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DIFFUSIVITY AND DISSOLUTION RATE IN POLYMERIC SOLUTIONS

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ABSTRACT

The diffusivity of benzoic acid was measured in various concentrations of aqueous solutions of methylcellulose, hydroxypropyl cellulose and guar gum. An increase in concentration of the polymer increases the viscosity of the polymeric solution to a greater degree than it decreases diffusivity. Dissolution rates of benzoic acid in various concentrations of polymeric solutions were measured. An equation is presented for calculating the relative dissolution rates in polymeric solutions.

INTRODUCTION

Transport through aqueous polymeric solutions is slowed as the concentration of the polymer is increased (1-4). Structural models of diffusivity through polymeric solutions have been reviewed by Li (5) and Osmers (6). The absolute rate theory

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developed by Eyring et al. (7,8) has been used by a number of investigators (5,6,9,10) as a basis for predicting diffusivity in polymeric solutions. Difficulty in obtaining accurate experimental values, such as the heat of mixing values for use in the equation of Li (5) and values of excess volume of mixing for use in the equation of Osmers (6), somewhat restrict the use of their predictive equations. In the equation of Navari et al. (9) experimental viscosities may be used to calculate terms involving polymeric-solvent and solvent-solvent interactions.

The purposes of this investigation were to study the dissolution in solutions of some common pharmaceutical suspending agents and to develop a relation suitable for predicting dissolution rates of a solute in aqueous polymeric solutions by use of parameters that are available in the literature and measured viscosities.

EXPERIMENTAL

The methodology and procedures have been reported, and the data are summarized in Table 1 (11). The bulk viscosity was measured at 25°C by a Brookfield model LVT Syncho-lectric viscometer operating at 60 rpm.

RESULTS AND DISCUSSION

Diffusivity. Navari et al. (9) employed the Eyring absolute rate theory (7, 8) as a basis for developing a quantitative predictive theory for diffusivities in dilute polymeric solutions. The relationship has been successfully applied to eleven polymeric solutions and to mixed polymeric systems (12) and is

Table I. Solubility, Diffusion Coefficient and Dissolution Rate of Benzoic Acid in Various Concentrations of Polymeric Solutions at 25°C

Weight Fraction	Solubility mg/ml	Density g/cm	η, cps[a]	$f(\eta)$[b]	10^5D_{exp}, cm /sec	R, mg/cm /hr Experimental	R, mg/cm /hr Predicted
			Methylcellulose				
0.001	3.25	0.9976	3.7	0.958	1.036	32.41	35.75
0.003	3.26	0.9979	6.5	1.164	0.678	22.79	23.65
0.005	3.32	0.9983	12.5	1.511	0.298	18.82	20.45
0.006	3.31	0.9985	19.0	1.740	0.240	16.36	20.56
			Hydroxypropyl cellulose				
0.001	3.32	0.9978	5.75	1.111	0.650	26.79	25.80
0.002	3.29	0.9979	13.6	1.560	0.372	20.39	17.88
0.003	3.30	0.9981	33.0	1.718	0.186	11.66	13.10
			Guar gum				
0.001	2.96	0.9975	4.8	1.042	1.055	29.26	37.85
0.002	3.18	0.9982	12.7	1.520	0.446	23.51	19.23
0.003	2.75	0.9983	37.0	1.582	0.167	8.15	4.48

[a] measured by Brookfield at 60 rpm; [b] calculated by Eq. 18;
[c] calculated by Eq. 19

$$\frac{D}{D_o} = \left(\frac{V_S}{V_B}\right)^{1/3}\left(\frac{M_S}{M_B}\right)^{1/2} \exp\left(\frac{E^H_{BB} - E^H_{(BB + PB)}}{RT}\right) \qquad \text{(Eq. 1)}$$

where D and D_o are the diffusion coefficients of the solute in the polymeric solution and in pure solvent, respectively; V_S and V_B are the molar volumes of polymeric solution and pure solvent, respectively; M_S and M_B are the molecular weights of polymeric solution and pure solvent, respectively; E^H_{BB} is the energy required for cage deformation or vacancy formation caused by breaking of solvent-solvent bonds, $E^H_{(BB + PB)}$ is the energy required for cage deformation or vacancy formation caused by breaking solvent-solvent bonds and solvent-polymer bonds, R is the gas constant, and T is the absolute temperature.

