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A novel method to measure the glass and melting transitions of pharmaceutical powders

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ABSTRACT

A method to measure thermo-mechanical properties of pharmaceutical and polymeric powders was developed. The measurements are conducted by characterizing the material's response to applied acoustic waves. Measurements were performed using griseofulvin, felodipine and indomethacin as model drugs and polyethylene oxide (MW = 200,000, 900,000, 2,000,000 Da) as model polymers. The method employed measures the mechanical impedance enabled the calculation of the powder rheological and thermo-mechanical properties. Measurements attained with this new technique are compared with measurements made using differential scanning calorimetry (DSC) and dynamic mechanical analysis (DMA). The new method detects the melting and glass transitions events while providing complementary information to that provided by DSC and DMA.

1. Introduction

Thermo-mechanical properties of materials are of critical relevance into the formulation and processing of pharmaceutical products. Such properties are typically measured using analytical techniques that capture the changes in either their mechanical or thermal properties when it is subjected to controlled temperature sequences. Dynamic mechanical thermal analyses (DMTA or DMA) are used to monitor mechanical properties, whereas differential scanning calorimetry (DSC) is the most widely used thermal analysis technique in pharmaceutical and food sciences. These methods yield important and complementary information on the molecular order and transitions, generally temperature dependent, of the tested materials. DMA is a frequency response analysis that uses a constant, non-destructive oscillatory strain (or stress) at selected frequencies under controlled temperature conditions while recording the resulting stress response (or strain) of the material (Brent et al., 1997a). This method is widely used to determine the glass transition and viscoelastic properties of polymeric amorphous materials. Under tension/compression the measured viscous component is referred to as the loss modulus (E''), while the measured elastic component is referred to as the storage modulus (E') of such viscoelastic properties. The ratio of the loss modulus to the storage modulus is referred to as the loss tangent (E''/E'), tangent delta or tan delta (Brent et al., 1997b). In general, the temperature the tan delta exhibits a maximum is considered as the glass transition temperature (T_g) of the material. However, many pharmaceutical materials do not exhibit a glass transition sufficiently sharp as to unequivocally assign it a temperature value (Angell and Green, 2004). The glass transition is a temperatures range in which the material undergoes drastic changes in its thermo-mechanical properties (Peleg, 1994). The shape and position is affected by factors such as the thermal history of the material (Mao et al., 2010), as well as the presence of residual water or other plasticizing substances. In biological and pharmaceutical glasses, residual water as a plasticizer is of considerable importance (Makower and Dye, 1956; Saleki-Gerhardt and Zografi, 1994). The presence of a plasticizer favors the mobility of large molecules lowering the T_g, thus influencing the thermo-physical properties of the material. At either low temperatures or low plasticizer content, cooperative molecular motions are limited in the glassy state. Upon heating through the glass transition, the material changes into the rubbery (as commonly referred to for polymers) or supercooled liquid (as referred to for molecular glasses) state, with much greater degree of molecular motion; sufficiently high as to result in a material in structural equilibrium. The glass transition temperature range of a sample depends on its composition and the

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compatibility of the components in its amorphous matrix (Fox and Flory, 1950; Gidley et al., 1993; Gordon and Taylor, 1952; Roos and Karel, 1993). Concerning the T_g range, increasing the molecular weight of a polymer typically results in a higher temperature necessary for its mobility or flow. This is attributed to an increased degree of entanglement taking place between the molecular chains resulting from their increasing length (Fox and Flory, 1950).

The DSC technique is typically used to assess the enthalpic changes associated with the phase transitions undergone by drugs, polymers and biomaterials, as a function of temperature. Like the DMA, DSC is also used for the detection of the material T_g range. It is characterized by a change in heat capacity, i.e. a shift in the DSC heat flow curve, as the material passes through the glass transition temperature. Even though the two methods reveal similar information, the two instrumental techniques vary significatively, not only in their analyses and sample preparation, but also in their sensitivity. For DMA analysis, the first step is to prepare structurally homogeneous tablets loaded into a mold and pressed under very high pressure (5000 lbs or more) to avoid the fracture of the samples during the measurements. That raises questions as to how the sample material is affected due to sample preparation. An alternative testing set-up, a DMA powder cell designed by TA Instruments, was used to test active pharmaceutical powders. The powder cell can be attached to the dual cantilever clamp on the DMA. The cell enables the characterization of transitions in powders by determining changes in the apparent elastic and viscous complex moduli. Since the geometry is not well defined and the material is in a powdery state, the obtained moduli values are indicative of the elastic and viscous character of the sample but do not provide a true measurement of those parameters. In other words, the storage modulus and the loss modulus measured using the powder cell are only semi-quantitative measurements. For this reason, they are referred to as apparent moduli. Nevertheless, use of the powder cell is of great value in pharmaceutical applications since it allows measurements to be made APIs, excipients and formulations in the unaltered powder form of interest, precluding the need of making a compact of the material of interest in order to enable the measurement.

