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Effect of triacetin and polyethylene glycol 400 on some physical properties of hydroxypropyl methylcellulose free films

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Summary

Free film techniques were used to study the effect of two plasticizers with different aqueous solubilities, triacetin and polyethylene glycol 400 (PEG 400), on the properties of hydroxypropyl methylcellulose (HPMC) free films cast from aqueous solutions. Thermomechanical and mechanical analysis of the films demonstrated that both additives were effective plasticizers for HPMC. PEG 400 was found to enhance water vapor permeability of the free films while triacetin slightly decreased water vapor permeability. Furthermore, triacetin significantly reduced the amount of water absorbed by HPMC films while PEG 400 had no significant effect. The results of these studies can be useful for designing soluble aqueous film coating systems when one or more of the tablet components is sensitive to water.

Introduction

Polymers are used extensively in pharmaceutical tablet coating formulations. The polymer films coated on tablet cores can mask bitter taste, protect ingredients from environmental extremes, aid in swallowing and enhance appearance. However, tablet film coatings often experience microscopic cracks, peeling and bridging of intagliations (Porter, 1981). Therefore, compounds known as plasticizers are added to polymer film coating formulations to make the films more pliable and tougher (Porter et al., 1982). Plasticizers, which have molecular weights much smaller than the polymer's, enhance the mobility of the polymer molecules in the film (Sakellariou et al., 1986). Therefore, the glass transition temperature (T_g) of the polymer, or temperature where the polymer molecules change from a glassy solid to a supercooled liquid state, is lowered when a plasticizer is added (Martin et al., 1983).

While these polymer film formulations may be aqueous or organic solvent based, aqueous-based polymer film formulations have obvious environmental and safety advantages over those based on organic solvents. Recently, several patents have been issued for the aqueous coating of tablets containing compounds highly prone to degrada-

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tion due to moisture (John et al., 1981; Franz, 1989). These patents cite triacetin as the plasticizer of choice in the application of aqueous based, water soluble HPMC films. Triacetin, which is only slightly soluble in water (Weast, 1976), is more hydrophobic than polyethylene glycol (PEG), a water soluble polymer (Windholz et al., 1983) commonly used to plasticize aqueous HPMC film formulations (Enwistle and Rowe, 1979; Aulton and Abdul-Razzak, 1981). In this study, the physical properties, especially mechanical, of aqueous based, water-soluble HPMC films plasticized by PEG 400 are compared with aqueous based, water soluble HPMC films plasticized by a hydrophobic plasticizer, triacetin, that could result in improved stability for moisture sensitive compounds.

Free film techniques have been used extensively to measure the mechanical properties and the permeability of polymer films (Woodruff et al., 1972; Aulton and Abdul-Razzak, 1981; Okhamafe and York, 1983, 1985b). The films can be formed by spreading or spraying a polymer solution onto plates, then drying (Swarbrick et al., 1972). The effect of the two plasticizers, triacetin and PEG 400, on the T_g of aqueous based HPMC free films was measured by thermomechanical analysis (TMA), tensile strength and dynamic mechanical thermal analysis (DMTA). In addition to being a detailed mechanical study on a triacetin-plasticized aqueous polymer film formulation, this work, for the first time, compares the results for T_g obtained using these different techniques on free films with identical components and cast by the same method.

The presence of a plasticizer has the potential to alter more than just the mechanical properties of a polymer film. Plasticizers can affect diffusion pathways in the polymer film and, therefore, alter its permeability (Okhamafe and York, 1989). This may have a significant effect on the stability of moisture sensitive tablets coated with water-soluble, aqueous based polymer films. Therefore, in addition to the mechanical properties, the water vapor permeability through cast free films of HPMC was studied as a function of plasticizer (triacetin or PEG 400) concentration. Furthermore, the amount of water absorbed by films containing the different plasticizers was also determined.

Materials and Methods

Reagents

HPMC (2910, 6 cps, Shin-Etsu), PEG 400 (Eastman Kodak) and triacetin (Eastman Kodak, USP, Food Grade) were used as received.

Film preparation

The percent plasticizer in the system is expressed as the ratio of the plasticizer to polymer weights. Aqueous solutions of the polymer/plasticizer combination were prepared so that the total solids concentration was 7.7% by weight. Films were cast on a glass plate using a stainless-steel blade (Paul Gardner Co., Inc., Pompano Beach, FL) and then dried by one of two techniques. In process 1, the films were dried at room conditions for approx. 12 h then conditioned in a humidity controlled cabinet at 25°C and 50% relative humidity (R.H.) for 24 h. A phase separation occurred (as demonstrated by blooming or haziness in the film) in films dried by this method when triacetin concentrations were higher than 10%. Therefore, a second drying process (process 2) was used where the films were cast, dried at 60°C for one h, then conditioned for 72 h at 25°C and 50% R.H. No phase separation was observed when the second drying process was used. Dry film thicknesses were measured by a micrometer and ranged from 50 to 90 μm.

