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Research Article

Prediction of Physical Aging in Controlled-Release Coatings: The Application of the Relaxation Coupling Model to Glassy Cellulose Acetate

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The effect of physical aging on both the water transport properties and the mechanical properties of glassy cellulose acetate was investigated. Results indicate a reduction in the mechanical rate of relaxation as well as a reduction in the water permeability as the glass ages. A model which describes the low-frequency relaxation behavior of condensed, amorphous systems is used to quantitate the mechanical relaxation data. Systematic changes in key parameters from this model signify alterations in the microscopic or short-range structure as the glass physically ages. Predictions from this model correlate quite closely with the observed water permeability reductions and thus indicate that the transport properties of glassy polymers are dependent on the structure of the glass. This approach may provide further insight into the effects of nonequilibrium behavior on pharmaceutically important properties and may serve as a basis for predicting aging and permeability changes in controlled-release dosage forms.

KEY WORDS: physical aging; water transport; controlled-release coating; mechanical relaxation; cellulose acetate.

INTRODUCTION

As more controlled- and sustained-release dosage forms are introduced into product development, pharmaceutical scientists are currently addressing the long-term stability of these formulations (1). While the use of accelerated testing conditions such as elevated temperatures for conventional dosage forms are quite successful, its use in testing dosage forms containing glassy polymeric materials needs to be examined. Both nonpolymeric and polymeric glasses are systems which are not in thermodynamic equilibrium. Common polymeric materials utilized in the pharmaceutical industry such as hydroxypropyl methylcellulose (T_g = 177°C), hydroxypropyl methylcellulose phthalate (T_g = 133°C), cellulose acetate (T_g = 191°C), ethyl cellulose (T_g = 133°C), cellulose acetate phthalate (T_g = 171°C), polyvinyl alcohol (T_g = 75°C), and polyvinyl acetate phthalate (T_g = 55°C) are glassy at room temperature and therefore not in an equilibrium state.

Nonequilibrium behavior is manifested as the nonlinear and asymmetric response to varying pressure and temperature histories, the breakdown of Fick's Law as a description of transport processes, and the phenomenon known as physical aging (2). Physical aging is a time-dependent relaxation toward a lower-free energy state and is the primary cause for macroscopic property changes such as reductions in specific volume, enthalpy, mechanical rate of response, dissolution rate, and gas permeability (3–5).

Above the glass transition temperature, T_g, large-scale translational and rotational motion governs the segmental mobility of a polymer (6). As the temperature of the macromolecule is lowered through the glass transition region, translational and large-scale rotational motion freezes out, leaving only hindered rotation and vibration (6). This freezing of the translational and rotational contribution to segmental mobility thus slows molecular relaxation in the glass and has been identified as the cause of the reduction in heat capacity that is observed at T_g (7). The lack of segmental motion prevents the system from attaining equilibrium below T_g, even at very slow cooling rates, because there is not enough mobility for the polymer to move into its lowest-free energy state. The difference between the free energy of the polymer and its lowest-free energy state provides the thermodynamic basis for physical aging.

The aging of amorphous materials has been extensively studied (3–5). These studies have focused mainly on the time-dependent changes in mechanical properties or in thermodynamic extensive variables such as volume or enthalpy. A graphical description of the aging time dependence of enthalpy for a glass-forming material is shown in Fig. 1. Aging induced changes in the mechanical properties involve an increase in brittleness, critical strain for shear yielding and

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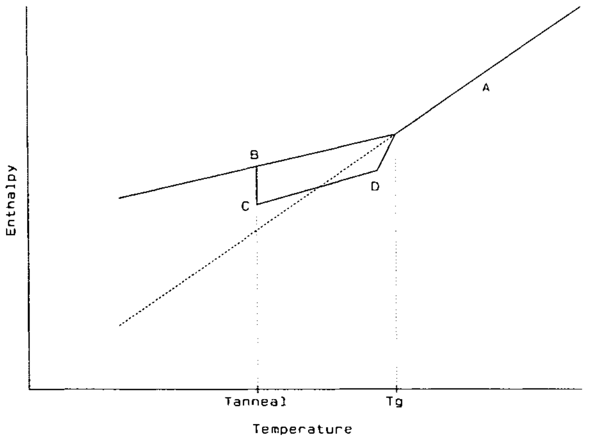

