J Therm Anal Calorim (2012) 108:227–233
DOI 10.1007/s10973-011-1423-y

Solid state studies of drugs and chemicals by dielectric and calorimetric analysis

Dhruthiman R. Mantheni · M. P. K. Maheswaram · Hany F. Sobhi · Naullage Indika Perera · Alan T. Riga · M. Ellen Matthews · K. Alexander

Received: 4 January 2011 / Accepted: 18 February 2011 / Published online: 11 April 2011

Abstract Novel dielectric behavior of a linear increase in ionic conductivity prior to melt temperature was observed for active pharmaceutical ingredients (APIs), organic chemicals, amino acids, and carbohydrates. Though, there are solids like polyolefins and long chain organic compounds (tetracosane, pentacosane) which do not exhibit this premelt behavior (i.e., the temperature where the onset of increase in ionic conductivity to melt temperature). We have discovered novel electrical conductivity properties and other physical analytical variations which can lead to unique synthetic routes of certain chemical entities. The above-mentioned unique variations are not related to solid–solid transitions which are quite often observed in pharmaceutical crystalline solids. These new properties are related to amorphous crystalline behavior of a solid. We have also studied the effect of various experimental variables: such as amount of mass tested, applied frequency at a given electric field and heating rate, which results in varying the onset temperature of the increase in ionic conductivity. Melting of the solids was correlated using differential scanning calorimetry (DSC). Activation energies for all the solids were measured in the premelt region using an Arrhenius plot at a specific frequency since we observed changes in the conductivity with frequency. This study focused on frequencies 0.1 to 10 Hz, since the conductivity at these frequencies related to surface analysis. This new physical properties are leading to new electro synthetic procedures to modify or prepare chemicals.

Keywords Dielectric thermal analysis · Differential scanning calorimetry · Premelt · Activation energy · Active pharmacy ingredients · Amino acids · Carbohydrates · Polymers · Organic compounds

D. R. Mantheni · M. P. K. Maheswaram · H. F. Sobhi · N. I. Perera · A. T. Riga (✉)
Department of Chemistry, Cleveland State University, Cleveland, OH 44115, USA
e-mail: a.riga@csuohio.edu

H. F. Sobhi
Department of Natural Science, Coppin State University, Baltimore, MD 21216, USA

A. T. Riga · M. E. Matthews
Buckeye Diagnostics, Beachwood, OH 44122, USA

A. T. Riga · K. Alexander
College of Pharmacy, University of Toledo, Toledo, OH 43606, USA

Introduction

In 2005, there were number of drugs evaluated by DEA and DSC in a preliminary study by Riga and Alexander [1]. Various active pharmaceutical ingredients (APIs) were analyzed by DEA, the resulting log conductivity versus temperature curve in °C revealed new electrical signatures of each drug. A very complete review was performed by Hilfiker et al. [2] on the relevance of solid state properties for pharmaceutical products but they did not include dielectric properties which were initiated in 2005. The bio pharmaceutics classification system was reviewed and did not include any electrical properties to understand the effect of solid state properties [3, 4]. A well-reviewed paper in 2006 on solid state pharmaceutical compounds and impact of ICH on Q6 guidelines did not include any information on dielectric properties [5].

The above-mentioned reviewed papers should have included the dielectric properties in order to complete a quality review on solid state properties of chemicals.

Thermal analysis studies in pharmaceuticals uses instrumentation like DSC, DEA, and TG (thermogravimetry). They were employed to study solid dispersion systems, time for drug disintegration, prediction of drug–excipients compatibility, and analysis of enantiomers, and racemates [6]. Introduction of DEA as part of thermal analysis of drugs was initiated by Dr. Riga. This opened a new door for studying many more properties of drugs and other chemicals, like premelt behavior and the determination of the amorphous and crystalline content in a solid dosage form.

The premelt behavior is significant in understanding solid state stability and reactivity. Premelt temperature range can identify residual moisture. A crystalline solid drug, e.g., sulphapyridine and acetanilide had a conductivity of about 10^{-2} pS/cm and when the drug melted the liquid amorphous drug had a conductivity of 10^{6} pS/cm as well as organic salts had conductivity of 10^{8} pS/cm [1]. Our lab has observed this striking variation of 10^{-2} to 10^{8} for a wide variety of chemicals drugs and ionic salts. Many chemicals such as drugs, organics, amino acids, and carbohydrates undergo 3 to 4 orders of electrical conductivity change prior to melting. In the solid state, the premelt variations detected by DEA and were not observed by DSC.