Water vapor permeability

Water vapor permeation through the polymer films was measured at 25°C and 50% R.H. according to ASTM method E96 using stainless-steel permeability cups (Paul Gardner Co., Inc.) containing $CaCl_2$. The conditioned films were mounted on the permeability cups then placed in a humidity and temperature controlled cabinet. Over a 30 h period, the cups were periodically removed from the cabinet, weighed, then replaced. The experiment was performed three times on any free film formulation. The slopes of cup weight vs time plots were calculated and the correlation coefficients were always greater than 0.99. This slope (g/24 h) was divided by the film area (25 cm^2) to give the flux (F). The permeability was then calculated by the following equation:

$$P = \frac{(F)(L)}{\Delta p} \tag{1}$$

where L is the thickness of the film (cm) and Δp is the water vapor pressure difference across the film. Assuming the air on the $CaCl_2$ side was dry (i.e. 0 mmHg of water), the vapor pressure difference of water across the film was 11.9 mmHg (Perry et al., 1963) (assuming the pressure in the cabinet was 1 atm). The units of P are metric perms cm and allow the reader to compare water fluxes reported for films having different thicknesses or water vapor pressure differences across them.

Thermal mechanical analysis

The penetration probe of a Perkin Elmer Model TMA7 was used to measure the glass transition (T_g) and thermal softening point (T_s) of the polymer films dried by process 2. T_g measurement is based on the principle that at the glass transition temperature, the atoms and groups in the polymer molecule acquire an increasing amount of thermal energy, causing them to vibrate and move about. This results in the brittle/ductile transition phase of the polymer. T_s indicates the point at which the polymer softens prior to melting and usually lies between T_g and the melting point. At T_s, polymer mobility is so high that some intersegmental bonds are ruptured and as a result, the polymer matrix is more porous and resistance to penetration becomes low.

A quartz probe with 0.51 mm radius was applied with 15 mN force while the sample was heated at 10°C/min. As the sample expands, contracts or softens, the position of the probe will change; and this position is accurately monitored by a linear variable differential transformer (LVDT). This LVDT provides a signal which is proportional to the probe displacement. Hence, for a given weight on the loading platform, the penetrating pressure can be readily calculated, and from the TMA output the amount of penetration can be read directly.

Experiments were performed in triplicate. The first and second infection points were taken as T_g and T_s, respectively (Masilunga and Lordi, 1984).

Dynamic mechanical thermal analysis

This method uses small strain sinusoidal deformation as the probe to modulus and damping (tan δ). Changes in these parameters are studied as a function of temperature and impressed frequency. Internal molecular mobility, secondary relaxations in the glassy state as well as the glass transition (T_g) relaxation process can be detected. Thermal mechanical spectra of the films were obtained using the Dynamic Mechanical Thermal Analyzer (DMTA) from Polymer Laboratories (Amherst, MA). For a visco-elastic material, the storage modulus, E', is the elastic response and corresponds to completely recoverable energy whereas the loss modulus, E'', is the viscous response corresponding to energy lost through internal motion. The tangent of the loss angle, tan δ, is dimensionless and is equal to the ratio of energy lost (dissipated as heat) to energy stored per cycle,

$$\tan \delta = \text{loss modulus/storage modulus} = E''/E' \tag{2}$$

Essentially, the response of the material changes with temperature at a fixed frequency. Hence, the elastic component of the tensile modulus (E') and the mechanical loss (tan δ) are tracked as a function of temperature. When the glass transition occurs, a sharp drop in modulus results and a peak is observed for tan δ. This allows the determination of T_g by DMTA.

Sample size was 5 mm long × 10 mm wide. Since the thickness of the cast film was variable between 0.05 and 0.09 mm, each sample was individually measured. Experiments were performed in the tensile mode at × 1 strain (16 μm nominal peak-to-peak displacement in the sinusoidal strain wave generated by the DMTA equipment) and at 1 Hz from 80 to 200°C at 3 degree/min in the reducing mode. A preset force in the tensile mode is applied to the sample held in the measurement head. This force is maintained at a steady level by the electronics unit of the DMTA. For valid measurements, the tensile force utilized must be large enough to avoid buckling of the sample during dynamic loading. As the sample softens, the force is reduced to minimize sample draw, hence the sample is run in the reduced mode. The minimum tensile force (F_τ) is set according to the modulus (E) of the sample and may be calculated as follows:

$$E = \text{stress/strain} = \frac{(F_\tau/A)}{(\Delta l/l_0)} \tag{3}$$

where A is the cross-sectional area of the specimen, Δl is the elongation of the sample and l_0 is the initial length of the sample. Knowing the sample modulus (E), cross-sectional area (A), length (l_0) and dynamic strain ($\Delta l/l_0$), the minimum tensile force (F_τ) to avoid sample buckling can be calculated. In the experiments, the minimum tensile (F_τ) force range was calculated to be 1.5–3.5 N based on the modulus (E) of the formulations tested. Three replicates were performed using an unplasticized HPMC film. Reproducibility of the T_g was within ±1°C, therefore a single trial was used in evaluation of additional formulations.