Some events like the glass transition are more easily detected by DMA than by DSC, as mechanical changes that accompany the glass transition are more clearly observable than the change in heat capacity of the materials. DMA starts to detect short range motion before the onset of the (cooperative) main chain motion associated with the calorimetric glass transition (Kalichevsky et al., 1992). DSC has also shown to be limited in its use to determine T_g of some biomaterials, such as flours and starches (Pereira and Oliveira, 2000; Tester and Debon, 2000). This is attributed to the fact that starch contains both amorphous (in where a T_g is observed) and crystalline components in where melting is observed. In starches, which are used as excipients in numerous pharmaceutical products, the melting and glass transition events occur at very close temperatures (BeMiller and Whistler, 1996). The fact that the energy associated with melting is significantly greater than that associated with the glass transition makes the DSC determination of glass transition extremely hard in these cases, thus DMA is a preferred method for testing starchy materials.

The objective of this study was to apply a novel device for the detection and measurement of thermo-mechanical properties of powders. The device, referred to as Oscillatory Squeezing Flow (OSF), has been successfully tested in characterizing the rheology of semi-solid and semi-liquid materials (Mert and Campanella, 2008). We compare data obtained using the OSF with data obtained from DSC and DMA, in order to assess the information obtained from the new device in terms of commonality and complementariness with the established methods DSC and DMA.

2. Materials and methods

2.1. Materials

The powder materials used for this study include polyethylene oxide (PEO), a polymer, with three different molecular weights (200,000, 900,000, and 2,000,000 Da). The PEO samples were obtained from Sigma–Aldrich (St. Louis, MO, USA). The active pharmaceutical ingredients used as model drugs in this study include griseofulvin (Hawkins Pharmaceutical Group, Minneapolis, MN, USA), felodipine (Astra Zeneca Mölndal, Sweden) and indomethacin (Sigma–Aldrich, St. Louis, MO, USA). These APIs were selected for the known differences in their physicochemical properties. Griseofulvin is a crystal for which there are no reported polymorphs and does not easily convert turn amorphous upon milling. Indomethacin is a very extensively studied compound so that it can be used as benchmark for measurements of thermo-physical properties. Amorphous indomethacin is easily produced from the crystal. Felodipine is an API with physicochemical properties positioned between those of griseofulvin and indomethacin.

The properties of the API's were investigated in their crystalline and amorphous states. The glassy form was obtained by melt-quench cooling of the samples. The melt quenching was done by heating the drug samples to a temperature slightly above their melting point and held for 3 min. The heated melt was then dropped in liquid nitrogen for 10 min until. The quenched solids were then gently crushed using a mortar and pestle and then stored in a Drierite® desiccator – low relative humidity ~5% and kept refrigerated at 4 °C. All testing on the APIs was done within 24 h of sample preparation to avoid re-crystallization of the amorphous powders as much as possible. Fig. 1 shows XRPD data for the three API's before and after melt quenching. The values of the glass transition (T_g), re-crystallization and the melting temperatures (T_m) of the materials used in this study as well as those reported in the literature (Rowe et al., 2003; Ahmed et al., 1998; Trojak et al., 2001; Correia et al., 2001) are presented in Table 1.

