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Influence of Physical Aging on Mechanical Properties of Polymer Free Films: The Prediction of Long-Term Aging Effects on the Water Permeability and Dissolution Rate of Polymer Film-Coated Tablets

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The effects of physical aging on the water permeation of cellulose acetate and ethylcellulose, the mechanical properties of ethylcellulose, and the dissolution property of hydroxypropyl methylcellulose phthalate were investigated. The water permeabilities of cellulose acetate and ethylcellulose and the dissolution rate of hydroxypropyl methylcellulose phthalate were found to decrease with physical aging time after being quenched from above the glass transition temperatures to sub-T_g temperatures. The gradual approach toward thermodynamic equilibrium during physical aging decreases the free volume of the polymers. This decrease in free volume is accompanied by a decrease in the transport mobility, with concomitant changes in those properties of the polymer that depend on it. The effects of long-term aging on the dissolution rate and water permeabilities of these polymers can be estimated from a linear double-logarithmic relationship between the mobility properties and physical aging time. The existence of the linear double-logarithmic relationship can be derived from the Williams–Landel–Ferry (1) equation, the Doolittle (2) equation, Struik's (3) model, and Fujita's (4) relationship between diffusion and free volume.

KEY WORDS: physical aging; creep compliance; permeability; dissolution rate; glass transition temperature.

INTRODUCTION

Film coating by polymers is a method for producing controlled release preparations. Generally, the film-controlled release of medicaments is determined by either of two basic factors: the dissolution of the film in gastrointestinal media or the permeability by the media. Hence, in selecting polymer coatings for sustained- or controlled-release systems, the dissolution rate and water permeability of the polymer must be considered.

Since amorphous polymers are not in thermodynamic equilibrium at temperatures below their glass transition temperature, they undergo a slow transformation toward equilibrium. The process by which the glass contracts toward the lowest free-energy state is known as physical aging (5). This gradual approach to equilibrium affects many properties of amorphous polymers. The temperature range in which aging occurs generally is not restricted to a narrow band just below the glass transition temperature, T_g, but can occur between T_g and the first secondary transition or below (3). In most of its aspects, aging can be explained in a straightforward way with the free-volume concept (6–9). When a polymer is cooled below its T_g, the mobility is small but not zero. Since at this stage the free volume is greater than it would be at equilibrium, the volume will continue to decrease slowly. This decrease in volume and free volume is accompanied by a decrease in the transport mobility, with concomitant changes in those properties of the polymer that depend on it. Since most of the polymers used in pharmaceutical film coatings are in the glassy state during storage and use, the effects of aging on the dissolution and permeation behavior should be fully assessed.

Physical aging effects in pharmaceutical film coatings have been widely reported. Thermal activation with respect to the increase in the disintegration time of enteric coated tablets was observed by Wagner *et al.* (10). They found, for example, that the disintegration time for tablets stored at 47°C for 1 month correlated very closely with that for tablets stored at room temperature for 2 years. The effects of aging on the physical and chemical properties of free cellulose acetate phthalate films were studied by Delporte (11). He found that the water vapor permeability constant of these films decreased with time, and the films continuously contracted with aging also. The effect of physical aging on the dissolution rate of anionic polyelectrolytes was investigated by Sinko and co-workers (12). By using creep compliance and dissolution rate studies, they found that a limiting density was approached with time for hydroxypropyl methylcellulose phthalate, and the dissolution rate also was observed to approach a limiting value.

In this study, we attempt to correlate the effects of physical aging on the dissolution and permeation properties with changes in the mechanical properties of these polymer films. By means of this correlation, we can estimate long-term aging effects on the dissolution rates and water permeabilities of the controlled-release polymer film coatings.