The diffusion coefficients of benzoic acid in pure water and in various concentrations of aqueous methycellulose, hydroxypropyl cellulose and guar gum solutions were determined experimentally at 25°, and the molar volumes and molecular weights are easily measured or calculated. The only unknown quantity is $\Delta E = E^H_{BB} - E^H_{(BB + PB)}$, which is a function of the concentration and type of polymer and is a measure of the strength of the polymer-solvent bond.

As shown in Fig. 1 a plot of logarithm ΔE against the reciprocal of weight fraction (C) is linear with logarithm ΔE_{max} and -k the intercept with the ordinate and the slope, respectively. Mathematically, this may be stated

$$\Delta E = \Delta E_{max} \exp\left(-k/C\right) \qquad \text{(Eq. 2)}$$

The maximum activation energy difference (ΔE_{max}) is solely a function of the polymer and could be called a polymer constant.

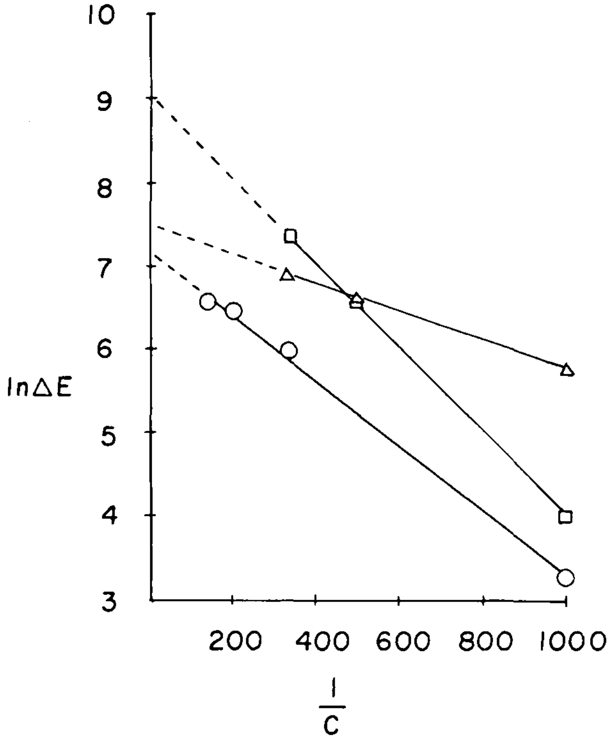

FIGURE 1

Variation of activation energy difference in polymeric solutions with concentration at 25°. Key: o, methylcellulose, Δ, hydroxypropyl cellulose; and, □, guar gum.

The solution constant (k) is a measure of the polymer-solvent interactions and is related to the properties of the solution.

For a polymer in solution the root-mean-square end to end distance ($\overline{r^2}$) between the ends of a polymer chain involves two factors. One factor depends on the nature of the polymer. The other is independent of the nature of the polymer and is dependent only on chain length (13, 14); it may be expressed in terms of molecular weights as

$$\frac{l^2}{M_o} = \frac{\overline{r^2}}{M_p} \qquad \text{(Eq. 3)}$$

where l is the effective bond length of repeating units of the polymer, M_o and M_p are the molecular weight of the repeating unit of the polymer and the polymer molecular weight, respectively. If l or M_o can not be determined experimentally, the term (l^2/M_o) may be estimated from the intrinsic viscosity (15).

A plot of ΔE_{max} against l^2/M_o is linear, and

$$\Delta E_{max} = C_1\ (l^2/M_o) + C_2 \qquad \text{(Eq. 4)}$$

where C_1 and C_2 have been determined to be -22.75 kcal/mole/Å^2 and 15.50 kcal/mole, respectively (9, 16).