Mechanical properties

The force and elongation at break for the films dried by process 2 were measured using a mechanical stress/strain analyzer (Instron Model 4501). The sample was 5 mm wide and 30 mm long. The gauge length was 10 mm and the jaw and chart speeds were 2.5 and 50 mm/min, respectively. Tensile strength is defined as the maximum tensile stress ($\sigma_{\max}$) which a material is capable of sustaining and is calculated from the maximum force applied during a tension test carried to break ($F_{\max}$) and the original cross-sectional area of the specimen (A), where:

$$\sigma_{\max} = F_{\max}/A \tag{4}$$

The tensile modulus at break is calculated using the ratio of tensile strength ($\sigma_{\max}$ in Pa) to the dimensionless strain (Van Vlack, 1980), where dimensionless strain is the ratio of change in length of the sample to the original length of sample. Six film samples for each formulation were tested.

Water absorption

The equilibrium concentration of water absorbed by the film at 25°C and 50% R.H. was measured by Karl-Fisher analysis (Mitsubishi KF-05) of films suspended in a controlled temperature and humidity cabinet for 24 h. The films used in this study were dried by process 2 and all experiments were performed in triplicate. In the cabinet, the weight of a dried HPMC film increased and reached a constant value after approx. 2 h.

Results and Discussion

Water vapor permeability

The results of water vapor permeability experiments with HPMC films prepared by drying process 1 are presented in Fig. 1. Since triacetin levels greater than 15% caused blooming in films prepared by this process, no permeability experiments were performed above this level. Over the range of triacetin levels tested, the permeability of these films decreased as triacetin level increased. Process 1 films containing PEG 400 show an initial decrease in permeability at the 5% plasticizer level followed by an increase in permeability, significantly greater than unplasticized HPMC films, at the 15% plasticizer level. The initial decrease in permeability could be due to densification of the HPMC polymer film by the addition of the smaller plasticizer molecules. This mechanism has also been postulated for HPMC and polyvinyl alcohol films plasticized by citric acid and urea (Okhamafe and Iwebor, 1987).

To explore the effect of higher triacetin levels on permeability, films were also prepared using drying process 2 (see Materials and Methods). The results for these experiments are shown in Fig. 2, where the range of plasticizer levels was

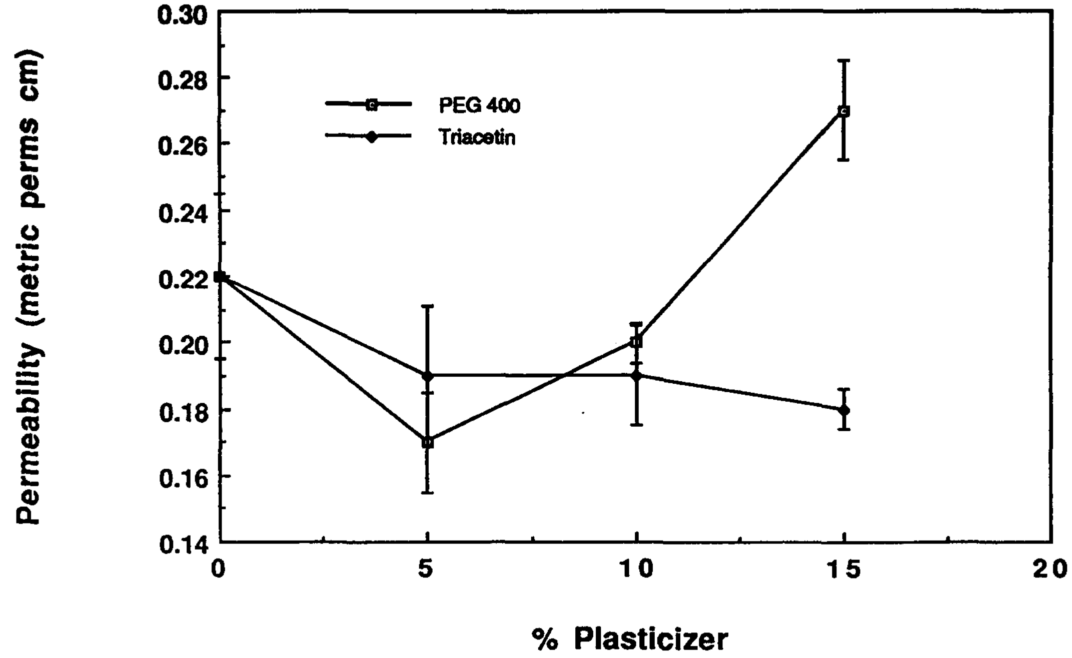

Fig. 1. Water vapor permeation through HPMC films as a function of plasticizer concentration. Films were prepared by drying process 1.

