Pharmaceutical Research, Vol. 7, No. 6, 1990

Report

The Effect of Physical Aging on the Dissolution Rate of Anionic Polyelectrolytes

Christopher M. Sinko,[1,3] Albert F. Yee,[2] and Gordon L. Amidon[1]

Received April 24, 1989; accepted December 19, 1989

The effect of physical aging on the dissolution and mechanical properties of hydroxypropyl methylcellulose phthalate (HPMCP) was investigated. Dissolution rate measurements were performed on films which, initially above the glass transition temperature, T_g, were quenched to a sub-T_g storage temperature, aged at that temperature for a period of time and then quenched again to 25°C. Within the time scale of observation, reductions in the dissolution rate to a limiting value were observed. HPMCP was also found to age in the same storage temperature range as determined by a creep compliance technique. These mechanical results indicate a change in glass structure and show that a limiting density was approached. Parallel changes were observed in the dissolution rate studies suggest that dissolution rate is governed in part by glass density. Therefore, mechanical changes of glassy films can yield pharmaceutically relevant information about the extent of physical aging and serve as an indicator of the effect of aging on dissolution rate.

KEY WORDS: physical aging; dissolution; enteric coating; creep compliance; hydroxypropyl methylcellulose phthalate.

INTRODUCTION

The accurate prediction of the dissolution rate of an enteric-coated dosage form requires a fundamental understanding of both the mechanism of dissolution and the physicochemical properties of the coating. Although attempts at identifying the mechanism of dissolution have been made, little attention has been devoted to the physics and chemistry of the glass structure and its effects on dissolution rate (1–3). Recent descriptions of the dissolution of a glassy matrix showed the importance of solvent penetration and swelling in the dissolution process (4,5). Since most enteric coatings, and pharmaceutical film coatings in general, exist as glasses during storage, knowledge of the effects of glass structure on dissolution behavior is necessary in order to develop an accurate mechanistic description of polymer dissolution.

The distinctiveness in properties of glasses arises from the general nonequilibrium behavior that is characteristic of a metastable amorphous solid which shows no long-range order (6). Short-range order, typically under 5 Å, does exist and can significantly change the physical properties of the glass (7). Differences in short-range order are dependent on the mechanism of disorder or, simply, how the randomness is generated and frozen into the system (6). An example of a mechanism of disorder would be the locking-in of excess energy over that of a crystal by suddenly moving a thermodynamic intensive variable such as temperature (thermal quenching) or pressure (pressure densification) (6). Randomness can also be produced by destroying crystalline order via high mechanical shear stresses and oxidation (6). In the pharmaceutical industry, randomness in materials is frequently generated by solvent removal in a film coating process or by freeze-drying drug formulations for parenteral delivery.

A substantial reduction in mobility occurs when a glass forming system is thermally quenched from above its glass transition temperature or upon solvent evaporation. This reduced mobility decreases the rate at which the solid approaches its more stable (lower energy) state at this new temperature. If the time scale of the relaxation at this new temperature falls within the time of observation, then the mechanical, as well as other, properties affected by this molecular relaxation will change.

The temperature range for physical aging generally extends from the glass transition, T_g, down to the first major secondary relaxation temperature (9). Aging is also thermoreversible, e.g., the effects of aging can be completely erased by bringing the material above its T_g. Furthermore, aging is a thermally activated process. Evidence for this can be found in the work by Foltz and McKinney, who found that peaks appeared at T_g on DSC thermograms of physically aged polyvinylchloride. The energy associated with these peaks was plotted versus reciprocal temperature on a semilogarithmic plot, where an apparent Arrhenius behavior was

---

[1] College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48109-1065.

[2] Department of Materials Science and Engineering, The University of Michigan, Ann Arbor, Michigan 48109-1065.

[3] To whom correspondence should be addressed at Drug Delivery R&D-Pharmaceutics, The Upjohn Company, Kalamazoo, Michigan 49001.

0724-8741/90/0600-0648$06.00/0

found (10). Although these peaks, which are the result of a phenomenon known as enthalpy recovery, have been described mathematically, a theory to explain the thermal activation has yet to be developed (11,12).

