Drug Development and Industrial Pharmacy, 24(9), 827–834 (1998)

RESEARCH PAPER

Thermal and Mechanical Characterization of Cellulose Acetate Phthalate Films for Pharmaceutical Tablet Coating: Effect of Humidity During Measurements

Anders Karlsson and Satish K. Singh*

Pharmaceutical Development, Pharmacia & Upjohn AB, S-751 82 Uppsala, Sweden

ABSTRACT

Films from a polymer used in pharmaceutical coating (cellulose acetate phthalate) were analyzed by thermomechanical techniques including dynamic mechanical thermal analysis (DMTA) and tensile tests. Emphasis was placed on relative humidity (RH) at the measurement site (as opposed to storage or conditioning RH). The films were plasticized with either triethyl citrate or diethyl phthalate. The results show that the films respond rapidly to changes in the environmental humidity. This in turn influences the data obtained from DMTA and tensile testing; thus, good control of the humidity is essential. Absorption isotherms have been obtained for the two types of films, and the results were interpreted in terms of the equilibrium moisture content which is determined by the polar nature of the plasticizer. This factor must be considered when formulating a film composition because moisture can, apart from its influence on mechanical properties, also speed the chemical degradation processes. When the stability of a film composition during storage is studied, the actual measurements on the films should preferably be done at 0% RH, irrespective of the storage RH. At 0% RH, the mechanical testing results will reflect the chemical stability correctly, without interference from plasticizing effect of absorbed water. A functionality test for films has been suggested: DMTA under isothermal conditions

* To whom correspondence should be addressed. Fax: +46-18-166480. e-mail: satish.singh@eu.pnu.com

using either step or continuous humidity scans. Isothermal dynamic humidity scans on the DMTA were performed for the first time, and the utility of these measurements is discussed.

INTRODUCTION

Background

Film coatings by polymers of tablets, pellets, and even capsules is a standard practice in the pharmaceutical industry. The objective of the coating varies widely: to improve the aesthetics of the product, mask taste and odor, improve product stability, facilitate swallowing, minimize cross-contamination during packaging, and enable drug-release characteristics to be modified in a predictable and reproducible manner. A wide variety of film-forming polymers are used for this purpose, the important ones being cellulose derivatives (ethyl cellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, and cellulose acetate phthalate [CAP]), and acrylate-based systems.

Knowledge of the thermomechanical properties of these polymers is important because these properties determine polymer behavior in film-coating formulations during the coating process, and during subsequent storage of the product. The pharmaceutical literature is therefore replete with studies of these polymers, both as free films and as coated products, at ambient conditions and at elevated temperatures and humidities. Free films are often used as models to analyze the effect of polymer type (solution/dispersion), composition, plasticizer, solvent system, process conditions, and storage conditions; the properties of the film are obviously easier to study in a free-film form than when coated on a substrate.

Among the variables that are often studied are storage temperature and humidity (see, e.g., references 1–3); among the methods commonly used to study the resulting properties of these films is tensile testing (see, e.g., references 2–5). Dynamic mechanical thermal analysis (DMTA) has also been used to study these films, although to a much lesser extent (see, e.g., references 6–12). Tensile testing provides information about the elasticity, breaking strength, and elongational ability of the film. DMTA enables detection of thermal events which can cause subtle changes in the mechanical properties of the films, usually connected to glass transitions and related phenomena.

Humidity and Mechanical Testing of Films

The purpose of studying the effect of storage humidity on the thermomechanical parameters is to examine the physical and chemical stability of the polymer, plasticizer, and film to heat and moisture. The effects that are involved include degradation, evaporation, coalescence, curing, and aging. Water is also known to have a plasticizing effect on hydrophilic polymers. Water molecules can be incorporated into the films during storage (see, e.g., references 13, and 14), thus affecting the strength of the film by lowering its glass transition temperature, T_g. An aspect to this function of water that seems to have been partly ignored is the water that may be absorbed/desorbed during the actual measurements, and which may thereby influence the results obtained. Environmental conditions in the room where tensile testing has been performed is not often stated in the literature, although there are exceptions (see, e.g., references 3, 15, and 16). It is a reasonable supposition that the apparatus is placed in at least a controlled-temperature area, but humidity can also vary widely if not controlled. The American Society for Testing and Materials specifies 23°C and 50% relative humidity (RH) in method ASTM D 882-90a for tensile testing of thin plastic sheeting.