Riga and Alexander identified this premelt as related to its defect structure. Later, our studies showed that the premelt was either due to formation of modified Zwitter ions or an excimer. The novel premelt behavior was related to electrical conductivity variations and not permittivity values, i.e., no premelt activity was recorded in the permittivity versus temperature plot. Determining amorphous and crystalline phases in a drug is a very challenging assignment. Properties like bioavailability, feasibility, stability depend on the amorphous content of the solid dosage form. The amorphous phase in drugs was studied using DSC, X-ray diffraction, micro-calorimetry, and DSC [7]. XRD of crystalline chemicals will yield sharp peaks and the amorphous content will be represented by broad diffused bands and amorphous short range ordering produces multiple bands, therefore, XRD can be used to differentiate crystalline, semi crystalline, and amorphous content [8].

These studies cannot identify quantitatively the amount of amorphous and crystalline content present in the solid dosage form. Prior studies in our laboratories revealed the amount of amorphous and crystalline content in the solid state by DEA and DSC. The amorphous content was determined by the conductivity–activation energy in the solid state. Major premelt behavior has been attributed to the solid–solid transition as described by Mesaros et al. [9]. Temperature-dependent variations in the proton NMR of hexa hydro-1,3,5-trinitroso-s-triazine were observed in the premelt solid phase of this chemical and were related to activation of substantial motion of the molecules in the crystal lattice[10]. Dielectric thermal analysis of amino acids also exhibited an enhanced electrical linear conductivity increase prior to the melt. Matthews and Riga [10] referred to these new properties as dielectric viscoelastic behavior.

Tryptophan, a hydropathically neutral amino acid as a neat and heat treated sample, showed no premelt behavior. Cystine the most hydrophobic amino acid of all the three amino acids studied in our work has the largest difference in premelt activity. Mathews et al. characterized the 20 L-amino acids and 9 D-amino acids. Anthracene, a hetero-cyclic organic chemical, forms an excimer, while undergoing fusion this may be one of the causes for the premelt variations (Fig 2). Premelt charge transfer complexes in organics were studied using DEA and DSC by Riga and Alexander [1].

The activation energy is calculated for all the chemicals using an Arrhenius plot, where the slopes of the plot log conductivity versus $1/T$ (K) * 1000 at a particular frequency is considered and multiplied by constant yielding activation energy in J/mol. A dielectric analyzer (TAI 2970), a thermal analytical instrument can be used to study the changes in materials due to the dielectric viscoelastic transition as well as other fundamental electrical properties. Those measured are permittivity (e'), which is related to dipole content, loss factor (e'') which is the energy required to align the dipoles, AC conductivity which is (loss factor or e'' * frequency * constant) in pS/cm, activation energy in J/mol (using an Arrhenius plot). Correlation of DEA and DSC plots highlights the solid state properties which can clearly explain where the onset of increase conductivity is initiated (Fig. 4). Given below is the list of chemicals tested along with their melting temperatures (Table 1).

Table 1 Chemical compounds studied by DEA and DSC

Compound	Melting point/°C
Acetanilide (API)	116
Caffeine (API)	235
Sulfapyridine (API)	191
Acetophenetidin (API)	135
Dextrose (carbohydrate)	148
Arginine (amino acid)	221
Histidine (amino acid)	282
Anthracene (organic)	218
Naphthalene (organic)	078
Polyethylene (polymer)	130

Experimental

Experimental procedures include studying a range of chemicals such as APIs, carbohydrates, amino acids, organics, and polymers by DEA and DSC, and then further study the effect of key experimental variables (frequency, sample mass and heating rate) on the onset and the continuation of the ionic conductivity as a function of temperature in the premelt phase.