Fig. 1. Graphical depiction of physical aging. Point A: An amorphous material at $T > T_g$ is in thermodynamic equilibrium. A glass will then form upon cooling at $T = T_g$. Point B: At $T_{\text{anneal}} < T_g$, the glass will physically age. This is manifested by a reduction in enthalpy to Point C. As the temperature of the glass is raised, the enthalpy will increase until Point D is reached. At this point the enthalpy will "recover" in a narrow temperature range until equilibrium is reached.

modulus, and decreases in compliance and rate of mechanical response (3,5,8). Reductions in enthalpy can be observed using a differential scanning calorimeter. When the physically aged glass is reheated through T_g, the enthalpy will "recover" in a narrow temperature range near T_g, resulting in the appearance of a sharp endothermic peak on the DSC thermogram (8,9). The origin of this sharp endothermic peak is shown in Fig. 1, where the rather sharp increase in the enthalpy of a physically aged glass occurs at point D near T_g. Increases in the density of a glass as a function of time have also been attributed to physical aging (3).

Time-dependent reductions in the gas transport properties of glassy films have been recently reported. Studies of physically aged substituted polycarbonates and polysulphones have demonstrated reductions in the permeability and lag time of helium, carbon dioxide, nitrogen, and methane (10). Dissolution rate reductions have been reported for physically aged hydroxypropyl methylcellulose phthalate (5).

The temperature range for aging extends from Tg down to the first major secondary relaxation in the glass. This secondary, or low-energy, relaxation has been associated with the local motions of main chain segments or side chains (11). It has been proposed and shown experimentally that, without this motion, the relaxation of the glass caused by aging will cease (3). Physical aging has also been shown to be a thermally activated process (9).

In this report, the impact of physical aging on the osmotic pressure-induced water transport properties and the mechanical properties of cellulose acetate is evaluated. The kinetics of physical aging are estimated from the mechanical data using a model which describes the relaxation behavior of condensed systems (12,13). Finally, the kinetic description of aging is correlated with the observed water permeability changes.

THEORY

A relaxation process is generally defined as the decay of a macroscopic variable such as stress, strain, volume, enthalpy, or electric field with time (14). The significant changes in physical properties which occur during the relaxation can critically affect that material's performance. A qualitative description of the relaxation behavior of a glassy polymer should include general features of relaxation such as memory effects, asymmetry, nonlinearity, and nonexponentiality (15). In the past, the characterization of relaxation processes in glasses and rubbers has been largely phenomenological. A distribution of relaxation times had been used to describe mechanical and dielectric relaxation because a simply Debye relaxation term, with a single relaxation time, generally failed. The notion of a distribution of relaxation times was justified by assuming that variations in local environments permitted the existence of a sequence of mechanisms which contributed to this distribution (12). This time-dependent relaxation could then be described by

$$\Phi(t) = \int_o^\infty g(\tau)e^{-t/\tau}dt \qquad (1)$$

where $\Phi(t)$ is a macroscopic variable which is normalized by its instantaneous ($t = 0$) value, τ is the relaxation time, and $g(\tau)$ is a relaxation spectrum associated with τ. This model has been used to characterize mechanical response (16), dielectric response (12), and volume relaxation (17).

The main drawback with this model, and with mechanical analogues such as spring and dashpot configurations in general, is that it is empirical and cannot be physically verified (12). If a distribution function or relaxation spectrum was determined for a particular system, one would expect it to be dependent on the physical or chemical composition of that system. In fact, it has been shown that the time dependence of the relaxation of macroscopic variables such as stress or electric field for a broad spectrum of materials is quite similar (18). The similarity of these functions between materials of widely different chemical type, physical state, and bonding character, though, would seem to rule this out (12).

A theory first proposed by K. L. Ngai (12) offers a way to describe the relaxation of complex, condensed systems without relying on any molecular details. This model, known as the relaxation coupling model, describes the modification of the microscopic transition rate, W_o, of a relaxing species by the interaction of that species with its complex environment. The species could be a molecular moiety or a structural unit that exists in a domain of short-range order, an environment that is a characteristic of a liquid, supercooled fluid, or glass (19). The modification of the microscopic transition rate, $W(t)$, is described as

$$W(t) = \tau_o^{-1}(\omega_c t)^{-n} \qquad (2)$$

where n represents the coupling strength or strength of interaction between the relaxing species and its surroundings, ω_c is an upper cutoff frequency or the time at which coupling must be taken into account, and $W_o = \tau_o^{-1}$. Increasing values of n indicate a greater interaction between the relaxing species and its surrounding environment, resulting in an enhanced reduction in the time-dependent transition rate (13,14). If, during the time scale of observation of the relaxation process, the key parameters in Eq. (2) do not change, the relaxation of a complex, condensed system is described as