MATERIALS AND METHODS

Preparation of Free Films and Film-Coated Tablets

Three polymer solutions were prepared. Hydroxypropyl methylcellulose phthalate, HP-55 (T_g = 135°C, M_n = 20,000, Lot No. 13001, Shinetsu Chemical Co., Japan) was dissolved in a 1:1 (v/v) methylene chloride/methanol mixture at a concentration of 4% (w/v). Cellulose acetate (T_g = 190°C, 398-10, FMC Corp., Lot No. SA 740, M_w = 177,000, M_n = 58,500, 39% acetyl) was dissolved in acetone at a concentration of 4% (w/v). Ethylcellulose (T_g = 128°C, Lot No. 104F-0689, 48.5% ethoxy, Sigma Chemical Co., St. Louis) was dissolved in 4:1 (v/v) methylene chloride/acetone mixture at a concentration of 4% (w/v). Two milliliters of ethylcellulose solution was poured into an aluminum evaporating pan and covered with an inverted funnel to prevent

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solvent removal by convection. After drying, the free films were lifted off the pan and cut into 15 × 2-mm rectangular pieces. The samples were stored in a desiccator for a minimum of 1 week. Tablets (450 mg, containing sorbitol, Magnesium stearate, etc.) were coated by using the three polymer solutions prepared above in a 20-cm spherical coating pan, respectively. The tablets were spray-coated by an air-spray unit (glass spray unit, Sigma Chemical Company, Pennsauken, NJ), and the loading amount of polymer for each tablet is 49 ± 4 mg. All film-coated tablets were placed in an oven at 35°C for 24 hr after coating and then stored in a desiccator for a minimum of 1 week.

Mechanical Experiments

Creep compliance tests of the ethylcellulose film samples were performed with a Mettler TMA40 Thermomechanical Analyzer (Mettler Instruments, Hightstown, NJ) at 37°C. Film samples (thickness in 0.0186 ± 0.0017-mm range), were fixed between two stainless-steel clamps with emery paper placed between the clamp and the sample to avoid slippage. The samples were placed in a dry nitrogen environment in the TMA 40 and equilibrated at 133°C, 5°C above the glass transition temperature, for 15 min. Following this, the sample was quenched to 37°C and annealed at this temperature for 30 hr. After elapsed times of 1, 3, 5, 10, 20, and 30 hr, the creep compliance behavior was measured, the creep compliance being the ratio of the relative extension to the applied stress.

Permeability Measurements

The ethylcellulose and cellulose acetate film-coated tablets were equilibrated at 5°C above the glass transition temperatures for 15 min and then quenched to the annealing temperature of 37°C and annealed. After being annealed for a predetermined time, up to 300 hr for ethylcellulose film-coated tablets and 100 hr for cellulose acetate film-coated tablets, the tablets were quenched to room temperature, held for 20 min, and tested. One aged tablet was place in a 100-ml vial that was filled with deionized water. The weight of the tablet was measured periodically over a period of 4 hr. The water permeability coefficient of the polymer film was calculated from

$$P \cdot S \cdot \Delta C = \frac{dM}{dt} \qquad (1)$$

where P is the water permeability coefficient, S is the surface area of the tablet, ΔC is the concentration difference of water between the tablet and the medium (ΔC is equal to 1 g/ml in this case), and dM/dt is the weight change of the tablet with respect to time.

Dissolution Measurements

The hydroxypropyl methylcellulose phthalate film-coated tablets were equilibrated at 140°C, 5°C above the glass transition temperature, for 15 min and then quenched to the annealing temperature, either 80 or 100°C. After being annealed for a predetermined time, the tablets were quenched to room temperature, held for 20 min, and tested. The individual annealed tablets were placed into 120-ml vials that were filled with nearly 100 ml of pH 6.0 phosphate buffer (310 mosm) solution and put on the shaker (Shaker Bath, Lab-Line Instruments, Inc., Melrose Park, IL) at speed 100 rpm. During the first half-hour, 200 µl of the dissolve solution was taken from the vial every 5 min, and the same volume of the dissolve solution was taken every 15 min for the next 1.5 hr. The sample solutions were monitored by a Lambda 3B UV/VIS Spectrophotometer (Perkin Elmer Instruments, Norwalk, CT) at 210 nm.

RESULTS

The creep results of ethylcellulose tested after different physical aging times are presented in Fig. 1. At the annealing temperature of 37°C, which is 91°C below the T_g, significant reductions in creep compliance with modest aging times are observed, but aging appears not to influence the shape of the creep curves. By shifting the data in Fig. 1 horizontally, a master curve or superposition of the creep curves is obtained, and this is shown in Fig. 2. This master curve is adequately smooth. The deviation from a single curve may have been caused by temperature variation during the aging. The shifting required to obtain the master curve is plotted against aging time in Fig. 3. In this double-logarithmic plot, an almost-linear relationship between the shift factor and the physical aging time is obtained, and the slope of the line is 0.821 (correlation coefficient = 0.997).

