

The influence of solution viscosity on the dissolution rate of soluble salts, and the measurement of an "effective" viscosity

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The rate of solution of KCl and NaCl from compressed discs has been determined under controlled conditions, in water at 25° and in solutions of varying concentrations of polyvinylpyrrolidone (molecular weight 360 000), polyoxyethylene glycol 6000 and cetomacrogol 1000. Dissolution rate constants decrease with increasing bulk solution viscosity, as expected, but no one equation relating rate constant and bulk viscosity fits the results for the systems studied. Calculation of an effective viscosity from the diffusion coefficients of the salts in water and the diffusion coefficients of the salt in the polymer solutions enables an empirical correlation of the results to be made. The relation of the effective viscosity to the microscopic viscosity is discussed in an Appendix.

Methods of delaying the rate of solution of freely soluble drugs are of obvious pharmaceutical importance. The use of inert, insoluble polymer matrices to modify the release of drugs from dosage forms has been studied in some detail (Desai, Simonelli & Higuchi, 1965; Desai, Singh & others, 1966). Soluble, hydrophilic polymers can affect the solution behaviour and transport properties of both large and small drug molecules and hence can be used to decrease the rate of solution of soluble drugs from compressed tablets. Probably the most important solution effect caused by hydrophilic macromolecules is an increase in solution viscosity. There has been considerable interest in the relation between bulk solution viscosity and the rate of dissolution of a wide range of materials (Braun & Parrott, 1972a, b). A number of empirical equations have been proposed (Roller, 1935; Wagner, 1949) to describe the decrease in dissolution rate with increase of viscosity, but no unanimity of expression has been found. One of the problems has been the calculation of the "effective" viscosity, that is, a viscosity which is a true reflection of the resistance to flow experienced by small ions or molecules in the solution. In solutions of macromolecules the bulk viscosity does not reflect the viscosity of the solvent through which the solute molecules travel.

In this paper we have studied the effect of a polyoxyethylene glycol, a polyvinylpyrrolidone and cetomacrogol 1000, a non-ionic surface-active agent, in retarding the solution rate of the soluble salts, sodium chloride and potassium chloride. The dissolution of NaCl in aqueous solutions is a diffusion-controlled process (Cooper & Kingery, 1962; Zdanovskii, 1951). The Noyes-Whitney (1897) equation

$$\frac{dc}{dt} = k(c_s - c) \quad \dots \quad (1)$$

applies in a variety of experimental arrangements when dissolution is diffusion

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controlled. Here c is the concentration of dissolving solute, c_s is its saturation solubility, t is time and k is the rate constant for the dissolution process. According to Nernst (1904) the rate constant (per unit volume of solution, per unit area of dissolving solute) is related to the solute diffusion coefficient, D , by

$$k = \frac{D}{\delta} \quad \dots \quad \dots \quad \dots \quad \dots \quad (2)$$

where δ is the thickness of the diffusion layer. The diffusion layer is assumed to be a practically stationary liquid layer through which the solute must diffuse to reach the bulk solution. At distances greater than δ from the surface the stirring is efficient and the thermodynamic activities of the various species are assumed to be equal to bulk activities (Anderson & Eyring, 1970). Levich (1947) showed that for a rotating dissolving disc (equivalent in effect to a stationary disc in a stirred solvent)

$$\delta = 1.611 D^{1/3} \nu^{1/6} \omega^{1/2} \quad \dots \quad \dots \quad \dots \quad \dots \quad (3)$$

where ν is the kinematic viscosity of the system and ω is the speed of rotation in radians s^{-1} .

It is apparent, then, that the rate of solution is a complex function of the viscosity of the homogeneous solvent, i.e.

$$k = f(D, \nu^{-1}, U) \quad \dots \quad \dots \quad \dots \quad \dots \quad (4)$$

U being the fluid velocity, D and ν being dependent variables. Addition of polymer to the system increases ν and decreases the diffusion coefficient of the solute in the bulk medium (Wang, 1954). The nature of the relation between k , ν and D is studied here, and an approach is made to the measurement of the effective viscosity and microscopic viscosity in solutions of a polyoxyethylene glycol and a polyvinylpyrrolidone.

