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Pharmaceutical applications of dynamic mechanical thermal analysis

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Abstract

Dynamic mechanical thermal analysis (DMTA) is an analytical technique which involves the measurement of the rheological properties of a sample over a range of temperatures. The theoretical and practical principles of the technique are outlined, including a description of dynamic mechanical measurements and the types of measuring mode currently available. A series of examples are given in which DMTA has been used to characterise the rheological properties and glass transition behaviour of materials of pharmaceutical interest. These include synthetic polymeric samples such as film coats, gels such as pectin–water systems, polysaccharides such as hydroxypropyl methylcellulose and proteinaceous materials such as elastin. A discussion of how the technique could be used in the future to characterise pharmaceutical samples is given.

Keywords: DMA; DMTA; Gel; HPMC; Polymer

1. Introduction

Dynamic mechanical testing methods have been widely used in the characterisation of viscoelastic materials, particularly in the polymer sciences. Furthermore, there is growing interest in the use of these methods as a means of characterising pharmaceutical materials. The methods generally involve subjecting samples to an oscillating force and assessing the relationship between that force and the subsequent deformation as a function of both frequency and temperature. From such

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measurements, a more detailed idea of the rheological properties of samples may be obtained than is possible using conventional linear viscosity techniques. Furthermore, by examining the rheological properties over a range of temperatures, glass transitions and related phenomena may be detected. In this review, an introduction to both the theory and the available methodologies will be given, along with an idea of how the technique is currently used in the characterisation of materials of pharmaceutical interest. The ways in which dynamic mechanical analysis could be used in the future will also be discussed.

Before outlining the theoretical and practical aspects of the field, it is necessary to place the review in the context of the wide range of thermomechanical techniques that are currently available. Daniels [1] has reviewed these techniques and has classified them into three broad groups. Thermodilatometry involves measuring the change in the dimensions of a sample over a range of temperatures, with no external stress being applied to the material. Thermomechanical analysis (TMA) involves the application of a non-oscillatory stress to a sample and the measurement of the resulting deformation over a range of temperatures. Dynamic mechanical analysis (or dynamic themomechanometry) involves the application of an oscillating stress to a sample over a range of temperatures. It is the last category that will be discussed here.

2. Theory of dynamic mechanical testing

The theories relating to the measurement of viscoelastic materials has been described in detail [2–4] and only a brief outline will be given here. In order to understand viscoelasticity, it is necessary to first consider the rheological behaviour of simple solids and liquids. For perfectly elastic solids, the behaviour is described by Hooke's law, whereby the applied stress is proportional to the strain. The classic example is the loaded spring, whereby the extension of the spring (strain) is directly proportional to the applied weight (stress). This system does not involve any time dependent behaviour, i.e. the response to changing the weights is instantaneous. For liquids, the response to an applied stress must be considered in terms of the rate of strain, as the sample will flow rather than exhibit an instantaneous deformation. For perfectly Newtonian liquids, the rate of strain will be proportional to the applied stress, the constant of proportionality being the viscosity. In these two extreme cases, therefore, solids respond instantaneously to an applied stress, while for liquids the response is time dependent in that it is the rate of strain, rather than the strain itself, that is proportional to the stress.

A number of deviations from this ideal behaviour have been described and these may be classified into two categories. Firstly, stress anomalies, whereby the relationship between the stress and strain in solids, or the stress and rate of strain in liquids becomes non-linear. This is seen, for example, when a solid exceeds the elastic limit, or when a liquid behaves in pseudoplastic (shear thinning) manner. Secondly, the stress may depend on both the strain and the rate of strain. In other words, the sample will behave like a liquid in that it will flow, but also like a solid in that there

is not a constant rate of deformation on application of the stress. Materials which exhibit this type of behaviour are termed viscoelastic. Qualitatively, viscoelastic solids can be considered to deform over a period of time; hence if one holds such a solid at a constant deformation and measures the stress required to hold that solid in this position, the stress would decrease over a period of time. In contrast, to hold a liquid at a constant deformation would require no stress at all, as the stress is proportional to the rate of strain (deformation), not the strain itself which in this case is constant; an elastic solid, in contrast, would require a constant stress which would show no time dependence. Viscoelastic behaviour therefore combines elements of both these types of behaviour. Now considering the situation whereby a constant stress is applied to a sample and the strain is measured, that strain will increase over a period of time as the sample deforms. This phenomenon is known as creep and is the basis for a widely used method of measuring the rheological properties of materials.

If one increases the stress applied to a viscoelastic material, then up to a specific value the proportionality between the stress and strain will remain constant, even though the strain may vary with time. In other words, up to this value, the sample is showing time anomalies, but not stress anomalies. The range of stress/strain ratios over which this is true is known as the linear viscoelastic region. When studying viscoelastic behaviour, it is usual to ensure that one is using conditions whereby the sample is within the linear viscoelastic region in order to simplify interpretation of the results.

The measurement of the deformation of solids may involve one of a number of approaches. These include shear stress, whereby a force is applied laterally to a sample; bulk compression, whereby a normal force is applied each side of a sample; simple extension, whereby a sample is extended in one direction; and bulk longitudinal deformation, whereby a thin plate-like sample is compressed along the thin side. In terms of the methods used to measure viscoelasticity, a number of approaches may be used. Firstly, constant stresses or strain may be applied to the sample and the response measured. For example, creep testing involves applying a constant stress to a sample and the strain is measured over a period of time, as mentioned above. Alternatively, stress relaxation involves bringing the sample to a given deformation and measuring the stress required to maintain that strain as a function of time. Samples can also be subjected to a linearly changing stress or strain and the corresponding parameter measured.