The experimental water permeability coefficients for ethylcellulose and for cellulose acetate film-coated tablets vs physical aging time at 37°C are presented in Figs. 4 and 5, respectively. The water permeability coefficients for both ethylcellulose and cellulose acetate film-coated tablets were found to decrease with aging time. The slopes for these double-logarithmic plots are 0.32 (correlation coefficient = 0.996) and 0.022 (correlation coefficient = 0.983), respectively.

The experimental dissolution rates of hydroxypropyl methylcellulose phthalate film-coated tablets vs physical aging times at the temperatures of 100 and 80°C are illustrated in Figs. 6 and 7, respectively. As with the permeability coefficients of ethylcellulose and cellulose acetate, the dissolution rate of hydroxypropyl methylcellulose phthalate decreased with the physical aging time. The slopes for these double-logarithmic plots are 0.082 (correlation coefficient =

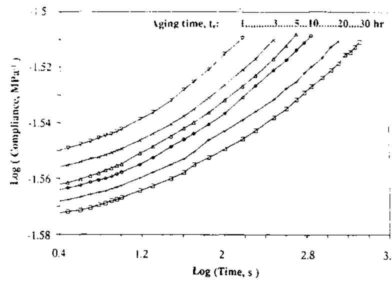

Fig. 1. The effect of physical aging on the creep compliances of ethylcellulose free films: (▽) 1 hr of aging, (×) 3 hr of aging, (△) 5 hr of aging, (◇) 10 hr of aging, (+) 20 hr of aging, and (□) 30 hr of aging.

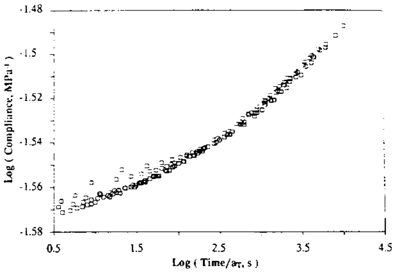

Fig. 2. The master curve of compliances of ethylcellulose obtained by shifting the data in Fig. 1 horizontally.

0.967) and 0.074 (correlation coefficient = 0.966), respectively.

DISCUSSION

When the temperature is above the glass transition temperature of the polymer, T_g, the distribution of mechanical retardation times is shifted by changes in temperature through the temperature-induced change in free volume (13). By relating the Williams–Landel–Ferry and Doolittle equations (1,2), a relationship between the shift factor a_T and the fractional free volume f can be expressed by the following equations:

$$\ln a_T = B\,[f^{-1}(T) - f^{-1}(T_0)] \tag{2}$$

where f is the fractional free volume (V_f/V), V_f is the free volume, V is the specific volume, T_0 is the reference temperature, T is the experimental temperature, and B is a constant. Kovacs *et al.* (14) and Meyer *et al.* (15) studied the time dependence of the free volume of amorphous polymers when the temperature was below the T_g. The shift factor is given by

$$\ln a_{T,t_e} = B\,[f^{-1}(T,t_e) - f^{-1}(T_0,\infty)] \tag{3}$$

in which $f(T_0,\infty)$ is the equilibrium fractional free volume at the reference temperature T_0 and $f(T,t_e)$ is the fractional free volume after being quenched to the experimental temperature T, an elapsed time t_e. The reductions in the creep curves of ethylcellulose with aging time shown in Fig. 1 can be explained by the continuous decrease in volume and free volume. Since the decrease in volume and free volume will be accompanied by an increase in the compaction of the polymer structure, the creep compliance will decrease with aging time. The superimposability of the creep curves shown in Fig. 2 is confirmation that aging does not influence the shape of the creep curves, and it shows that an increase in aging time changes all relaxation times by the same factor. Struik (3) observed that the shifts between successive creep curves were about constant and that the effect of aging could be expressed by the double-logarithmic shift rate μ defined as

$$\mu = -\frac{d \ln a_T}{d \ln t_e} \tag{4}$$

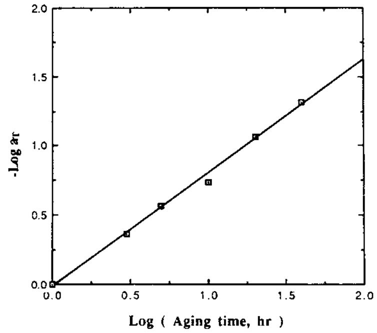

Fig. 3. The shifting of the creep curves of ethylcellulose-free films.