Changes in physical and mechanical behavior because of aging include increases in density, yield stress, and modulus and decreases in creep and stress relaxation rate (8,9). Physically aged glasses become more embrittled and show reductions in impact strength (13). Transport properties also change in an aged system with reductions in gas permeability (14,15), decreases in lag time (15), and reductions in the rate of sorption of a solvent (14,16). Reductions in sorption rate are illustrated in Fig. 1 for polyvinylchloride aged at 65°C for 100 hr and at 90°C for 96 hr. The sorption mechanism also seems to shift with aging temperature from Fickian to concentration-dependent or anomalous diffusion (17).

The most popular and one of the most sensitive methods for testing physical aging is the creep compliance test. In a creep test a constant stress is applied to the sample and deformation, or strain, is monitored. The material parameter, creep compliance, is then calculated using Eq. (1).

$$J(t) \equiv \gamma(t)/\sigma_o \qquad (1)$$

where $\gamma(t)$ is the time-dependent strain and σ_o is the applied stress. The creep test has been extensively used to study the physical aging behavior of both polymeric and nonpolymeric glasses. Diverse materials such as polystyrene, cellulose acetate butyrate, sugar, shellac, lead, borosilicate glass, margarine, and wool have been tested mechanically and all show physical aging behavior (9,18).

Given the large changes in some of the physical and mechanical properties as a result of aging, it is important to be able to identify nonequilibrium behavior and to understand its effects on pharmaceutically important properties such as dissolution rate and permeability. In this study we have mechanically evaluated the physical aging behavior of hydroxypropyl methylcellulose phthalate with a creep compliance test in uniaxial tension. The effects of aging and thermal history on the dissolution rate behavior of this polymer are also studied. Finally, a correlation between dissolution rate and mechanical response is made.

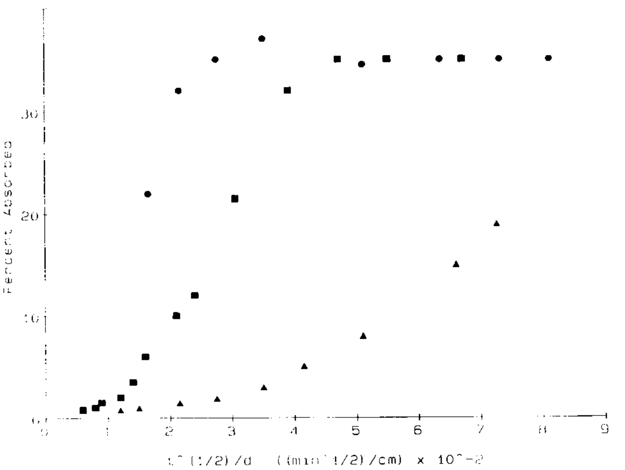

Fig. 1. Effect of physical aging on the sorption of benzene in polyvinyl chloride. (●) Unaged; (■) 96 hr at 65°C; (▲) 96 hr at 90°C (from Ref. 14).

MATERIALS AND METHODS

Film Preparation

Two solutions were prepared by dissolving hydroxypropyl methylcellulose phthalate, HP55 (T_g = 135°C, MW_n = 20,000, Lot No. 13001, Shinetsu Chemical Co., Japan) in a 1:1 (v/v) methylene chloride/methanol mixture at concentrations of 2.5 and 5% (w/w). The solution with the lower concentration of polymer was used to generate films of suitable thickness for the mechanical measurements. Two-milliliters portions were poured into an aluminum evaporating pan and placed in an oven at 35°C for 20 min. The films were easily lifted off the pan and cut into 15 × 2-mm rectangular samples for the mechanical experiments and into 1.5-cm-diameter samples for the dissolution experiments and then stored in a desiccator for a minimum of 2 weeks. Solvent removal was verified by testing the films mechanically. The procedure, which is described below, is very sensitive to the presence of slight amounts of plasticizer or solvent. The results of these tests indicated that there were no differences in the compliance of the films after the 2 weeks of storage. As explained below, the films were brought above 135°C for 20 min, which is substantially higher than the boiling points of the solvents used. If solvent were present, rapid desorption from the rubbery polymer would obviously occur at this temperature resulting in the formation of bubbles in the film. No bubbles were observed within the film samples.

