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Research Article

Temperature Dependence of Non-Fickian Water Transport and Swelling in Glassy Gelatin Matrices

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The effect of temperature on the swelling kinetics of glassy gelatin matrices exposed to water was studied. The movement of two distinct and characteristic swelling boundaries was measured directly using an optical microscope. Swelling rate constants associated with these moving boundaries demonstrated Arrhenius behavior over the temperature range of 15 to 40°C. The apparent activation energy for non-Fickian water transport into the gelatin glassy core was determined to be 8.1 kcal/mol, and 3.5 kcal/mol was found for the outer expansion of the swelling gelatin network due to water sorption. These findings are compared with activation energies for other solvent–glassy polymer systems, and possible reasons for the unexpectedly low value for non-Fickian water transport in the glassy gelatin solid are considered.

KEY WORDS: non-Fickian transport; water swelling; glassy gelatin; Arrhenius; activation energy.

INTRODUCTION

Rate processes such as polymer dissolution and the swelling of polymeric materials with water have important implications in drug delivery research. For example, the swelling rates of glassy polymers loaded with therapeutic agents have been studied (1–3) in the development of swelling-controlled drug delivery devices. Also, in a recent report (4) the significant role of polymer dissolution in drug release from compressed tablets containing a hydrophilic polymer was addressed and analyzed in terms of a predictive mathematical model.

Because drug release and polymer swelling may be interdependent rate processes in some pharmaceutical systems, baseline parameters are needed to identify the variable(s) that determines the primary drug release mechanism. Therefore, solvent transport into a polymer with or without matrix swelling would provide information about the structural features of the system and, with the establishment of temperature dependence, would permit the comparison of activation energies in resolving the mechanism.

Activation energies have been widely used in mechanistic studies of solvent transport into polymeric materials. One important determinant of the ensuing transport mechanism is the physical state of the polymer. When the polymer is rubbery, or above its glass transition temperature during solvent sorption, mass transport obeys Fick's law. However, when the polymer is an amorphous glassy solid, non-Fickian solvent transport may be exhibited. Transport behavior is also sensitive to the physical state of the solvent (5) where, at low penetrant activities, Fickian behavior may often arise in glassy polymers (6,7).

In general, non-Fickian transport is the more highly activated process in which a solvent penetrates a glassy polymer and, at the point of contact, increases chain mobility and induces mechanical relaxations. The rate of chain relaxation resulting from solvation may depend on specific polymer–solvent interactions and polymer flexibility. On the other hand, Fickian transport typically exhibits a lower activation energy, because the polymer is a rubbery solid in which the chains are highly mobile and react instantaneously to solvent perturbations.

The experimental parameter usually evaluated for temperature dependence in Fickian transport is the diffusion coefficient. A true activation energy may be determined if there is no significant polymer swelling. For non-Fickian transport, two experimental parameters may be examined: (i) the rate constant of solvent weight uptake (sorption) and (ii) the velocity of the solvent front in cases where a visually distinct boundary can be measured as it advances into the glassy matrix (penetration). A true activation energy for non-Fickian transport may be derived from the first parameter when equilibrium sorption is also measured, and an apparent activation energy is directly obtained with the second (8).

To evaluate the true activation energy (E_{act}) of non-Fickian transport from the apparent activation energy given by penetrant front kinetics, the following relationship was derived by Nicolais *et al.* (8). The temperature dependence of the initial penetrant velocity, V_o, was expressed as

$$V_o = A' \exp[-(E_{act} + m\,\Delta H_s)/RT] \quad (1)$$

where A' is the preexponential factor, R is the gas constant, ΔH_s is the heat of sorption, m is the order of the rate process,

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and the sum (E_{act} + $m\Delta H_s$) is the apparent activation energy. When solvent mixing with a polymer is an endothermic process, the apparent activation energy from the front velocity data overestimates the true E_{act}. Conversely, an exothermic enthalpy of sorption underestimates this value. The true E_{act} is directly obtained from the penetrant velocities only when solvent sorption is isothermal. Examples of activation energies for the mass transport of solvents into rubbery and glassy polymers are presented in Table I.