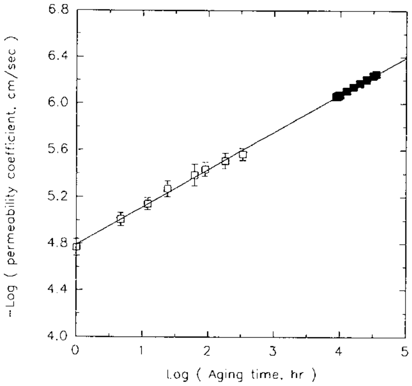

Fig. 4. The effect of physical aging on the water permeability coefficient of ethylcellulose film-coated tablets. The dotted lines represent the 95% confidence limit lines ($n = 4$). (☐) Experimental data; (■) long-term predicted data.

The shifting behavior of the creep curves of ethylcellulose, shown in Fig. 3, is consistent with that observed by Struik (3). The shift rate μ for ethylcellulose, the slope of the line in Fig. 3, is equal to 0.821. Struik (3) also found, and it has been confirmed many times since, that aging effects are very similar in all amorphous glassy polymers. Hence, aging is a basic feature of the glassy state, and the creep curves of cellulose acetate and hydroxypropyl methylcellulose phthalate are expected to shift with aging time in a way similar to those of ethylcellulose.

A basic relationship between the mobility of a diffusant and the free volume of the medium through which the diffusant moves was presented by Fujita (4). This relationship can be expressed in the form

$$m_d = A_d \cdot \exp(-B_d/f) \tag{5}$$

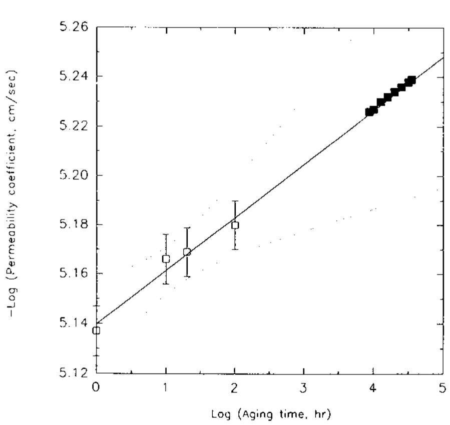

Fig. 5. The effect of physical aging on the water permeability coefficient of cellulose acetate film-coated tablets. The dotted lines represent the 95% confidence limit lines ($n = 4$). (☐) Experimental data; (■) long-term predicted data.

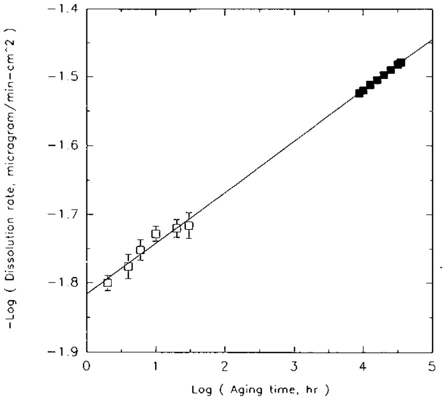

Fig. 6. The effect of physical aging on the dissolution rate of hydroxypropyl methylcellulose phthalate film-coated tablets (annealed at 100°C). The dotted lines represent the 95% confidence limit lines ($n = 4$). (□) Experimental data; (■) long-term predicted data.