Mechanical Measurements

Stainless-steel clamps were placed on the ends of the rectangular strips with emery paper between the clamp and the sample. The presence of the emery paper removes the extraneous deformation that usually occurs at the contact site (19). The sample was then placed in a Mettler TMA40 thermomechanical analyzer (Mettler Instruments, Hightstown, NJ) and equilibrated at 140°C for 20 min. Following equilibration the sample was quenched to 100°C and aged for up to 30 hr. At elapsed times of 3, 6, 10, 15, 20, and 30 hr the sample was tested for structural change due to aging by applying a uniaxial tensile stress in the range of 1–3 MPa at 100°C. In all of the experiments performed, initial strains of 0.09–0.15% were observed. The TMA40 thermomechanical analyzer records the time-dependent displacement of the film, which is converted directly to the time-dependent compliance. The resultant compliance was monitored for 18 min, after which the load was removed to allow for recovery. This experiment was repeated for aging temperatures of 25, 50, and 80°C.

Extraneous effects due to such factors as mechanical interference, aging during the mechanical test, and recovery were avoided by controlling the experiment in the following manner. Mechanical-induced changes in the structure of a glass have been reported to occur at values of strain above 0.004 (20). This was avoided in our experiments by keeping the tensile stress low because the strain is directly dependent on the stress applied. Since aging is a continuous process, consideration was made for possible interferences during the mechanical test by keeping the duration of the test ten times less than the previous aging time (9). For the test described above, at an aging time of 3 hr, the length of the creep experiment was kept to 18 min. Experiments for the longer aging times permitted longer measurements, e.g., aging times of 6 hr were tested for 36 min, but all the time lengths for mechanical testing were kept consistent. Recovery effects were minimized by allowing sufficient time for the process to complete. In this case the time length was 10 times as long as the previous mechanical test (9).

The second set of mechanical tests differed only in the thermal history applied. The sample was equilibrated at 140°C for 20 min and then quenched to the aging temperature (50, 80, and 100°C). After aging for a predetermined time the sample was then quenched to 25°C, held for 1 hr, and tested mechanically. The aging times studied in this test were 3, 10, 30, and 60 hr.

Dissolution Measurements

The same thermal history used in the second set of mechanical experiments was utilized for the dissolution evaluation. The aging temperatures studied were 25, 50, 80, and 100°C, while the aging times considered were 10, 30, 60, and 100 hr. After quenching down to 25°C the sample was held for 1 hr, placed on a disk with silicone grease for adhesion, and lowered into a pH 6.0 phosphate buffer (0.019 *M*, *I* = .05) dissolution medium at 25°C. The disk was rotated at 30 rpm while the amount dissolved was monitored continuously at 232 nm using a Masterflex pump drive (Cole Parmer Institute, Chicago) in conjunction with a Lambda 3B UV/VIS spectrophotometer (Perkin Elmer Instruments, Norwalk, CT). The pH was also monitored throughout the run with a PHM62 pH meter (Radiometer Copenhagen, Westlake, OH) and a Ross combination pH electrode (Orion Research Inc., Cambridge, MA).

RESULTS AND DISCUSSION

First Mechanical Experiment

The effect of aging at 100°C on the mechanical response of HP-55 is shown in Fig. 2. A substantial reduction in the compliance of the film can be observed by evaluating the isochronal value of compliance at 612 sec. This behavior correlates quite well with the physical aging of other materials (9,21,22). A comparison of mechanical responses at 3 and 30 hr also illustrates the change in the time dependence. Both curves show a high initial rate of deformation but exhibit significant differences in the rate within 200 sec. The response at the aging time of 30 hr shows a much greater deceleration than the response at 3 hr.

These changes in the deceleration can be used to quantify the effects of physical aging on the structure of the material by using a method of data analysis first suggested by Chai and McCrum in their study on semicrystalline polypropylene (22). The first derivative of the compliance–time curve was plotted on a log–log plot and regressed. A physically aged material will show reductions in the intercept and increases in the negative slope. Increases in the negative slope serve as an estimate of the increase in deceleration.