In addition to these linear methods, dynamic loading patterns may also be used, whereby the stress or strain is applied sinusoidally. It is this approach that forms the basis of dynamic mechanical testing methods and hence will be described in some detail. If we take a system whereby the sample is being subjected to a sinusoidally varying tensile strain ε, the strain at any point in time may be described by

$$\varepsilon = \varepsilon_0 \cos \omega t \tag{1}$$

where ε_0 is the maximum amplitude of the strain, ω is the angular frequency and t is the time. The strain will follow the stress σ if the system is in the

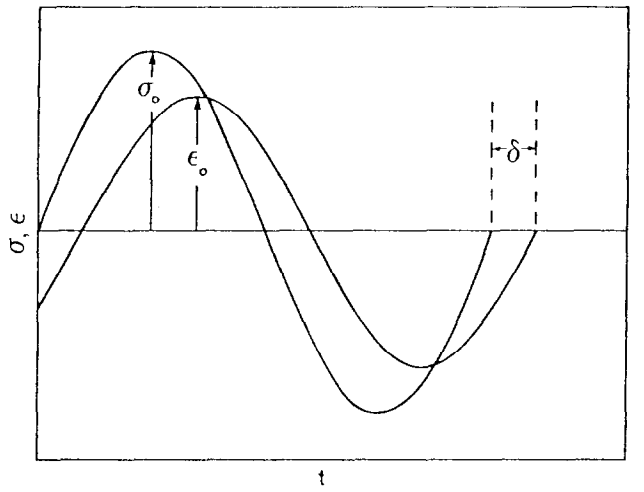


Fig. 1. Variation in the stress and strain of a sample subjected to an oscillating signal with time [3].

linear viscoelastic region, but there will be a phase lag between the two, given δ; hence

$$\sigma = \sigma_0 \cos(\omega t + \delta) \tag{2}$$

The relationship between the two may be visualised with reference to Fig. 1. This can be resolved into in-phase and out-of-phase components via

$$\sigma = \sigma_0 \cos \delta \cos \omega t - \sigma_0 \sin \delta \sin \omega t \tag{3}$$

One may now see how this approach may be used to study viscoelastic behaviour. Comparison of Eqs. (1) and (3) shows that there will be a stress component which is in-phase with the strain: this component will have an amplitude of $\sigma_0 \cos \delta$. There will also be a stress component which will lead the strain by 90° (as it varies as sin ωt, rather than cos ωt) and will have an amplitude of $\sigma_0 \sin \delta$. A further consequence of this analysis is that the out-of-phase component is the first derivative of the strain. This shows that the in-phase component represents the relationship between the stress and the instantaneous deformation of the sample (i.e. the solid response) while the out-of-phase component shows the relationship between the stress and the rate of strain (i.e. the liquid response). Consequently, it is possible to deconvolute these two components of the response with one measurement.

The response is conveniently expressed in terms of the storage E and loss E moduli, where

$$\sigma = \varepsilon_0 E' \cos \omega t - \varepsilon_0 E'' \sin \omega t \tag{4}$$

where the moduli are given by

$$E' = \frac{\sigma_0}{\varepsilon_0} \cos \delta \tag{5a}$$

and

$$E'' = \frac{\sigma_0}{\varepsilon_0} \sin \delta \tag{5b}$$

The storage modulus is so called because it represents the energy stored per cycle within the system (as the "solid" response is elastic), while the loss modulus represents the energy dissipated per cycle (as the "liquid" response is a non-reversible deformation). The two components may also be expressed in complex form, where

$$E^*(\omega) = E'(\omega) + iE''(\omega) \tag{6}$$

with E^* representing the complex modulus at any frequency ω and i being the square root of -1. The relationship between the two components is

$$E''/E' = \tan \delta \tag{7}$$

While the example of tensile measurements has been used here, the same principles apply to other types of deformation described earlier. Measurement of these parameters under a defined set of conditions comes under the broad term of dynamic mechanical analysis (DMA). However, all three terms in Eq. (6) are dependent on the temperature and frequency of measurement, and it is this dependence, particularly on the temperature, that forms the basis of dynamic mechanical thermal analysis (DMTA). The use of the technique in the temperature domain is preferred to frequency scans because of the limited frequency range available on any single instrument, while the available temperature range can cover all the transitions of interest.

3. Methods of testing and instrumentation

Dynamic mechanical analysis (DMA) has become increasingly popular not only due to the wide applicability of the information obtained, but also due to the wide range of measuring methods that may be used, often within a single instrument. There are several approaches to the measurement which can be divided into four subgroups [3].

3.1. Forced vibration non-resonance methods

This method of material characterisation includes what is considered classical DMA and DMTA. Samples are typically subjected to a dynamic force (stress) or deformation (strain) over a frequency range of 0.01–100 Hz. The dynamic modulus and loss factors are calculated directly from the measured amplitude of and phase angle between the force and displacement curves. Data may be obtained over a wide temperature range, depending on the specifications of the equipment being employed. Measurements are generally made at frequencies other than the resonance frequency of the system, as this frequency may vary during the course of an

experiment due to the material structure changing on heating or cooling. It is this method that will be discussed in detail in this review as it represents the most widely used approach for materials of pharmaceutical relevance.

One of the advantages of the equipment currently available is the versatility of the measuring systems. These may include the following geometries:

(a) Parallel plates, whereby a material is placed between two plates and a compression force applied. This mode is particularly useful for semisolids such as gels and foams.

(b) Extension analysis involves the sample being clamped at either end and the material examined under tension. This is widely used for low modulus solids such as thin films and fibres.

(c) Single and dual cantilever modes, whereby the sample is clamped at one or, more usually, two points along the specimen and a measuring head applied to the sample. In the case of the dual cantilever mode, the head will be placed between the two clamps. This type of assembly is useful for materials with mid-range moduli such as elastomers and materials above their glass transition temperatures.

(d) Three point bending is used for high modulus materials and involves placing the sample on two knife edges. A measuring head is then placed between these edges and a vertical, downward force applied.

3.2. Torsion pendulum

This method involves the application of a torque to a sample, typically a rod-shaped material. The oscillations of the sample on removal of the angular force are measured, particularly in terms of measuring the damping of the signal with each cycle. While the technique is less versatile than forced-vibration methods, it does allow a more accurate characterisation of several classes of material, particularly high modulus samples for which the displacement using, for example, three point bending may be small.

3.3. Audiofrequency resonance techniques

At frequencies between approximately 20 Hz and 20 kHz, the moduli of rigid, low loss materials may be measured by audiofrequency resonance techniques. If one applies a signal to a sample over this range of frequencies and measures the vibrational amplitude of the material, maxima will be observed at certain frequencies (resonance frequencies). The storage modulus and tan δ can be calculated from the sample dimensions and the resonance behaviour.