APPARATUS AND METHODS

Dissolution apparatus. This consisted of a Pyrex vessel (700 ml capacity, 15 cm external diameter) maintained at $25^\circ \pm 0.1^\circ$. A four bladed polythene stirrer was operated by one of a series of synchronous motors (5–120 rev min^{-1} , Crouzet Ltd., Brentford). The compressed disc of salt was placed in a titanium holder sunk in a block of Perspex which eliminated as far as possible the effects of dead space. Only one face of the tablet was exposed to the dissolution medium. Degassing of the dissolution medium was essential to preclude bubble formation at the tablet surface. A precision conductance bridge (Wayne Kerr Universal Bridge B221 with autobalance adaptor AA 221) monitored the conductivity of the solution. The conductivity cell was positioned at a depth of 0.6 cm from the liquid surface, where most reproducible results were obtained.

Methods

The conductivity cell constant was obtained using standard solutions and literature data (Shedlovsky, 1932; Chambers, 1956). The rate constant of dissolution was obtained as follows. A weighed tablet was located in its holder and about 600 g of freshly distilled water at 25° placed in the flask, the exact weight of the water added being determined. The maximum error in timing the progress of dissolution is about 20 s, the time taken to complete the filling procedure.

From equation (1) when $c_s \gg c$

$$\frac{dc}{dt} = kc_s \quad \dots \dots \dots (5)$$

Therefore, under sink conditions, a convenient method of obtaining k is from the the equation obtained by expansion of the exponential form of equation (5), neglecting terms in k higher than the square:

$$c/t = kc_s - k^2c_s t/2 \quad \dots \dots \dots (6)$$

k is therefore obtained from a plot of c/t versus t , the intercept giving kc_s .

Viscosity measurements were made using a suspended level viscometer, thermostatted at $25^\circ \pm 0.01^\circ$.

Solubilities were obtained in a percolation cell as described by Elworthy & Lipscomb (1968).

Density measurements were made with a Lipkin pycnometer of 10 ml capacity.

Diffusion coefficients were obtained using a membrane apparatus after the design of Goldberg & Higuchi (1968), following their procedures. A silver membrane (Flotronics, 37 mm diameter) separated two flasks of about 250 ml capacity. The cell was calibrated with KCl and the mean diffusion coefficient calculated for NaCl was $1.468 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, the literature value being $1.473 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$. The reproducibility of repeat results was estimated to be $\pm 3\%$. Values of diffusion coefficients in the presence of the polymers were obtained by adding polymer to the flasks on both sides of the membrane to obviate osmotic effects.

Materials

Sodium chloride and potassium chloride were Analar grade (BDH); the moisture content of each, determined by drying to constant weight at 110° , was 0.095% for NaCl and 0.042% for KCl. As single size fractions produced friable discs 180–250 μm and 125–180 μm fractions (Endecott test sieves BS 410) were mixed in the ratio 2:1. This mixture (15 g) was compressed in an evacuable die in a hand operated hydraulic press (Research & Industrial Instrument Company, model C-30). The powder was evacuated for 5 min and a pressure of up to 0.15 kg m^{-2} applied for 4 min. The diameter of the resulting disc was 3.5 cm and its thickness 0.8 cm. The average weight was 15 g with limits of 14.9 to 15.05 g.

Cetomacrogol 1000 B.P.C. (Macarthy's Ltd.), polyoxyethylene glycol 6000 (BDH Ltd.) and polyvinylpyrrolidone (mol wt 360 000) (Sigma Chemical Company (PVP-360)) were all used as received.

RESULTS

Dissolution of salts in water

The conditions of the experiment were optimized so that the rate constants in water ($k_{\text{H}_2\text{O}}$) would serve as a baseline for the results obtained in polymer solutions. Stirring speed and stirrer blade design, compaction pressure and position of the stirrer were chosen to avoid artifacts. As at high speeds pitting of the disc surface occurred, experiments were carried out at 60 rev min^{-1} after initial experiments. It seemed pertinent to make *in vitro* measurements under these low agitation conditions as these approximate more closely to *in vivo* conditions.