A survey of the literature on solvent transport into glassy polymer matrices reveals a lack of research on the transport of water into glassy protein solids. Investigations such as the one presented in this report are needed to address this specific area. Compared with synthetic polymers, the preparation and study of protein matrices have some special considerations. For example, the important relationship between proteins and water has long been recognized (9,10), in which water molecules play a critical role in stabilizing polar groups with the solvation of charges and the formation of hydrogen bonds. Complete dehydration of proteins has been associated with irreversible structural changes such as the formation of covalent bonds by condensation reactions between carboxylic and amino groups (11). This, in addition to other degradation reactions, may lead to permanent protein denaturation. Accordingly, a finite water content is needed to maintain the structural integrity of a particular protein matrix under examination.

Another difficulty in the study of protein swelling is the inability of protein matrices to attain equilibrium swelling in water. The method of equilibrium swelling, which is commonly used as a measure of solvent interactions with synthetic polymers, cannot be used with the protein–water pair. The time required for a protein to approach equilibrium swelling in water would permit significant hydrolysis of peptide chains and, hence, a continuous alteration in its matrix structure. However, for investigations of water-sensitive protein matrices, the kinetic analysis of moving boundaries associated with swelling over short time periods offers a viable alternative to solvent sorption studies that require the measurement of an equilibrium swelling value. The only limitation of penetrant velocity data is that an apparent activation energy is obtained, rather than the true value for water transport into the glassy solid.

In a previous study (12), the profiles of the moving boundaries associated with water transport and swelling in glassy gelatin beads have been established. Two dynamic physical processes occur simultaneously when a glassy gelatin matrix is exposed to water. The first is a transition from the glassy to the rubbery state of gelatin (devitrification) as water penetrates the glassy solid. Generally, the rate of chain relaxation at a glass–gel boundary determines the rate of solvent penetration, and if the latter rate is constant, then mass transport is characterized by Case II kinetics, a limiting form of non-Fickian behavior (13). A region with such a constant penetration rate was demonstrated in the spherical glassy gelatin matrix.

The second dynamic process is the continual swelling of the outer rubbery gelatin network as more water is absorbed. Outward expansion of the swelling gelatin front is limited by the number of chemical crosslinks existent in the matrix.

The present investigation was undertaken to examine the influence of temperature in both aspects of the swelling process of glassy gelatin matrices. The rate of each moving boundary was studied as a function of temperature in terms of the Arrhenius rate law. From this law, the activation energy for both rate processes may be determined and may be used to gain insight into the process of water sorption by glassy gelatin matrices.

Arrhenius analysis of this system requires the measurement of rate constants for both dynamic swelling fronts. Because the water front was found to advance into a glassy gelatin bead at a constant velocity over a significant length of the radius (12), its steady-state velocity, v_{ss}, was used as the rate constant for analyzing the inner moving boundary. The rate constant for the outer boundary was obtained by fitting the swelling data to the following empirical equation:

$$r_t = r_o + k_s t^{1/2} \quad (2)$$

where r_o is the initial dry radius, r_t is the outer radius measured at time t, and k_s is the swelling rate constant.

Table I. Activation Energies for Solvent Transport into Polymer Matrices

Polymer	Solvent	kcal/mol: True E_{act}	kcal/mol: App. E_{act}	ΔH_s	Ref. No.
Rubber state					
Neoprene	Water	2.6		Exothermic	26
Cellulose acetate	Water[a]	5.6		Exothermic	27
Polyethylmethacrylate	Water[a]	15.1		Exothermic	28
Polymethylmethacrylate	Ethanol		14.6	Endothermic	8
Glass state					
Polymethylmethacrylate	Ethanol		54	Endothermic	8
Polymethylmethacrylate	*n*-Butanol		102	Endothermic	8
Polystyrene	*n*-Hexane		43	Isothermal	25
Polystyrene	*n*-Pentane		50	Isothermal	6
Poly(styrene-cophenyleneoxide), 75/25	*n*-Hexane		66	?	25

[a] Solvent maintained at a low activity.

EXPERIMENTAL

Glassy gelatin beads were made from type A gelatin (Bloom 203, *p*I 8.9, Battista Research Institute) using a hot extrusion method described elsewhere (12). They were crosslinked in a chilled solution of 18.5% formaldehyde (Fisher Scientific Co.). The beads were dried and aged at 25°C in a sealed chamber with a constant relative humidity of 32% and were not used until they attained the corresponding equilibrium moisture content of 11% (w/w). The drying stage requires a minimum of 50 days, after which reproducible swelling can be demonstrated for a period up to 2 years (12). The mean diameter for this batch was 1.640 ± 0.061 mm.