3.4. Ultrasonic wave techniques

This allows the extension of the frequency range available from the other techniques and involves the application of a sound wave through a material and measurement of the time of flight and reduction in amplitude of the wave over a

specified path, from which the storage and loss components of the complex modulus may be determined for the material.

4. Pharmaceutical uses of DMTA

In general terms, dynamic mechanical analysis offers a number of possibilities and advantages over other techniques. It is excellent for detecting thermal events which involve subtle changes in the mechanical properties of samples and is usually associated with the measurement of glass transitions and related phenomena. It is also highly useful for measuring the rheological properties of a range of samples over and above the detection of thermal transitions. Finally, it is extremely versatile, with a wide range of samples being measurable using the one technique. Furthermore, it may measure the moduli of samples on a template such as paint films on a solid sample, although surprisingly this advantage has not yet been fully exploited pharmaceutically.

The principal disadvantages of the technique lie in the sample preparation and the interpretation of the results. In all cases, the method by which the sample is presented to the instrument and the experimental conditions used must be thoroughly explored in order to obtain reproducible and accurate results. In particular, care must be taken when clamping the sample; if the material is too loosely clamped the sample will slip on softening, while our experience has been that very tight clamping leads to poor reproducibility. Furthermore, given the range of frequencies, heating rates and initial stresses that may be applied to a sample, it is necessary to perform fairly extensive preliminary studies prior to carrying out the main investigation. However, as DMA (or DMTA) is a highly sensitive technique, it is hardly surprising that care needs to be taken in determining the optimal measuring conditions.

The second disadvantage is that the interpretation of the results may not always be straighforward, particularly when multicomponent systems are under study. It is not always obvious whether the phenomenon under observation is a main chain glass transition, a side chain transition, a thermal event associated with the crystalline regions of the sample or one of a number of other possibilities. The system currently used whereby the peaks are assigned using the Greek alphabet in decreasing order of temperature (see below) is useful in that it is a widely used nomenclature, with the α peak generally being associated with the main glass transition. However, it may lead to some confusion because, for example, the highest temperature peak is not necessarily the glass transition, as some materials decompose before this thermal event takes place or else may show events about the T_g.

The previous and potential uses of the technique for the study of pharmaceutical materials rest largely on two factors. Firstly, the technique can measure glass transitions and related thermal events with great clarity. This is important not only for polymeric systems such as film coats, but also for considerations of stability [5], water sorption [6] and collapse phenomena in lyophilised products [7]. Secondly,

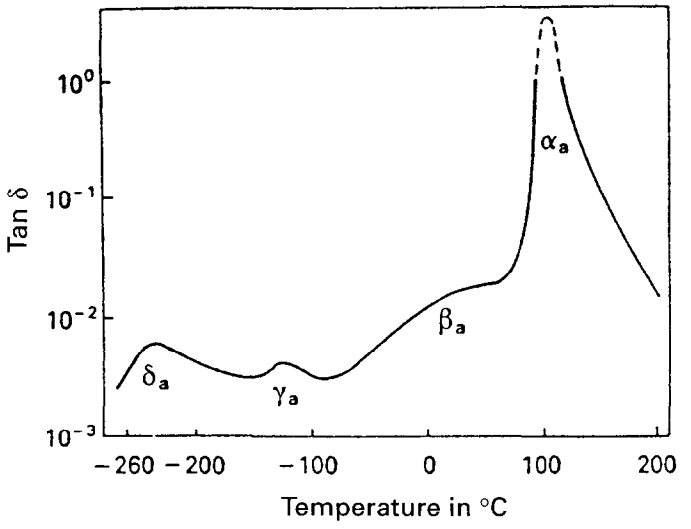
the method provides a means of assessing the rheological properties of a wide range of materials isothermally. In particular, the technique is useful for semisolid and solid materials which may be too rigid for instruments such as cone and plate controlled stress rheometers and may also exhibit behaviour which may be too subtle for detection using less sensitive equipment such as may be used to measure the moduli of compressed tablets. In this section, the term "pharmaceutical" has been interpreted loosely in order to include studies whereby materials of pharmaceutical interest have been tested even if that was not the primary concern of the authors, in order to highlight the potential of the technique.

4.1. Synthetic polymers

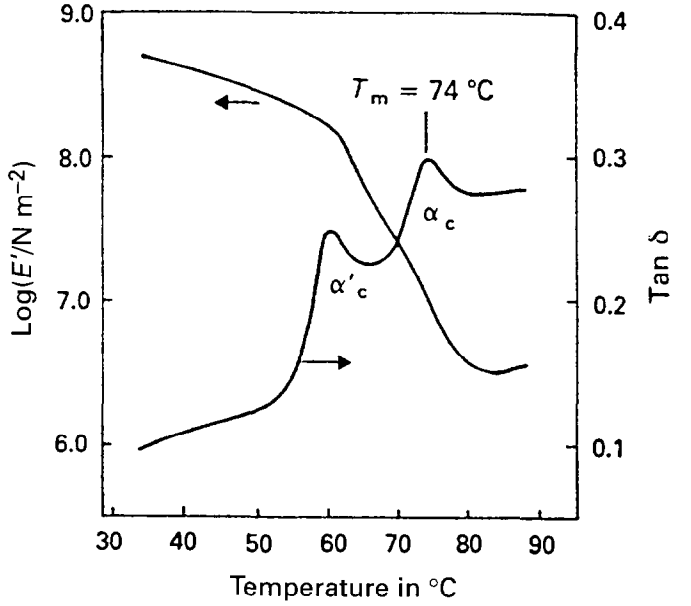
The principal use of dynamic mechanical testing methods has been in the characterisation of polymers, particularly in terms of glass transition phenomena. Several reviews are available on the application of the technique to polymeric system (for example, Refs. [4,8,9]) and only a brief summary will be given here.

