J Therm Anal Calorim (2012) 108:283–287
DOI 10.1007/s10973-011-1859-0

# Solid-state mechanical properties of crystalline drugs and excipients

## New data substantiate discovered dielectric viscoelastic characteristics

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Received: 20 April 2011 / Accepted: 10 August 2011 / Published online: 24 November 2011


**Abstract** Thermal mechanical analysis (TMA) of crystalline drugs and excipients in their pre-melt temperature range performed in this study corroborate their newly found linear dielectric conductivity properties with temperature. TMA of crystalline active pharmacy ingredients (APIs) or excipients shows softening at 30–100 °C below the calorimetric melting phase transition, which is also observed by dielectric analysis (DEA). Acetophenetidin melts at 135 °C as measured calorimetrically by DSC, but softens under a low mechanical stress at 95 °C. At this pre-melting temperature, the crystals collapse under the applied load, and the TMA probe shows rapid displacement. The mechanical properties yield a softening structure and cause a dimensionally slow disintegration resulting in a sharp dimensional change at the melting point. In order to incorporate these findings into a structure–property relationship, several United States Pharmacopeia (USP) melting-point standard drugs were evaluated by TMA, DSC, and DEA, and compared to the USP standard melt temperatures. The USP standard melt temperature for vanillin (80 °C) [1], acetophenetidin (135 °C) [2], and caffeine (235 °C) [3] are easily verified calorimetrically via DSC. The combined thermal analysis techniques allow for a wide variety of the newly discovered physical properties of drugs and excipients.

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**Keywords** Thermomechanical analysis · Active pharmaceutical ingredients · Mechanical properties DSC · DEA · Pre-melt · Softening

## Introduction

Most of the active pharmaceutical ingredients (APIs) known today are crystalline. An amorphous material can be substantially more soluble than the corresponding crystalline material, and thus more readily bioavailable, but the crystalline structure is often preferred because of better shelf stability [4]. Because of the dichotomous nature of the two morphologies, there are myriad drug applications that could possibly benefit from a combination of the two morphologies, as well as many others where the presence of a particular morphology could be detrimental to the formulation.

In previous studies, methods employed to determine the extent of crystallinity of APIs and excipients included the use of solution calorimetry and others [5], but these methods did not incorporate multidimensional analysis and do not completely describe the morphology of the drug compounds and excipients through the various stages of dissolution.

This lack of a complete description of the physical characteristics of APIs and excipients exemplifies the fundamental gap between the current techniques used and the extent of information required to truly define the morphology of these compounds. As such, it is essential to develop methods by which we can use multiple instruments to map the physical properties of the drugs and excipients more accurately. Our approach involves using a multi-instrumental route, where we show that the crystalline APIs soften well below their melting temperatures, and that they

also show differences in their electrical properties, which can indicate a potentially significant discovery in the properties of APIs. To pilot this study, three common USP standards are used: vanillin USP (80 °C) [6–8], acetophenetidin USP (135 °C), and caffeine USP (235 °C). The above mentioned APIs were characterized by three thermal analytical techniques.

Thermomechanical analysis (TMA), because of its known usefulness in studying the elastic and viscous properties of many materials including polymers [9] and pharmaceutical APIs and excipients [10–12], is used for measuring the changes in the physical dimensions (length or volume) of a sample as a function of temperature and/or time under a non-oscillatory load. In this study, TMA will be used for determining the softening point of the three USP ingredients.

We also characterize the ingredients by differential scanning calorimetry (DSC), which has been used extensively to study glass transition temperature ($T_g$), crystalline melting temperature ($T_m$), heats of fusion ($\Delta H_f$), and thermal stability of materials including pharmaceuticals and polymers [13–15]. DSC will provide both qualitative and quantitative data on the three USP ingredients based on the endothermic (heat-absorbing) and exothermic (heat-evolving) processes.

Finally, dielectric analysis (DEA) is used for measuring the dielectric properties of the three USP ingredients [16]. DEA has been used extensively to characterize a wide variety of materials such as polymers, food products, pharmaceuticals, and proteins, which may be in the form of solids, liquids, or gels [16, 17]. As DEA is a thermal analysis tool, it compliments DSC by allowing a measurement of molecular motion initiated by the alternating current (AC) Electric field.

