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Research paper

The use of dynamic mechanical analysis (DMA) to evaluate plasticization of acrylic polymer films under simulated gastrointestinal conditions

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ABSTRACT

Purpose: Glass transition temperature (T_g) measurements of polymers are conventionally conducted in the dry state with little attention to the environment they are designed to work in. Our aim was to develop the novel use of dynamic mechanical analysis (DMA) to measure the T_g of enteric polymethacrylic acid methylmethacrylate (Eudragit L and S) polymer films formulated with a range of plasticizers in the dry and wet (while immersed in simulated gastric media) states.

Methods: Polymer films were fabricated with and without different plasticizers (triacetin, acetyl triethyl citrate, triethyl citrate, polyethylene glycol, propylene glycol, dibutyl phthalate, dibutyl sebacate). T_g was measured by a dynamic oscillating force with simultaneous heating at 1 °C/min. This was conducted on films in the dry state and while immersed in 0.1 M HCl to simulate the pH environment in the stomach.

Results: The T_g of unplasticized Eudragit L and S films in the dry state was measured to be 150 and 120 °C, respectively. These values were drastically reduced in the wet state to 20 and 71 °C for Eudragit L and S films, respectively. The plasticized films showed similar falls in T_g in the wet state. The fall in T_g of Eudragit L films to below body temperature will have far-reaching implications on polymer functionality and drug release.

Conclusions: Immersion DMA provides a robust method for measuring T_g of polymer films in the wet state. This allows better prediction of polymer behaviour *in vivo*.

1. Introduction

Polymer film coatings are applied to tablet formulations for a variety of reasons, from protecting the active ingredient from light, air and moisture to achieving controlled release of the drug [1]. Many pure coating polymers form brittle films, which would crack around any sharp edges of the tablet; plasticizers are therefore frequently added. These are usually high-boiling point, neutral and stable fluids [2], which act by configuring between the chains and altering polymer intermolecular interactions thus increasing molecular mobility of the polymer and, consequently, film flexibility [3]. The effect of plasticizers is manifest in changes in mechanical properties of the film that include an increase in strain or film elongation, a decrease in elastic modulus and a decrease in tensile strength [4–6]. However, perhaps one of the most important physicochemical changes induced by inclusion of plasticizers is lowering of the glass transition temperature (T_g).

Studies comparing different plasticizers and their influence on T_g and mechanical properties of polymer tablet film coatings have been performed. Gutierrez-Rocca and McGinity [6] compared the plasticizing efficiency of citrate plasticizers on acrylic polymer films. A good correlation was found between the T_g and mechanical properties of the films. Tarvainen et al. [7] developed a computational approach for prediction of plasticizer efficiency based on the three-dimensional structure of the molecule. They concluded the desirable structural properties for plasticization of starch acetate to be strong hydrogen bonding capacity and a definitive hydrophobic region on the plasticizer molecule.

The T_g is characterised by an increase in the molecular mobility of the polymer chains, which changes the observed mechanical strength of the material from a hard glass to a softer rubber. Improvement in polymer flexibility infers several processing advantages, including the use of lower temperatures during hot melt extrusion or tablet film coating [8]. The segmental chain movements that arise above the T_g allow interpenetration of the chains and therefore film formation. For aqueous polymer dispersions, latex particle deformation and coalescence at lower temperatures are facilitated [9]. The T_g is also critical for storage stability; optimal plasticizer levels are required to prevent films from becoming brittle during storage.

Polymeric materials are strong glass formers and therefore have small changes in heat capacity over the T_g, which makes it difficult to detect and measure the T_g with differential scanning calorimetry

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(DSC) [10]. Dynamic mechanical analysis (DMA) has about 1000 times greater sensitivity for detecting T_g compared with DSC [11] and hence is more appropriate for polymeric samples. We have previously compared T_g measurements of plasticized methacrylic polymers using DSC, DMA and thermally stimulated depolarisation currents (TSDC) [12]. While the same trends in the T_g values were achieved for the different formulations using the three techniques, the absolute values obtained were different, since each technique detects different changes in the sample. DSC reflects polymer chain movement by detecting changes in specific heat capacity of the sample, DMA reflects the global nature of the sample by measuring mechanical changes, and TSDC detects the T_g through dipolar rearrangements. Consequently, the T_g measured by each technique was different and increased in the following order: TSDC < DSC < DMA.