2.2. Methods of characterization

2.2.1. Oscillatory Squeezing Flow (OSF) methodology

The Oscillatory Squeezing Flow (OSF) method, originally presented by Mert and Campanella (2008), is a technique for studying the viscoelastic properties of semi-liquid and semi-solid materials. A modification of the OSF technique is used in this report for the study of the thermo-mechanical properties of powders. The method is based on the same principles and concepts as the well-known rheological technique called squeezing flow (Campanella and Peleg, 2002). However, the OSF method offers technological improvements in obtaining mechanical behavior as the powder is compressed in real time. It involves small amplitude oscillations at random frequencies up to 10 kHz and the testing apparatus can be attached to a texture analyzer or a universal testing machine in order to control the force or stress exerted by the upper plate on the powder sample. In this case, the testing unit was attached to the Sintech 1/G Universal Texture Analyzer (MTS-Sintech, Cary, NC, USA). The design uses a low voltage piezoelectric crystal stack (Piezo Systems, Inc., Cambridge, MA, USA) attached to an impedance head Type 8001 (Brüel & Kjær, Nærum, Denmark). A picture of the system is illustrated in Fig. 2. A voltage is applied to the piezoelectric stack using the SigLab dynamic signal analyzer and function generator model 20-42 (Spectral Dynamics, San Jose, CA, USA). Upon the application of voltage, the upper plate oscillates; force and acceleration values are measured by the impedance head and through a Fourier Transformation, the frequency response specific to the sample is obtained (SigLab-MATLAB Interface, The Mathworks, Natick,

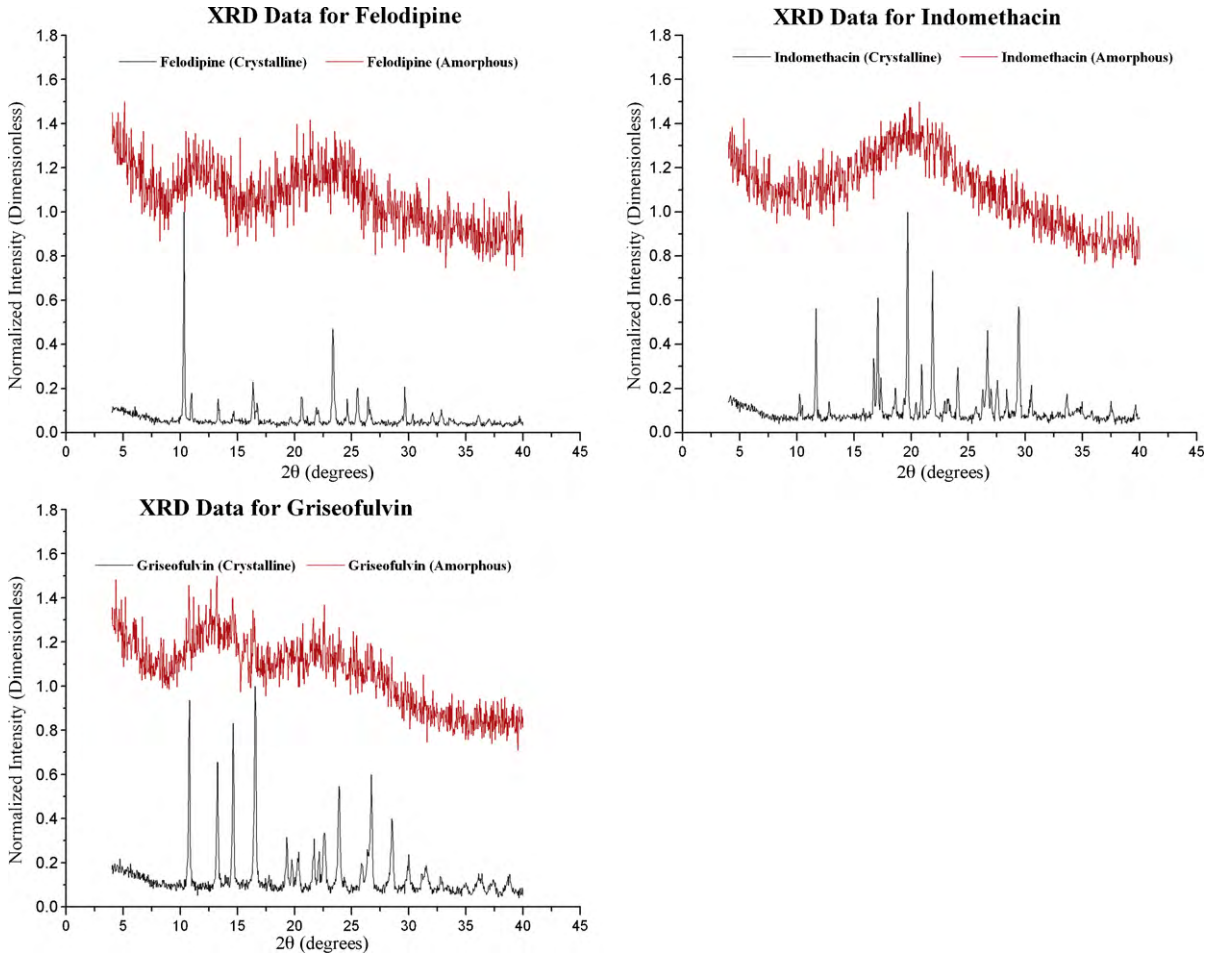

Fig. 1. X-ray powder diffraction for the melt quenched felodipine, griseofulvin and indomethacin.