$$\Phi(t) = \exp(-t/\tau^*)^{1-n} \quad (3)$$

where τ^*, the apparent relaxation time, is defined as

$$\tau^* = [(1 - n)\omega_c{}^n\tau_o]^{1/1-n} \quad (4)$$

Equations (3) and (4) are coupled through n, the coupling parameter. The significance of Eq. (4) is that microscopic events represented by ω_c, τ_o, and n can be interpreted in the form of a macroscopic measurement, τ^*. The effect of coupling strength on the relaxation of a macroscopic variable is shown in Fig. 2. Small changes in n result in substantial changes in the time profile of relaxation.

Ngai has presented experimental evidence for both Eq. (3) and Eq. (4) (18). This model was also used to describe the kinetics of physical aging by taking into account the aging temperature and aging time dependence of τ^* and n (20):

$$\Phi(t) = exp\left[- \int_o^t \tau_o{}^{-1}(\omega_c t')^{-n} dt' \right] \quad (5)$$

In most cases ω_c remains constant. In the present analysis, we characterize physical aging as a relaxation process which can be described through $\Phi(t)$. The values of τ_o (through τ^*) and n are evaluated experimentally by measuring the viscoelastic properties of cellulose acetate at different aging temperatures and aging times. The extent of aging is then calculated using Eq. (5).

EXPERIMENTAL

Film Preparation

Cellulose acetate was chosen in this study due to its high water permeability and ion selectivity, as well as for its strength (21). Another important reason, particularly for the organic solvent-based system, is that water will only slightly change the structure of the glass (21,22). Cellulose acetate, 398-10 (FMC Corp., Lot SA740; MW_w = 177000, MW_n = 58500, 39% acetyl), was dissolved in acetone at a concentration of 2.5% (w/w). Two-milliliter portions were poured onto a glass plate and covered with an inverted funnel to prevent solvent removal by convection. The films were allowed to dry for a period of 24 hr at room temperature prior to their removal from the glass plate. The films lifted easily off the plate and were cut into 2.0-cm-diameter circular and 15 × 2-mm rectangular samples. The samples were stored in a desiccator for a period of 1 week. Since the boiling point of acetone is 6°C, it was assumed that no residual solvent was present. This was checked by subsequent creep compliance measurements, where it was found that no difference was observed in the mechanical response as a function of time. This procedure does not indicate that no solvent was left, only that there were no changes in solvent concentration.

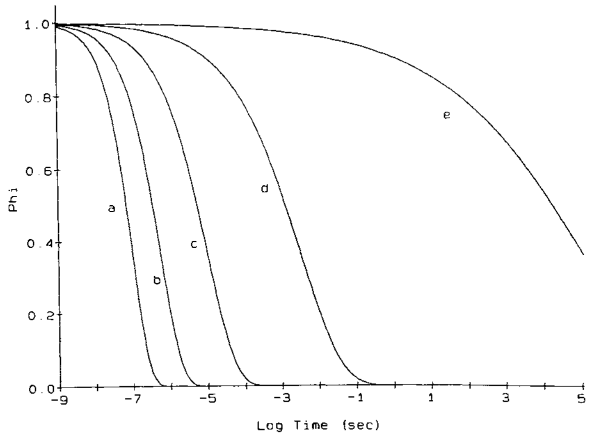

Fig. 2. The impact of coupling or constraint on the relaxation behavior of a condensed, amorphous system. $\tau_o = 10^{-7}$ sec, $\omega_c = 10^{10}$ sec^{-1}. (a) $n = 0$; (b) $n = 0.2$; (c) $n = 0.4$; (d) $n = 0.6$; (e) $n = 0.8$.

Transport Studies

The osmotic pressure-induced water transport studies were performed in a standard diffusion cell system that was preequilibrated at 37°C. The system included a MGW Lauda M3 water circulator (Messgerate-Werk Lauda, Lauda-Konigsofen, West Germany) and 3-ml Side bi-Side diffusion cells (Crown Glass Co., Vineland, NJ). The thickness of the film was measured before each permeability experiment was performed. Two 3-mm Silastic gaskets were placed on each side of the circular film and placed between each half of the diffusion cell. The cells are then clamped to ensure no leakage. A saturated sodium chloride solution in the presence of excess NaCl was placed in the receiver side of the system, while distilled water was added to the donor side. Both of these solutions were preequilibrated at 37°C overnight. Stirring bars were added in order to reduce boundary layer effects.