DEA (TA Instruments 2970) was used to determine electrical conductivity profiles. A single surface gold ceramic electrode (Fig. 1) was calibrated by the instrument fixtures. For each chemical tested, a sample size of $\sim$10 to 15 mg was taken so that it covered the entire interdigitated gold ceramic electrode. Samples were heated from room temperature (28 °C) at a heating rate of 3 and 10 °C/min accordingly. The experiment was carried out in an inert atmosphere of nitrogen at a flow rate of 50 mL/min. The samples were heated 20 °C above the melting temperature. Conductivity profiles were measured at a frequency range of 0.1 to 10^5 Hz at all temperatures.

DSC (TA Instruments 2920) was used to characterize melting and crystallization properties of the various chemical entities described above. Each chemical was analyzed in an aluminum pan (both crimped and open according to the sample specifications) using a sample size of 10 to 15 mg. Samples were subjected to heat–cool–heat cycle with a heating and cooling rate of 10 °C/min. Samples were heated to 20 °C above the melt temperature in the heat cycle and in cool cycle samples were cooled to 50 °C below the melt temperature. Heat flow (W/g) values versus time and temperature were generated and plotted along with the DEA graphs to better understand the premelt activity (with Universal Analysis software).

The DEA conductivity was evaluated as a function of temperature. The activation energy for electrical charging in the premelt state was calculated based on two specific ranges of frequencies, for example, a low frequency of 1 to 10 Hz and a higher frequency of 100 to 1000 Hz. The selection of the frequencies used was based on attaining a correlation coefficient approaching 0.999. The activation energy was evaluated in the premelt state for all the various chemicals studied and were defined by the overlay of DEA and DSC curves which marked the solid liquid transition. Macro photography for all the samples was recorded with a Sony® digital SLR camera at 3 to 5× magnification. An eye piece reticule was used to calibrate the macro photography system.

Fig. 1 DEA electrodes with anthracene in crystalline form (*left*), and amorphous form (*right*)

Results and discussions

We have observed multiple unique solid state variations in the chemicals tested by DEA. The phenomenon observed is attributed to the electrical change (ionic conductivity) not a crystalline change in the solid state. In order to better understand the process, we measured the effect of the applied critical frequency, the sample mass and heating rate, on this behavior of the suspected dipolar character of the chemicals. A wide variety of crystalline materials were used to define and characterize their premelt and melt temperature profile. Examples are drugs, sugars, amino acids, and organics. Those chemicals or polymers which do not exhibit premelt behavior were linear polymers low density and high density polyethylene (LDPE, HDPE), and long chain alkanes did not exhibit this premelt electrical behavior.

The Arhennius plot was used to calculate activation energy in the premelt state. The activation energy for materials varied from 35 J/mol (naphthalene) to 1600 J/mol (Acetophenetidin), the rest are listed in Table 2.

Anthracene, a polycyclic organic compound, composed of three fused rings undergoes dimerization when heated through its melt temperature (Fig. 2).

The dimerization and excimer formation is relevant in the DEA heating curve since there is no abrupt transition seen in the further heating profile. DEA electrical

Table 2 Activation energy studies of selected chemicals

Compound	Activation energy/J mol^{-1}
Caffeine	300
Sulfapyridine	950
Lidocaine	060
Acetophenetidin	1600
Dextrose	180
Arginine	340
Histidine	350
Anthracene	800
Naphthalene	035

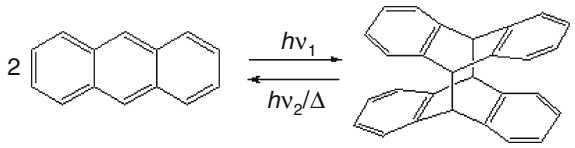


Fig. 2 Anthracene showing excimer formation

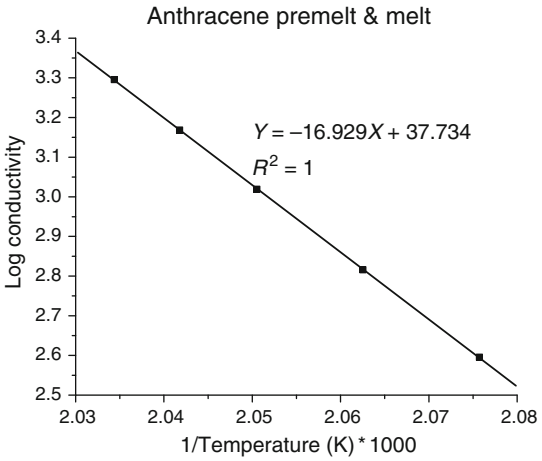


Fig. 3 Log conductivity versus $1/T$ (K) * 1000 for anthracene (2.035 melt, 2.075 premelt)