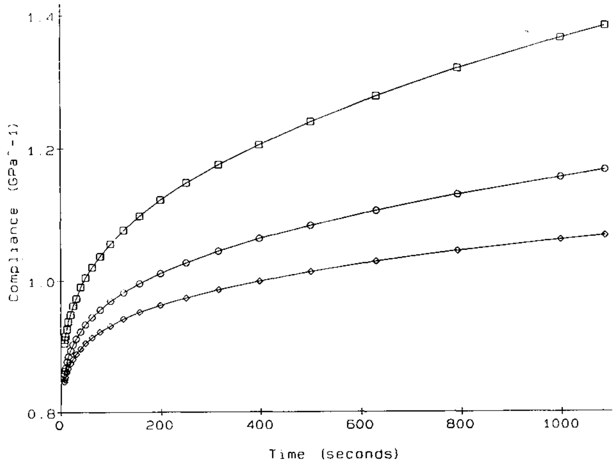

Fig. 2. Effect of physical aging at 100°C on the creep compliance curves of HP-55. Aging times: (□) 3 hr; (○) 10 hr; (◇) 30 hr.

The data presented in Fig. 2 is plotted in this manner and shown in Fig. 3. The characteristic decrease in the intercept and increase in negative slope with respect to aging time are seen. A possible physical interpretation of these data is as follows: when an external stress is applied to a viscoelastic material, the time scale of response depends on the material's ability to relax that stress. In this case, relaxation occurs in the form of displacement or deformation, which, in turn, depends on the material's ability to undergo local readjustment. Molecular crowding increases as the glass densifies with aging, thus requiring a greater amount of cooperation between neighboring molecules. This leads to a longer time scale for local readjustment to occur, which is physically observed as a greater deceleration in mechanical response.

The value of this slope has been shown to estimate a critical parameter in a recently developed model that describes the low-frequency relaxation behavior of condensed amorphous materials (23). This parameter, originally called a coupling parameter, describes the coupling strength between a relaxing mode or primary species and its surroundings,

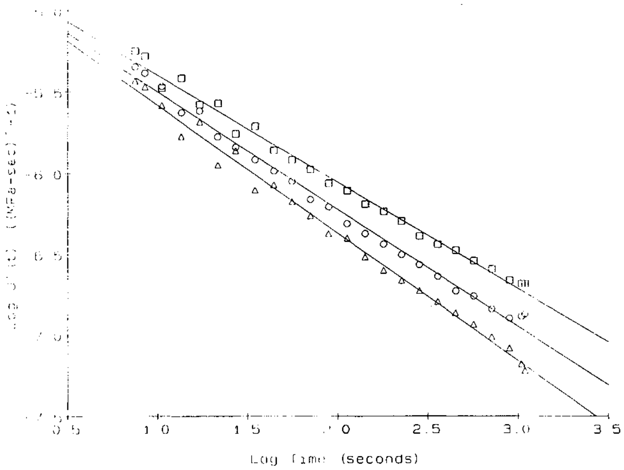

Fig. 3. Creep compliance data presented in Fig. 1 using Chai and McCrum's method of analysis (22). Reductions in the intercept and increases in the negative slope with respect to aging are observed. Aging times: (□) 3 hr; (○) 10 hr; (△) 30 hr.

usually in the form of low-energy excitations that have been observed in glasses, polymers, and amorphous metals (24). The coupling can be viewed as a measure of the constraint on motion within the glass, thus slowing down the relaxation as well as giving it an apparent distribution of relaxation times. In the context of this model the relaxation of a quantity, Q, that is perturbed from equilibrium can be represented as

$$Q(t) = Q_0 \exp[-(t/\tau^*)^{1-n}] \tag{2}$$

where Q_0 is the instantaneous value of the relaxing quantity, n is the coupling parameter, and

$$\tau^* = [(1 - n)\omega_c{}^n\tau_0]^{1/1-n} \tag{3}$$

Here τ_0 is the microscopic relaxation time, and ω_c is the cutoff frequency or time at which coupling dominates the relaxation process. An increasing relationship between the coupling parameter and density due to aging has been interpreted through this model with glassy polystyrene (21).