Discs prepared under a variety of compaction pressures were examined. Results did not vary within experimental error when the applied pressure was greater than

$0.127 \mu\text{g m}^{-2}$. The discs used in these reported experiments were prepared at 0.148 kg m^{-2} , the resultant NaCl and KCl discs having void space content of 4 and 0.8% respectively.

Using the standard conditions described, six repeat experiments of NaCl gave $k = 4.52 \pm 0.13 \times 10^{-5} \text{ min}^{-1} \text{ cm}^{-2}$.* The reproducibility is $\pm 2\%$ ($P = 0.95$). Three repeat experiments with KCl gave a mean $k = 5.02 \times 10^{-5} \text{ min}^{-1} \text{ cm}^{-2}$ **.

Dissolution in the presence of polymers. The procedure for the measurement of rate constants for dissolution in the polymer solutions was identical to the procedure given above. Calibration graphs of specific conductivity vs salt concentration were prepared for each polymer at each concentration used because of the so-called "obstruction" effect, which we have discussed elsewhere (Elworthy, Florence & Rahman, 1972).

Fig. 1 shows the rate constants observed in the presence of the polymer solutions as a function of polymer concentration. At the highest concentrations of additive

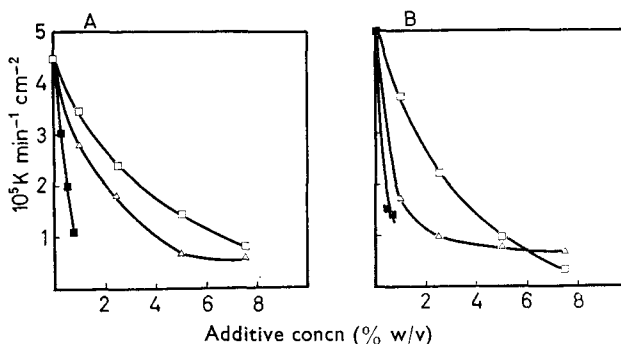


FIG. 1. Rate constant for dissolution (k , $10^5 \text{ min}^{-1} \text{ cm}^{-2}$) plotted as a function of additive concentration A, NaCl; B, KCl. Additives: \blacksquare PVP 360, 000; \triangle cetomacrogol 1000; and \square PEG 6000.

studied (7.5%) the rate constant may be decreased by a factor of 10. The solubility of the salts is not markedly affected by the presence of any of the polymers (Rahman, 1972). A maximum reduction in rate of solution of only 10% would be accounted for by this decreased solubility, according to equation 5.

Fig. 1 illustrates the additive decrease in dissolution rate constant with increasing

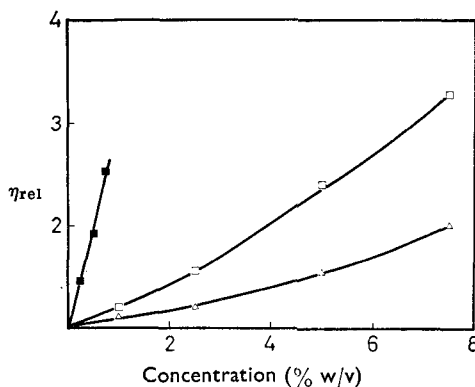


FIG. 2. Relative viscosities of \blacksquare polyvinylpyrrolidone, \square polyoxyethylene glycol 6000, and \triangle cetomacrogol 1000, as a function of concentration in water at 25° .

* $7.53 \times 10^{-3} \text{ s}^{-1} \text{ m}^{-2}$.

** $8.36 \times 10^{-3} \text{ s}^{-1} \text{ m}^{-2}$.

Table 1. Diffusion, viscosity and rate constant relations in water at 25°.

Salt	$10^6 D_0$	$10^6 D_s$	$10^4 \nu_0$	$10^4 \nu_s$	$10^6 k$	k/D_0	k/D_s	$\frac{k D_0^{1/3} \nu_0^{1/6}}{D_0}$	$\frac{k D_s^{1/3} \nu_s^{1/6}}{D_s}$
NaCl	1.610	1.59	0.8930	1.463	4.52	2.807	2.843	3.231×10^{-2}	3.536×10^{-2}
KCl	1.993	2.22	0.8930	0.8374	5.02	2.524	2.261	3.11×10^{-2}	2.849×10^{-2}

Units of $D = \text{cm}^2 \text{s}^{-1}$, data from Robinson & Stokes (1965). Units of $K \text{min}^{-1} \text{cm}^{-2}$.