Since k is related to properties of the solution, a viscosity parameter could be used to provide a measure of the polymer-solvent interaction. The viscosity parameter (η_R) is related to k

$$\eta_R = \frac{2\eta}{\eta_o C} - \frac{1}{\eta_o}\frac{d\eta}{dC} \qquad \text{(Eq. 5)}$$

A plot of logarithm k against logarithm η_R is linear and may be represented by

$$\ln k = C_3 \ln \eta_R + C_4 \qquad \text{(Eq. 6)}$$

where C_3 and C_4 have been determined to be -1.186 and -3.54, respectively (9, 16). For large values of η/η_o, the intrinsic viscosity approximates η_R.

Using methylcellulose solutions as an example, the intrinsic viscosity is calculated by plotting $\eta-\eta_o/\eta_o C$ against concentration as shown in Fig. 2 in which η and η_o are the viscosities of the methylcellulose solutions at concentration C in g/100 ml and of water, respectively (17). Extrapolating to intercept the ordinate,

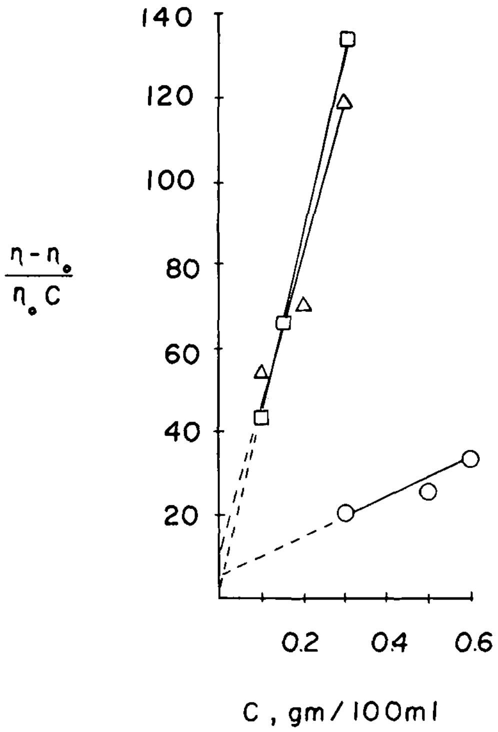

FIGURE 2

Evaluation of intrinsic viscosity of polymeric solutions. Key: o, methylcellulose; Δ, hydroxypropyl cellulose; and □, guar gum.

the intrinsic viscosity is 6 dl/g, which is in agreement with the value of 5.7 dl/g reported by Savage (18). Similarly the intrinsic viscosities of hydroxypropyl cellulose and guar gum were found to be 11.0 and 4.4 dl/g, respectively.

The intrinsic viscosity is used to calculate the molecular weight of the methylcellulose by use of the equation described by Neeley (17)

$$[\eta] = 3.16 \times 10^{-3} M^{0.536} \qquad \text{(Eq. 7)}$$

$$6 = 3.16 \times 10^{-3} M^{0.536} \qquad \text{(Eq. 7a)}$$

$$M = 1{,}321{,}600$$

The term (l^2/M_o) is calculated by use of the equation (16)

$$[\eta] = 4.291 \times 10^{23} \; (\alpha^3 \; \zeta^3 \; l^3/M_o^{3/2}) \; M^{1/2} \qquad \text{(Eq. 8)}$$

where $[\eta]$ is the intrinsic viscosity in cm^3/g, α is an empirical expansion factor for polymer dimensions, l is the effective bond length in the polymer chain, ζ is a parameter, M_o is the molecular weight of the repeating units of the polymer, and M is the molecular weight of the polymer. The parameter ζ, as calculated from the Flory-Fox parameter of 2.15×10^{21}, is 0.794 for methylcellulose (17). The factor α may be estimated for the molecular weight of the polymer (15)