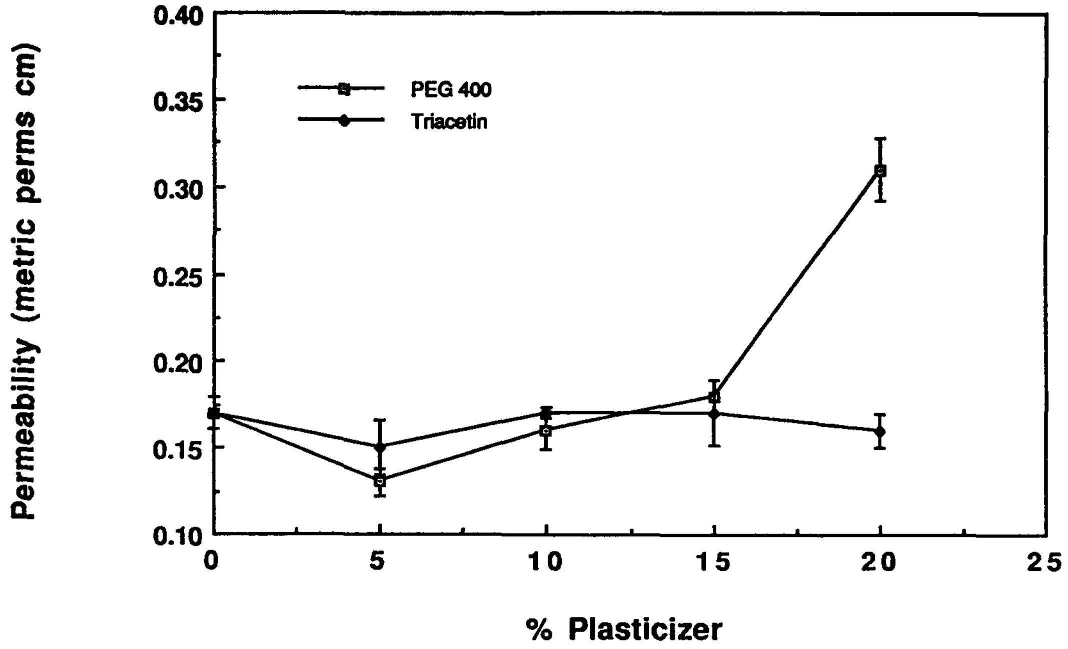

Fig. 2. Water vapor permeation through HPMC films as a function of plasticizer concentration. Films were prepared by drying process 2.

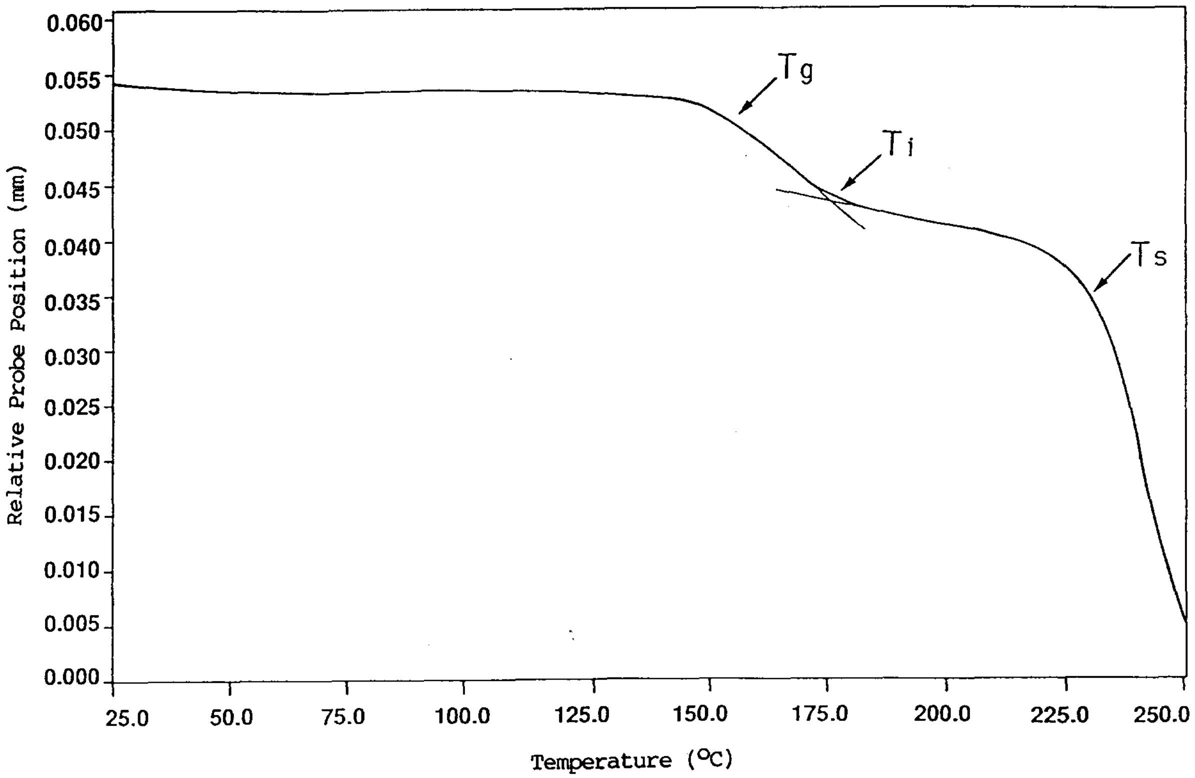

Fig. 3. Plot of relative probe position as a function of temperature (for an HPMC film prepared by drying process 2) using thermal mechanical analysis. T_g was taken as the first inflection point and T_s was taken as the second inflection point.