A specially made 2-mm-ID graduated capillary tube with a 7/25 male fitting was inserted in the sampling port of the receiver side. Silicone grease was added to the surface of the fitting to prevent leakage. The whole connection was then wrapped in parafilm. Parafilm was placed over the sampling port of the donor side without the glass stopper. Insertion of the glass stopper was found to exert a hydrostatic pressure gradient which directly affected the reading of the water level in the capillary tube. Level readings were taken periodically over a period of 4 hr. These readings can be converted to volume, from which volume flux can be directly calculated.

After the experiment, the films were removed, cleaned, and stored in a desiccator for 24 hr. They were then placed in an oven at a specified temperature for a specified period of time. The effect of aging time at 100°C was studied at 10, 30, 60, and 100 hr. The effect of aging temperature was evaluated for 10 hr at 50, 75, 100, 125, and 150°C. The literature value of T_g for this material was identical to the experimentally determined value of 191°C (23). The films were removed from the oven and allowed to stand for 1 hr before another permeability test was run. There were no statistical differences between the thickness of the film before and that after the aging step.

The apparent non-Fickian behavior of cellulose acetate has been previously reported (24). Thickness effects were observed to affect the permeability measurement and this was removed in our experiments by dividing the volume flux of the aged film by that of the untreated film. The effect of the thickness variation was removed by using the film as its own control. Reverse osmosis measurements confirm that the reflection coefficient (a measure of salt permeability) tends to be dependent on pressure, with the coefficient being one at zero applied pressure on the high-salt concentration side (21). Salt transport across solvent cast cellulose acetate films has been shown experimentally to be very low in comparison to water transport (21,22).

Mechanical Measurements

The mechanical measurements were performed in order to evaluate the coupling parameter and apparent relaxation time–temperature/aging time profiles. Thus, a slight change in the aging experiments from our previous studies on hydroxypropyl methylcellulose phthalate was made (5). The film was brought to 194°C for 20 min and then cooled at 2°C/min to various aging temperatures. Mechanical experiments were performed at 3, 6, 10, 15, and 20 hr for 18 min. The aging temperatures that were studied were 175, 150, 125, 100, 75, and 50°C.

The mechanical testing technique used in this study was a uniaxial tensile test. All of the measurements were made on a Mettler TMA40 Thermomechanical Analyzer (Mettler Instruments, Hightstown, NJ). A uniaxial tensile stress between 1 and 3 MPa was applied to the film, while the initial strains were observed to be between 0.065 and 0.12%. Mechanical and aging interference in the tests was minimized using the same testing criteria for our previous studies (5). The interference of the primary relaxation on the mechanical response was also evaluated and found to be minimal (2).

RESULTS

Permeability Measurements

Water transport was found to be linear with time for the entire time period studied. The lowest r^2 value which was recorded was 0.991. The lag times, although all were positive, showed substantial variation and could not be reliably analyzed. A plot of permeability ratio versus aging time at 100°C is shown in Fig. 3, while that of permeability ratio versus aging temperature for an aging time of 10 hr is shown in Fig. 4. These figures reveal a monotonic decrease in permeability with aging time as well as thermally activated reductions in permeability. Both of these effects point to a physical aging/structural change within the system.

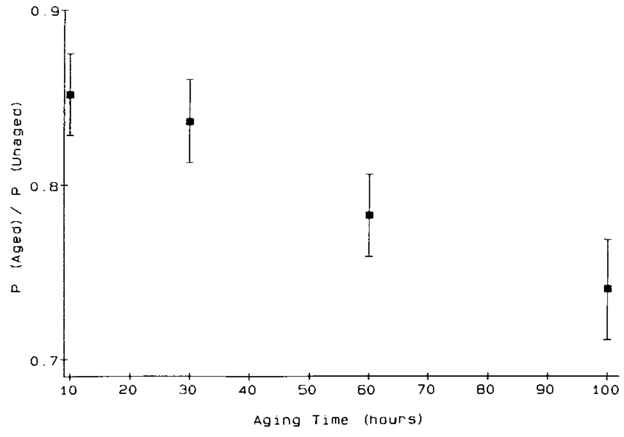

Fig. 3. Aging time dependence of the water permeability of cellulose acetate. T = 100°C. Error bars represent standard error of the mean.