It is common practice to label major loss transitions α, β, γ and δ in decreasing order of temperature of appearance, sometimes with a subscript a or c to indicate whether the transition is occurring in the amorphous or cystalline phase of the sample (if known). Amorphous polymers such as polystyrene exhibit a major (glass) transition related to the mobility of the main chain, while secondary (β, γ and δ) transitions may also occur due to side chain motions or localised motions in the main chain. Crystalline polymers may also exhibit transitions which are related to motions associated with the amorphous regions between lamellae, but may also exhibit transitions which are related to the behaviour of the crystalline lamellae themselves such as melting or premelting. Examples of these transitions are shown for an amorphous polymer (polystyrene) and a crystalline polymer (high molecular weight polyethylene glycol) in Figs. 2(a) and (b). DMTA may also be used to assess the degree of crystallinity in an amorphous polymer, because amorphous materials show a sharp drop in storage modulus at the glass transition, while a gradual decline in modulus associated with multiple transitions suggests a semicrystalline structure.

The degree of crosslinking present in a polymer may be estimated using the technique, because an increase in crosslinking produces an increase in the glass transition temperature and a broadening of the tan δ peak. The uses of DMTA as a means of assessing cure processes has been reviewed by McCrum et al. [4] and Skrovanek [10]. These include the possibility of assessing the optimum conditions for a cure process by measuring the modulus over a range of temperatures, because the crosslinking process will result in an increase in the modulus, hence indicating the minimum cure temperature. Measurements may also be made over a period of time at a single temperature in order to assess the kinetics of the process [11–13]. An example of such a study with pharmaceutical implications is that of Oysæd [14] who examined the influence of five different crosslinking agents on the dynamic mechanical properties of acrylic systems such as polymethlmethacrylate (PMMA) which are commonly used for bioengineering purposes, finding that the glass



(a)



(b)

Fig. 2. Dynamic mechanical data for, (a) polystyrene in the temperature domain at approximately 1 Hz; (b) high relative molecular mass poly(ethylene oxide) fast cooled from the melt at 1 Hz [9].

transition behaviour is highly dependent on the quantities of crosslinking agents used. The effect of plasticisers on a polymer may also be assessed using DMTA, because these materials may cause a decrease in the glass transition temperature and a broadening of the tan δ peak. Jones [15] examined Eudragit films containing the antibiotic metronidazole for use as wound dressings using the technique, reporting

that the presence of the drug had a plasticising effect on the film. For example, incorporation of 2.4% w/w metronidazole into film of Eudragit RL100 reduced the temperature of the main α transition from 52°C to 36°C and from 42°C to 32°C for Eudragit RS100. Because these films are designed to be applied to wounded skin, the moduli of the samples are of clear relevance to their performance as products; hence a knowledge of the plasticising effects of the incorporated drugs is of importance when choosing the most suitable polymer for these dosage forms.

DMTA may also be used to analyse fibres in the tension mode. This has been used in the study of suture materials [16]. The authors examined the properties of four suture materials (Prolene, Maxon, Vicryl and silk) in order to assess the changes in their modulus with time, as this may have a dramatic effect on the surgical outcome. For example, relaxation of a surgical loop around a blood vessel may lead to haemorrhage, while alternatively the relaxation of sutures may be beneficial in settling wounds, as it is known that overtight sutures can result in a greater degree of scarring. The authors studied the stress relation of the materials and reported a β transition in Prolene (composed of a polypropylene monofilament) which was associated with the amorphous region of the polymer. This transition occurred just below room temperature as indicated in Fig. 3. The authors argued that the frequency dependence of the transition indicates that this material may show time-dependent behaviour, possibly leading to changes in modulus with time. In

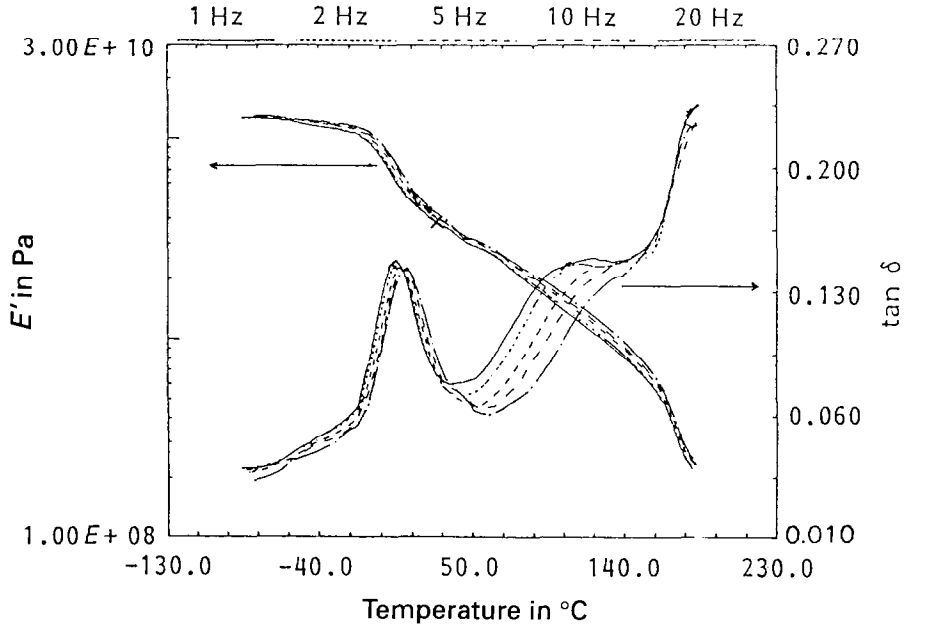


Fig. 3. Dynamic mechanical analysis of prolene (polypropylene monofilament suture). The lines refer to different measuring frequencies, as indicated at the top of the diagram. Measured under tensile deformation at 2°C min^{-1}. (From Ref. [16].)

contrast, the main softening temperature for silk was 221°C, with a relatively flat response being seen at lower temperatures. This material was therefore considered to be stable at room temperature. The study shows how DMTA may be used to predict the stability of polymeric materials, which suggests a number of pharmaceutical applications such as predicting changes in the structure, and hence release characteristics of implants, film coats and other polymeric preparations.

A number of studies have been performed using DMTA to characterise dental materials. For example, Clarke [17] studied heat-cured polymethylmethacrylate-based materials. In addition to being able to compare the moduli of various materials, the author was able to calculate the activation energies of the transitions by plotting the logarithm of the frequency of the rubber–glass and β transitions against the inverse temperature, as shown in Fig. 4. In later studies, the author examined the properties of bis-phenol A-related resins and heterocyclic methacrylates [18,19]. These studies are of importance in characterising and comparing dental materials whose efficacy relies heavily upon their rheological properties.