MA). The calculated complex mechanical impedance obtained is used to assess the mechanical properties of the material.

For the analysis it is assumed that the mechanical properties of the sample can be described by dashpot (viscous) and spring (elastic) components, as depicted in Fig. 3. According to standard theory on vibration, with the oscillation of the top plate, the damping (associated to the viscous component), is closely related to the amplitude of the vibration, whereas the stiffness (associated to the elastic component of the material), is related to the natural frequency of the vibration:

$$\hat{Z} = \frac{\hat{F}}{\hat{u}} = R + i \cdot \left(\omega \cdot m - \frac{s}{\omega}\right) \quad (1)$$

where $\hat{Z}$ is the impedance of the sample, R is the mechanical resistance responsible for the damping of the vibration, ω is the angular frequency, m is the mass of the system, s is the spring stiffness responsible for the elasticity of the sample, and i is $\sqrt{-1}$. The impedance is in turn defined as the Fourier transformed force divided by the Fourier transformed velocity. These Fourier transformed variables are complex numbers and denoted as $\hat{F}$ and $\hat{u}$, respectively.

Accordingly, the resonance frequency of the sample associated with the stiffness (elasticity) of the sample $\left(f_{res} = \sqrt{s/m}\right)$ can be determined as the frequency at which the inverse of the impedance, also known as mobility reaches a maximum. In addition, the shape of the resonance peak describing the mechanical resistance, R, of the powder can be identified. As a result, the viscoelastic properties of the powder can be evaluated from the obtained frequency response spectra (Kinsler et al., 2002). The OSF plots show stiffness values normalized to the maximum stiffness in that run, are used for

Table 1
Glass transition (T_g), re-crystallization and melting onset temperatures (T_m) of the powders used in this study.

Pharmaceutical drugs/additives	Glass transition temperature (°C) T_g	Re-crystallization temperature (°C)	Melting onset temperature (°C) T_m
PEO (MW 200,000 Da)[a]	–		65–70
PEO (MW 900,000 Da)[a]	–		65–70
PEO (MW 2,000,000 Da)[a]	–		65–70
Griseofulvin[b]	–	121–124	220–225
Felodipine[c]	~43	~98	140–145
Indomethacin[d]	~42		155–162

[a] Rowe et al. (2003).
[b] Ahmed et al. (1998).
[c] Trojak et al. (2001).
[d] Correia et al. (2001) and Sigma–Aldrich.

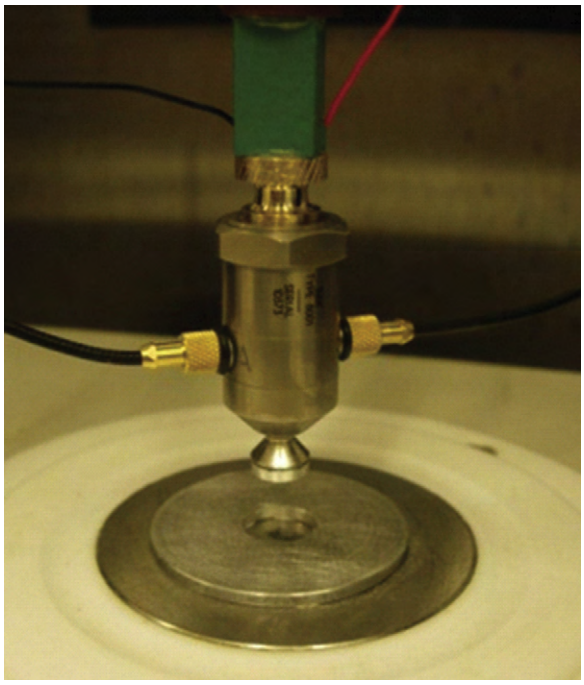

Fig. 2. Photograph of OSF device testing set-up.

comparison with DMA data. In thermo-mechanical analysis, as the temperature increases, a sudden decrease in the stiffness (N/m) of a crystalline material is indicative of melting. For amorphous materials, a decrease in stiffness with increasing temperature is indicative of the glass transition. Measurements were done in triplicate.