For DMTA, the sample is placed in an enclosed thermal chamber, often with a nitrogen or helium purge. The humidity in the chamber will be low, and if the sample has been equilibriated at a higher storage humidity, the sample will dry out during measurement. Because the film samples in both of these tests are often small and thin, it is reasonable to suppose that they can respond rapidly to humidity changes in the environment surrounding them. In fact, this suggests the possibility of a new type of experiment with the DMTA, namely isothermal dynamic humidity scan.

Aim of This Work

Based on the above observations, we examined the effect of humidity on pharmaceutical coating films *during* thermomechanical measurements. The magnitude of this effect and the potential of such measurements was examined. The dynamic humidity scan in DMTA was tested. Complementary tensile tests with a humidity step were performed. The aim was to obtain information that can assist in designing relevant experiments for film formulation development work.

Cellulose acetate phthalate was used as the film-forming polymer with diethyl phthalate and triethyl citrate as plasticizers.

MATERIALS

CAP and diethyl phthalate (DEP) were obtained from Eastman Chemical Company, Kingsport, TN. Triethyl citrate (TEC) (Eudraflex) was from Rohm Pharma (Darmstadt, Germany).

METHODS

Preparation of Free Cast Films

CAP was dissolved in acetone to a concentration of 10% w/w, with 2% w/w plasticizer (to give 20% w/w of polymer dry weight). The solution was stirred for 16 hr before varying volumes of the solution were poured into 10 cm diameter polymethylpentene Petri dishes. The solution was then dried at room temperature and humidity to obtain cast films which could be peeled off from the Petri dishes. The films were stored at 20°C and 50% RH.

Some films were also prepared from CAP latex dispersion at the same concentrations as described. The Petri dishes were treated with chromic acid for 2 min and rinsed before the dispersion was poured into them. The dispersion was dried at room temperature.

Moisture Absorption

Free film samples were equilibriated at either 0 or 100% RH for a week and then placed in a microbalance at 20°C and 50% RH. The weight of these samples was recorded at different times, and the final films were immediately analyzed for equilibrium water content by Karl Fischer (coulometry) analysis (Metrohm 737 KF Coulometer, Metrohm Ltd., Herisau, Switzerland).

DMTA of Free Films

DMTA was performed on a Netzsch (Netzsch-Gerätebau GmbH, Selb, Germany) DMA 242 in the tensile mode at 1 Hz and a maximum dynamic force of 0.7 or 0.8 N. Samples, 6 mm wide, were cut out of the films for analysis; thickness of the samples varied between 0.02 and 0.3 mm. Glass transition temperatures were determined at a scanning rate of 3°C/min over the range 20–150°C.

For isothermal humidity scan experiments, the temperature of the sample compartment was held at 25°C. The humidity in the sample compartment was controlled by a simple home-built apparatus in which a stream of dry air (200 ml/min) is divided into two parts. One part is bubbled through water to saturate it and is then remixed with the other part in a three-necked bottle, from which it flows into the DMTA sample compartment. Changing the proportion of the two divided flows enables different final humidities to be obtained, and changing the volume of the bottle allows different humidity ramp slopes to be obtained. The humidity was measured at the mixing point by an HMI36 Humidity Data Processor containing a psychrometer probe (Viasala OY, Helsinki, Finland).

No reference to such dynamic humidity scan experiments was found in the literature. However, some work was done on thermomechanical characterization of, e.g., paint (17) and protein (18) at different moisture levels, in which the sample was protected from dehydration by coating it with mineral/silicone oil during testing.

Tensile Testing of Free Films

A Lloyd LRX tensile tester (Lloyd Instruments Ltd., Fareham, UK) with a 50-N cell and a gauge length of 7 mm was used for tensile testing of free cast films. The films were cut into strips 6 mm wide; thickness was measured inductively by a Fischer Permascope MPO(S) (Helmut Fischer GmbH, Germany), and were an average of 0.3 mm thick. The measuring speed was 0.1 mm/min. Data evaluation was done by the Windup ver. 1.0 software package, which was also used for operating the instrument.