The effect of temperature on the physical aging behavior of HP-55 is shown in Fig. 4 in terms of the coupling parameter, n. Lower values of the coupling parameter appear at higher temperatures, thus supporting a density–coupling parameter relationship. An apparent thermal activation in the rate of aging is also seen, with greater changes in the coupling parameter occurring at higher temperatures. This is qualitatively in agreement with Foltz and McKinney's study on polyvinyl chloride (10).

Dissolution Experiment

The method of dissolution analysis was selected on the basis of the number of variables that could be held constant during the dissolving process. In the rotating disk system, the most important variable which can be controlled is the shear rate at the interface of the dissolution medium and the disk (25). The unique shear rate-viscosity behavior of a concentrated polymer solution makes this a particularly critical factor when evaluating the dissolution of a polymer. Another reason for selecting this system was the description of dissolution rate in terms of flux in order to make rates independent of surface area and hence directly comparable.

The effects of aging time and temperature on the dissolution rate of HP-55 are shown in Fig. 5. Within the time scale of our observation a temperature-independent limiting dissolution rate of approximately 24 μg/min/cm^2 is approached. The major effect of aging temperature arises in the rate that this limiting dissolution rate is approached. At 100°C, aging times greater than 10 hr give this limiting rate, while at 50°C it takes times greater than 60 hr. Since aging is a continuous process the limiting value we have observed may actually be lower. It is interesting to note that the effects of aging on the water vapor transmission properties of cellulose acetate phthalate seem to follow this same pattern (26). This thermal activation in the change of the dissolution properties of enteric coatings is consistent with the findings of Wagner and co-workers, where similar disintegration times of coated granules were observed between those aged at 47°C for 1 month and those aged at room temperature for 2 years (27). To understand the presence of this limiting rate and the differences due to aging temperature, a more mechanistic description of the dissolution process of a glassy polymer must be made.

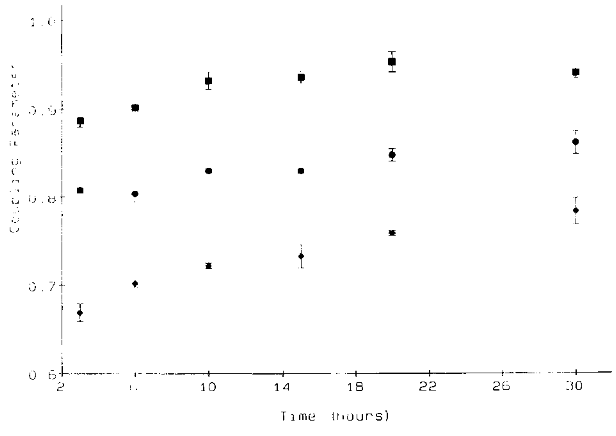

Fig. 4. Effect of temperature on the physical aging behavior of HP-55. (◆) 100°C; (●) 80°C; (■) 50°C.

An illustration of the dissolution process has recently been presented in which the dissolution of a glassy polymeric matrix is described as a two stage process (4). The first stage is the swelling step in which water penetrates the glass, increasing mobility to the point that the glass transition temperature is lowered to the process temperature. The second stage is the "true dissolution" step in which the chains disentangle and are removed from the surface (28). The true dissolution step will occur in the rubbery phase of the polymer, and since this phase is in equilibrium, previous thermal history and physical aging should not affect any properties. The effects of aging most probably occur in the swelling stage. Reductions in the rate of sorption in a physically aged glass have been reported and this may lead to the reduced rate (14).