2.2.2. DMA methodology

A DMA instrument (RSA III, TA Instruments, New Castle, DE, USA) was used for T_g determination of the API powders. Approximately 100 mg of each sample was placed in the powder cell. The cell was then attached to the clamped three point bending tool on the instrument. Felodipine and indomethacin samples were heated from 30 °C to 120 °C, whereas griseofulvin was heated from 30 °C to 150 °C. The temperature was ramped at 10 °C/min with an applied frequency of 1 Hz and a strain level of 0.02%, ensuring that the samples were tested within the linear viscoelastic region. To determine the T_g values, the normalized complex modulus (E^*) was plotted as a function of temperature. The normalized complex modulus was obtained by taking the ratio of the complex measured moduli at different temperatures for a given sample and the value of the maximum modulus observed for that sample. Sample testing was done in triplicate.

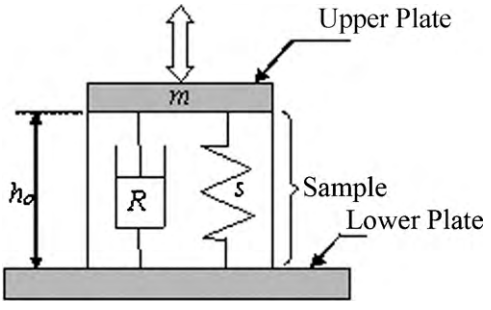

Fig. 3. Schematic of the spring-dashpot system, where h_o, R, and S are the height, the resistance, and the stiffness of the fluid sample, respectively.

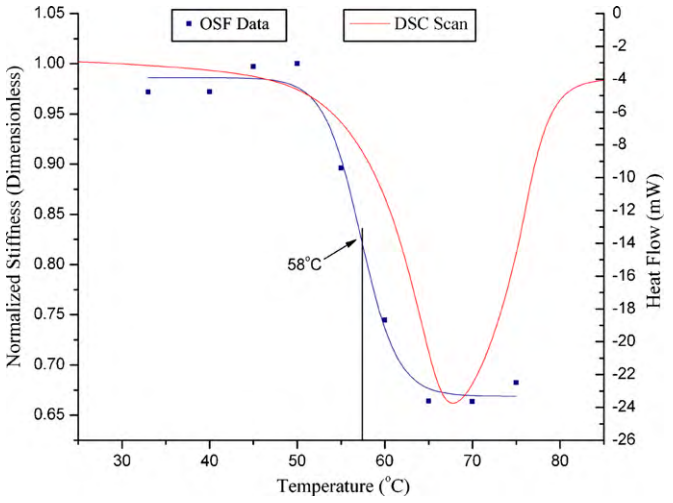

Fig. 4. Melting of PEO MW 200,000 in terms of OSF stiffness overlaying respective DSC melting endotherm.

2.2.3. DSC methodology

Approximately 4 ± 1 mg samples were placed in sealed aluminum pans and scanned at 10 °C/min in a DSC instrument (Model Q10, TA Instruments, New Castle, DE, USA) under a nitrogen gas flow of 50 mL/min. The temperature range varied, depending on the sample being tested. A temperature range from 25 °C to 100 °C was used to determine the melting temperatures of PEO. Scans with temperatures ranging from 30 °C to 240 °C were used for griseofulvin samples, a range of 25 °C to 175 °C was used for indomethacin, and a range of 25 °C to 160 °C was used for felodipine. All runs were done in triplicates.

2.2.4. X-ray powder diffraction

X-ray diffraction was performed using a Siemens Kristalloflex D-5000 diffractometer (Siemens, Haan, Germany) with Cu K_α radiation at 40 kV/40 mA. The samples were step-scanned at 0.04° intervals from 4.0° to 40.0° (2θ) at the rate of 4.0° per minute. Scans for each sample were run in triplicate.