## Methods

### *Calibration*

The calibration of the TA Instrument (TAI) TMA 2940 was performed based on ASTM method E1363. At the transition temperature of the test specimen, there is a change in dimensional stability and a measured change in the coefficient of thermal expansion is recorded by the instrument. From the TMA thermal curve recorded, extrapolated onset temperature is calculated by extending the pre-transition portion of the curve which to the point of intersection with a line drawn tangent to the steepest portion of the curve which describes the probe displacement [3].

The calibration for the DSC instrument TAI 2920 was done based on Standard Test method for temperature calibration, adapted from ASTM method E967-03.

The calibration for the DEA instrument TAI 2970 was done based on the standard test method for temperature calibration of DEA using the prescribed fixtures. The sensor is calibrated to a permittivity of zero. At the thermodynamic melt transition temperature, an abrupt change in DEA permittivity is observed. The temperature observed for this transition is recorded by the instrument. From the resultant DEA thermal curve, the following parameters are measured to determine the property variation associated with the transition: frequency, permittivity, log permittivity, temperature, derivative of permittivity, and log permittivity with respect to temperature.

## Experimental protocol

### TMA protocol

The TAI TMA 2940 was used for evaluating the pharmaceutical samples. The probe in this study is a flat probe made of quartz which has an expansion coefficient of $0.6 \times 10^{-6}$ $K^{-1}$ which is negligible when compared to that of the samples studied. [12] TMA tests are run in heating mode at controlled heating rates. A sample was packed into a standard DSC aluminum pan and weighed. On being placed in the TMA apparatus, quarts probe was lowered on to the sample, and then heated at the heating rate of 5 °C/min in nitrogen at a flow rate of 50 mL $min^{-1}$ up to the melting temperature. The length of the sample measured before heating the TAI software varied from 0.90 to 1.30 mm. Probe displacement profile is recorded using a linear variable differential transducer (LVDT). Subsequently, the data are analyzed in terms of thermal expansion coefficients, softening temperatures, and melting temperature.

### DSC protocol

The TAI 2920 was used for DSC studies. Ten mgs of sample was weighed into an aluminum pan. The sample in the open pan was heated at the heating rate of 10 °C/min in nitrogen at a flow rate of 50 mL $min^{-1}$.

### DEA protocol

To generate DEA data, the TAI 2970 was used varying the frequencies ranging from 0.1 to 1,000 Hz. The sample was spread on the surface of a gold ceramic-interdigitated (IDA) electrode and heated in the dielectric analyzer at the heating rate of 5 °C $min^{-1}$ with nitrogen gas purge at a flow rate of 50 mL $min^{-1}$.

## Results

As described earlier, the TMA measures the changes in the physical dimensions of a sample as a function of temperature and/or time under a constant load.

The TMA melting of the standard indium is at 158 °C which matched with the literature value of 157 °C; see Fig. 1. The baseline before melting was flat and, at the melting temperature, it dimensionally deviated vertically with no pre-melt activity. However, acetophenetidin, with the literature melting temperature of 134 °C, should produce a sharp vertical displacement at its melting temperature, but as seen in Fig. 2, the baseline starts to deviate downward well before its melting temperature at 95 °C which infers the sample solid structure is weakening. We termed this phenomenon as softening, and the temperature—where this starts is the onset of softening—$T_{os}$. When this sample was examined by DEA known to measure the electrical properties of a sample, acetophenetidin, in this case showed an increased pre-melt conductivity [18] from $10^{-1}$ to $10^{3}$ pScm$^{-1}$; see Fig. 2. The DSC curve in contrast to this did not exhibit any enhanced activity but only the classical melting, $T_m$ at 135 °C. The TMA melting paralleled the increase of DEA conductivity of $10^{3}$–$10^{5}$ pScm$^{-1}$; see Fig. 2. The DSC test was also used for verifying the purity of the drug samples. The DEA and TMA are thermal analytical techniques which are more sensitive in nature, by virtue of which the softening was observed.