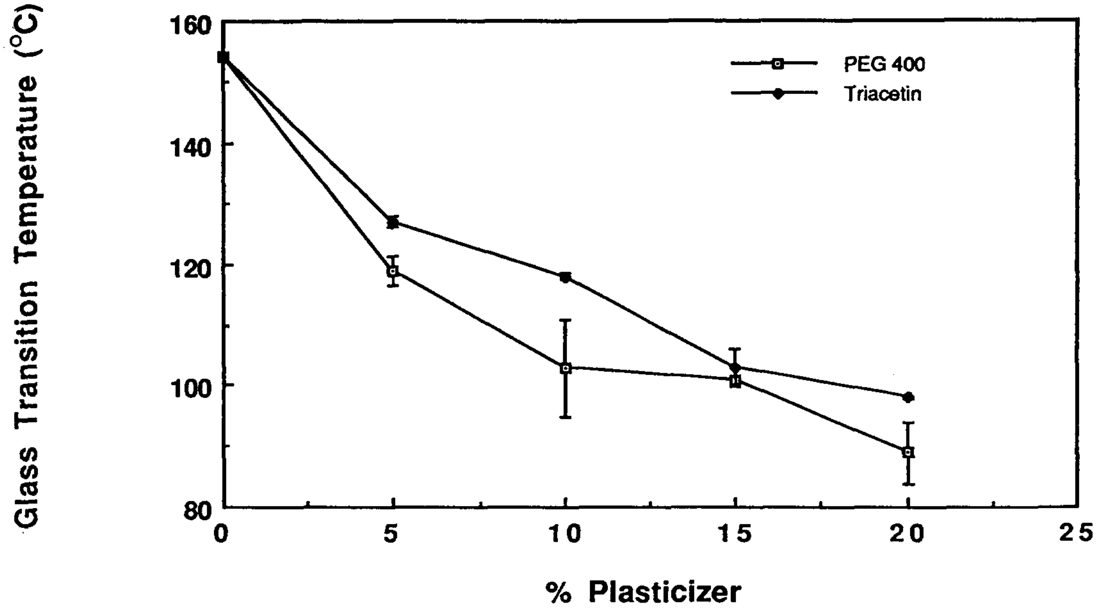

Fig. 4. Glass transition temperature determined using TMA as a function of plasticizer concentration for HPMC films. The films were prepared by drying process 2.

varied from 0 to 20%. As the triacetin level was increased, the permeability of films prepared using drying process 2 remained essentially unchanged. As with films prepared using drying process 1, films plasticized by PEG 400 showed an initial permeability decrease at the 5% plasticizer level, followed by an increase in permeability at the highest plasticizer level (20%). The permeability at the highest plasticizer level (20%) was significantly greater than unplasticized HPMC films.

At the highest plasticizer levels, films containing PEG 400 were significantly more permeable than those containing triacetin. Furthermore, while the values of film permeability were different for the two drying processes, the effect of plasticizer level followed the same trend. In general, film permeabilities were lower for films dried by process 2. Since the drying conditions for process 2 simulated conditions used in a typical aqueous coating process and allowed the incorporation of additional triacetin in a homogeneous film, the remainder of this study focused on films prepared by drying process 2.

Thermal mechanical and dynamic mechanical thermal analysis

Fig. 3 is a plot of the probe penetration into an HPMC film as a function of temperature during thermal mechanical analysis (TMA). The glass transition and thermal softening point were taken as the first and second concave-down inflection points, respectively. Values of T_g and T_s calculated using TMA for polymer films (drying process 2) having different plasticizer concentrations are presented in Figs 4 and 5, respectively. At the highest plasticizer level (20%) PEG 400 and triacetin lowered T_g by 65 and 56°C, respectively. Also, at the 20% plasticizer level, PEG 400 and triacetin lowered T_s by 67 and 53°C, respectively. Based on the ability to lower T_g and T_s, the results of this study indicate that PEG 400 is more efficient than triacetin in plasticizing aqueous based, water soluble HPMC films.

A sample DMTA spectrum for a HPMC film is presented in Fig. 6, where the elastic component of the tensile modulus (E') and the mechanical loss (tan δ) are plotted as a function of temperature. For unplasticized HPMC films,