3. Results and discussion

3.1. Melting of polyethylene oxide (PEO)

Figs. 4–6 show the melting of PEO with molecular weights of 200,000, 900,000, and 2,000,000 Da, respectively. The graphs show overlays of the melting profiles obtained by the DSC and OSF methods. The DSC plots show the characteristic melting endotherm, while the OSF plots exhibit their (characteristic) drop in stiffness as the materials begin to melt. The DSC curves for the three PEO samples used in the study are overlaid in Fig. 7, showing the increase in onset melting temperature with increasing molecular weight. In the OSF technique, the inflexion in the curve is associated with the melting temperature value. It is noteworthy that Figs. 4–6 show that as the temperature approaches the melting temperature, the materials become measurably softer before the calorimetric transition is observed. Figs. 4–6 also show that the increase in melting point accompanying the increasing molecular weight also results in a relatively wider gap between the beginning of the observable mechanical softening and the calorimetric onset of melting. The melting temperatures obtained by the OSF and DSC methods are listed in Table 2. The temperatures determined by the OSF method were 58 °C, 60 °C, and 62 °C for the 200,000 MW, 900,000 MW and 2,000,000 MW, respectively. The corresponding DSC onset temperatures were observed at 61 °C, 63 °C, and 66 °C.

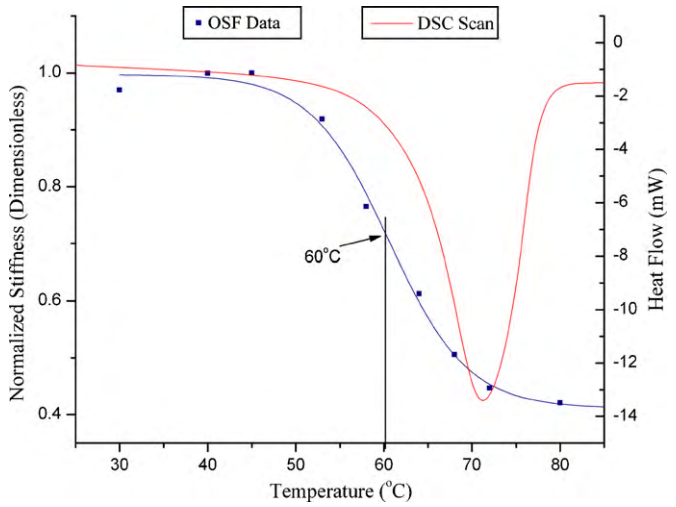

Fig. 5. Melting of PEO MW 900,000 in terms of OSF stiffness overlaying respective DSC melting endotherm.

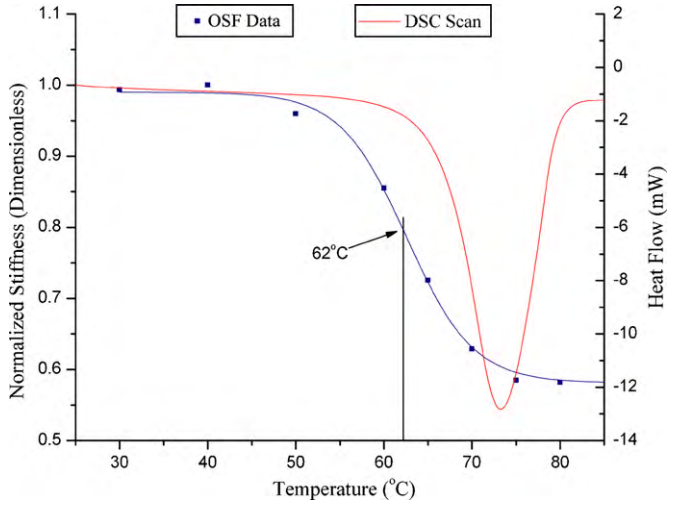

Fig. 6. Melting of PEO MW 2,000,000 in terms of OSF stiffness overlaying respective DSC melting endotherm.