$\nu = \text{Stokes}$, data from *International Critical Tables* 5; 17; 19.

The saturation values (D_s and ν_s) are extrapolated values.

concentration and hence viscosity. However, the order of effectiveness in decreasing the rate constant is $\text{PVP} > \text{CMG} > \text{PEG}$, whereas the effectiveness of increasing bulk viscosity is $\text{PVP} > \text{PEG} > \text{CMG}$. Fig. 2 shows the relative viscosity of the solutions as a function of concentration. It is obvious that no equation relating rate constant and bulk solution viscosity will explain the change in observed rate constant.

DISCUSSION

The differences in the dissolution rate constants of NaCl and KCl in water can be rationalized using Levich's equation (3) and equation (2), which suggest that

$$(k/D)(D^{1/3}\nu^{1/6}) = \text{constant} \quad \dots \quad (7)$$

if the values of diffusion coefficient and kinematic viscosity chosen are those for infinite dilution (i.e. D_0, ν_0) and not the saturation concentration values. The analysis in Table 1 shows that using the former values the rate constants for dissolution of NaCl and KCl agree to within 3.7%. Use of the saturation values leads to a divergence of about 20%. When polymer molecules are present in the bulk solution, bulk viscosity is increased and the dissolution rate falls. The dissolution rate constants in the aqueous polymer solutions cannot be explained by use of equation (7); this is not surprising as the bulk viscosity is not a true indication of the actual resistance encountered by ions and small molecules moving between the polymer chains. The dissolution rate constant is not a simple function of D as δ also depends on diffusion coefficient. Hence a simple relation between k and η_{rel} will not be found.

A satisfactory explanation of the results requires that the experimental dissolution rates in the presence of PVP, PEG and CMG of all concentrations fall on or near the same line. Fig. 3 shows the scattered nature of the experimental rate constants when

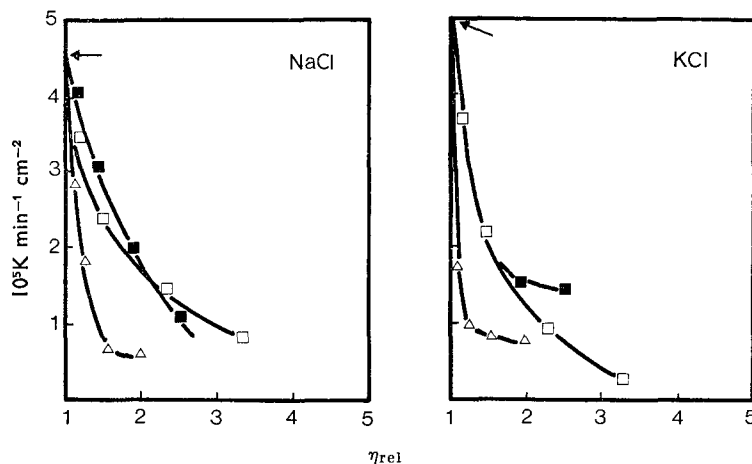


FIG. 3. Rate constants for dissolution plotted as a function of solution viscosity, relative to water (η_{rel}): ■ PVP □ PEG △ CMG.

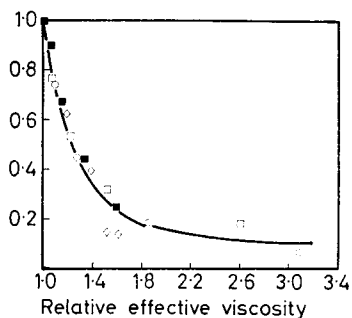


FIG. 4. Rate constants for dissolution of the two salts as a ratio of the measured value to value in absence of additive (k_{H_2O}) plotted as a function of the calculated relative effective viscosity. \square NaCl/PEG; \blacksquare NaCl/PVP; \circ KCl/PEG; \diamond NaCl/CMG.

plotted against solution viscosity (η_{rel}). However the discrepancy between the points is largely eliminated if the "effective" viscosity of the solvent (see Appendix) is used in place of bulk viscosity.