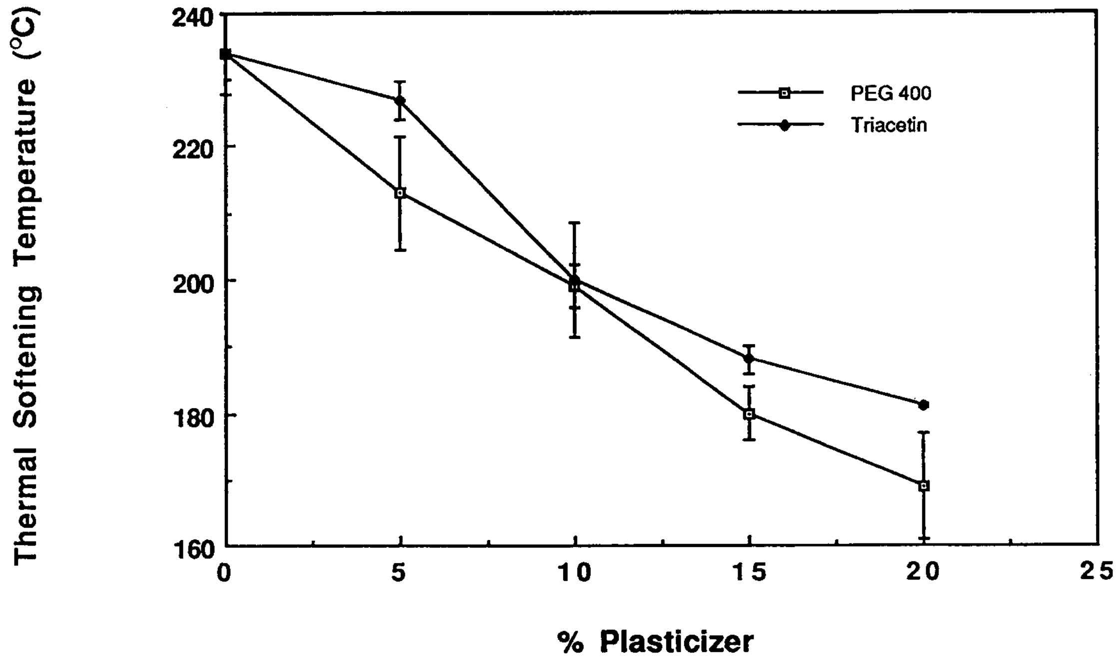

Fig. 5. Thermal softening temperature determined using TMA as a function of plasticizer concentration for HPMC films. The films were prepared by drying process 2.

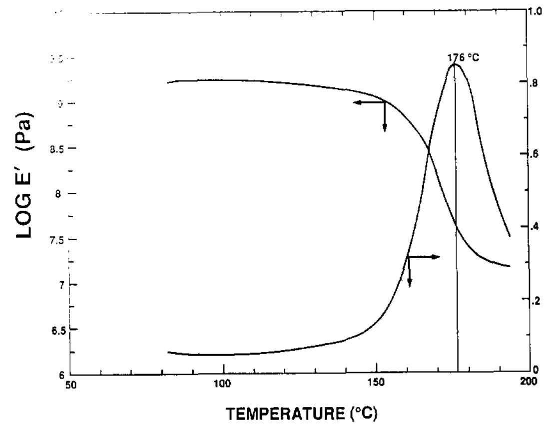

Fig. 6. Plot of the elastic component of the tensile modulus (E') and mechanical loss (tan δ) as a function of temperature for an unplasticized HPMC film dried by process 2. The peak in tan δ indicates that the film has reached the glass transition temperature.

tan δ peaks at 176°C which correlates to the glass transition temperature. The data from DMTA experiments on HPMC films are presented in Fig. 7. Both PEG 400 and triacetin reduced the glass transition of HPMC, which was also shown using TMA. The DMTA results further confirmed TMA results by showing that for the same percentage of plasticizer, PEG 400 reduces the glass transition of HPMC to a greater extent than does triacetin. At 5, 10, 15, and 20% plasticizer levels, PEG 400 reduced the glass transition temperature of HPMC films by 14, 25, 30, and 37%, respectively, while triacetin reduced the glass transition temperature of HPMC films by 10, 18, 20, and 26%, respectively (see Fig. 7). Plasticizer efficiency can be assessed by the greatest decrease in the glass transition temperature per unit amount incorporated (Rowe et al., 1984) and hence PEG 400 is a more efficient plasticizer than triacetin in these films. Generally, the addition of an efficient plasticizer increases the free volume of the polymer matrix which results in increased chain mobility, causing the glass transition temperature to decrease (Billmeyer, 1971).

Comparing values of T_g from different techniques

While TMA and DMTA data showed that PEG 400 and triacetin reduced T_g, the values of