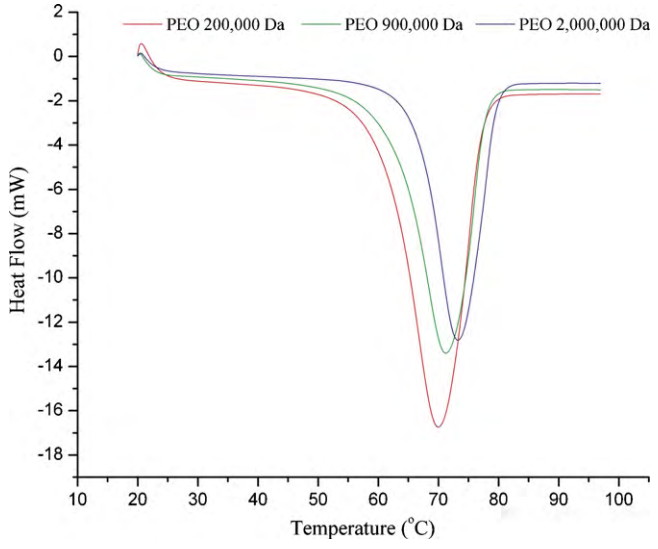

Fig. 7. DSC melting endotherms of PEO 200,000 Da, 900,000 Da, and 2,000,000 Da.

Table 2
Melting onset temperatures for polyethylene oxide powders as obtained using the broadband frequency squeezing flow (BBFSF) and differential scanning calorimetry (DSC).

Material	Melting onset temperature (°C)	
	DSC	OSF
PEO (MW 200,000 Da)	61	58
PEO (MW 900,000 Da)	63	60
PEO (MW 2,000,000 Da)	66	62

Table 3
Summary of glass transition temperatures obtained using the DSC, DMA and the OSF.

Drug Powders	DSC	DMA	OSF
Felodipine	Range: 43–47 °C Average: 45 °C STD: 2.72 °C COV: 6.04%	Range: 45–47 °C Average: 46 °C STD: 1.25 °C COV: 2.72%	Range: 49–51 °C Average: 50 °C STD: 0.85 °C COV: 1.7%
Indomethacin	Range: 44–47 °C Average: 45 °C STD: 1.66 °C COV: 3.69%	Range: 46–48 °C Average: 47 °C STD: 1.22 °C COV: 2.60%	Range: 50–52 °C Average: 51 °C STD: 0.70 °C COV: 1.37%
Griseofulvin	Range: 80–83 °C Average: 81 °C STD: 0.41 °C COV: 0.51%	Range: 79–87 °C Average: 83 °C STD: 3.73 °C COV: 4.49%	Range: 75–85 °C Average: 80 °C STD: 7.78 °C COV: 9.73%

These results indicate that overall, the mechanical and thermal methodologies agree in terms of detecting the melting transition. However, they provide somewhat different and complementary information about the same event.

3.2. Glass transition temperature for the active pharmaceutical powders

Table 3 summarizes the glass transition temperatures of the model drugs obtained by the various testing methods; DSC, DMA, and OSF. The T_g results obtained with the three methods are in good agreement. Figs. 8 and 9 show results obtained for felodipine using the three methods; other APIs showed a similar behavior. Locating the glass transition temperature using the mechanical (DMA and OSF) methods is straightforward, as the assigned T_g corresponds to

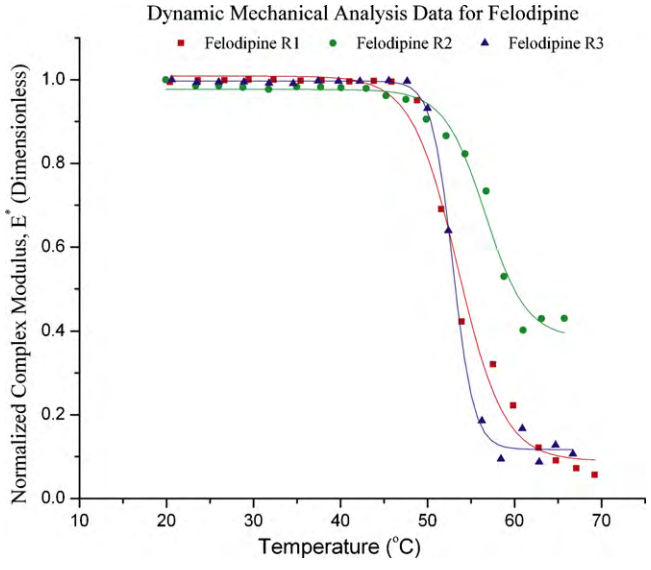

Fig. 8. DMA data for felodipine showing the dimensionless modulus versus temperature.