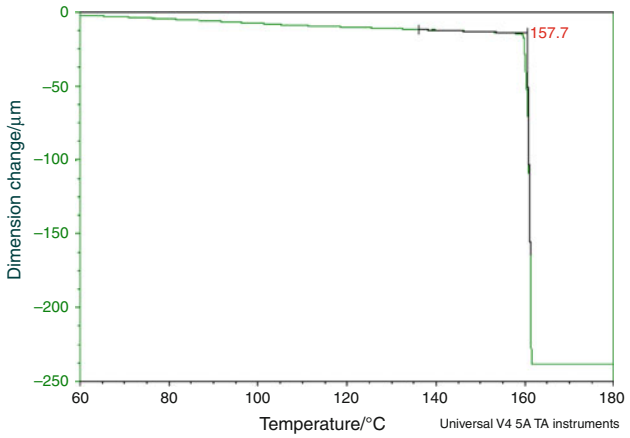


**Fig. 1** TMA curve of indium standard

Vanillin with the literature melting temperature of 81 °C produced a baseline which initially deviates dimensionally downward well before its melting temperature at 72 °C. The TMA melt temperature was 84 °C, or the sample softened 12 °C below the melt temperature. The onset of enhanced electrical conductivity, $T_{dc}$ of vanillin was 60 °C with increased conductivity from $10^{-1}$ to $10^{3}$ pScm$^{-1}$; see Fig. 3. The DSC curve did not exhibit any enhanced activity but only the classical melting at 81 °C. The TMA melting paralleled the increase of DEA conductivity of $10^{3}$–$10^{5}$ pScm$^{-1}$. Again, the DEA and TMA are more sensitive to property changes than the DSC.

The literature melting temperature of Caffeine was 237 °C. This baseline deviates dimensionally downward well before its melting temperature at 176 °C, i.e., the $T_{os}$; see Fig. 4. The TMA melting temperature was 226 °C, the sample softened 31 °C below the melting temperature. Part of the decrease in the transition temperature of 31 °C is due the sublimation of caffeine in an open pan. The TMA is tested in an open environment, while the DSC test is typically done in a closed cell. Therefore, the DSC is prone not to exhibit the effects of the sublimation, while the TMA is affected by the sublimation.

The onset of softening temperature and melting temperature observed by TMA are summarized in Table 1. The melting temperature determined by DSC compares well