DMTA can be used to assess the homogeneity of polymer blends and copolymers. The response of random copolymers generally falls in between those corresponding to the homopolymers, while the presence of blocks of either species in the chain may result in maxima at temperatures corresponding to those of the homopolymer. The response of blends is similar, in principle, with incompatible blends showing characteristics of both species while miscible blends may show a single response which is between that of the individual components. The miscibility of polymer blends has been discussed in detail by Utracki [20]. In a study investigating the properties of Eudragit film coats, Lafferty [21] studied cast films of Eudragit NE30D and Eudragit NE30D/Aquacoat mixed systems, typical results being shown in Fig. 5. Changing the composition of the film results in changes in the glass transition characteristics, with the peak at approximately 30°C being ascribed to the Eudragit component and the peak at approximately 115°C to the Aquacoat component. The author was able to study the miscibility of the two components using the technique, hence aiding the understanding of the performance of these polymers as film coats.

4.2. Gels

The rheological evaluation of gels is of considerable pharmaceutical importance in understanding product performance, particularly in terms of drug release properties. One problem associated with these systems is that they may occur with a wide range of moduli; hence many rheological techniques may be inappropriate for more rigid gels. The versatility of measuring systems afforded by DMTA may be exploited in this case, allowing measurement of a wide range of materials with the one instrument.

In the food industry, the technique has been used to characterise a number of gel systems. Watase and Nishinari [22] studied the properties of methoxyl-pectin gels, particularly with a view to understanding the effects of pH and added dimethyl

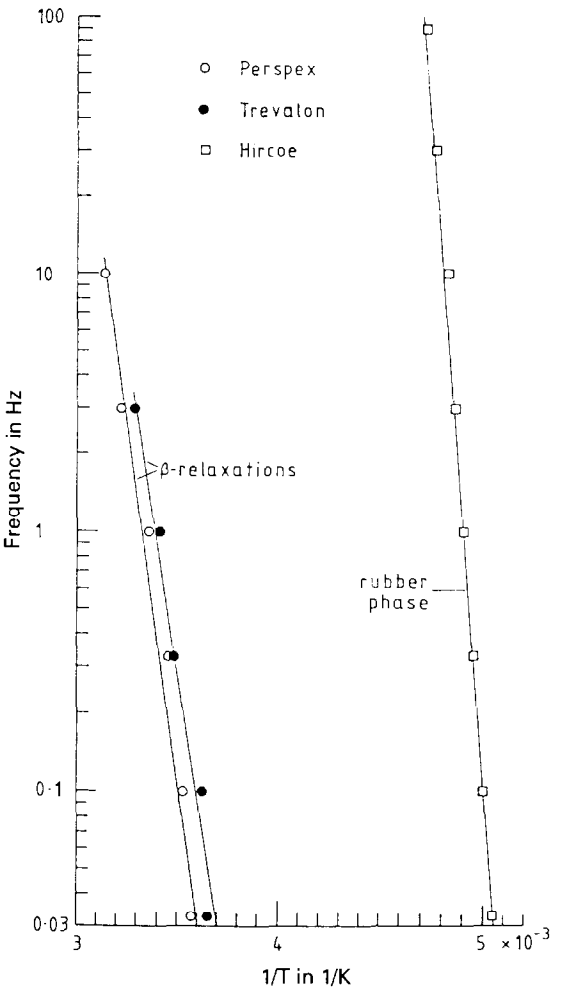


Fig. 4. Frequency as a function of $1/T_{\beta}$ and $1/T_{\text{rubber}}$. Dual cantilever mode, 4 C min^{-1}. (From Ref. [17].)

sulphoxide (DMSO) on gel structure. DMSO is known to alter water binding within gels, resulting in changes in the gel properties of agarose and poly(vinyl alcohol) systems [23,24]. By using the technique in conjunction with differential scanning calorimetry, the authors were able to characterise not only the rheological properties of the system under a range of pH values and DMSO concentrations but also the sol–gel transition temperature, from which information on the bonding thermodynamics could be obtained. The pectin itself formed a gel with a high elastic modulus, with a maximum being seen at a DMSO mole fraction of approximately 0.2.

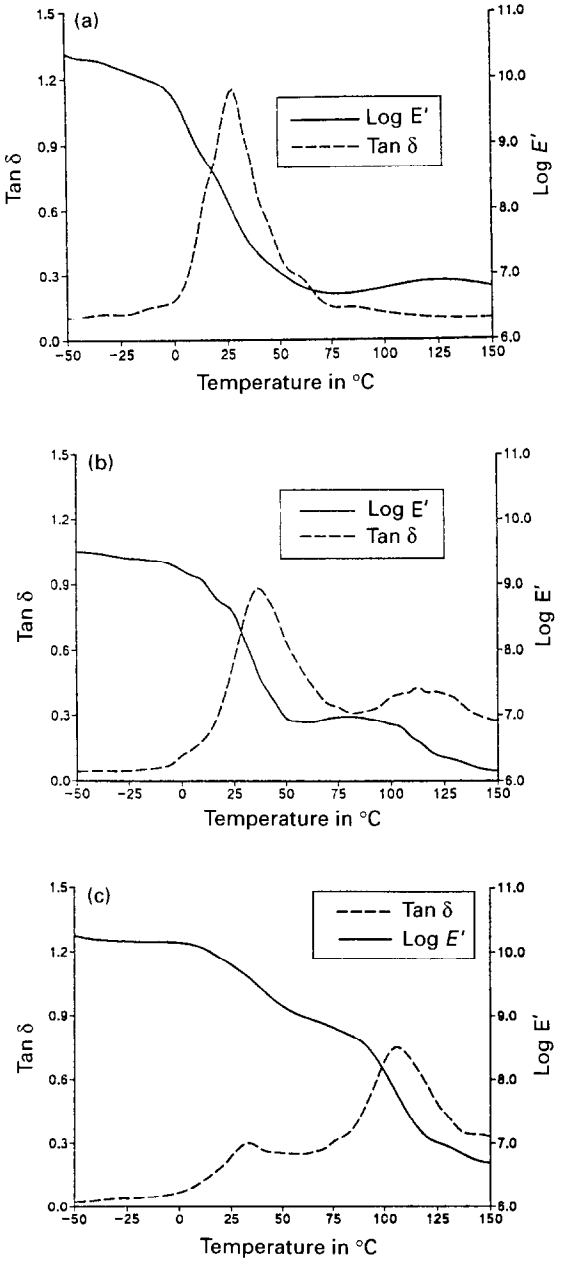


Fig. 5. Eudragit NE30D/Aquacoat films measured at 1 Hz in single cantilever mode at 3°C min^{-1}: (a) 100% Eudragit NE30D; (b) 70% Eudragit NE30D; (c) 50% Eudragit NE30D. (From Ref. [21].)