The apparatus was installed in a controlled-environment room which was held at 25°C. The relative humidity in the room was held at 20% and at 70%.

Thermal Analysis of Free Films

Free film samples (CAP + TEC) were analyzed by differential scanning calorimetry (DSC) on a Mettler (Mettler-Toledo, Greifensee, Switzerland) DSC30 with a TA4000 operating system. Sample masses were approximately 10 mg, placed in aluminum pans with crimped lids and also lids with pin holes. Heating rates were 10°C/min in an atmosphere of nitrogen. The samples were preequilibriated at 67% RH at room temperature (20°C) by placing them in a dessicator containing saturated $CuCl_2$ solution.

RESULTS AND DISCUSSION

Moisture Absorption

CAP + TEC and CAP + DEP films prepared from acetone were equilibriated either at 0 or 100% RH at 20°C, and then moved to a room with 50% RH. The changes in water content of these films as a function of

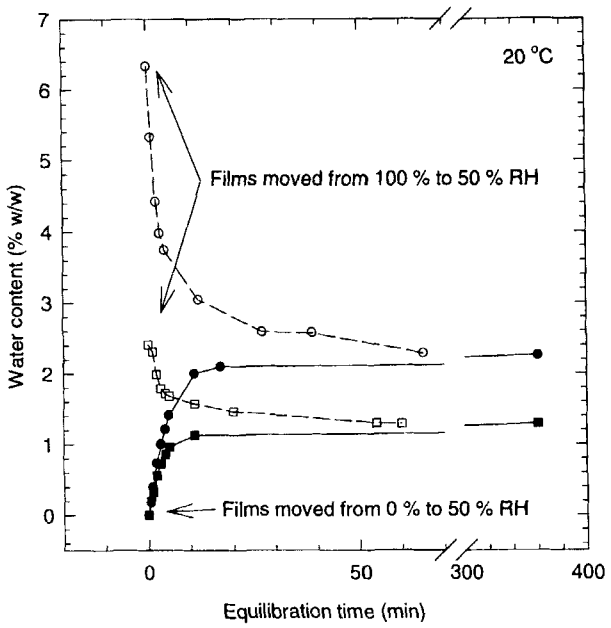

Figure 1. Change in water content of CAP + TEC (○) and CAP + DEP (□) films when the films are moved at time zero from 100 to 50% RH (open symbols) and from 0 to 50% RH (closed symbols).

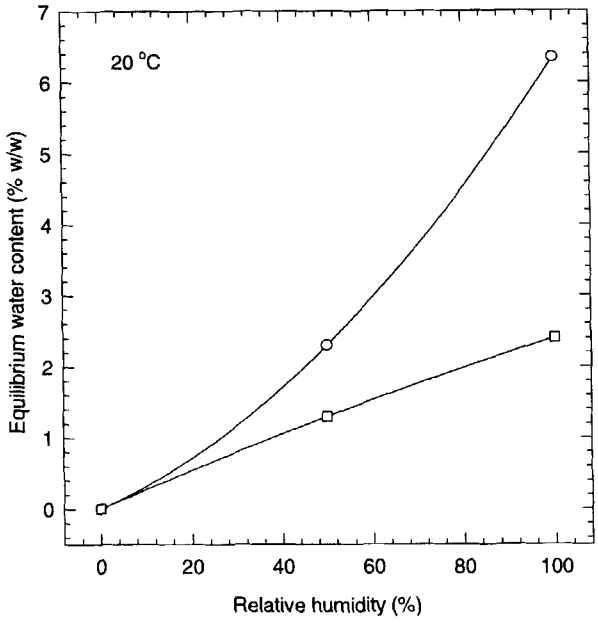

Figure 2. Equilibrium water content in CAP + TEC (○) and CAP + DEP (□) films at different relative humidities at 20°C.

time are shown in Fig. 1. The results show that the films respond rapidly to changes in the humidity of the environment. Dry films respond faster, approaching more than 90% of final value at 50% RH within 20 min. Wet films are somewhat slower in drying out but also reach over 90% of final value at 50% RH within 30 min.