If the reduction in solution rate constant calculated as k/k_{H_2O} is plotted as a function of the effective viscosity (η_e) as in Fig. 4 a line can be drawn through most of the experimental points, although there is some scatter when the relative viscosity of the system is high. The equation of the line is

$$\frac{k}{k_{H_2O}} = c(\eta_e)^{-3.15}$$

We can provide no theoretical basis for this equation which, however, satisfactorily explains the results in 4 different polymeric systems (3 different polymer solutions) whose bulk viscosities vary widely. We conclude that at low bulk viscosity effective viscosities are more useful parameters than bulk viscosities when predicting the extent of solution retardation in solutions of large solute molecules or surfactants, although more work is required before universal applicability of the concept is claimed.

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APPENDIX

Measurement of an "effective" viscosity from diffusion data and its relation to the "microscopic" viscosity

The diffusion coefficient at infinite dilution, D , of a sphere of radius r moving in a continuum of viscosity η can be obtained from the Stokes-Einstein equation

$$D = \frac{kT}{6\pi\eta r} \quad \dots \dots \dots \quad (A1)$$

where k is Boltzmann's constant. Equation (A1) was derived on the assumption that there is no slip at the surface of the sphere. As the diffusing molecule moves with velocity v , it encounters an opposing frictional force, ζv . D is given by

$$D = \frac{kT}{\zeta} \left(1 + \frac{\partial \ln \gamma_2}{\partial \ln c_2} \right) T, P \quad \dots \dots \dots \quad (A2)$$

where γ_2 is the molar activity coefficient of the solute and c_2 is the solute molar concentration. If β is the coefficient of sliding friction between the surface of the sphere and the medium (Stokes, 1903)

$$\zeta = 6\pi\eta r \frac{\beta r + 2}{\beta r + 3} \quad \dots \dots \dots \quad (A3)$$

$\zeta = 4\pi\eta r$ when $\beta \rightarrow 0$ and $\zeta = 6\pi\eta r$ when $\beta \rightarrow \infty$. Hence equation (A1) is more correctly written as

$$D = \frac{kT}{n\pi\eta r} \quad \dots \dots \dots \quad (A4)$$

where $4 \leq n \leq 6$. For small molecules moving in a molecular medium, n varies with r , and is almost invariably less than 6 (Edward, 1970) at viscosities up to 1cP (10^{-3}N m^{-2}). If there is no change in n with bulk viscosity, and if $\partial \ln \gamma_2 / \partial \ln c_2$ is identical in the presence and absence of additive, then the ratio of diffusion coefficients of a solute in water and in an aqueous non-electrolyte solution should give an "effective" viscosity relative to water (η_e) i.e.

$$\frac{D_0}{D} = \frac{n\pi\eta r}{n_0\pi\eta_0 r_0} = \frac{\eta}{\eta_0} = \eta_e \quad \dots \dots \dots \quad (A5)$$

provided that $r = r_0$. Nishijima & Oster (1956) have previously suggested this approach. Values for the diffusion coefficients of NaCl and KCl in water and in solutions of polyvinylpyrrolidone, polyoxyethylene glycol and cetomacrogol 1000 are shown in Table A1. The ratios D_0/D or η_e are calculated and bulk relative viscosities are quoted in Table A1 for comparison.

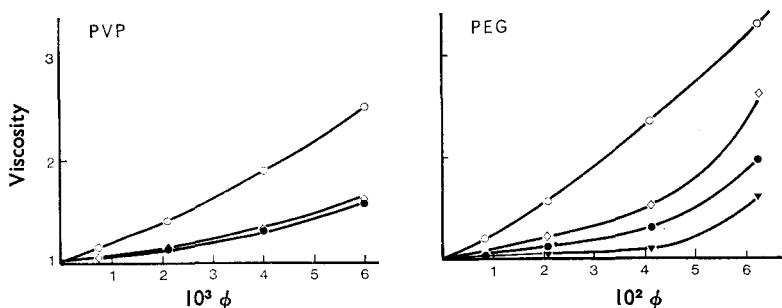


FIG. A1. Relation of the various relative viscosities to volume fraction of additive (ϕ). Note the lower concentrations of additive in the PVP systems. Top line in both diagrams (\circ) is measured bulk relative viscosity of the system; effective viscosities are shown thus: \diamond ; and microscopic viscosities calculated with the aid of Mackie and Meares' tortuosity factor are shown by \bullet ; in the PEG system \blacktriangledown denotes microscopic viscosities obtained using hydrated volume fractions in calculation of P , the tortuosity factor.