4.3. Polysaccharides

In addition to the analysis of gels, DMTA has also been used as a means of assessing the glass–rubber transitions of polysaccharides in the dry state. For example, Scandola et al. [25] examined the glass transitions of dextran, pullulan and amylose. The authors used DMTA in combination with thermogravimetric analysis to establish the characteristic water loss of the samples, and the mechanical changes corresponding to this loss of water. Due to the presence of strong intermolecular forces within solid polysaccharides, the glass transition of the amorphous phase tends to occur at a very high temperature, often above the temperature of decomposition. Consequently, often only secondary transitions are seen for these polymers, as shown for amylose in Fig. 6. The letters A to D refer to decreasing water contents within the sample. The higher temperature peak on curve A is associated with water loss, while the lower temperature peak is associated with a secondary transition. This peak increases in temperature as the material is dried, while for sample D a second, lower temperature peak is also seen. The authors argued that two hydration regions exist within the solid polysaccharide. At low

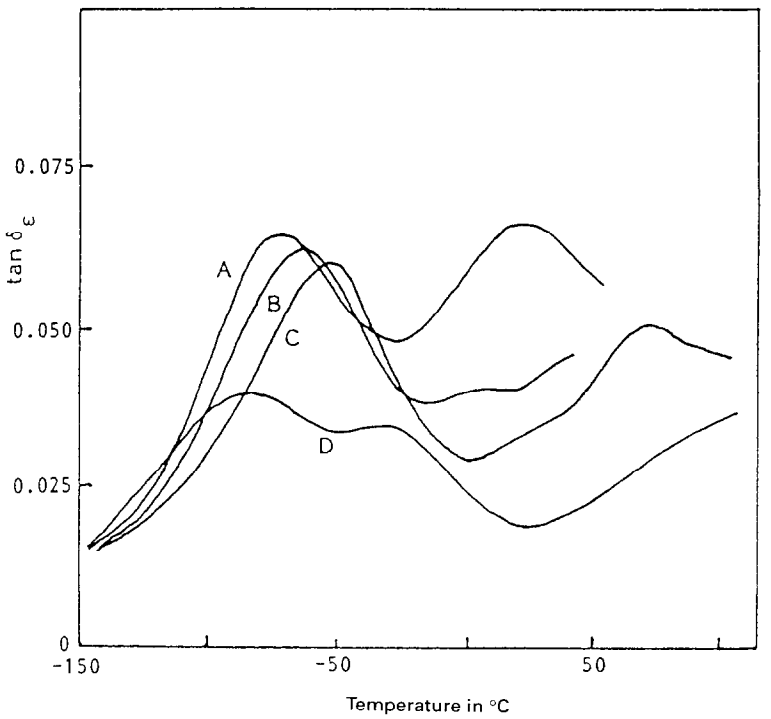


Fig. 6. Dynamic mechanical curves of amylose prepared under different conditions (measured at 3 kHz): curve A, conditioned under ambient conditions; curve B, stored under nitrogen at room temperature for 30 min; curve C, heating to 60°C under nitrogen; curve D, heating to 120°C under nitrogen. Tensile mode, 1°C min^{-1}. (From Ref. [25].)

levels of hydration, the water molecules form a hydrogen bonded network with the hydroxyl groups of the polysaccharide molecules, while at higher hydration levels the water is present in the free state. The dynamic mechanical spectra of these systems are a reflection of these interactions and hence DMTA may be used as a means of characterising water binding in solid polysaccharides.

A number of studies have examined cellulose and cellulose derivatives. Rials and Glasser [26] examined hydroxypropyl cellulose (HPC) films, particularly with a view to examining the effects of added crosslinking agents. The authors used DMTA with differential scanning calorimetry to show that hydroxypropyl cellulose consists of three phases (crystalline, amorphous and an intermediate phase) which show transitions at different temperatures. Kararli et al. [27] studied the behaviour of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and hydroxyethyl cellulose (HEC), all of which are used in the pharmaceutical and food industries. The authors showed DMTA to be a highly sensitive technique for the measurement of transitions in these systems. The authors suggested that the secondary transitions shown in these polymers could be associated with diffusion of relatively small molecules such as oxygen and water, which could affect the stability of formulations as well as effecting drug release patterns.

Starch products may be produced in a freeze-dried form in order to improve their durability, and recently this technology has been extended to the manufacture of starch capsule shells. The freeze-dried products are difficult to characterise using standard techniques. Poliszko et al. [28] used DMTA together with dielectric analysis to demonstrate different relaxations in the gel systems, as shown in Fig. 7(a) and (b). The mechanical behaviour is associated with weakening of rotational barriers which stabilise the conformational structure, leading to a decrease in storage modulus. The dielectric data show a loss peak at approximately 200 K associated with increased mobility of the hydroxymethylol groups, while the higher temperature response is associated with intramolecular hydrogen bond breakage and reorientation of polar segments of the chain. While a full discussion of dielectric analysis is outside the scope of this review, the study is an example of how this technique may be usefully employed in conjunction with DMTA.

4.4. Proteinaceous material

A number of materials that may be used in both the pharmaceutical and food industries are proteinaceous in nature. For example, gluten is obtained from wheat flour and contains a mixture of starch, lipid and protein. Gluten proteins are responsible for the viscoelastic properties of baked products; hence a knowledge of the glass transition behaviour is important in understanding product performance. This behaviour was studied by Kalichevsky et al. [29], including an investigation into the plasticising effect of water and the effects of sugars on the glass transition. The compatibility of lipids and emulsifiers with gluten was also later investigated by the same methods [30]. The study showed that the hydrophilicity and molecular weight of the additives are important in determining the effect it has on the glass transition of gluten. While the behaviour of gluten is in itself not of great

pharmaceutical interest, the investigation does demonstrate that the technique may be used to examine the effects of interactions of sugars, lipids and water on the structure of proteins.