$$\alpha = 0.492 \; M^{0.086} \qquad \text{(Eq. 9)}$$

$$= 0.492 \times 1{,}321{,}600 \qquad \text{(Eq. 9a)}$$

$$= 1.7$$

Substituting these values into Eq. 8 and solving for l^2/M_o

$$\frac{l^2}{M_o} = \left(\frac{600}{4.291 \times 10^{23} \times 1.7^3 \times 0.794^3 \times 1{,}321{,}600^{1/2}} \right)^{2/3} \qquad \text{(Eq. 10)}$$

$$= 6.254 \times 10^{-17} \; cm^2 \; (0.6254 \; Å^2)$$

The value of l^2/M_o calculated by Eq. 8 may be substituted into Eq. 4

$$-\Delta E_{max} = -22.75 \; (0.6254) + 15.5 \qquad \text{(Eq. 11)}$$

$$= 1.27 \text{ kcal/mole}$$

Since $\eta_R \rightarrow [\eta]$ at large values of η/η_o, $[\eta]$ may be substituted into Eq. 6

$$\ln k = -1.186 \ln 6 - 3.54 \qquad \text{(Eq. 12)}$$

$$= -5.665$$

$$k = \text{antilogarithm } -5.665 = 0.00346$$

The values of k and ΔE_{max} may now be substituted into Eq. 2 so that for methylcellulose solutions

$$\Delta E = -1270 \exp (-0.00346/C) \qquad \text{(Eq. 13)}$$

Combining Eq. 1 and 2 for solutions of methylcellulose yields

$$\frac{D}{D_o} = \left(\frac{V_s}{V_B}\right)^{1/3} \left(\frac{M_S}{M_B}\right)^{1/2} \exp\left[\frac{-1270 \exp (-0.00346/C)}{RT}\right] \qquad \text{(Eq. 14)}$$

which shows that the diffusivity of benzoic acid in aqueous methylcellulose solutions relative to that in water is a function of the concentration of methylcellulose. The ratios of the molar volumes and molecular weights approach unity since the concentrations of methylcellulose studied did not exceed 0.6%.

Using the data of Table 1 the experimental D/D_o in various concentrations of aqueous methylcellulose solutions is compared in Fig. 3 to the theoretical ratio calculated by use of Eq. 14. The comparison shows reasonable agreement between the calculated and experimental values.

The diffusivities of benzoic acid in aqueous solutions of hydroxypropyl cellulose and guar gum were treated similarly and are plotted in Fig. 3. Since some of the parameters of Eq. 8 are unknown, the values of ΔE were evaluated using experimental diffusion coefficients and Eq. 1. The ΔE_{max} was determined from Eq. 2 in its logarithmic form

$$\ln \Delta E = \ln \Delta E_{max} - k/C \qquad \text{(Eq. 15)}$$

as plotted in Fig. 1. The values of ΔE_{max} are -1720 and -8300 cal/mole for hydroxypropyl cellulose and guar gum, respectively. The values of k are 0.00169 and 0.0050 for hydroxypropyl cellulose and guar gum, respectively.