The appearance of a limiting rate may be attributed to the appearance of a limiting density that is dependent not only on the aging temperature but also on the rate of cooling. This result is expected because the physical properties of a

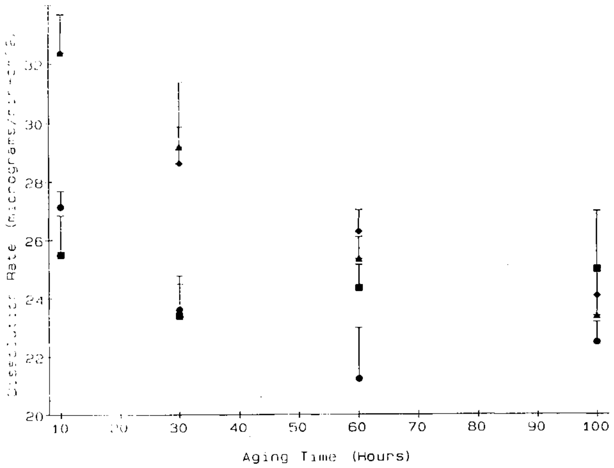

Fig. 5. Effect of aging temperature on the dissolution rate–aging time profile. A limiting dissolution rate of approximately 24 μg/min/cm^2 appears to be independent of temperature. (■) 100°C; (●) 80°C; (◆) 50°C; (▲) 25°C.

glass are a function of the material's complete thermal history, which includes both physical aging and the heating and cooling rate (11,12). In these experiments, the film is quenched to 25°C and held for 1 hr before the dissolution experiment, a step which should be taken into account when analyzing the effects of thermal history.

A physical interpretation of the effect of aging temperature on the approach to the limiting rate can be made by comparing the effects of aging at 50 and 100°C. As seen earlier, the greater rate of aging occurs at the higher temperature. Coupling this with the subsequent quench to 25°C, a critical density is reached whereby the material will no longer change. This statement applies only to the time scale of observation that was made because physical aging is a continuous process, although much slower at 25°C. Based on our mechanical measurements and by assuming no difference in the effects of cooling rate between treatments, the effects of aging at 50°C on the changes in properties measured at 25°C should be different because the approach to the critical density should be slower and this is what is indeed seen. Again, this argument is contingent on the measurement of the coupling parameters of HP-55 using the additional quench step.

Second Mechanical Measurement

The effects of the direct quench from the aging temperature to 25°C are shown in Table I. The presence of a limiting density seems to be supported by the appearance of a limiting coupling parameter. The coupling parameter is fixed at approximately 0.932 at aging times greater than 10 hr at 100°C, 30 hr at 80°C, and 60 hr at 50°C. Although the differences in the parameters may not be too large, the differences in measured relaxation times can be significant, leading to an altered mechanical response (29).

A comparison of the coupling parameter and dissolution rate observed from HPMCP samples that have identical thermal histories is shown in Fig. 6, and a decreasing relationship between the coupling parameter and the dissolution rate exists. While there is significant scatter, given the fine scale used for the coupling parameter, this result suggests that the dissolution rate may be dependent on the density as well as the structure of the glass.

ACKNOWLEDGMENTS

This study was supported by the Advanced Predoctoral Fellowship in Pharmaceutics from the Pharmaceutical Manufacturers Association Foundation and the Lilly Endowment Fellowship in Pharmacy.

Table I. Summary of Coupling Parameters Showing the Effect of Aging and Direct Quench on the 25°C Creep Curves of HP-55[a]

Aging time (hr)	Aging temperature 50°C	80°C	100°C
3	0.892 (0.004)	0.890 (0.003)	0.896 (0.01)
10	0.919 (0.006)	0.923 (0.003)	0.930 (0.006)
30	0.925 (0.004)	0.934 (0.003)	0.931 (0.015)
60	0.932 (0.013)	0.936 (0.002)	0.928 (0.01)

[a] Numbers in parentheses are standard deviations.

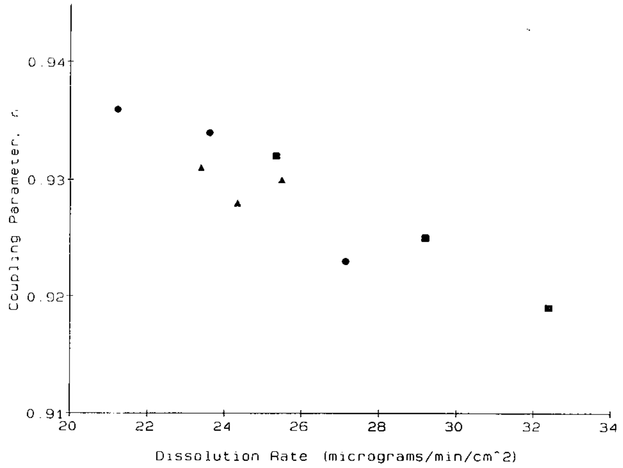

Fig. 6. Comparison of the coupling parameter estimated from the mechanical and dissolution rate measurements of HP-55 for identical thermal histories. (■) 100°C, (●) 80°C; (▲) 50°C.