At room temperature gelatin exists in a glassy state at all moisture levels below 25% (w/w) (14). However, the 11% residual water contained in the glassy gelatin matrix acts as a plasticizer and lowers the glass transition temperature from about 196 to 80°C (15). The last traces of tightly bound water were not removed from the gelatin molecules because prolonged heating at high temperatures would cause significant hydrolytic degradation of the peptide chains. Moreover, exhaustive dehydration of gelatin by any method induces irreversible structural changes with the formation of covalent cross-links (16). Therefore, the process of slow drying to an established low moisture content had been purposely selected for this work in order to obtain gelatin matrices with reproducible structures. The 11% (w/w) moisture content is well within the range for gelatin to exist in the glassy state, making this solid protein matrix an acceptable model for water transport.

After moisture equilibration, the gelatin beads were stored under identical temperature and humidity conditions until needed. Careful control of moisture content is necessary, because slight changes in the total amount of water have considerable impact on subsequent swelling rates (12).

The moving boundaries, inner water front and outer swelling gelatin front, were observed with a stereomicroscope (Wild M420, E. Leitz, Inc.) equipped with a scaled-filar eyepiece (Wild MMS 235 digital length-measuring set and printer). The eyepiece automatically records the distance traversed by either swelling front by moving a cursor line over the length of the specimen. This device is precise to within 0.001 mm. The bead under study and the swelling medium were maintained at a constant temperature using a jacketed beaker placed on the microscope stage, which was connected to a thermostatically controlled water bath.

The moving boundaries (inner and outer diameters) were measured alternately at 1-min intervals. A total of four to eight beads was examined at each of the following temperatures: 15, 20, 25, 30, 35, and 40°C. It was previously established (12) that the solution pH does not affect the velocity of either boundary during the time required for complete devitrification. For this reason, double-distilled water was selected as the swelling medium.

RESULTS AND DISCUSSION

Inner Moving Boundary

The temperature dependence of non-Fickian water transport into glassy gelatin beads is demonstrated in Fig. 1. Measurements of the extent of water penetration began at the bead's initial perimeter, $r = 0$, and continued until the center was reached, $r = r_o$ (see Fig. 2). In the graphical