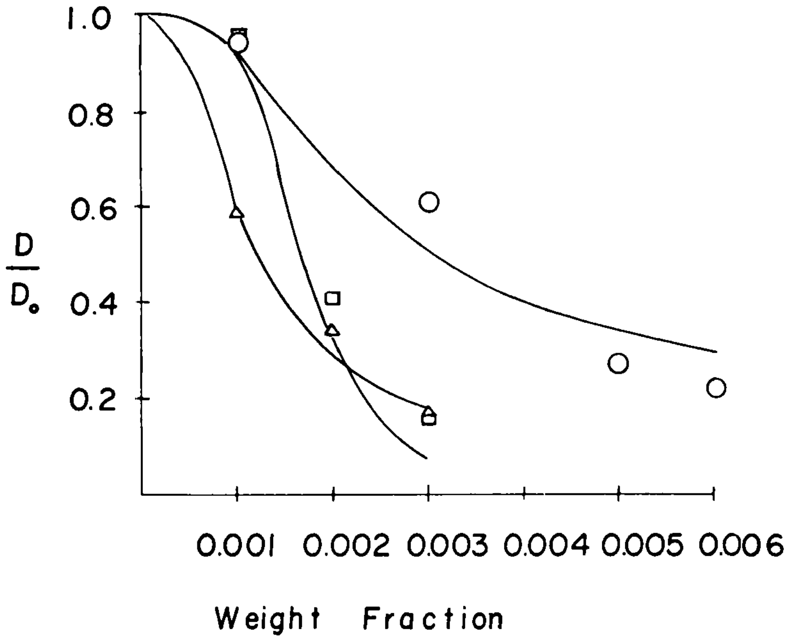

FIGURE 3

Comparison in various concentrations of polymer of the experimental D/D_o to the precited D/D_o as calculated by Eq. 1 and represented by the solid line. Key: o, methylcellulose; Δ, hydropropyl cellulose; and □, guar gum.

As illustrated in Fig. 3 for benzoic acid at 25° the experimental D/D_o in various concentrations of aqueous solutions of methylcellulose, hydroxypropyl cellulose and guar gum are reasonably similar to the theoretical values represented by the solid curve.

Dissolution Rate. When the dissolution of a one-component, nondisintegrating sphere occurring in a non-reactive medium at sink conditions is diffusion controlled, the dissolution rate (R) may be expressed

$$R = \frac{DC_s}{h} \qquad \text{(Eq. 16)}$$

where h is the effective diffusion layer thickness and C_s is the solubility. The conditions used to determine the dissolution rate suggest that the diffusion layer model is operative (4).

The Noyes-Whitney concept as expressed in Eq. 16 assumes that terms other than those expressed in the equation (agitation, temperature, viscosity) are constant. Obviously, the viscosity of a solution of a polymer is a function of the concentration. It has been shown that at a fixed viscosity the dissolution rate is not a linear function of the experimental diffusion coefficient (11). As the concentration of the polymer is increased, the decrement in the diffusion coefficient of the solute is considerably less than the increment in solution viscosity, which is increased markedly (6). Thus, a viscosity function f (η) may be introduced into Eq. 16 to consider variations of viscosity (11)

$$R = \frac{DC_s}{h} f(\eta) \qquad \text{(Eq. 17)}$$

From the experimental data in Table 1 the values of f(η) were calculated by Eq. 17. The relationship of the viscosity function to viscosity is shown in Fig. 4, and the equation for this relationship is

$$f(\eta) = 0.642 + 0.092\eta - 0.0018\eta^2 \qquad \text{(Eq. 18)}$$

Substitution of D of Eq. 1 into Eq. 17 yields

$$R = \frac{D_o C_s f(\eta)}{h} \left(\frac{V_S}{V_B}\right)^{1/3} \left(\frac{M_S}{M_B}\right)^{1/2} \exp\,(\Delta E/RT) \qquad \text{(Eq. 19)}$$

in which the dissolution rate is related to the bulk viscosity since both the viscosity function and the activation energy difference are determined using measured viscosity. Clearly the

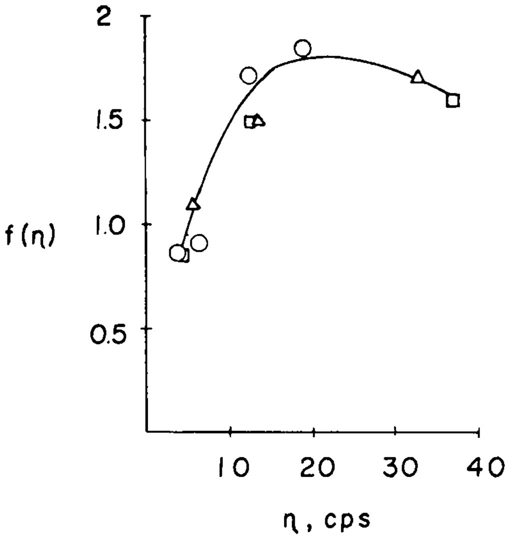

FIGURE 4

Relation of viscosity to viscosity function. Key: o, methylcellulose; Δ, hydroxypropyl cellulose; and □, guar gum.