A number of more pharmaceutically relevant proteinaceous materials such as keratin have been studied using the technique, particularly with a view to studying the plasticising effects of water [31]. Elastin is a rubber-like protein which is an essential mechanical component of many tissues including skin, lung and arterial walls. While the material is brittle in the dry state, it has low modulus viscoelastic properties when hydrated. Furthermore, changes in behaviour of elastin have been associated with arterial disease, because elastin binds to lipids, notably cholesterol esters, especially in the vicinity of atherosclerotic plaques. An understanding of the mechanical properties of this material is therefore extremely helpful in understanding these disease processes. A thorough study by Lillie and Gosline [32] has examined the effects of hydration on the dynamic mechanical response of aortic elastin using a series of frequency sweeps at a range of temperatures. The data were analysed using the method of reduced variables [2]. For the frequency sweeps taken at different temperatures, the profiles were shifted along the frequency axis at a

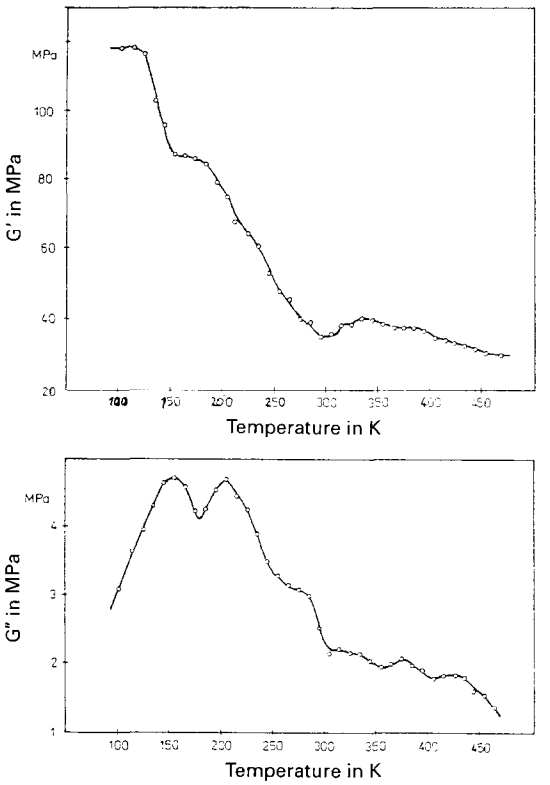
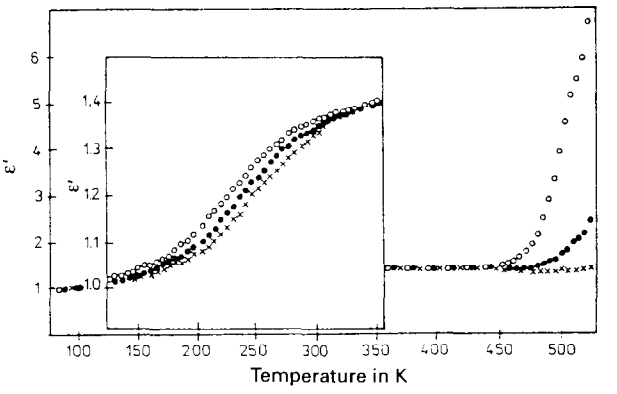
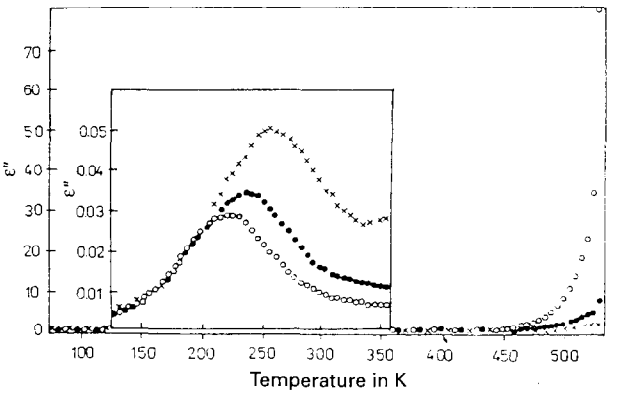


Fig. 7. (a).





(b)

Fig. 7. (a) Mechanical storage (G') and loss (G'') moduli for freeze-dried starch gels using the torsion pendulum method at 0.25 Hz. (b) Dielectric permittivity (ε') and loss (ε'') for freeze-dried starch gels; ○, 0.4 kHz; ●, 2 kHz; ×, 10 kHz. (From Ref. [28].)

distance a_T until the curves overlapped. This displacement may be related to the difference in the temperature of measurement and the glass transition temperature Williams–Landel–Ferry (WLF) equation [2], where

$$\log a_T = -C_1^g(T - T_g)/(C_2^g + T - T_g) \tag{8}$$

with C_1^g and C_2^g being constant and T_g being the glass transition temperature of elastin at each water content. The glass transition temperature is obtained from previous studies [33] using the equation

$$T_g = 201 - 126 \log c \tag{9}$$

where c is the water content; hence it was possible to calculate the two constants in Eq. (8) and so predict the shift in the curves at any temperature. The data derived from Eqs. (8) and (9) were found to show excellent agreement with the experimentally derived values of a_T. For samples measured at different humidities, the displacement distance was designated a_C. The total shift factor (indicating the dependence of the response on both temperature and concentration) is given by

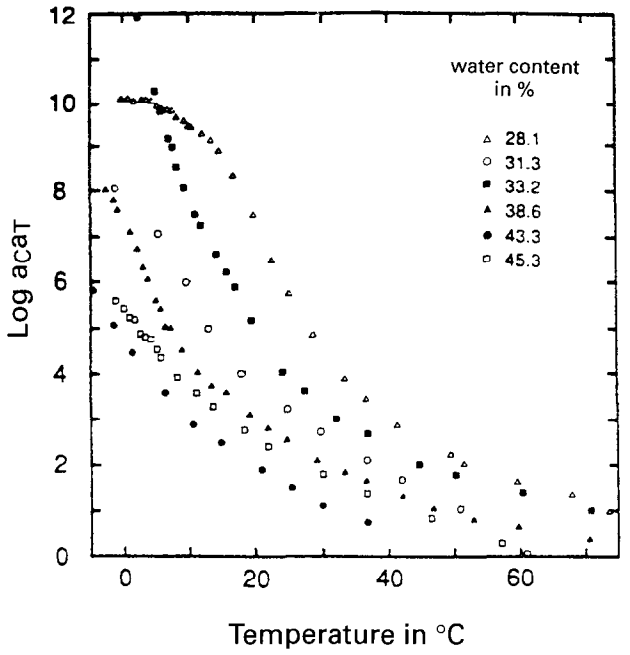


Fig. 8. Total shift factor $a_C a_T$ of elastin against temperature for six water contents, measured in tensile mode. (From Ref. [32].)

