for comparison purposes.

$T_f = T_0 - xRT_0^2/\Delta H_f$

T_f = melting point of the impure sample
T_0 = melting point of the pure substance
x = mole fraction of impurity in liquid phase
R = gas constant
ΔH_f = heat of fusion of the pure substance

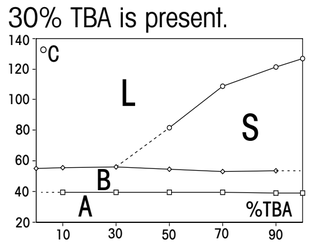
This method is only valid for low levels of impurity in eutectic systems that are close to thermal equilibrium. As an example, the purity of different mixtures of phenacetin and p-aminobenzoic acid (PABA) is determined. The samples measured show the following purity levels: 99.97, 99.29, and 98.39 mol% respectively.



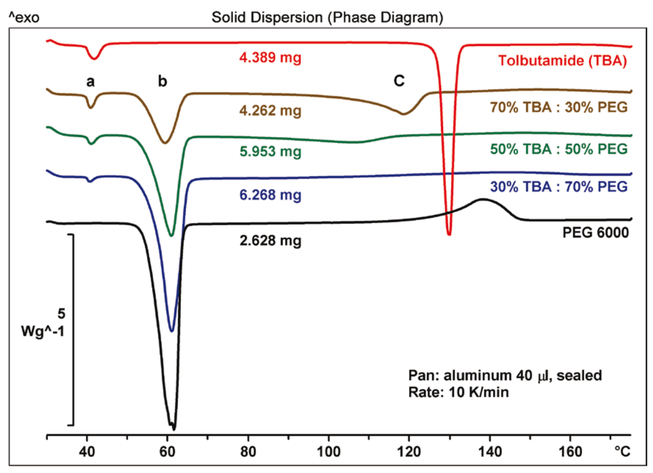
DSC measurements and purity evaluation of phenacetin samples with different levels of impurity.

Phase diagram of a solid dispersion by DSC

Tolbutamide (TBA) forms a solid dispersion with PEG 6000 (PEG), but not a solid solution. The phase diagram determined by DSC shows the following: TBA and PEG form a eutectic with a composition of 30% TBA and 70% PEG with the same melting point as the PEG used (55 °C). The peak at 39 °C corresponds to a solid-solid transition of tolbutamide that melts at 127 °C. Above 54 °C (peak b), either the liquid or the solid phase is present, depending on the TBA concentration. Excess TBA melts (peak c) if more than 30% TBA is present.



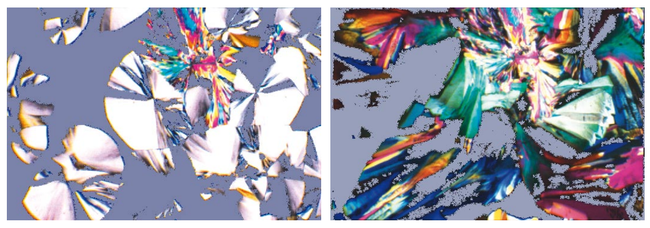
Phase diagram:
L = liquid
S = solid
B = TBA solid (mod II) + PEG solid
A = TBA solid (mod I) + PEG solid

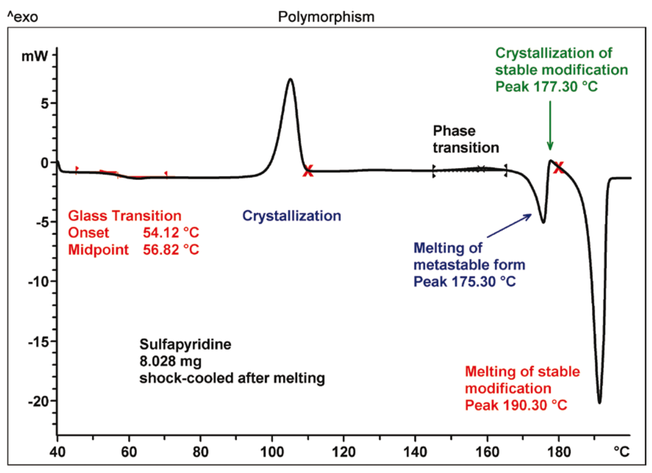


DSC curves of a solid dispersion with various concentrations (weight %).

Polymorphism by DSC and TOA

Different crystal modifications of a particular compound have different melting points, bioavailabilities and dissolution rates. DSC is used to detect polymorphism. Thermal microscopy can be used to observe and interpret the different crystal modifications and transitions between polymorphic forms.
As an example, the DSC curve shows the fusion and recrystallization of the different modifications of sulfapyridine. Photographs were taken at about 110 °C and 180 °C (marked with an x on the curve).