The equilibrium water contents at 20°C and 50% and 100% RH for films containing TEC and DEP differ significantly. This is illustrated in Fig. 2, in which the equilibrium moisture content is plotted against percent RH. The more polar character of TEC as compared to DEP results in a higher final water content of CAP + TEC films. This moisture content has an effect on the thermomechanical properties of the films. However, another factor is the chemical stability of CAP, which undergoes rapid hydrolysis above 6% moisture content (19). It is important, therefore, that such moisture absorption isotherms be drawn up when a film compostion is formulated. Hygroscopic or moisture-sensitive excipients/drugs in the tablet substrates will exacerbate this problem.

DMTA with Humidity Scanning

DMTA results of films while the humidity in the sample chamber is changed continuously are shown in Figs.

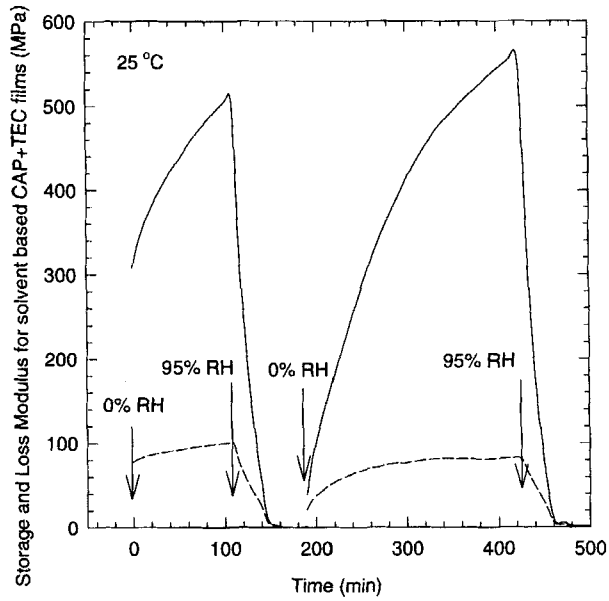

Figure 3. Effect of dynamic humidity change on the mechanical properties [storage modulus (—) and loss modulus (---)], of CAP + TEC films during isothermal measurements (25°C) on the DMTA. The points at which the 0 or 95% RH gas purge were started are indicated by arrows.

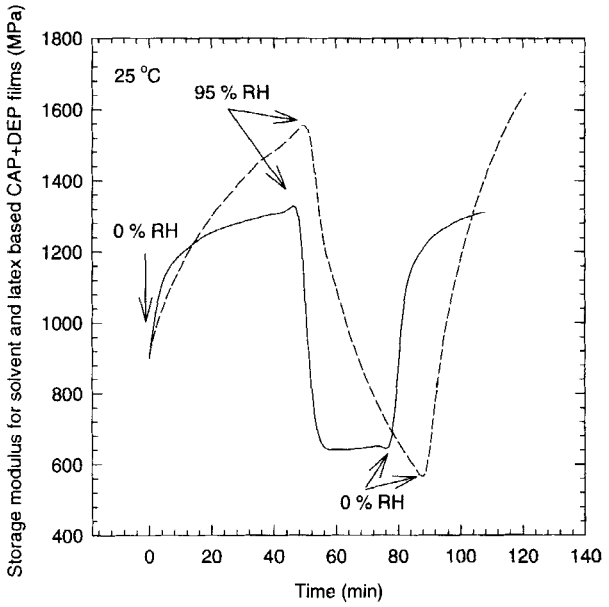

Figure 4. Effect of dynamic humidity change on the storage modulus of solvent- (—) and latex- (---) based CAP + DEP films during isothermal measurements (25°C) on the DMTA. The points at which the 0 or 95% RH gas purge were started are indicated by arrows.

3 and 4. The storage (E′) and loss (E″) modulus of CAP + TEC films under varying humidity (i.e., moisture content) show that the film responds very rapidly to environmental conditions (Fig. 3). The sample was placed in the instrument (after storage at room temperature and humidity) and the dry purge gas was started along with the measurements. The values of the moduli increased continuously as the film dried out. When the purge gas flow was switched from dry to that with 95% RH, the film responded immediately to the change in humidity; the values of the moduli became very low. However, when the dry gas was switched on, the film was dried out and recovered its original tensile properties.