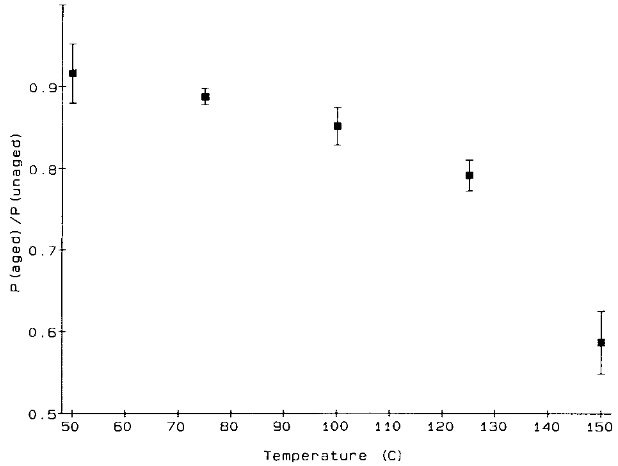

Fig. 4. Aging temperature dependence of the water permeability of cellulose acetate. Time = 10 hr. Error bars represent standard error of the mean.

An assumption that we have made is that the water molecule does not change the structure of the glass appreciably. Even though cellulose acetate will absorb water, the unplasticized polymer will remain as a glass (22). It is assumed here that water may change the structure slightly such that transport occurs through an "infiltration" layer, an assumption commonly made in gas transport measurements (25).

Mechanical Measurements

The creep compliance data for cellulose acetate is similar in its time profile to that of hydroxypropyl methylcellulose phthalate (5). The constants n and τ^* can be determined from the mechanical relaxation properties measured in tension through the following equation (4):

$$G(t) = G_o\exp(-t/\tau^*)^{1-n} \tag{6}$$

where $G(t)$ is the stress relaxation modulus, Go is the instantaneous value of the stress relaxation modulus, and n and τ^* retain their original definition. In our studies, the creep compliance data had to be converted to the stress relaxation form before it was fit with Eq. (6) by using Hopkins and Hammings's algorithm for the deconvolution of the linear constitutive equation for viscoelastic response (26):

$$t = \int_o^t J(t - \tau)G(\tau)d\tau \tag{7}$$

where $J(t)$ is creep compliance.

The converted data were then fit to Eq. (6) using nonlinear regression (BMDP, Statistical Software Consultants, Los Angeles, CA). The fits that gave the lowest residual sum of squares were labeled as best fits and the values of the apparent relaxation time and coupling parameter were recorded. The averages of these values (n = 3) are reported in Table I.

The increase in the coupling parameter with aging time

Table I. Summary of Parameters Taken from Best Fits of the Relaxation Coupling Model

Aging Time (hr)	50°C		75°C		100°C	
	n	τ^{*a}	n	τ^{*b}	n	τ^{*b}
3	.892 (.003)	203.2 (67.8)	.878 (.0015)	533.8 (125)	.875 (.002)	202.9 (64)
6	.892 (.004)	323.5 (113.2)	.886 (.001)	1187.9 (223)	.885 (.0006)	797.7 (156)
10	.897 (.0003)	556.1 (59.5)	.890 (.002)	1900.1 (586)	.888 (.003)	1437.5 (394)
15	.901 (.0007)	1044.5 (143)	.893 (.002)	3553.8 (1572)	.894 (.003)	2643.7 (642)
20	.899 (.001)	1001.9 (129)	.895 (.001)	4539.3 (1501)	.893 (.002)	3173.9 (580)

Aging Time (hr)	125°C		150°C		175°C	
	n	τ^{*b}	n	τ^{*c}	n	τ^{*}
3	.869 (.02)	281.7 (43.4)	.779 (.007)	434 (37.8)	.607 (.004)	551.7 (42.4)
6	.879 (.003)	898.6 (205)	.789 (.002)	696.1 (134)	.620 (.007)	861.5 (66.9)
10	.886 (.0006)	1620 (164)	.793 (.005)	1783.5 (573)	.625 (.001)	1083.5 (146)
15	.887 (.001)	2586.9 (229)	.801 (.002)	2262.7 (180)	.629 (.001)	1235.4 (219)
20	.891 (.002)	4891 (1382)	.811 (.004)	3817.7 (574)	.634 (.002)	1242.2 (217)