Water has a reported T_g of −135 °C and can act as a powerful plasticizer [13,14]. Water can also act as an antiplasticizer by forming stable bridges through hydrogen bonds [15]. The effect of a small amount of water acting as an antiplasticizer has been demonstrated with microcrystalline cellulose and soluble starch [16,17]. These plasticizing/anti-plasticizing effects have been shown to affect drug release from diffusion controlled polymeric drug delivery systems [16]. It is thus important, in order to develop *in vitro–in vivo* correlations, to be able to characterise the T_g of polymer systems while exposed to liquid dissolution media, yet we are not aware of any such studies in the literature. It is difficult to use TSDC or DSC to measure film properties in liquid, but it is possible with DMA, using a film-immersion clamp.

The objective of this study is thus to examine the use of immersion DMA for measuring the T_g of polymer films while immersed in a liquid environment and to compare the data with polymer films measured in the dry state. Methacrylic acid methyl methacrylate copolymer (Eudragit L and S) (Fig. 1) enteric films were selected as model polymers and formulated with a range of plasticizers from different classes.

2. Materials and methods

2.1. Materials

Methacrylic acid methyl methacrylate (1:1 and 1:2) copolymers, Eudragit L and S respectively, were donated by Evonik, Darmstadt, Germany. A range of plasticizers was selected from different classes (Table 1), and 0.1 M HCl was prepared from 5 M analytical grade HCl purchased from VWR. Ethanol (99%) was purchased from Hayman Ltd.

2.2. Preparation of polymer films by solvent evaporation

Eudragit L and S films were separately prepared with plasticizer weight concentrations that are typically recommended for organic tablet coating applications. Films were fabricated from polymer-plasticizer solutions in ethanol that were cast onto Teflon plates followed by solvent evaporation. Plasticizer (15% or 20% of polymer mass) was dissolved in 96% ethanol (100 g) over 30 min at room temperature in a beaker. DBS, having a low aqueous solubility, could only be included at a concentration of 15% of polymer mass before phase separation was observed. Eudragit S powder (8.5% w/w of solvent) was gradually added to the ethanolic solution with rapid stirring (Heidolph RZR1 overhead stirrer). The mixing vessel was sealed with Parafilm to prevent solvent evaporation, and the solution was stirred overnight for a further 12 h to ensure complete polymer dissolution. Aliquots of solution (9 mL) were poured into separate Teflon® moulds (9 cm diameter) and allowed to dry at room temperature for eight hours. The films were then peeled from the Teflon moulds and placed in an oven at 50 °C for 48 h to remove residual ethanol/water and subsequently stored until use under vacuum in a desiccator. Thermogravimetric analysis (Pyris 6, Perkin-Elmer Ltd., UK) showed less than 2% residual solvent post-desiccation, data not shown. Film thickness was measured at different points using a micrometer (Mitutoya, Japan) and was found to be 130 ± 10 μm.

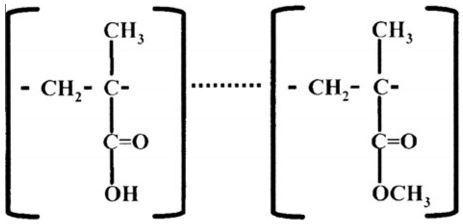

Fig. 1. Structure of poly(methacrylic acid methylmethacrylate) copolymers (Eudragit L and S). For Eudragit L, the ratio of carboxylic acid to ester groups is 1:1, and for Eudragit S the ratio of carboxylic acid to ester groups is 1:2.

Table 1
Plasticizers used in this study.

Class	Plasticizer	Supplier
Citrate	Triacetin (TA)	Sigma–Aldrich
Citrate	Acetyl triethyl citrate (ATEC)	Sigma–Aldrich
Citrate	Triethyl citrate (TEC)	Fluka
Polyol	Polyethylene glycol 6000 (PEG)	Fluka
Polyol	Propylene glycol (P-diol)	Fluka
Phthalate	Dibutyl phthalate (DBP)	Sigma–Aldrich
Sebacate	Dibutyl sebacate (DBS)	Sigma–Aldrich

2.3. Dynamic mechanical analysis

A Q800 Dynamic Mechanical Analyser (TA Instruments LLC, Delaware, USA) was used throughout the study. A film-clamp was used both in dry and immersion modes. A slow heating rate of 1 °C/min was employed throughout to ensure that the sample was in thermal equilibrium with the instrument. The temperature range used in the immersion mode was 7–80 °C (the maximum allowed by the instrument software), and the range for the dry mode was 25–180 °C. The oscillating frequency was set at 1 Hz. Films were exposed to the liquid medium only for the duration of the glass transition measurements.