The above reversible phenomenon is also true for CAP + DEP films in Fig. 4. Both solvent-based and latex-based CAP films were tested and showed qualitatively similar behavior (only the storage modulus is presented here). Differences in the maximum values of the modulus obtained for the two types of films can be attributed to errors in the measured thickness of the very thin films.

Note that in the above experiments, the dry gas purge was run only as long as was required to illustrate the phenomena. Running the dry purge longer will lead to increasing values of the moduli and finally to a plateau as the film dries out completely. Hence, the maximum values of E′ (and E″) in Figs. 3 and 4 are not absolute. It is apparent, however, that the CAP + TEC film became increasingly elastic with decreasing moisture content because the rate of increase in the storage modulus was much higher than that of the loss modulus (Fig. 3). The same holds true for CAP + DEP films in Fig. 4, although the E″ data are not shown here.

A comparision of the minimum values of E′ obtained for the films containing TEC and DEP (Figs. 3 and 4) shows that the TEC film apparently became much softer than the DEP films. Fig. 2 shows that the DEP-containing films have a more hydrophobic nature than the TEC-containing films. The plasticizing effect of moisture is therefore more apparent in the TEC-containing films. This may have implications in the choice of plasticizer in coating formulations.

Tensile Testing at Different Humidities

Complementary results from tensile testing on the same CAP + TEC films as in Fig. 3 are presented in Fig. 5. Tensile testing was carried out with the room at 25°C and at two RHs (20 and 70%). The dramatic effect of increased humidity in the room was obvious. The film at 70% humidity was very plastic and showed an extreme degree of elongation before breaking. A rough estimate of the difference in water content of the films (between 20 and 70% RH) can be obtained from Fig. 2, although the isotherm was obtained at 20°C. We estimate this difference to be in the range of 3–5%; this amount of extra moisture then results in almost complete plasticization of the film.

Glass Transition Temperature and the Efficacy of Plasticizers

Plasticizer functional efficacy is often estimated by examining the reduction caused in the T_g. However, if an incompletely dried sample is placed in the DMTA, it will continue to dry in an uncontrolled manner in the sample compartment and will reduce the validity of the results. (This is illustrated in Fig. 6, in which a DSC run on CAP + TEC film in an open pan shows that water is lost from this film over a very broad temperature range. The same film in a sealed pan shows no water loss and exhibits reversible thermograms; these thermograms resemble those obtained from second runs made in open pans.) DMTA scans on such ill-defined samples are therefore meaningless. In our own studies, T_g values ranging between 84 and 97°C for CAP + TEC films, and between 87 and 109°C for CAP + DEP films were obtained, when