[a] $\times 10^{-6}$.
[b] $\times 10^{-5}$.
[c] $\times 10^{-3}$.

reflects the greater interaction between relaxing species within the glass. Physically, this means that as the glass ages, a longer time is needed to respond to the mechanical state of stress. In the case of a glassy polymer a greater amount of segmental cooperativity is required to relax the applied stress. This result is consistent with similar measurements made on physically aged polystyrene and hydroxypropyl methylcellulose phthalate (4,5). Figures 5 and 6 show the characteristic dependencies in both parameters with temperature at an aging time of 3 hr. The coupling parameter and the apparent relaxation time show a negative dependence on temperature with logarithmic changes in the apparent relaxation time. The same trend has been seen with the temperature dependence of the stress relaxation behavior of glassy polycarbonate (27). Higher values of the coupling parameter at the lower temperatures indicates a greater interaction between the relaxing species and its surroundings, which would be the expected result because the density of the system also increases in the same temperature range.

DISCUSSION

$\Phi(t)$ as an Indicator of Aging

The quantity $\Phi(t)$ describes the time-dependent decay of a macroscopic variable. In the following analysis, we use this quantity to describe the extent of structural change in cellulose acetate as a function of aging time. Physical aging is treated as a relaxation toward equilibrium and thus an equation of the form of Eq. (5) is utilized.

The progression of physical aging was monitored with our mechanical probe, in this case creep compliance measurements, and changes in the microscopic, or local, envi-

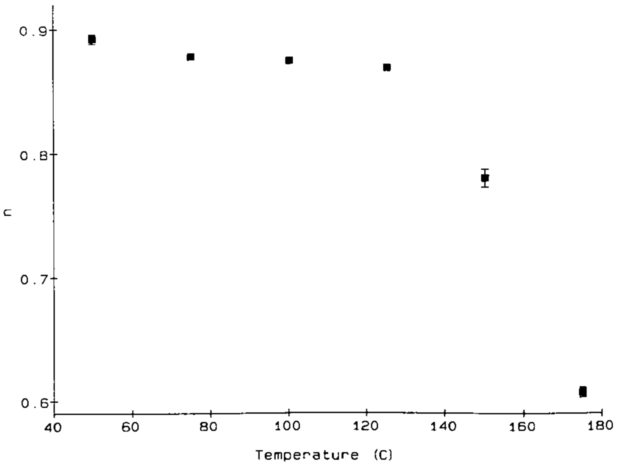

Fig. 5. The aging temperature dependence of the coupling parameter for cellulose acetate; time = 3 hr. The parameters were obtained from the fits of the converted mechanical relaxation data. (See text.) Error bars represent standard error of the mean.

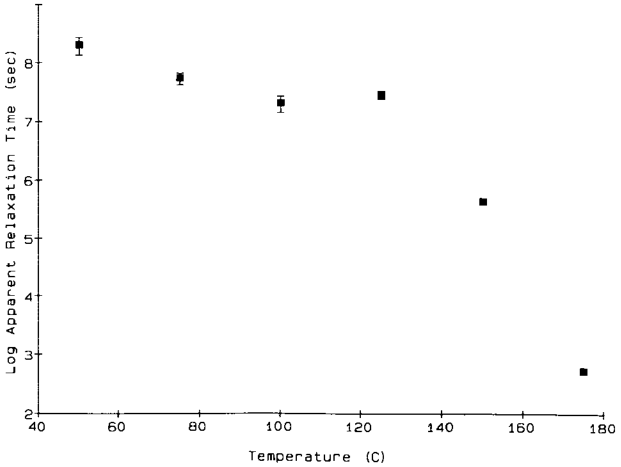

Fig. 6. The aging temperature dependence of the apparent relaxation time for cellulose acetate; time = 3 hr. The relaxation times were obtained from the fits of the converted mechanical relaxation data (see text). Error bars represent standard error of the mean.

ronment in terms of the parameters in Eq. (6) were recorded (see Table I). With this information it is possible to calculate the extent of structural change or aging by inserting the time profiles of n and τ_0 (through τ^*) into Eq. (5). The time profile of Φ is calculated by numerically integrating Eq. (5) (2). The estimates of structural change through $\Phi(t)$ as function of aging time are given in Fig. 7.