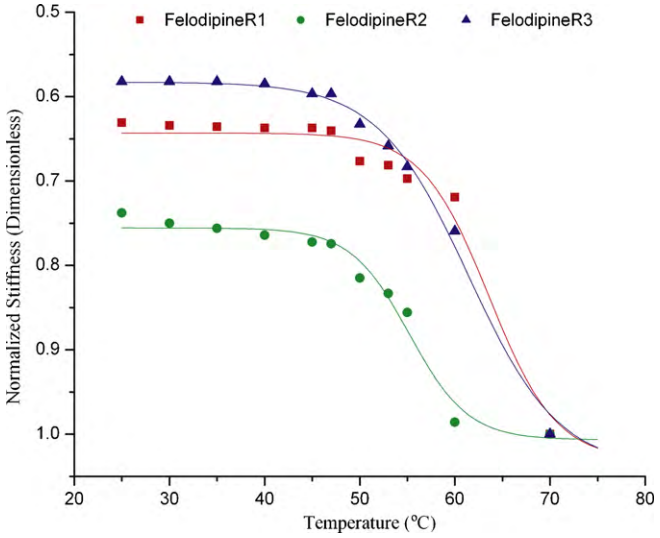

Fig. 9. OSF data for felodipine.

the inflexion of the profile. Precise assignment of the T_g value by DSC is not as straightforward. This is by no means a disadvantage of the DSC method, however. The shape and location of the glass transition detected by DSC carries information regarding the aging and relaxation of the material (Saleki-Gerhardt and Zografi, 1994). Overall, the thermal and mechanical methods agree as to the location of the glass transition. Mechanical methods provide a simpler means of assigning a T_g value, whereas the DSC method provides complementary information about the sample. Even though DMA and OSF both are based on the thermo-mechanical response of the tested material, there are some important differences between the two. In a typical DMA test, the measurement reflects the properties of a purposely made compact, rather than those of the originating powder. In contrast, the OSF method is based in applying a constant force to the powder of interest, such that the technique measures the changes in stiffness of the powder itself as it responds (consolidates) to the applied force. In pharmaceutical and food applications the physico-mechanical properties of the powders themselves are of central interest. Measurements performed directly on powders provide characterization information that can be associated to their performance (e.g. flowability, compressibility in tableting machines, etc.) during processing.

In the OSF method, as the temperature approaches the T_g, the powder particles become softer. Under the applied constant force (approximately 2N), the sample begins to compact. Under these circumstances, the measured stiffness of the sample increases so that the T_g of the powder samples is determined when an abrupt change in stiffness is observed. The DMA and OSF data shown in Figs. 8 and 9 are actually reverse normalized, by dividing the measured stiffness by the highest stiffness value of the same run. Reversing the normalization is done simply for convenience so that the glass transition by OSF and by DSC (with the particular instrument used here) both appear as down shifts in the profiles.

Another consideration is that powders are inherently not well defined; they lack a continuous, precisely defined geometry. Therefore, mechanical testing on powdered samples reflects a combination of the mechanical properties of the solid as affected by the geometrical and discontinuous nature of the sample. Fundamental mechanical properties of solids such as the complex modulus (E^*) are exactly defined in terms of a continuous solid of known geometry. Consequently, when the material of interest is a powder, and the powder itself (as opposed to a compact from it) is tested, a method like OSF provides a precise profile of the relative change in mechanical properties but does not give precise values of E^*, for example.

4. Conclusion

The T_g values obtained with the OSF method agree well with those values obtained from currently used instruments such as DMA and DSC. One practical difference between the OSF and DMA methods is that in OSF, the same analysis cell is used for directly analyzing samples, whether powders or compact. The OSF method was successful in measuring the melting and glass transition temperatures for a variety of powder materials ranging from polyethylene oxide having different molecular weights to active pharmaceutical ingredients including griseofulvin, felodipine and indomethacin. With the OSF method, melting temperatures were identified by a sudden decrease in the measured stiffness, which becomes measurable before the onset of the calorimetric onset of melting. The T_g values are identified by an increase in the apparent stiffness of the sample. The OSF concept of measuring the thermo-physical properties of powders when they undergo thermal transitions has practical advantage as compared with DMA and DSC methods since little or no sample preparation is required. The OSF method can be easily implemented in a Universal Testing Machine at a cost significantly lower than those associated with the DMA and DSC methods. Mechanical properties of the samples measured with the OSF methodology upon heating offer some distinctive behavior while transitioning the glass transition range that could be exploited to determine functional characteristics of the powders such as powder flowability and compactability.

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