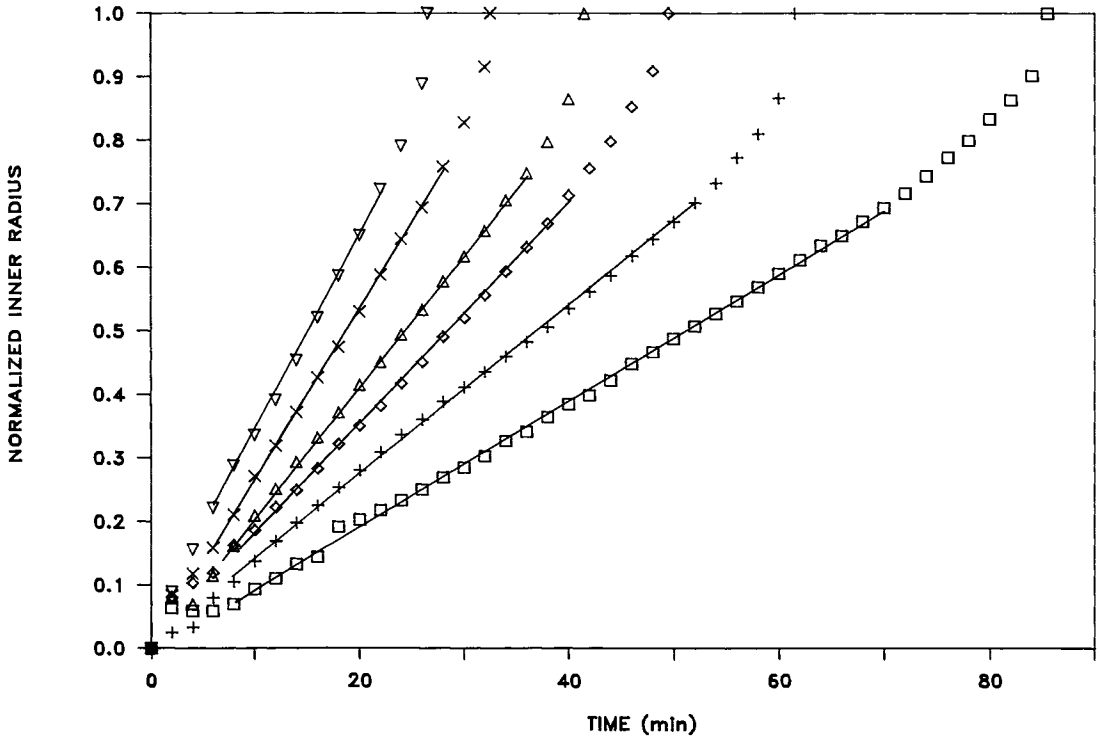

Fig. 1. Normalized radial distance for the water front as it advances into a glassy gelatin bead from the perimeter, $r = 0$, to the center, $r = 1$. The steady-state region is shown for each temperature studied. Curves from right to left are 15, 20, 25, 30, 35, and 40°C.

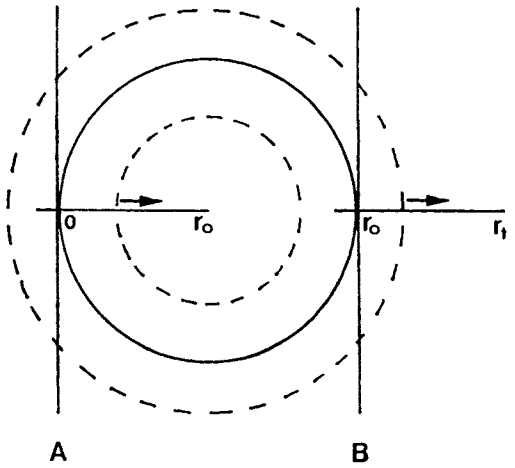

Fig. 2. Diagram of a swelling gelatin bead where the solid line represents the initial dry perimeter, and the dashed lines represent the two moving boundaries. The frames of reference for the graphical presentation of data are shown: (A) inner water front and (B) outer swelling gelatin front.

presentation of data, radial distances were normalized with respect to the initial dry radius. The central region of the profiles illustrates the steady-state velocity, v_{ss}, for the advancing water front. The slope of the central region (not normalized) was calculated by linear least-squares analysis to obtain v_{ss}, and the data were averaged for each temperature. The mean velocities are listed in Table II, and their coefficients of variation range from 2 to 10%.

The Arrhenius rate law was used to determine the apparent activation energy associated with the water front movement into the gelatin glass. Expressed in its general form, the law is given as

$$k = Ae^{-E_{act}/RT} \tag{3}$$

Here k is the rate constant for the process, A is a preexponential "frequency" factor, R is the gas constant (1.987 cal/K-mol), T is the absolute temperature, and E_{act} is the apparent activation energy. When applying Eq. (3) to the present work, k represents v_{ss} (steady-state velocity) for inner boundary kinetics and k_s for outer boundary kinetics. No physical meaning is attributed to the preexponential factor, A.

Figure 3 shows $\ln(v_{ss})$ plotted as a function of reciprocal temperature. A linear relationship for the inner boundary velocities (lower data) is clearly demonstrated over the selected range of temperatures. The apparent activation energy for water transport was calculated directly from the

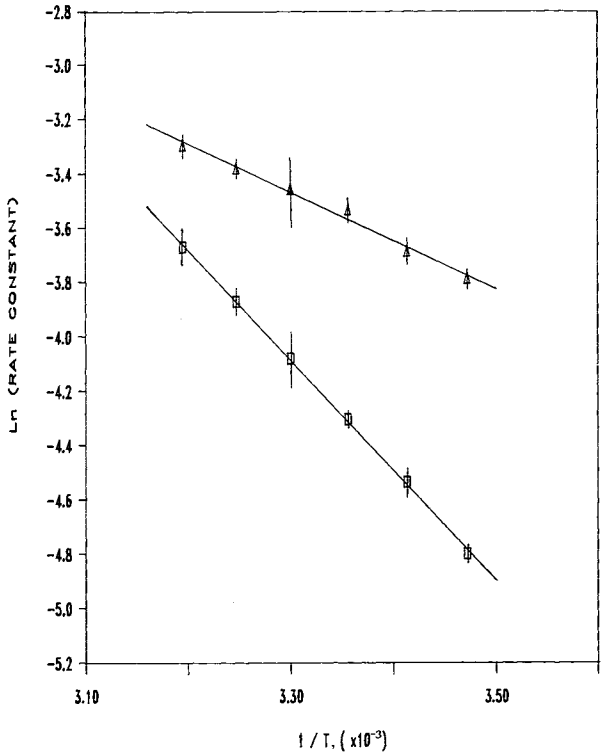

Fig. 3. Arrhenius plot of the swelling rate constant associated with each moving boundary: (□) inner water front (v_{ss}) and (△) outer swelling gelatin front (k_s).

slope of the fitted regression line ($r = -0.9997$). It was found that 8.1 (±0.1) kcal/mol is needed by liquid water to penetrate a glassy gelatin matrix that is plasticized by an initial equilibrium moisture content of 11% (w/w).