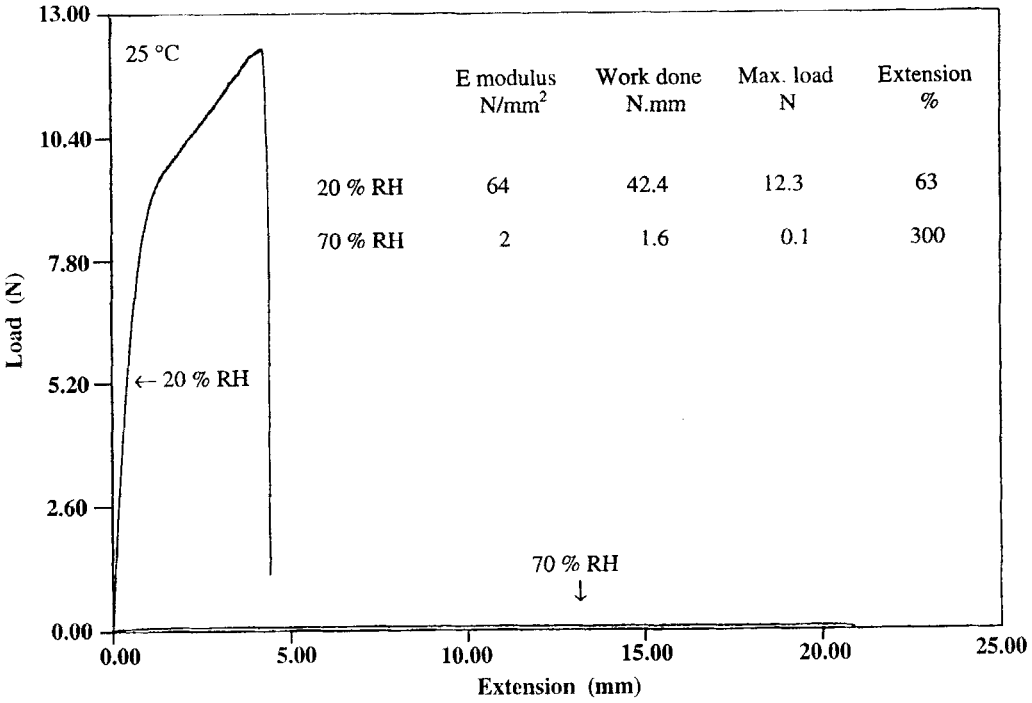

Figure 5. Load-extension profiles of CAP + TEC films obtained from tensile testing carried out at 20 and 70% RH at 25°C.

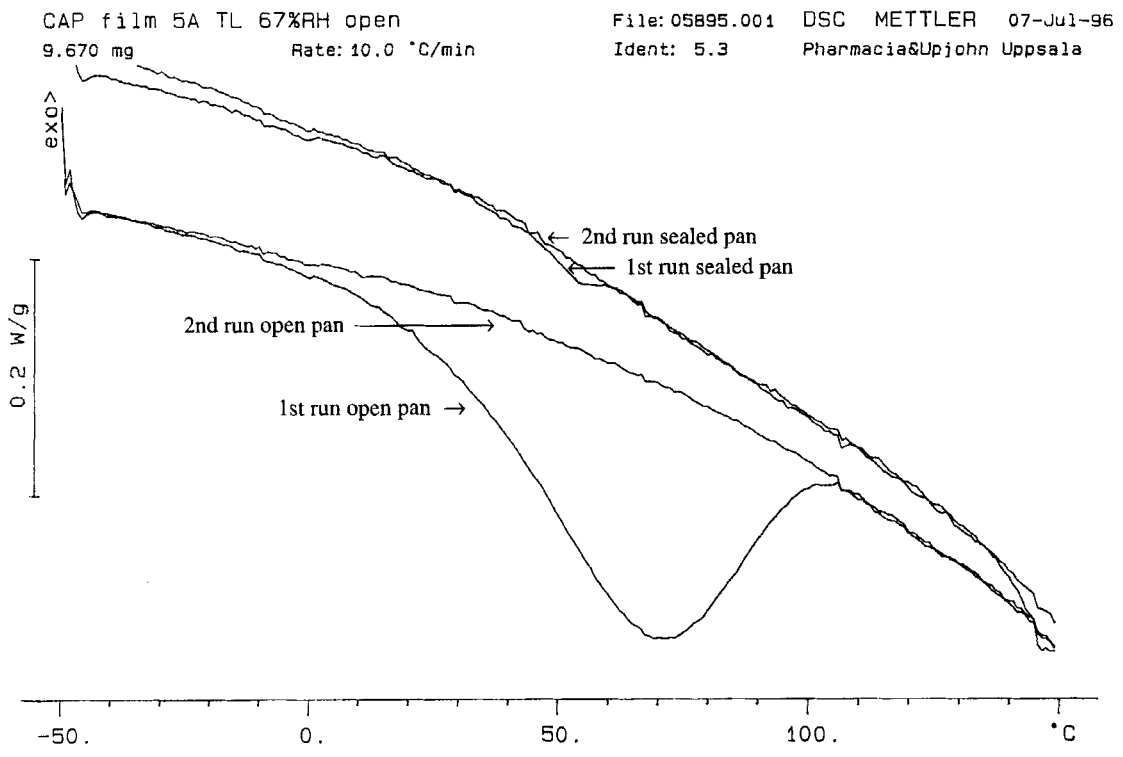

Figure 6. Typical DSC thermograms on CAP + TEC films stored at 20°C and 67% RH. Shown here are results for a sample run in an open DSC pan and the second run on the same sample. Corresponding runs for a sample run in a sealed pan are also given.