$a_C a_T$. Fig. 8 shows the variation in $a_C a_T$ with temperature for a range of water contents, demonstrating the dependence of the moduli on both these parameters. The results indicate that the technique may be used as a basis for understanding the mechanical properties of elastin with a view to relating these properties to arterial disease states.

5. Conclusions

This review has attempted to demonstrate how DMA is presently used pharmaceutically and, more importantly, how it could be used in the future. At present, the technique is underexploited in this field and it is clear that DMTA may be of use in the characterisation of a number of dosage forms and in the study of certain disease states. In particular, the technique is well established as a means of characterising the transitions in polymers. While the relevance of the glass transition is reasonably well known, Kararli et al. [27] have pointed out that the relevance of secondary transitions to product performance, particularly with a view to pharmaceutical considerations, has not been extensively studied and represents a very interesting area for future investigation. Furthermore, the technique may be particularly useful in examining the performance of pharmaceutical packaging materials, as both their rheological properties at room temperature and their thermal properties

are of importance. The study of gels is also an area of pharmaceutical interest; the method may yield information on sol–gel transitions as well as assessing the rheological properties of the gels in their own right. The transitions in dry (or partially hydrated) polysaccharides are of clear relevance in understanding the behaviour of, for example, HPMC matrices, while the use of the technique to study the properties of biomolecules such as elastin represents an extremely exciting new area of application for the technique. These diverse possibilities should ensure that DMTA becomes considerably more established within the pharmaceutical sciences in the future.

References

[1] T. Daniels, Anal. Proc., 18 (1981) 412.
[2] J.D. Ferry, Viscoelastic Properties of Polymers, 3rd edn., Wiley, New York, 1980.
[3] B.E. Read, G.D. Dean and J.C. Duncan, Determination of dynamic moduli and loss factors, in B.W. Rossiter and R.C. Baetzold (Eds), Physical Methods of Chemistry, Vol. VII, Determination of Elastic and Mechanical Properties, John Wiley, London, 1991, Chap 1.
[4] N.G. McCrum, B.E. Read and G. Williams, Anelastic and Dielectric Effects in Polymeric Solids, John Wiley, London, 1967.
[5] A.R. Berens and H.B. Hopfenberg, J. Memb. Sci., 10 (1982) 283.
[6] H. Levine and L. Slade, in F. Franks (Ed.), Water Science Reviews, Vol. 3, Cambridge University Press, Cambridge, 1988, pp. 79 185.
[7] L. Mandelkern and P.J. Flory, J. Am. Chem. Soc., 73 (1951) 3206.
[8] G.P. Koo, Plast. Eng., 30 (1974) 33.
[9] R.E. Wetton, Thermomech. Methods, (1981) 416.
[10] D.J. Skrovanek, Prog. Org. Coat., 18 (1990) 89.
[11] M.B.M. Mangion and G.P. Johari, J. Polym. Sci., Part B, Polym. Phys., 28 (1990) 1621.
[12] M.B.M. Mangion and G.P. Johari, Macromolecules, 23 (1990) 3687.
[13] M.B.M. Mangion and G.P. Johari, J. Polym. Sci., Part B, Polym. Phys., 29 (1991) 437.
[14] H. Oysæd, J. Biomed. Mat. Res., 24 (1990) 1037.
[15] C.E. Jones, Preparation and characterisation of polymer films for the release of metronidazole, Ph.D. Thesis, School of Pharmacy, University of London, 1990.
[16] J.A. von Fraunhofer and W.J. Sichina, Biomaterials, 13 (1992) 715.
[17] R.L. Clarke, Biomaterials, 10 (1989) 494.
[18] R.L. Clarke, Biomaterials, 10 (1989) 549.
[19] R.L. Clarke, Biomaterials, 10 (1989) 630.
[20] L.A. Utracki, Polymer Alloys and Blends: Thermodynamics and Rheology, Hanser, Munich, 1989.
[21] S.V. Lafferty, Evaluation of properties of polymers used as controlled release membranes, Ph.D. Thesis, School of Pharmacy, University of London, 1992.
[22] M. Watase and K. Nishinari, Carbohydr. Polym., 20 (1993) 175.
[23] M. Watase and K. Nishinari, Polym. J., 20 (1988) 1125.
[24] M. Watase and K. Nishinari, Polym. J., 21 (1989) 567.
[25] M. Scandola, G. Ceccorulli and M. Pizzoli, Int. J. Biol. Macromol., 13 (1991) 254.
[26] T.G. Rials and W.G. Glasser, J. App. Polym. Sci., 36 (1988) 749.
[27] T.T. Kararli, J.B. Hurlbut and T.E. Needham, J. Pharm. Sci., 79 (1990) 845.
[28] S. Poliszko, G. Hoffmann and R. Rezler, Acta Aliment. Pol., 17 (1991) 351.
[29] M.T. Kalichevsky, E.M. Jaroszkiewicz and J.M.V. Blanshard, Int. J. Biol. Macromol., 14 (1992) 257.
[30] M.T. Kalichevsky, E.M. Jaroszkiewicz and J.M.V. Blanshard, Int. J. Biol. Macromol., 14 (1992) 267.
[31] H. Maeda, Biophys. J., 56 (1989) 861.
[32] M.A. Lillie and J.M. Gosline, Biopolymers, 29 (1990) 1147.
[33] S.R. Kakivaya and C.A.J. Hoeve, Proc. Natl. Acad. Sci. USA, 72 (1975) 3505.