dissolution rate is related to bulk viscosity by a complex relationship. Using the data in Table 1 and Fig. 1 the dissolution rates of benzoic acid were calculated using Eq. 19 at various concentrations of methylcellulose. The diffusion coefficient of benzoic aicd in water at 25° is 1.102×10^{-5} cm^2/sec, and the value of h is 32.3×10^{-4} cm (4).

For example, with 0.3% methylcellulose solution having an experimental viscosity of 6.5 cps,

$$R = \frac{1.102 \times 10^{-5} \times 3.25}{32.3 \times 10^{-4}} \times [0.642+(0.092 \times 6.5) - (0.0018 \times 6.5^2)]$$

$$\times \exp\left[\frac{-1270 \exp(-0.0046/0.003)}{1.987 \times 298}\right] \qquad \text{(Eq. 20)}$$

$$= 6.57 \times 10^{-3} \text{ mg/cm}^2\text{/sec } (23.7 \text{ mg/cm}^2\text{/hr})$$

The calculated dissolution rate in 0.3% methylcellulose is 4% faster than the experimental rate.

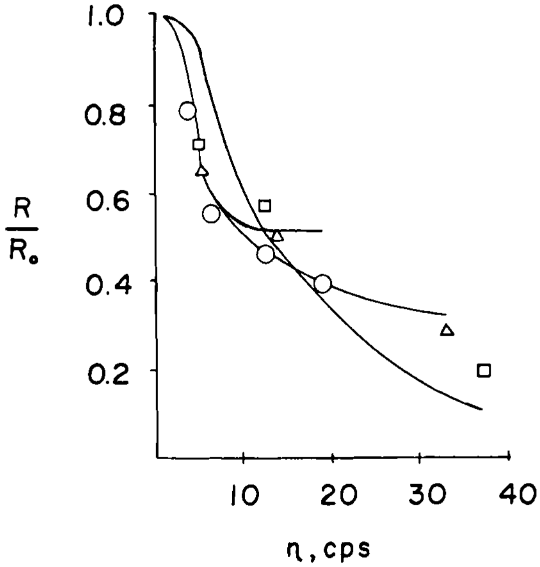

FIGURE 5

Comparison of the experimental R/R_o to the predicted R/R_o as calculated by Eq. 21 and represented by the solid line against viscosity. Key: o, methylcellulose; Δ, hydroxypropyl cellulose; and □, guar gum.

For the systems studied the terms f(η) in pure solvent, $(V_S/V_B)^{1/3}$ and $(M_S/M_B)^{1/2}$ approach unity and as shown in Table 1 the solubility of benzoic acid is not significantly changed by the addition of methylcellulose; thus, assuming that the thickness of the diffusion layer does not change, the ratio of the dissolution rate in a polymeric solution to the dissolution rate in pure solvent (R/R_o) may be predicted if Eq. 19 is divided by Eq. 17

$$\frac{R}{R_o} = f(\eta)\ \exp\ (\Delta E/RT) \qquad \text{(Eq. 21)}$$

For example, the ratio of dissolution rate of benzoic acid in 0.3% methylcellulose to dissolution rate in water is approximately

$$\frac{R}{R_o} = 1.164 \times \exp(-400/1.987 \times 298) \quad \text{(Eq. 22)}$$

$$= 0.592$$

Similarly the ratios predicted by Eq. 21 were calculated for other concentrations of methylcellulose and for solutions of hydroxypropyl cellulose and guar gum. In Fig. 5 the predicted ratios are plotted against viscosity as a solid line for comparison to the experimental ratios represented by various symbols.

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