conductivity versus $1/T$ (K) is linear in the premelt temperature range through to the fusion as seen in the (Fig. 3). Anthracene is our model for excimer or Zwitter ion formation in our additional DEA results. For example, Sulfapyridine undergoes a strong linear ionic conductivity change in the premelt observed below in the superimposed DSC fusion curve (Fig. 4). Further, an Arrhenius plot of Sulfapyridine (log conductivity vs. $1/T$ (K) * 1000) has the linear fit for the curve of 0.965 a better choice of premelt values yielded a correlation coefficient of 0.999 (Fig. 5).

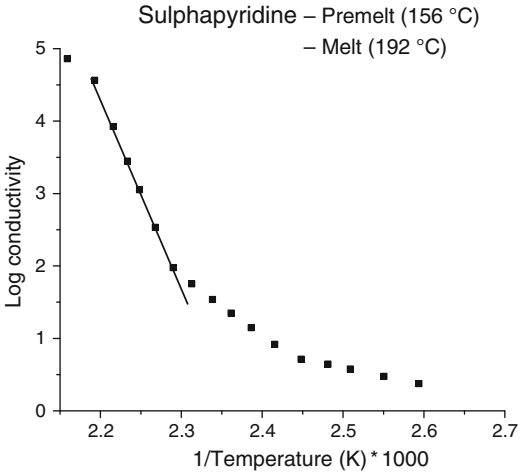
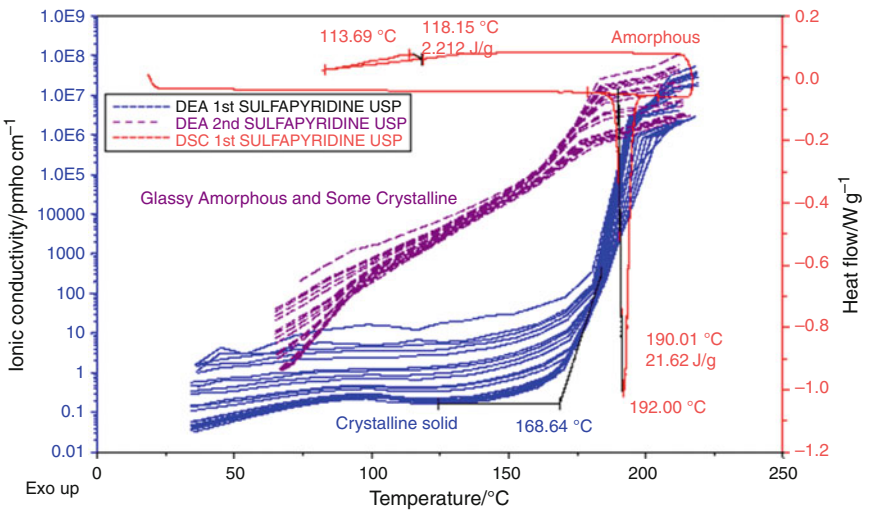


Fig. 5 Increase of ionic conductivity for sulphapyridine in the premelt region

DEA profile of polymers and long chain alkanes clearly shows the onset of increase in ionic conductivity due to the formation of amorphous entity was initiated after melt temperature of the sample (Fig. 6). The amorphous form is known to be highly conductive (10^5 to 10^8 pS/cm) Comparing these results to any other samples studied will noticeably delineate those that are undergoing the unique solid state behavior as observed for acetanilide (Fig. 7). The reason behind these polymers and long chain alkanes not showing the activity might be their molecular weight or their long chain structures. The Arrhenius plots for the chemicals show that the ionic conductivity increase in the premelt region is very linear. Conductivity values in the premelt region were taken and plotted against $1/T$ (K) * 1000 which gave a coefficient of correlation of ~0.99. Dextrose a carbohydrate is shown in (Fig. 8) and amino acid Histidine is shown in (Fig. 9).