According to our calculations, cellulose acetate is almost at equilibrium [$\Phi(t) = 0$] within 20 hr of annealing at 175°C, which is 16°C below its glass transition temperature. At 150°C the system is much farther away from equilibrium and the relaxation profile starts to flatten out after 20 hr. At the lower annealing temperatures, the value of $\Phi(t)$ is much higher, indicating the trend of the inverse dependence of the time the system needs to relax toward equilibrium on the aging temperature. In the temperature range between 50 and 100°C, the flattening of the relaxation curve is much more pronounced. At these temperatures, in the time scale of observation of 3 to 20 hr, the changes in structure are slight. These small structural changes are reflected in the slight changes in the coupling parameter at these temperatures as shown in Table I.

Since these profiles are plotted on a log time scale the structure of the glass may change, though these changes may not be seen at convenient time scales of observation. The changes at lower temperatures may occur over the period of months or years and not over hours. The implications of this on temperature accelerated stability testing are discussed below.

Permeability and Aging

A number of authors have concluded that water transport through cellulose acetate is by diffusion through a single phase (22,28). Electron micrographs of cast cellulose acetate films revealed a very dense structure with no pores (22). Even plasticized films did not show a porous structure, which would almost certainly be detected by whitening due to contact with water and subsequent drying (28). The general view is that water transport is governed by density fluctuations of the macromolecular chains (22,28).

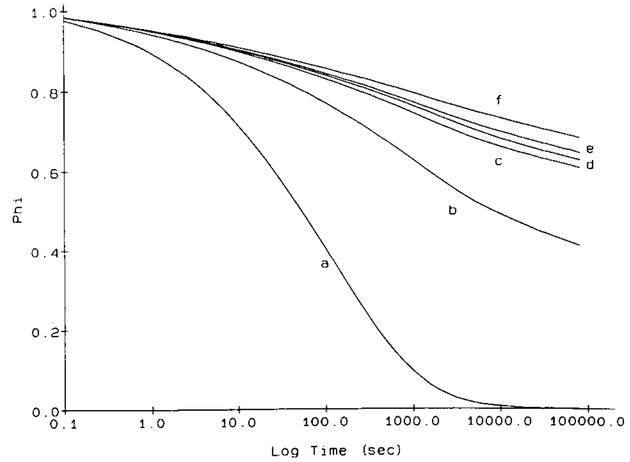

Fig. 7. Estimates of the structural change of cellulose acetate as a function of time as calculated from Eq. (5). The isothermal aging time profiles of the coupling parameter and the apparent relaxation time were inserted in Eq. (5) and numerically integrated (2). (a) 175°C; (b) 150°C; (c) 125°C; (d) 100°C; (e) 75°C; (f) 50°C.

Chain mobility determines the rate of diffusion of a small solvent molecule in a polymeric system. Some variations of a free volume-type theory have been frequently invoked to describe the impact of chain mobility on the diffusion rate of small molecules. Density fluctuations are induced by thermal energy acting against bulk compliance. Free volume or "holes" are thought to arise from these density fluctuations. Extensions of free volume theory describe cooperative motion between neighboring segments as the controlling factor in the formation of a hole that is large enough to allow small molecule transport (29). An example of this would be the theory developed by Fujita, which explicitly uses Cohen and Turnball's description of free volume and the probability of the appearance of a "hole" of appropriate size which will allow molecular motion (30,31).

Physical aging has been interpreted in terms of free-volume theory by correlating reductions in specific volume and reductions in mechanical rate of response (3). Struik proposed that aging was a self-retarding process wherein free volume determines the mobility of segments in the glass, and this in turn governs the rate at which free volume is reduced (3). The permeability reductions we observed could be interpreted as either the loss or the reduction of density fluctuations during aging.

Objections concerning the application of free-volume theory to the glassy state have been raised over the past 20 years and have been recently reviewed (2). In the case of gas transport, the critical hole sizes or the free volume required for the transport of certain gases through glassy polymers is much greater than the values of free volume which have been measured using small-angle X-ray scattering or photochrome isomerization techniques (29,32,33). The question of whether the size of the holes formed by density fluctuations could affect water transport in cellulose acetate can be answered only when the volume range of these density fluctuations is compared with the volume required for water transport.

There is evidence that the physical properties of a glassy material are more dependent on local structural order than on specific volume, a measure of the density of the "holes" (32). Cooperativity of segmental motion within this local structural order significantly contributes to the mobility of the system (18). Macroscopic measurements of mobility such as viscosity, mechanical response, and ion conductivity have been accurately described within the framework of the relaxation coupling model (18). It follows that diffusivity and transport processes in general, which also manifest mobility, could be described by this model as well.