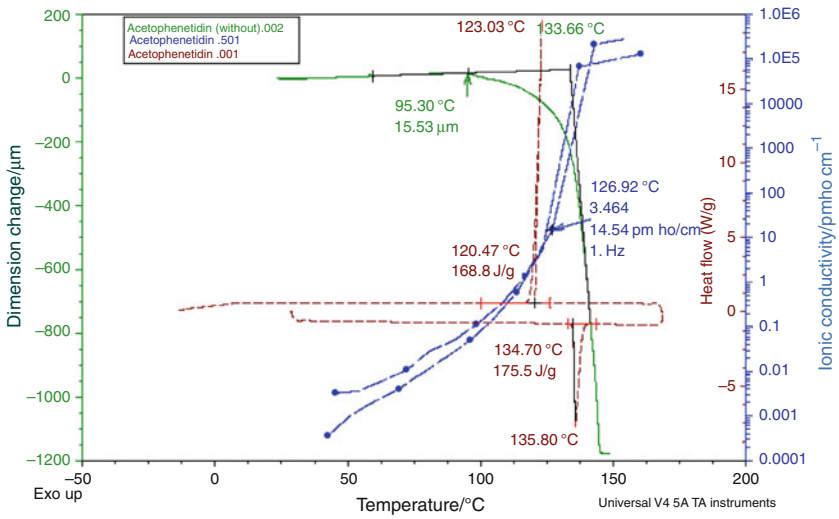


**Fig. 2** Acetophenetidin examined by TMA (*solid line*), DSC (*dash line*), and DEA (*dotted line*)

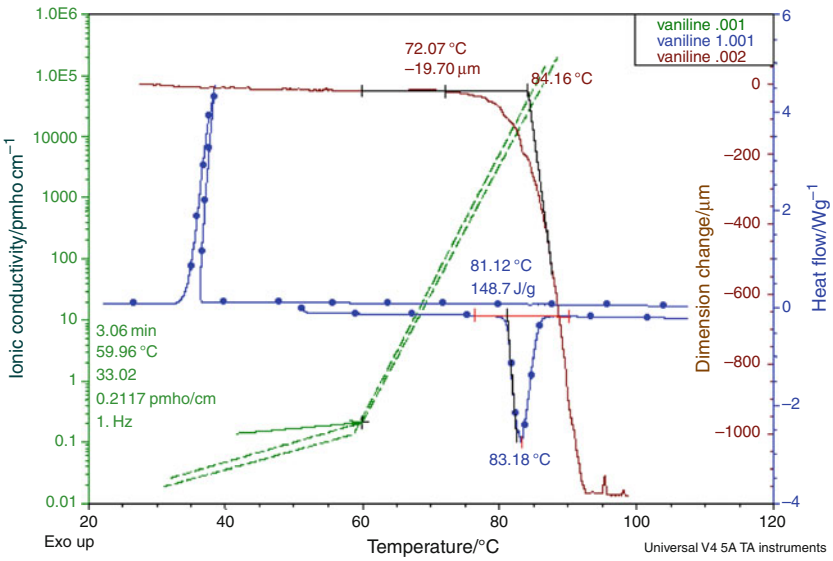


**Fig. 3** Vanillin examined by TMA (*solid line*), DSC (*dotted line*), and DEA (*dash line*)

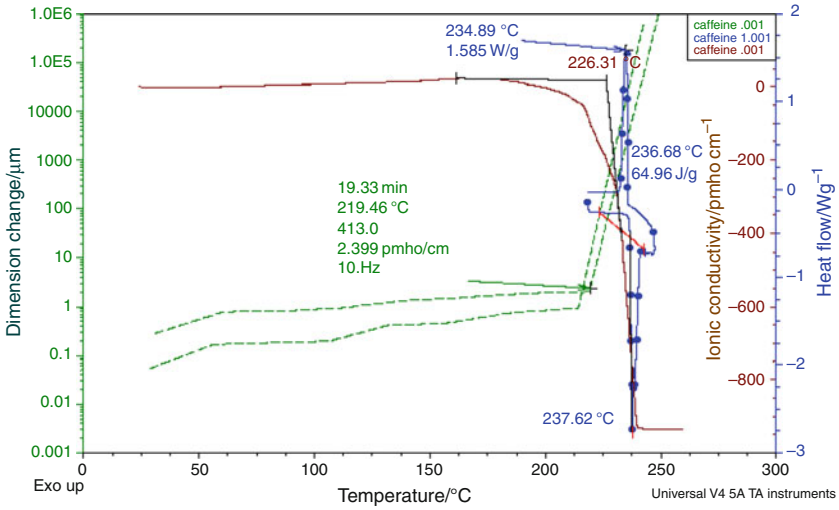


**Fig. 4** Caffeine examined by TMA (*solid line*), DSC (*dotted line*), and DEA (*dash line*)

**Table 1** Summary of the TMA, DSC, and DEA of vanillin, acetophenetidin, and caffeine

| Drug | TMA | | DSC | | | DEA $T_{dc}$/°C |
|---|---|---|---|---|---|---|
| | $T_{os}$/°C | $T_m$/°C | $T_m$ (lit)/°C | $T_m$/°C | $T_c$/°C | |
| Vanillin | 72 | 84 | 81–83 | 81 | 37 | 60 |
| Acetophenetidin | 95 | 134 | 134–136 | 135 | 123 | 127 |
| Caffeine | 176 | 226 | 235–237 | 237 | 234 | 219 |

$T_{os}$ onset softening temperature by TMA (first deviation)

$T_m$ melting temperature (significant vertical displacement)

$T_m$ (*lit*) the literature melting temperature

$T_c$ temperature of exothermic crystallization

$T_{dc}$ onset of conductivity by dielectric change

with the literature temperature values of the APIs and excipients as seen in Table 1 and the onset of dielectric permittivity change.

## Conclusions

The DSC melting temperature ($T_m$) of the APIs and the excipient correlates well with the DSC published values. The TMA shows the softening at a temperature ($T_{os}$) 12–50 °C lower than the $T_m$. At a temperature less than $T_m$, the electrical properties were observed using DEA, showing an increased conductivity which is associated with the softening. The relationship between $T_{os}$ and $T_{dc}$ is linear, and the correlation coefficient ($R^2$) was 0.95.

In conclusion, we observe a strong relationship between the DEA conductivity in the pre-melt and the TMA pre-melt. It is concluded that we have measured unique dielectric viscoelastic (DEA and TMA) properties of acetophenetidin, vanillin, and caffeine.

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