Fig. 4 Sulphapyridine DSC and DEA curve overlay and comparing conductivity in crystalline and amorphous samples



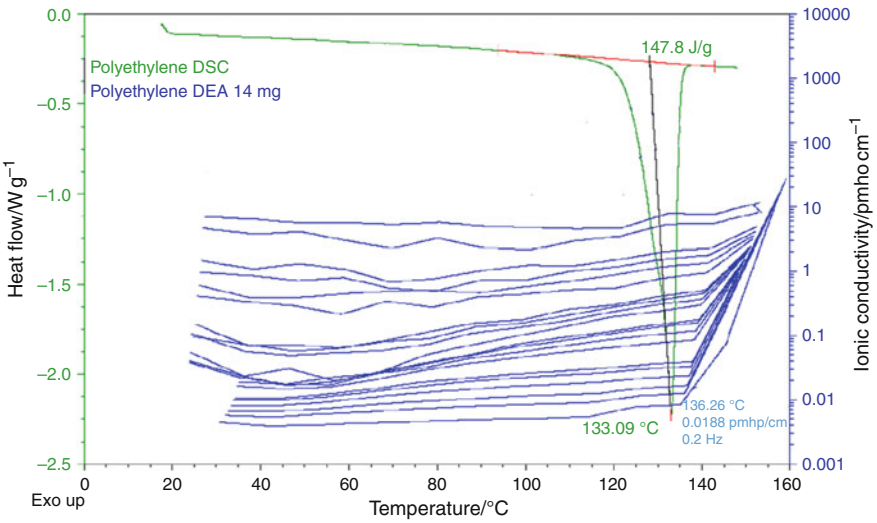


Fig. 6 DEA and DSC overlay for polyethylene showing increase in conductivity after melt. $T_{mp} = 133$ °C, $\Delta H_f = 148$ J g^{-1}; T_o = conductivity onset = 136 °C

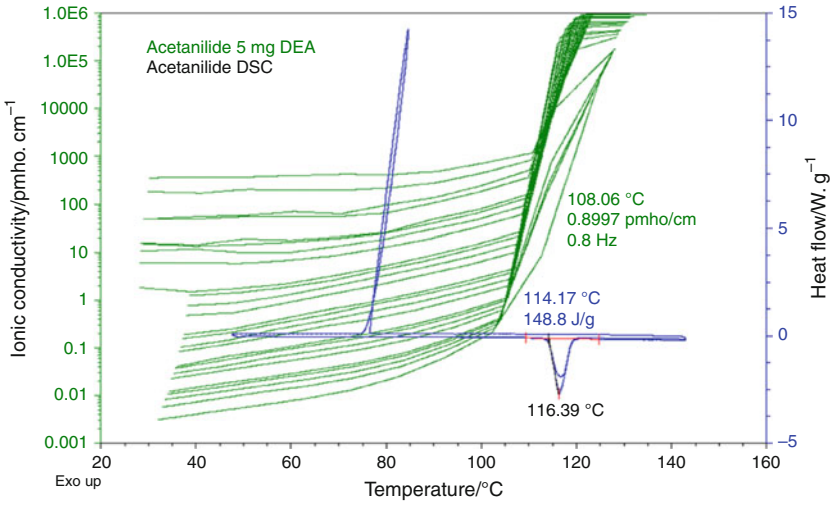


Fig. 7 DEA and DSC overlay for acetanilide showing increase in conductivity before melting in premelt region

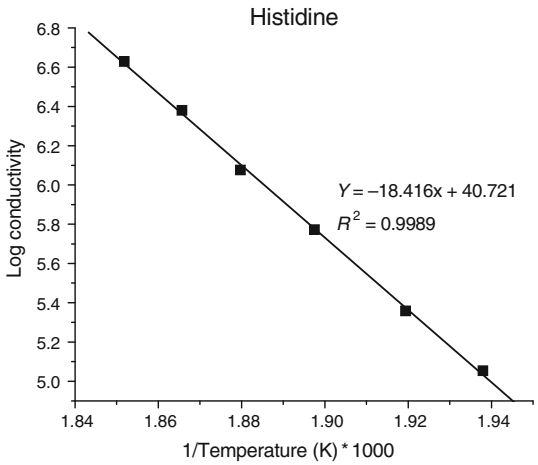


Fig. 8 Amino acid histidine showing ionic conductivity increase in the premelt region