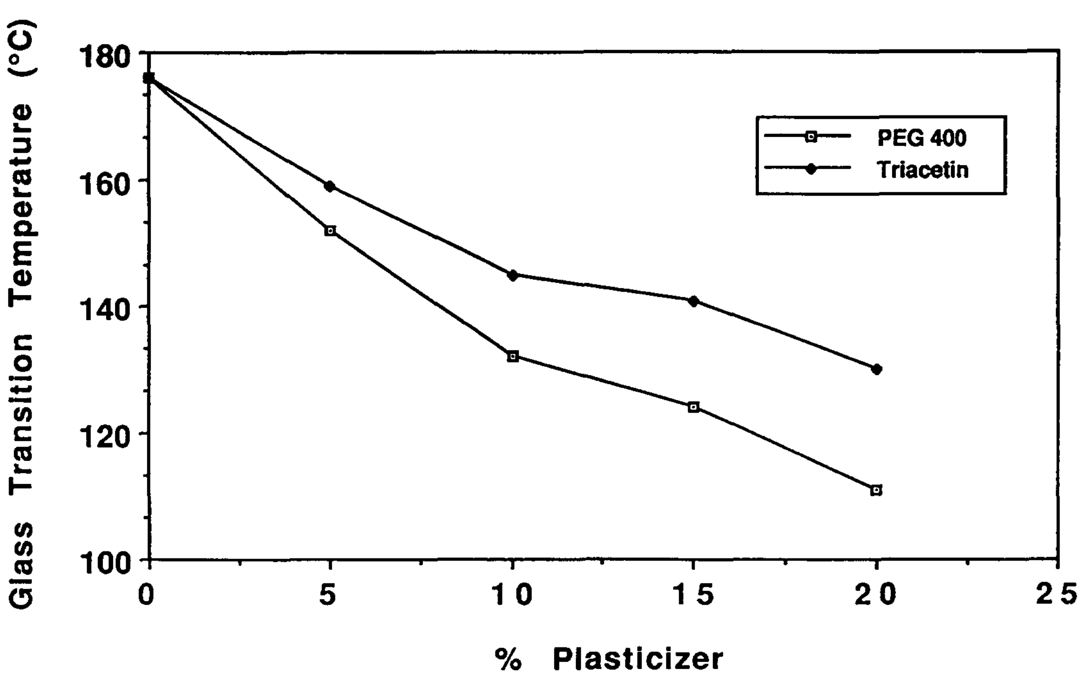

Fig. 7. Glass transition temperature determined using DMTA as a function of plasticizer concentration for HPMC films. The films were prepared by drying process 2.

T_g for the polymer film formulations varied based on the technique used.

The glass transition temperature is defined as the onset motion of chain segments in the amorphous region of a polymer (Bacon and Charles, 1971). Several techniques have been utilized to study these properties such as differential scanning calorimetry (DSC) (Enwistle and Rowe, 1979; Porter and Ridgway, 1983; Okhamafe and York, 1985a), differential thermal analysis (DTA), thermal mechanical analysis and the torsional braid pendulum (Osterwald et al., 1982; Masilunga and Lordi, 1984; Rowe et al., 1984; Sakellariou et al., 1985). The T_g results from these different measurement and sample preparation techniques ranged from 154 to 180°C for HPMC. It is worth noting that the T_g values for unplasticized HPMC films measured in this work are in agreement with previously reported values.

For unplasticized HPMC films, the T_g obtained by DMTA was approx. 20% higher than the values obtained by TMA (cf. Figs 4 and 7). This difference could be due to the load placed on the sample in the TMA instrument, hence depressing the glass transition temperature. With zero loading, penetration does not occur even above the softening point or glass transition temperatures. With heavy loading, penetration occurs at or slightly below the glass transition temperature for amorphous or semi-crystalline polymers (Cassel, 1977). On closer examination of the TMA penetration profile for unplasticized HPMC films (see Fig. 3), it was observed that the temperature between the T_g and T_s inflection points, T_i, was more representative of the T_g obtained by the DMTA method.

The glass transition temperature depends on molecular weight, on internal strain in the polymer, on residual solvents and also, to some extent, on heating rate (Nissan et al., 1965). Therefore, as indicated by the data presented using TMA and DMTA techniques, if film/polymer properties are to be compared, the same methodology and instrument parameters must be used.

Mechanical properties of films

Fig. 8 is a typical plot of the force required to elongate and break an HPMC film using the mechanical stress/strain analyzer (Instron). This data was used to calculate the tensile modulus at break (see Materials and Methods) for the HPMC films. Both PEG 400 and triacetin reduced the tensile modulus at break of the HPMC films as shown in Fig. 9. However, as Fig. 9 indicates, PEG 400 reduced the tensile modulus at break to a greater extent than did triacetin. This is further evidence that PEG 400 is a more efficient plasticizer of HPMC films than triacetin (Billmeyer, 1971). In general, chain mobility of the HPMC matrix is increased with the addition of both plasticizers as observed from thermomechanical data (e.g. TMA and DMTA).

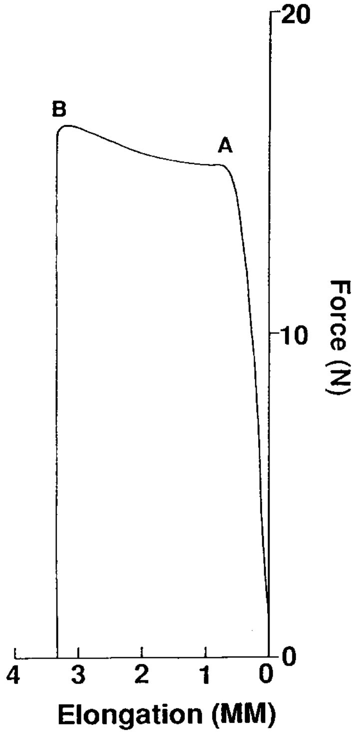

Fig. 8. Plot of force as a function of elongation using mechanical stress/strain analysis (Instron) for an HPMC film prepared by drying process 2. Point A: initial film deformation; point B: film breakage).