Experiments were performed with the film under tension. A static pre-load force (0.01 N) was applied to the sample prior to the dynamic oscillating force to prevent film buckling. During measurement, the instrument was programmed to maintain the static load at 125% of the force required to oscillate the sample. It is important that the film remained in its linear viscoelastic region during measurement (to ensure that the properties observed were independent of the deformation applied and truly reflected molecular motions), and so experiments were recorded maintaining constant strain. Generally, for thin polymer films, linear viscoelastic behaviour can be assured with a strain less than 0.1%, and so this limit was used.

For all the submersion studies, 0.1 M HCl was used as the liquid medium. This was chosen to simulate the stomach conditions through which the enteric-coated tablets are designed to remain intact.

2.4. Data analysis

In DMA, the sample is subjected to an oscillating stress, measured as force per unit area, which results in sample deformation (strain) [18]. If an oscillatory stress is applied to a perfectly elastic solid, then the deformation (strain) is exactly in phase with the stress. However, on applying stress to a viscoelastic solid then the deformation lags behind the stress by an angle of δ [19], the maximum lag being 90°. The data can be expressed graphically using two figures: modulus versus temperature or $\tan\delta$ versus temperature. The modulus is the ratio of applied stress to strain. As most materials are viscoelastic, the modulus has two components: (i) a component in phase with the applied stress (storage modulus, E'), which corresponds to the sample's elastic response and (ii) a component out-of-phase with the applied stress (loss modulus, E''), which corresponds to the sample's viscous component. The ratio of the dissipated mechanical energy to stored mechanical energy is represented by $\tan\delta$ (E''/E') [20]. There are many ways of characterising the T_g from DMA data. Since the use of polymers is generally dependent upon maintenance of mechanical strength, the peak loss modulus is generally taken as the reference temperature, since this value corresponds to the point at which the polymer starts to lose its mechanical strength [21]. Hence, the T_g values reported here are calculated from the peak loss modulus.

3. Results and discussion

The glass transition of an amorphous material is accompanied by a large change in its mechanical properties as a result of an increase in molecular mobility. Consequently, the loss modulus progresses through a maximum due to the increase in the dissipated mechanical energy, and there is a concomitant decrease in the storage modulus due to the reduced resistance of the material to deformation [11,18]. These changes act to drive $\tan\delta$ through a maximum (Fig. 2).

To date it has been difficult to measure the T_g of methacrylic acid methylmethacrylate copolymers as thermal degradation starts at a very similar temperature. T_g values have therefore been predicted by the Gordon–Taylor equation to be 144 and 128 °C for Eudragit L and S polymers, respectively [22]. With the DMA methodology we adopted, however, accurate and reproducible T_g values were achieved that are in close agreement with the predicted ones. The T_g of Eudragit L and S polymer films in the dry state was found to be 150 (±4) and 120 (±1.8) °C, respectively.

All the small molecule 'plasticizers' investigated lowered the T_g of Eudragit L and S films, with the exception of dibutyl sebacate (DBS) (Figs. 3 and 4). In general, plasticizers lower the T_g by configuring between the polymer chains, thus altering polymer intermolecular interactions and enhancing chain mobility [3]. Several theories have been proposed to explain the exact mechanism of

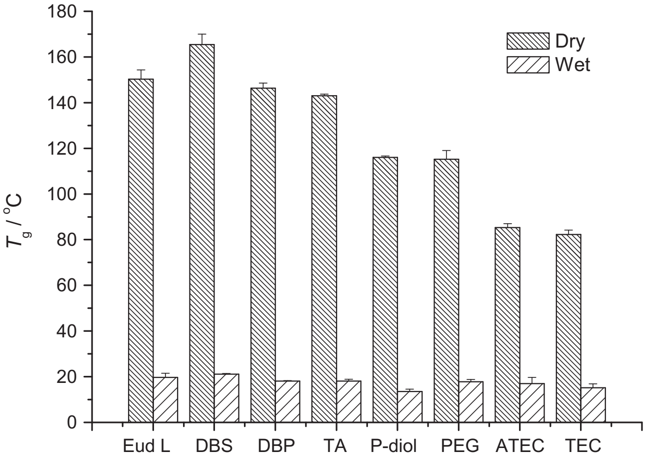

Fig. 3. Glass transition of Eudragit L films fabricated with different plasticizers in the dry and wet states.