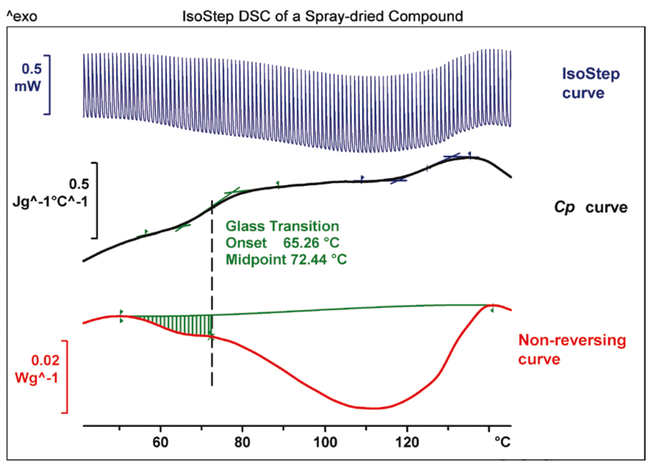




Phase transitions of amorphous sufapyridine measured by DSC and TOA.

Influence of moisture using IsoStep™ DSC

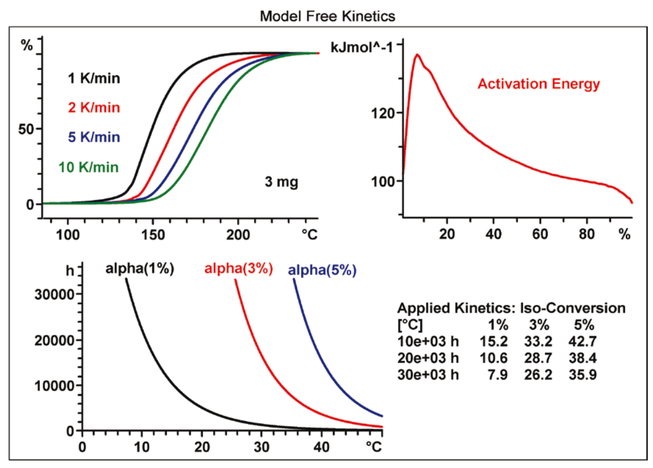
The properties of pharmaceuticals are often influenced by the presence of moisture. Water can for example act as a plasticizer and lower the glass transition temperature, T_g. This may cause a powdery material to become sticky, leading to processing problems.
IsoStep™ DSC allows heat capacity changes and evaporation to be determinded exactly as a function of the moisture content. The samples are pretreated in the DSC cell using pans with pierced lids to reach a well-defined moisture content (e.g. 4.3 % in the sample given below).



IsoStep™ DSC measurement and resulting curves of a spray-dried compound.

Determination of shelf life by TGA

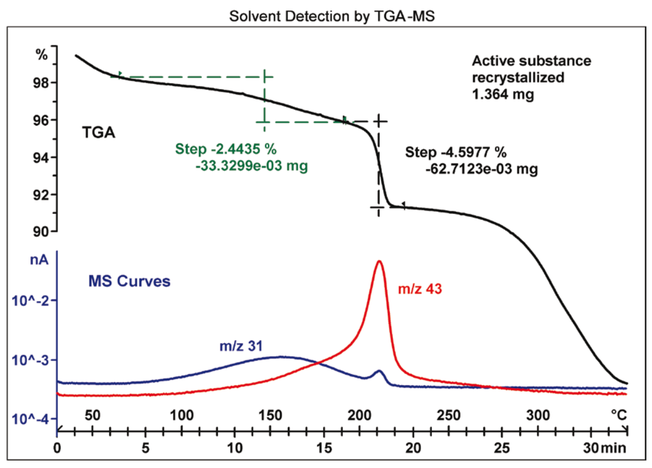
The shelf life of a material is usually checked by storing it for several months under defined conditions and analyzing it at regular intervals. It is however much less time consuming to screen materials at higher temperatures and make predictions based on kinetic models. The predictions can afterward be confirmed by long-term testing.
As an example, the thermal decomposition of acetylsalicylic acid is measured by TGA at four different heating rates. The curves are evaluated using Model Free Kinetics. The data obtained is used to predict the stability lifetime, i.e. the time taken to reach a certain conversion at a given temperature.



TGA measurements and kinetic evaluations are used to predict thermal stability.

Solvent analysis by TGA

Pharmaceutical substances are often recrystallized from different solvents during production processes. Any solvent residues left in the final product should be as low as possible.
A TGA-MS combination allows both the quantity and the composition of such residues to be determined.
The TGA curve of a pharmaceutical substance that had been recrystallized in methanol and acetone is shown below. The simultaneously recorded MS curves show that the mass-loss steps correspond to methanol (m/z 31) and to acetone (m/z 43), the main fragment ion of acetone).



TGA and MS curves of a pharmaceutical substance heated to 350 °C.

Literature

A more detailed description of the use of thermal analysis techniques in pharmaceutical analysis is given in the Collected Applications booklet Pharmaceuticals available from METTLER TOLEDO (ME-51725006).

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