Water absorption

The difference in film permeability at the highest plasticizer levels (see Fig. 2) does not agree with the thermomechanical and mechanical analysis of film plasticization. Those results indicate that either plasticizer is capable of lowering T_g. Even though triacetin was a less efficient plasticizer than PEG 400, some increase in permeability would be expected based on the T_g results. Therefore, chain mobility alone cannot explain the water vapor permeability data since there is a large difference in permeability at high plasticizer concentrations. PEG 400 is freely water soluble while one part triacetin is soluble in only 14 parts water (Windholz et al., 1983). Furthermore, PEG 400 is slightly hygroscopic. Overall, PEG 400 is a more hydrophilic plasticizer than triacetin. The effect of plasticizer hydrophilicity on free films was studied by measuring the amount of water absorbed by the film.

To determine the effect of plasticizer hydrophilicity on water transport through HPMC films, the amount of water absorbed by dried films was measured for those prepared by process 2 at the lowest and highest plasticizer levels. Using a Karl-Fisher titration, the amount of water in a film after completion of the drying process was approx. 2.5% regardless of the plasticizer. The results for dried films placed in a cabinet at 25°C and 50% R.H. for at least 24 h are presented in Table 1. Films plasticized by triacetin have a significantly lower capacity for water than un-plasticized or PEG 400-plasticized HPMC films.

TABLE 1

Water absorption by HPMC films stored at 25 ° C and 50% R.H.

Plasticizer	% Water absorbed
None	6.23 ± 0.44
20% PEG 400	6.65 ± 0.42
20% Triacetin	4.02 ± 0.20

For water to pass through the polymer film, it must first partition from the vapor phase (Cussler, 1984). With triacetin as the plasticizer, the film has a much lower capacity for water. Even though PEG 400 and triacetin are comparable in their ability to plasticize HPMC (see Thermal mechanical data), the film permeability can be much higher when PEG 400 is used as the plasticizer. This can be explained by the more hy-

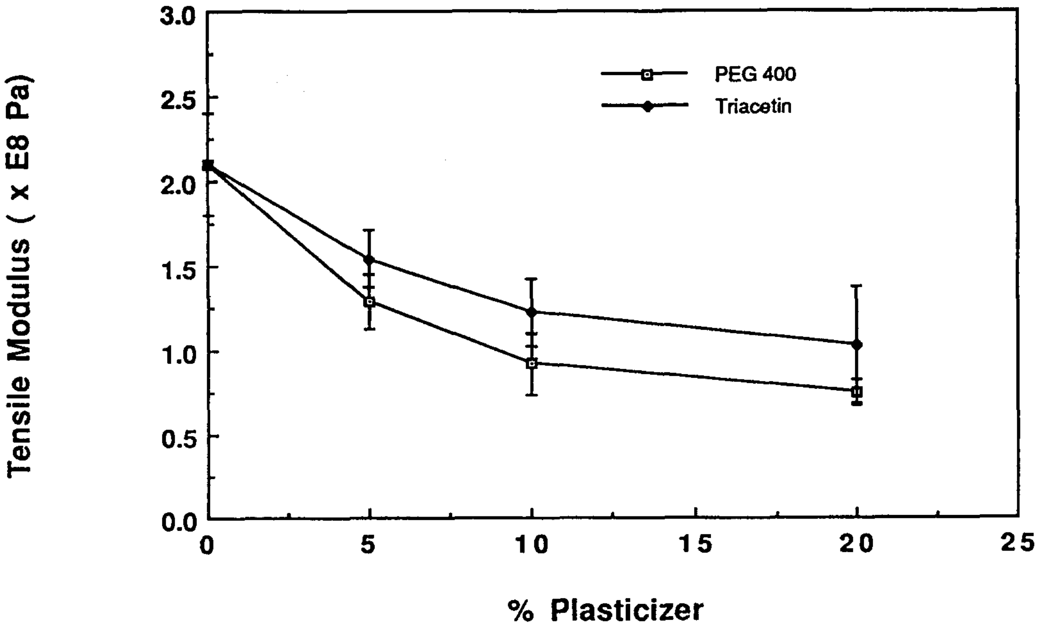

Fig. 9. Tensile modulus as a function of plasticizer concentration for HPMC films using mechanical stress/strain analysis (Instron). The films were prepared by drying process 2.

drophilic nature of PEG 400 when compared to triacetin.

Conclusions

Both triacetin and PEG 400 exhibited effective plasticization of HPMC films, as evidenced by T_g, T_s and tensile strength at break, with PEG 400 being a slightly more efficient plasticizer. However, there were large differences between the effect of the two plasticizers on water vapor permeability through HPMC films. The more hydrophilic PEG 400 significantly increased water vapor permeability at 15 and 20% levels while the less hydrophilic triacetin had little effect on permeability. The results of water absorption by the films at 20% plasticizer levels showed that triacetin significantly lowered the ability of the film to absorb water while PEG 400 had little effect. Since triacetin reduced water absorption by the films while plasticizing it, there was no significant effect on permeability as the amount of plasticizer was increased. However, since PEG 400 plasticized the film while maintaining its affinity for water, the permeability of the film increased at the higher PEG 400 levels. The conclusions from this study are in agreement with results described during the aqueous film coating of tablet cores containing a water-sensitive material (Franz, 1989).

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