The microscopic viscosity

The microscopic viscosity (η^*) is the viscosity of the surroundings in which the ions move. η^* differs from η_e (both calculated relative to water) because of the increased path length for

Table A1. Measured diffusion coefficients of NaCl and KCl in polymer solutions and calculated values of effective and microscopic viscosities.

Salt	Additive	$10^3\phi^a$	10^9D^b	η_{rel}	η_e	η^{*c}	η^{*d}
NaCl	—	—	1.47	1.00	1.00	1.00	1.00
NaCl	PEG 6000	0.83 ₅	1.38	1.19	1.06 ₈	1.03	0.99
		2.09	1.20	1.55	1.22	1.13	1.04
		4.17 ₅	0.96 ₈	2.30	1.52	1.28	1.08 ₅
		6.26	0.56 ₈	3.28	2.60	1.95	1.57
NaCl	PVP-360	0.08	1.38	1.16	1.06 ₈	1.06	1.06
		0.20	1.28	1.41	1.15	1.14	1.13
		0.40	1.10	1.92	1.34	1.31	1.28
		0.60	0.92	2.52	1.59	1.56	1.52
NaCl	CMG	0.92	1.24	1.08	1.19		
		2.29	1.06	1.18	1.39		
		4.54	0.98	1.60	1.52		
		6.84	0.92	2.03	1.60		
KCl	—	—	1.85	1.00	1.00	1.00	1.00
KCl	PEG 6000	0.83 ₅	1.68	1.19	1.10	1.06	1.03
		2.09	1.45	1.55	1.27 ₅	1.17	1.08
		4.17 ₅	0.99	2.30	1.85 ₅	1.57	1.33
		6.26	0.60	3.28	3.06	2.37	1.85

a. ϕ calculated from measured density values.

b. $m^{+2} s^{-1}$. Each value of D is a mean of at least 2 determinations. Values in water are mean of at least 3 determinations. For NaCl e.g. (i) 1.471×10^{-9} ; (ii) 1.468×10^{-9} ; (iii) 1.471×10^{-9} ($m^2 s^{-1}$).

c. With P calculated using volume fraction of unhydrated additive molecule.

d. With P calculated using hydrated volume fraction, $\omega = 1 g g^{-1}$ polymer.

diffusion in a heterogeneous medium and the resultant decreased concentration gradient (Meares, 1968). According to Mackie & Meares (1955), the path length P relative to that in water is

$$P = \frac{1 + \phi}{1 - \phi} \quad \dots \dots \dots (A6)$$

where ϕ is the volume fraction of the obstructions.

The diffusion coefficient in the microscopic environment (D^*) is thus related to the experimentally determined coefficient D_{exptl} by

$$D^* = D_{exptl} \left(\frac{1 + \phi}{1 - \phi} \right)^2 \quad \dots \dots \dots (A7)$$

Hence

$$\eta^* = \eta_e \left(\frac{1 - \phi}{1 + \phi} \right)^2 \quad \dots \dots \dots (A8)$$

If the water hydrating the polymer is considered to be inaccessible to the moving ions i.e. to be playing no part in the transport of the ion the volume fraction of the polymer should allow for the hydrating water. Results are presented for the microscopic viscosity calculated in this way in Table A1 and shown graphically in Fig. A1 for PVP and PEG. In the former the use of hydrated volume fractions has little influence on the results, because of the low volume fractions used.

Komiyama & Fuoss (1972) have recently obtained similar estimates of the internal viscosity of poly(vinyl alcohol) solutions from conductance measurements.

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