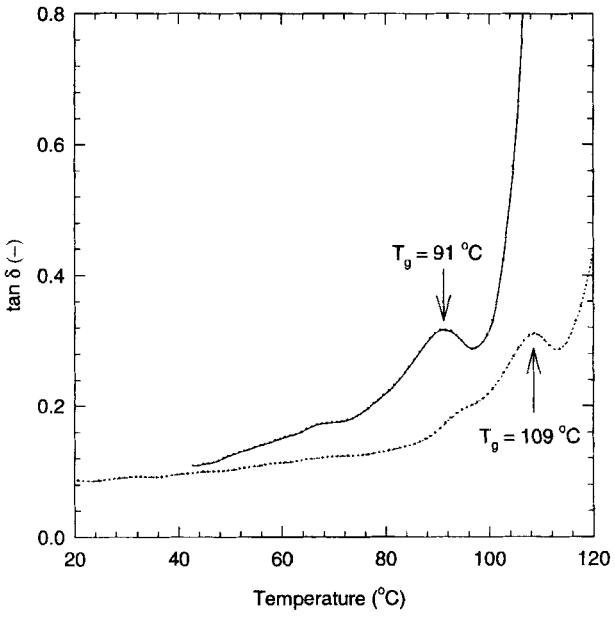

Figure 7. Determination of glass transition temperatures of CAP + TEC (—) and CAP + DEP (···) films by DMTA. The films were dried for 1 hr on the instrument before analysis.

tested directly without a drying step. This can be compared to the true T_g values of dry CAP + TEC film at ~90°C, and that of dry CAP + DEP films at ~110°C in Fig. 7. The lower values obtained when analyzing "moist" films obviously reflect the influence of water. Examples of tan δ versus temperature scans on the DMTA on CAP + TEC and CAP + DEP films are shown in Fig. 7. These films were dried for 1 hr after being mounted in the instrument, prior to the temperature scan.

True efficacy of the plasticizers can thus be compared when the influence of absorbed moisture has been removed. For the same concentration of plasticizer (20% with respect to dry polymer), TEC is more effective than DEP in its plasticizing ability because it causes a larger reduction in T_g (T_g of CAP itself is ~171°C). This can again be attributed to the more polar nature of TEC, which enables it to interact better with the CAP molecules. However, we can note that water is actually much more effective than either TEC or DEP. A water content of approximately 3–6% reduces the T_g to almost room temperature (see Fig. 5). Plasticization effect is not proportional to the weight fraction but to the mole fraction; 3–6% by weight water translates into a minimum of twice as many moles compared to 20% TEC or DEP. (The molecular weight of TEC is 276 and that of DEP is 222; thus, this same argument cannot be used to explain the higher efficacy of TEC in relation to DEP. The mole fraction argument may be used when comparing plasticizers of similar polarity only.)

CONCLUSIONS

The results discussed above show very clearly the function of moisture as a plasticizer for CAP films, and the rapid response of these films to changes in environmental conditions. This emphasizes the importance of having adequate control of the measurement conditions when performing the thermomechanical tests. In stability studies (see, e.g., references 3 and 20) in which films or coated tablets are stored at various humidities, it is important to dry the film completely before DMTA or tensile strength analysis. Any influence of chemical degradation could otherwise be masked by the effect of absorbed moisture during the measurement itself. This will be especially important when the aim of the study is to choose the best plasticizer (see, e.g., references 3, 4, 13, and 21–23), because equilibrium-absorbed moisture content will also depend on the type of plasticizer. Thus, even if the films are equilibriated at similar conditions before testing (e.g. those specified in ASTM D 882-90a) (2, 4, 11), the final moisture content of films containing different plasticizers will vary. The incremental plasticization effect resulting from this moisture will thereby be different, making the results difficult to interpret.

Isothermal dynamic humidity scan experiments on the DMTA have much potential. Considerable interest exists in finding suitable functionality tests for pharmaceutical excipients (24). For film coatings, one functionality test can be the determination of mechanical properties at various relative humidities, because this would mimic the conditions of use. These tests can be performed rapidly in the DMTA, using a humidification system of the type presented here to produce step or continuous RH changes under isothermal conditions. Accelerated conditions may be simulated by running these tests at higher temperatures. T_g at various absorbed moisture levels can also be determined.

The utility of the DMTA can be multiplied enormously by making step or continuous humidity scans; we have only shown the possibility of doing such experiments here.

ACKNOWLEDGMENTS

We acknowledge the skillful assistance of Tobias Lehtipalo in performing some of the early experiments.

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