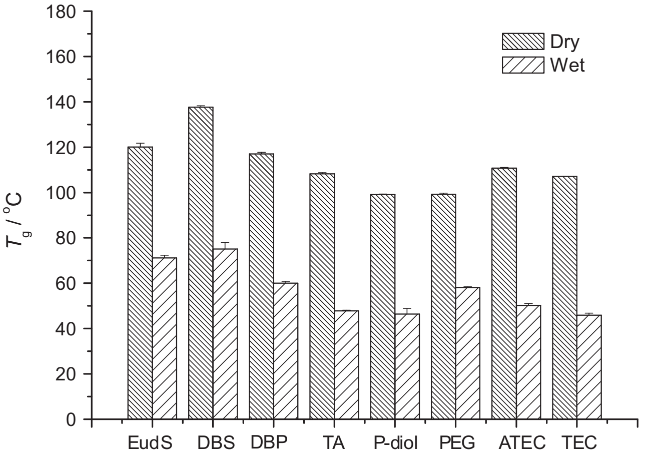

Fig. 4. Glass transition of Eudragit S films fabricated with different plasticizers in the dry and wet states.

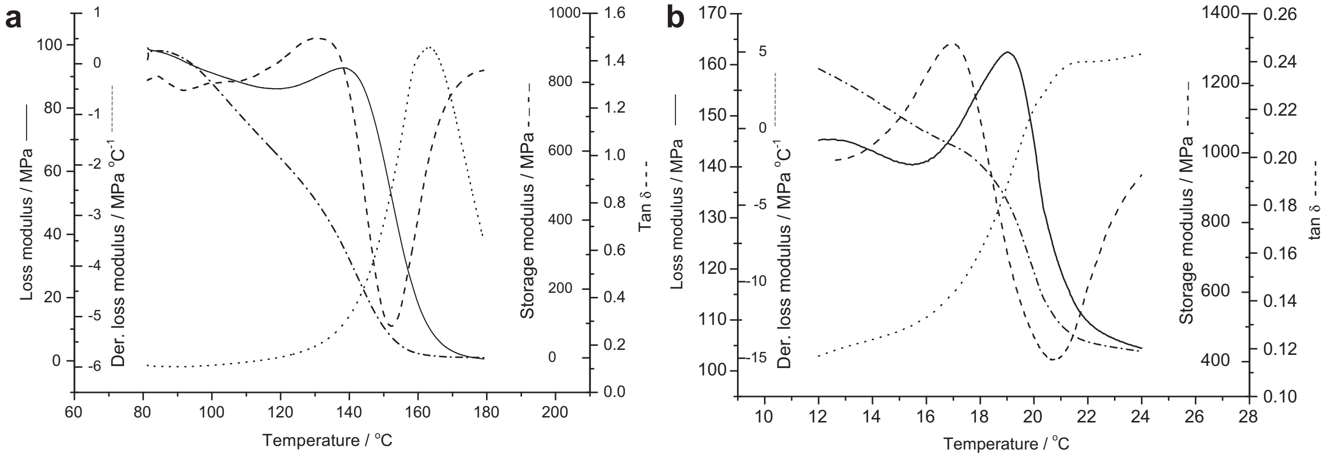

Fig. 2. (a) A typical DMA plot for a polymer film undergoing a glass transition. This represents Eudragit L polymer film plasticized with triacetin in the dry state. (b) A typical DMA plot for a polymer film undergoing a glass transition. This represents Eudragit L polymer film plasticized with triacetin in the wet state.

plasticizer action. The most prevalent and commonly cited in the literature include; lubricity theory, gel theory and free volume theory [23]. The lubricity theory envisages the polymers to exist as planes and the plasticizers orientate between the planes, thus reducing the friction between the polymer chains and the force necessary for them to glide past each other [24]. The gel theory considers polymers to form three-dimensional honeycomb structures sustained by loose attachments between the polymer molecules along their chains [25]. Plasticizers reduce these attachments between the polymer molecules by a dynamic and static mechanism. The free volume theory is based on the concept that between atoms and molecules, there is nothing but free volume that comes from three main sources: motion of chain ends, motion of side chains and motion of the main chain [26].

Plasticizer efficiency is dependent on a number of factors including molecular structure, size and physicochemical properties [6,7,12]. DBS however acts as an antiplasticizer, hindering the movement of the polymer chains and therefore raising the T_g of Eudragit L and S films by 15 and 17 °C, respectively. Antiplasticizers improve local packing; the molecular crowding that arises reduces mobility of the relaxing species [27]. Although both dibutyl phthalate and DBS are hydrophobic molecules with poor aqueous solubilities (0.04% and 0.01% m/v, respectively) [9], their different structures probably explain the converse effect they have on the T_g of methacrylic acid methyl methacrylate copolymer films. The long sebacate chains of DBS may configure between the polymer chains and improve the packing of the polymer network converting it into a stronger glass former. The rank order of plasticizer efficiency at reducing T_g for the Eudragit L polymer films in the dry state was found to be triethyl citrate > acetyl triethyl citrate > polyethylene glycol 6000 > propylene glycol > triacetin > dibutyl phthalate. The rank order for Eudragit S polymer films was different; polyethylene glycol > propylene glycol > triethyl citrate > triacetin > acetyl triethyl citrate > dibutyl phthalate. These different trends are unexpected based on the Gordon–Taylor equation as it indicates that small molecules with a lower T_g reduce the polymer T_g to a greater extent than diluents with a higher T_g. Our findings, however, illustrate that a more important determinant of plasticization efficiency is interaction of plasticizer with the host polymer which in turn is dependent on the molecular properties of both.