where A_d and B_d are constants, f is the average fractional free volume of the medium, and m_d is the mobility of the diffusant. According to Barrer and Fergusson (16), the relation between the diffusion coefficient D and the mobility is

$$D = R \cdot T \cdot m_d \tag{6}$$

where R is the gas constant and T is the absolute temperature. Equations (5) and (6) show that the diffusion coefficients for diffusants in the polymer depend on the instantaneous free volume of the polymer. Since the free volume depends on aging, the diffusion coefficient of a polymer film that has been annealed in the sub-T_g temperature region for a predetermined time can, by combining Eqs. (5) and (6), be expressed in term of the fractional free volume in the following form:

$$\ln D(T,t_e) = \ln D_0 - B_d[f^{-1}(T,t_e) - f^{-1}(T_0,\infty)] \tag{7}$$

where D_0 is the diffusion coefficient of the equilibrium polymer at the reference temperature T_0. By comparing Eqs. (3) and (7), the relationship between the diffusion coefficient and the aging time is seen to be similar to that between the shift factor and the aging time. Hence, a linear double-logarithmic relationship between the diffusion coefficient and the physical aging time is expected and is given by

$$\frac{d \ln D(T,t_e)}{d \ln t_e} = \frac{B_d}{B} \cdot \mu \tag{8}$$

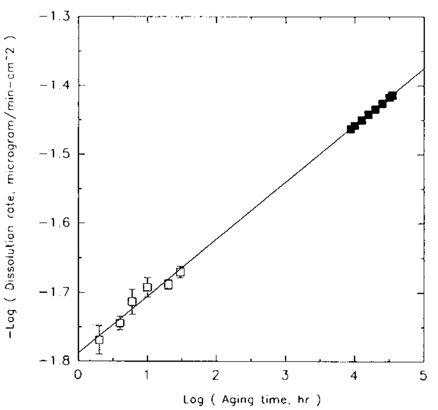

Fig. 7. The effect of physical aging on the dissolution rate of hydroxypropyl methylcellulose phthalate film-coated tablets (annealed at 80°C). The dotted lines represent the 95% confidence limit lines ($n = 4$). (□) Experimental data; (■) long-term predicted data.

According to the basic equation describing mass transfer through a membrane, the relation between the permeability coefficient P and the diffusion coefficient D is

$$P = \frac{(K \cdot D)}{h} \tag{9}$$

where K is the partition coefficient and h is the thickness of the membrane. Since the permeability coefficient is linearly proportional to the diffusion coefficient, by comparing Eqs. (8) and (9), a double-logarithmic relationship between the permeability and the physical aging time is expected also and is given by

$$\frac{d \ln P(T,t_e)}{d \ln t_e} = \frac{B_d}{B} \cdot \mu = \text{constant} \tag{10}$$

The linear double-logarithmic relation between the permeability and the aging time was found as seen in Figs. 4 and 5, in which the water permeability coefficients of ethylcellulose and cellulose acetate are plotted against aging time, respectively. By using a simple linear regression extrapolation of the experimental data in these two figures, the long-term, 1- to 4-year, aging effects on the permeability coefficients of ethylcellulose and cellulose acetate can be predicted and are shown in the same plots.

The dissolution process of a glassy polymer has been frequently studied (17,18). In general, the dissolution process is controlled by two steps: solvent diffusion and swelling, and the dissolution rate of a polymer should be proportional to the diffusion coefficient. Connecting this assumption with Eq. (8), a double-logarithmic relationship between the dissolution rate of a polymer and the physical aging time it has undergone also should exist. The linear double-logarithmic relationships between the dissolution rate of hydroxypropyl methylcellulose phthalate and the aging time at the annealing temperatures of 100 and 80°C are shown in Figs. 6 and 7, respectively. Hence, the long-term, 1- to 4-year, aging effects on the dissolution rate of hydroxypropyl methylcellulose phthalate also can be predicted by extrapolating the simple linear regression line for the experimental data, and this is shown in these two figures. The solid symbols in the lines represent the predicted 1- to 4-year behavior.

CONCLUSION

Following quenching from the glass transition temperature and annealing in the sub-T_g temperature range, the water permeability and dissolution rate of polymer film-coated tablets decrease with aging time. The results are consistent with the free volume and aging theories. The decrease in the mobility properties follows a linear double-logarithmic relationship with aging time. By extrapolating this linear double-logarithmic results, the long-term aging effects on the mobility properties of polymer film-coated tablets can be predicted.

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