The apparent activation energy obtained from the Arrhenius analysis was unexpectedly low compared with values reported for non-Fickian transport in other glassy polymer–solvent systems (Table I). When accounting for enthalpic effects, a typical true E_{act} will assume a value between 20 to 60 kcal/mol (8), which is significantly higher than Fickian transport of solvents into rubbery polymers. For the latter process, a value of less than 10 kcal/mol (5) is expected under ideal experimental conditions. Because the heat of sorption of water by gelatin is exothermic (17), the apparent activation energy should then be an underestimate of the true E_{act} as predicted by Eq. (1). However, recall that in this particular system 11% (w/w) water is already absorbed by the gelatin molecules, which is slightly greater than the established amount (8.7%, w/w) of water bound in the "first

Table II. Temperature Dependence of Rate Constants for Both Moving Boundaries

Temp. (°C)	Number of beads	v_{ss} (mm/min) $\times 10^2$	SD $\times 10^2$	k_s (mm/$\sqrt{}$min) $\times 10^2$	SD $\times 10^2$
15	4	0.82	0.02	2.27	0.07
20	4	1.07	0.06	2.51	0.11
25	4	1.34	0.03	2.93	0.13
30	8	1.69	0.17	3.16	0.42
35	4	2.09	0.09	3.41	0.11
40	6	2.55	0.17	3.71	0.13

layer" (17). Generally the first layer of solvent absorbed by a polymer accounts for about 84% of its total heat of sorption (18). Therefore, at this moisture level, it is unlikely that the relatively low apparent E_{act} is attributable simply to exothermic water penetration into the glassy gelatin solid.

On the other hand, the nominal moisture content of the glassy gelatin matrix should be partly responsible for the low apparent activation energy by a different mechanism. Because the initial equilibrium water content plasticizes or increases the mobility of gelatin chains, subsequent water transport into the glass would be facilitated and, thus, might be less temperature dependent.

It becomes clear when examining the published literature that water is unique from organic solvents in swelling polymer matrices. The transport behavior of water vapor was observed by Kishimoto *et al.* (19) to be less temperature dependent than organic solvents in the vapor state. They found that the activation energy required by water to diffuse into both glassy and rubbery films of polyvinylacetate averaged about 10 kcal/mol. However, a maximum value slightly above 10 kcal/mol did occur at the glass transition temperature. These relatively low values were attributed to the small size of the water molecule, leading to its failure to obey free-volume theory (19). Furthermore, as a result of water's small molecular size, its penetration into a polymer solid requires only the local cooperation of two or three monomers of a chain (20) and, consequently, would be a relatively less activated process.

Other evidence for the unusual transport behavior of water is provided by the penetration of liquid water into glassy polystyrene films (21) which undoubtedly exhibited sorption curves characteristic of non-Fickian behavior. A true activation energy of only 8.0 kcal/mol was calculated from the temperature–diffusion data available in the above work. In still another report (22), the true activation energy for the transport of water vapor into polyvinylchloride remained constant at 9.98 kcal/mol over a temperature range that included both rubbery and glassy states of the polymer. No break in the slope or maximum value was noted at the glass transition temperature.

Although the previous arguments concerning the low activation energies for non-Fickian water transport into glassy polymers seem convincing for water's unique behavior, an exception can be cited where the true activation energy for liquid water penetration into melamine–formaldehyde resins was measured at 34 kcal/mol (23).

Outer Moving Boundary

Radial measurements of the outer moving boundary over time, normalized with respect to the initial radius of the dry bead, are presented in Fig. 4. Moreover, the swelling profiles are examples of individual temperature trials. When the same data are replotted in Fig. 5 according to Eq. (2) in the rearranged form,

$$r_r/r_o = 1 + (k_s/r_o)t^{1/2} \quad (4)$$

an appropriate fit is demonstrated. The swelling rate constant, k_s, was calculated from the slope of the line, and mean values are listed in Table II. The coefficients of variation for the averages range from 3 to 13%.