The T_g of the plasticized films was shown to decrease further in the wet state arising from water imbibition into the films. It has been shown that water molecules absorbed into a polymer matrix act as an effective plasticizer causing changes in the physicochemical properties of amorphous solids [14]. Similar trends in plasticizer efficiency were observed in the dry and wet states, which may be explained by higher free volumes available in the well-plasticized films for water binding. One exception to this general trend however is seen with films plasticized with polyethylene glycol 6000. It may be that hydrogen bonding may arise between PEG, water and the polymer chains, forming stable bridges that overcome the increase in molecular mobility caused by the absorbed water.

In the case of Eudragit S films fabricated with different plasticizers, the T_g dropped by a mean of 56 °C, reaching 57 °C in the wet state. Interestingly, a more drastic drop in T_g was observed for Eudragit L films with T_g falling by a mean of 108 °C, reaching 18 °C. Eudragit L copolymer has a higher ratio of methacrylic acid groups in its polymer structure with ratio of methacrylic acid to methyl methacrylate of 1:1 in comparison with 1:2 for Eudragit S. The hydrophilic carboxylic acid groups are likely to attract more water compared with the more hydrophobic methyl ester groups, which will therefore give rise to a greater reduction in T_g. It has been proposed that the extent of water absorbed is dependent on not only the physicochemical affinity of the polymer groups to water but also the free space available in the vicinity of these sites [28]. Dittgen et al. have shown significant amounts of moisture to be absorbed by acrylic polymers and have correlated water uptake with polymer hydrophilicity [2]. Eudragit L was illustrated to have a higher water uptake compared with Eudragit S polymer at different relative humidities, which correlates with and explains our findings. Peeters and Kinget [29] have worked on the methylation of carboxylic groups of Eudragit S in aim of increasing the pH threshold of the polymer. Water vapour permeability was measured to be 50% higher in Eudragit S compared with the methylated version.

For all the Eudragit L films, including the unplasticized formulation, a drop in T_g to below body temperature was observed in the wet state (Fig. 3). In the gastrointestinal tract, the polymers will therefore be at a temperature above their glass transition and exist in the rubbery state, which has higher free volume and molecular mobility compared with the glassy state. This may compromise the functionality of these polymers. For enteric-coated tablets, it is important that the coat maintains its structural integrity in the stomach; if however the polymer is present at a temperature above its T_g, acid may imbibe through the coat into the tablet core, which may cause premature drug release or degrade acid-labile drugs.

This glassy–rubbery transition of polymers on hydration may pose a problem for nanoparticulate and multiparticulate systems. On coming into contact with each other, rubbery particles can deform or aggregate due to polymer interdiffusion as it observed in polymer colloids [30,31]. The extent of this aggregation depends on several material properties including T_g, degree of polymer cross-linking, molecular weight and hydrophilicity [31].

In a study on the mechanical properties of poly(lactic acid)/everolimus-coated stents, the Young's modulus was found to drop significantly in liquid media at 36 °C as measured by atomic force microscopy [32]. The authors speculate that *in vivo* the polymer is likely to exist above its glass transition altering the diffusion release profile. This highlights the importance of determining the T_g of polymer materials in the wet state, and we have demonstrated that immersion DMA is very suitable for making such measurements.

Studying the physical–mechanical properties of polymers in the dry state is important as it provides useful information on film formation during coating and compaction [33,34]. Understanding these properties, particularly the glass transition, in the wet state is equally important as it provides an insight into material properties and performance *in vivo*. This knowledge will provide a more mechanistic approach to formulation development.

4. Conclusions

Dynamic mechanical thermal analysis provides an accurate and reproducible means of measuring the glass transition temperature of plasticized polymer films in the dry state and while immersed in liquid media. Water imbibition into the polymer films was found to drastically reduce the T_g of methacrylic acid methyl methacrylate polymer films. This was particularly profound for Eudragit L films whereby the T_g dropped to below body temperature. This is likely to have far-reaching implications on polymer functionality and drug release. The technique of immersion DMA allows the physical–mechanical properties of pharmaceutical materials in the wet state to be determined and therefore better predictions to be made on the behaviour of dosage forms *in vivo*.

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