The reductions in water permeability should correlate with the changes in mechanical response if physical aging is indeed responsible for the change in local structural order of a glass. To check the validity of the preceding statement the values of Φ(10 hr), an estimate of the extent of aging via our mechanical measurements is plotted against the permeability ratio after aging for 10 hr in Fig. 8. The correlation suggests a local structure–permeability relationship exists and hence permeability displays an apparent sensitivity to segmental cooperativity. Although the line drawn in Fig. 8 implies a linear relationship, there is no evidence a priori suggesting

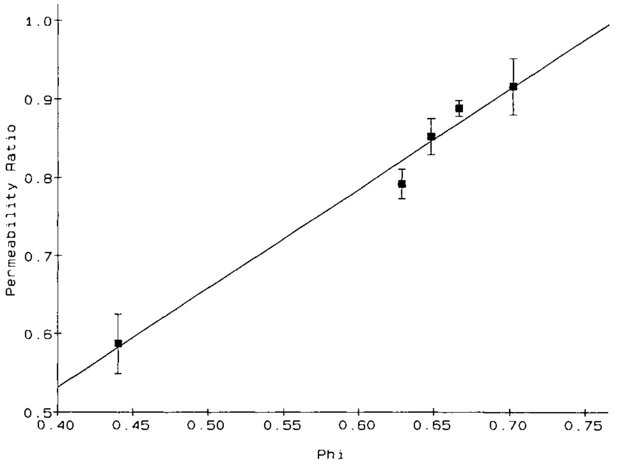

Fig. 8. Correlation between permeability reduction and structural change as estimated from Φ at an aging time of 10 hr. This correlation suggests that the structure of the glass may have a significant impact on its transport properties. Error bars represent standard error of the mean.

this to be the case. A sigmoidal relationship could also be used in the description of this relationship.

Aging and Polymer Performance

The embrittlement of physically aged polymers has been a cause for concern for many years in the areas of polymer production and application. Most, if not all, of the research on aging comes from these areas. With the growing use of polymers in the pharmaceutical industry, many of the same problems with respect to aging will be of interest even though the applications may be somewhat different.

In the case of film coating, the integrity and reproducibility of the polymer are of paramount interest. For some materials, aging could adversely affect its performance, particularly if the polymer's T_g was near its storage temperature. The relationship between the storage and the glass transition temperature is evident in Fig. 7. The closer the storage temperature is to T_g, the greater the extent of aging, which is consistent with previous observations of thermal activation.

Problems may also be encountered with the accelerated stability testing of coated dosage forms. Storage at a temperature close to T_g may "overage" the polymer and in turn overestimate the reduction in permeability or release rate with respect to storage at a lower temperature. Using Fig. 7, if the accelerated temperature was 45° below T_g, while room temperature was 90° below T_g (curves b and d in Fig. 7) the permeability reduction recorded for the higher storage temperature after 1 month would be equivalent to the reduction recorded after storage at room temperature for 10^5 years. Obviously, the strong temperature dependence of the aging of glassy polymers may have to be taken into account when one plans an accelerated stability study.

For most of the unplasticized polymers commonly used in the pharmaceutical industry, T_g is sufficiently high enough such that aging may not be a problem at room temperature. In many cases, though, plasticizers are incorporated into film coating formulations to modify the physical properties. Plasticizers can substantially reduce T_g, in some polymers up to 100°C, to the point where aging may play a role in the performance of the dosage form (34). Using cellulose acetate as an example, if plasticizer addition reduced T_g below 100°C, the dosage form could experience substantial aging during normal storage conditions over 2–5 years (see curves b and c in Fig. 7). The formulation scientist should balance the propensity for aging with other considerations in the decision on plasticizer addition.

As a rough guideline for the physical aging of cellulose acetate, the storage temperature should be either in the vicinity of T_g or no less than 60°C below T_g. If the storage temperature range is in the vicinity of the T_g of the polymer system, extensive aging would occur in a very short time period, e.g., hours as opposed to months, due to enhanced segmental cooperativity. By the time a dosage form made it to the marketplace, further aging would be minimal. Conversely, if the storage temperature is 60°C below T_g, the effects of physical aging would be minimal during a normal shelf life of 2–5 years.

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