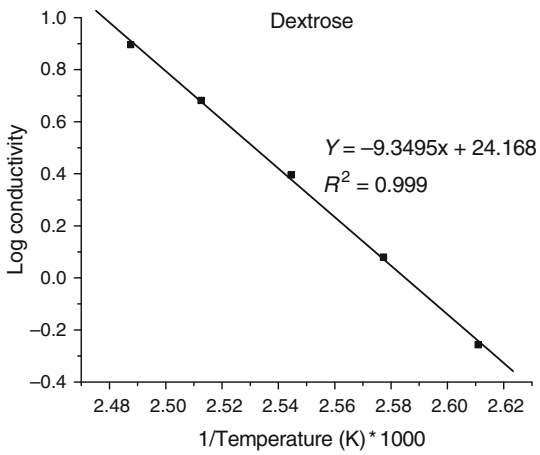


Fig. 9 Carbohydrate dextrose showing ionic conductivity increase in the premelt region

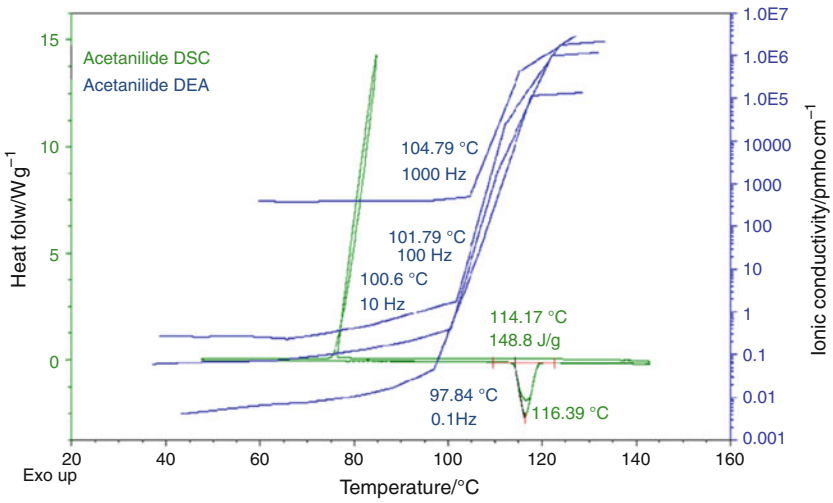


Fig. 10 DEA and DSC overlay showing the effect of frequency on the onset of conductivity in the premelt region. 0.1 Hz (97.84 °C) to 1000 Hz (104.79 °C)

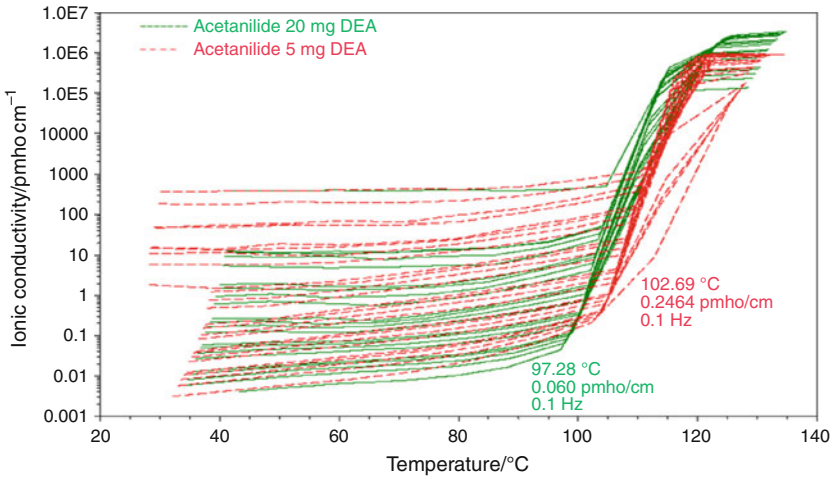


Fig. 11 Acetanilide DEA curves showing the effect of sample mass on onset of increase in conductivity in the premelt region (5 mg low sample mass, 20 mg high sample mass)