The activation energy for the swelling gelatin network was determined from its rate constants and the Arrhenius rate law as presented in Fig. 3. Similar to the result for the

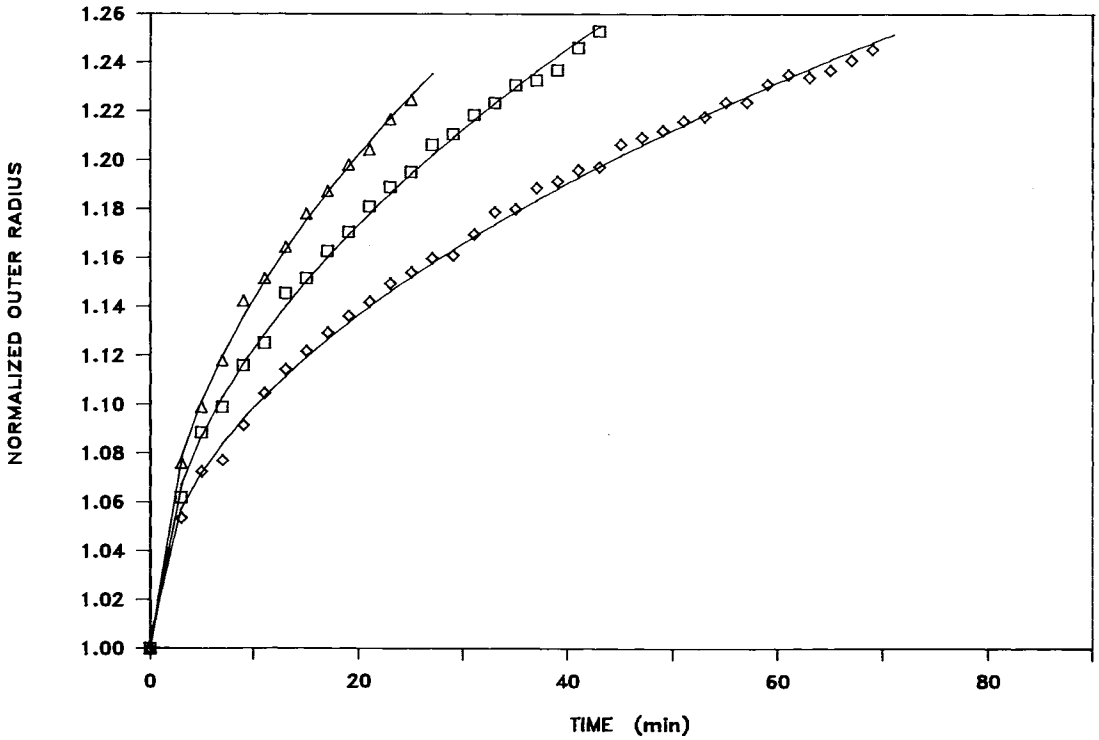

Fig. 4. Normalized radial distance for the swelling gelatin front as it expands outward during water sorption. The effect of temperature is demonstrated. Curves from right to left are 20, 30, and 40°C.