REFERENCES

1. J. Spitael and R. Kinget. *Pharm. Ind.* 39:502–505 (1977).
2. E. Shek. *Pharm. Ind.* 40:981–982 (1978).
3. S. S. Ozturk, B. O. Palsson, B. Donohoe, and J. B. Dressman. *Pharm. Res.* 5:550–565 (1988).
4. R. S. Harland, A. Gazzaniga, M. E. Sangalli, P. Colombo, and N. A. Peppas. *Pharm. Res.* 5:488–494 (1988).
5. P. I. Lee and N. A. Peppas. *J. Contr. Rel.* 6:207–215 (1987).
6. G. P. Johari. In K. L. Ngai and G. Wright (eds.), *Relaxations in Complex Systems,* Government Printing Press, Washington, DC, 1985, pp. 17–41.
7. S. B. Elliot. *The Physics of Amorphous Materials,* Longman, New York, 1983.
8. M. R. Tant and G. L. Wilkes. *Poly. Eng. Sci.* 21:874–895 (1981).
9. L. C. E. Struik. *The Physical Aging Behavior of Amorphous Materials,* Elsevier, New York, 1978, pp. 19–27.
10. C. R. Foltz and P. V. McKinney. *J. Appl. Poly. Sci.* 13:2235–2245 (1969).
11. I. M. Hodge and A. R. Berens. *Macromolecules* 15:762–770 (1982).
12. R. W. Rendell, T. K. Lee, and K. L. Ngai. *Poly. Eng. Sci.* 24:1104–1110 (1984).
13. L. C. E. Struik. In W. Brostow and R. D. Corneliussen (eds.), *Failure of Plastics,* Macmillan, New York, 1986, pp. 209–258.
14. K. H. Illers. *Makromol. Chem.* 127:1–33 (1969).
15. A. H. Chan. Ph.D. dissertation, University of Texas, Austin, 1978.
16. E. S. W. Kong. *Adv. Poly. Sci.* 80:125–171 (1986).
17. J. H. Kou. Ph.D. dissertation, University of Michigan, Ann Arbor, 1988, p. 22.
18. G. Levita and L. C. E. Struik. *Polymer* 24:1071–1074 (1983).
19. A. F. Yee. *Poly. Eng. Sci.* 17:213 (1977).
20. L. C. E. Struik. *Polymer* 21:962 (1980).
21. D. J. Plazek, K. L. Ngai, and R. W. Rendell. *Poly. Eng. Sci.* 24:1111–1116 (1984).

22. C. K. Chai and N. G. McCrum. *Polymer* 21:706 (1980).
23. K. L. Ngai. In T. V. Ramakrishnan (ed.), *Non-Debye Relaxations in Condensed Matter,* World Scientific Press, Singapore, 1985, p. 58.
24. A. K. Rajagopal, S. Teitler, and K. L. Ngai. *J. Phys. C Solid. State. Phys.* 17:6611–6622 (1984).
25. V. Levich. *Physicochemical Hydrodynamics,* Prentice Hall, Englewood Cliffs, NJ, 1962.
26. J. P. Delporte. *Pharm. Ind.* 41:984–990 (1979).
27. J. G. Wagner, G. W. Ryan, E. Kubiak, and S. Long. *J. Am. Pharm. Assoc.* (*Sci. Ed.*) 49:133–139 (1960).
28. F. Brochard and P. G. Degennes. *Physiochem. Hydrodynam.* 4:313–324 (1983).
29. R. W. Rendell, K. L. Ngai, and A. F. Yee. *Mat. Res. Soc. Symp. Proc.* 79:311–324 (1987).