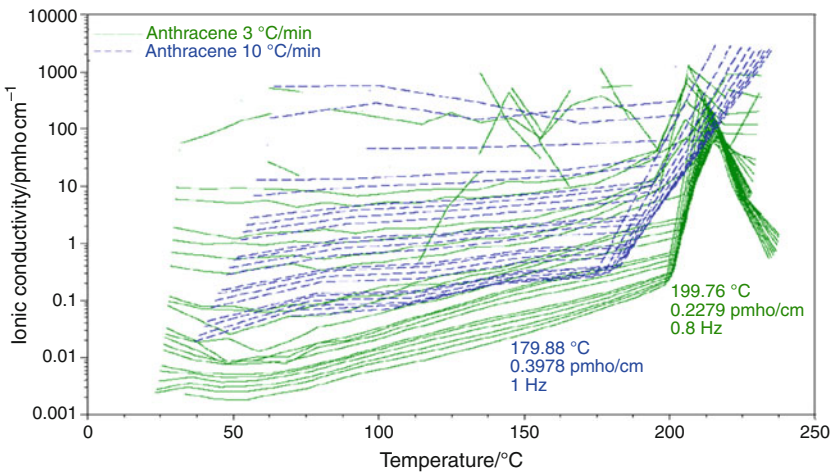


Fig. 12 Anthracene DEA curves showing the effect of heating rate on the onset of conductivity in the premelt region (heating rate 10 °C/min, heating rate 3 °C/min)

The experimental variables we studied were the sample mass, heating rate, and applied frequency. A fourfold increase in mass (5 to 20 mg) caused a 5 °C decrease in electrical onset (Fig. 10). The heating rate variation from 3 to 10 °C/min, a 3.3 increase in heating rate caused a decrease of 20 °C in the onset temperature for ionic conductivity (Fig. 11). A 10,000 fold increase in frequency (0.1 Hz to 1000 Hz) caused a 7 °C increase in the

conductivity onset (Fig. 12). These three factors tested are apparently not effective variations in dielectric analysis. The observed changes recorded are not paralleling DSC studies because of much higher sample surface area in DEA compared to DSC. It is our observation that DEA at less than one Hz is a measure of conductivity at the surface of the solid/electrode. Also, when analyzing calcium oxalate hydrate by DEA 12% loss of water (hydrate) was observed only at frequencies greater than 1000 Hz, i.e., bulk loss of water.

An increase in heating rate in DSC shifts the curve to higher temperatures, while in DEA it shifted to lower temperatures. The interdigitated electrode has more points of contacts than DSC. DEA can differentiate surface and bulk changes which cannot be seen in the DSC. The 5 to 20 °C change in the onset of conductivity by the three variables studied here are significant but not relevant since the rate of change of conductivity with temperature is the defining property (activation energy).

Conclusions

We observed unique dielectric viscoelastic, properties (Thermal Mechanical Analysis, Shravan NATAS 2010) in a variety of chemicals like carbohydrates, amino acids, APIs, and organics. This observation is confirmed by our DEA studies. LDPE and HDPE as well as long chain alkanes do not exhibit the premelt behavior. Molecular weight may be a factor in prohibiting premelt variations. This dielectric viscoelastic property observed in chemicals and drugs does suggest new synthesis routes. Activation energy, E_a (J/mol) varied based on source of chemicals from 36 J/mol (e.g., naphthalene) to 1600 (e.g., Acetophenetidin) at 1 Hz applied frequency (surface analysis—Table 2). The significance of the absolute value of the E_a is that it ranks the chemical's amorphous content. For the various crystalline and amorphous phases in the chemicals studied, the amorphous content is inversely related to activation energy. Work is in progress to define other factors that will affect the premelt activity. DSC analysis was done at 10 °C/min premelt behavior for small molecular weight materials (not polymers) can be caused by the eutectic melting. To investigate the potential of eutectic melting slower heating rates (2 °C/min) will be studied in the future. We are searching for reactive species that can produce new products for the future, e.g., a reaction of a sweetener and a fatty acid for the continuous presence of the sweetener.

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