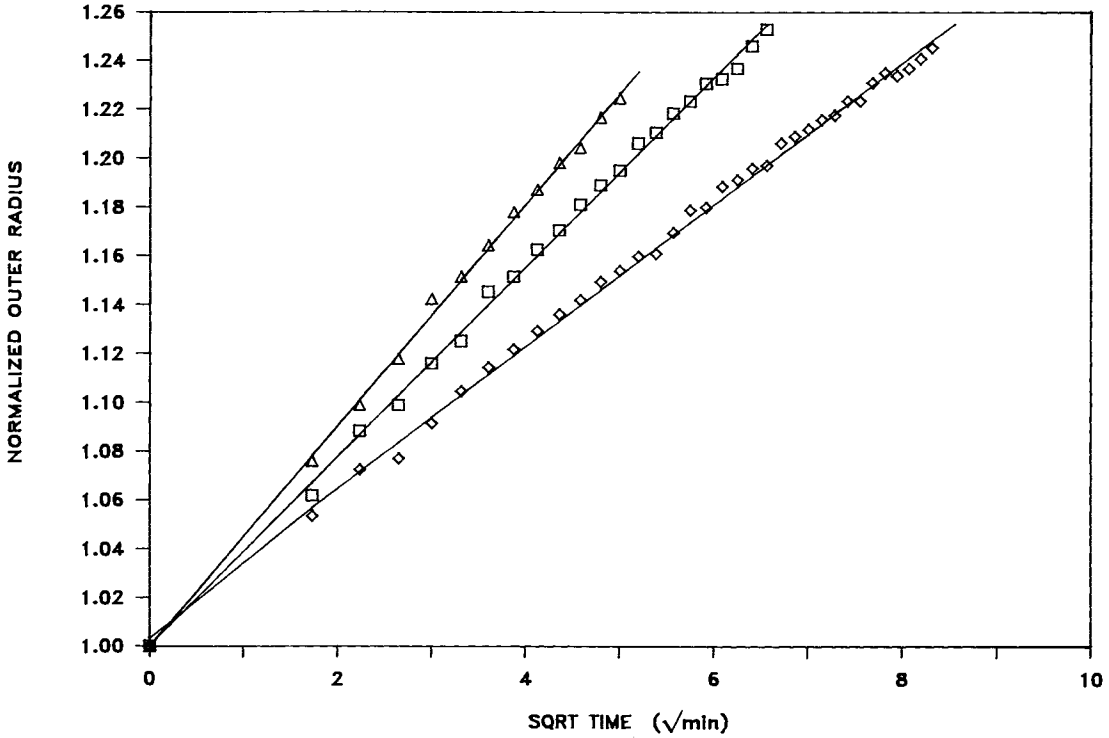

Fig. 5. The outer swelling gelatin front (data from Fig. 4) replotted as a function of the square root of time according to Eq. (4). The profiles from right to left represent swelling at temperatures of 20, 30, and 40°C.

inner moving boundary, the relationship was linear over the range of temperatures investigated. The apparent activation energy for the outer swelling front was 3.5 (±0.2) kcal/mol.

This apparent activation energy does not solely represent Fickian water diffusion into a rubbery gelatin matrix, because there is a considerable volume increase in the matrix with water influx. Unlike many synthetic hydrogel matrices that typically absorb from about 20 to 80% (24) of their weight in water, gelatin beads may absorb up to 300% of their weight, representing a highly expanded network structure. So by measuring dimensional changes during swelling as a function of temperature, the expansion rate of the gelatin molecules in an aqueous medium is actually determined. Consequently, the apparent activation energy, 3.5 kcal/mol, should be a composite of the activation energies for water diffusion and for the bulk movement, or viscous flow, of the long gelatin segments. The magnitude of the value should also be significantly dependent on the degree of covalent cross-linking of the particular gelatin network structure being studied.

CONCLUSIONS

In general, one can assume that non-Fickian solvent transport in glassy polymers is a more highly activated process than Fickian transport in rubbery polymers. Yet as noted previously with water transport behavior, there are reported exceptions to this generalization. Therefore, although the trend is clear, narrow guidelines for activation energies should not be used for distinguishing between Fickian and non-Fickian water transport in polymer matrices.

In this study, the apparent activation energy for the velocity of the penetrating water front into a glassy gelatin matrix was found to fall outside the typical range for non-Fickian behavior of organic solvents in synthetic polymers, but it was substantially greater than the apparent activation energy for the outer swelling gelatin front. The real utility of these activation energies does not necessarily lie in their absolute values but, rather, in their use for understanding the physical processes associated with water swelling when making relative comparisons. Clearly the absolute values are sensitive to inherent variables such as swelling history, rate of glass formation by solvent evaporation, cross-link density, and initial water content. A similar argument can be made for all polymer–solvent pairs listed in Table I.

Although the moving boundaries were analyzed independently, they are actually coupled processes linked by a continuum of gelatin chains in the network structure. The degree of mutual influence is yet to be assessed. Nevertheless, the two moving boundaries do exhibit different mechanisms of swelling and have distinctive rate constants. Therefore, the examination of the apparent activation energies of both processes would provide useful information about the integrated mechanism of swelling as long as the values are viewed collectively.

And finally, the findings of this report may have indirect application in dosage form design utilizing gelatin as a drug-loaded, glassy matrix. In an ideal swelling-controlled drug delivery system, drug release is controlled by the water front velocity. Because penetrant velocity is very sensitive to the structure of a polymer glass (13), possible alterations in the gelatin glass due to incorporation of drug molecules may be effectively assessed by comparisons of apparent activation energies with those evaluated herein.

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