Effects of Polyelectrolytes on Drug Transport I: Diffusion

K. F. FARNG and K. G. NELSON▲

Abstract □ The capillary method was used to determine the diffusive transport properties of radioactive salicylate ion in the presence of a commonly used polyelectrolyte, sodium carboxymethylcellulose. In a solution of this polymer, the self-diffusion coefficient of salicylate was found to decrease only moderately, even though the bulk macroscopic viscosity increased about two to three orders of magnitude. These data were evaluated with two theories from the literature. The tracer drug release rate out of the polymer solutions was also studied and was more rapid than if the polymer were not present. Increases of up to 40% were observed.

Keyphrases □ Diffusion properties, radiolabeled salicylate as co-ion in sodium carboxymethylcellulose—determined using capillary method □ Carboxymethylcellulose, sodium—effect on co-ion diffusion of radiolabeled salicylate, capillary method □ Salicylate, radiolabeled, diffusion coefficient and tracer release rate in sodium carboxymethylcellulose—determined using capillary method, co-ion effect □ Polyelectrolytes—effect of carboxymethylcellulose on salicylate co-ion diffusion □ Drug transport—effect of carboxymethylcellulose on salicylate co-ion diffusion

Hydrophilic polymers that are commonly added to pharmaceutical preparations can influence the transport properties of the system and, hence, the rate of drug absorption. Levy and Jusko (1) demonstrated that the increase in viscosity due to methylcellulose decreased the absorption rate of ethanol and salicylic acid in rats. Other investigators (2, 3) also reported similar viscosity–absorption effects.

The most widely known relationship between diffusive transport and viscosity is the Stokes–Einstein equation. This equation is based partly on the movement of a spherical solute through a continuous medium. With high molecular weight polymer solutions, however, the physical conditions are somewhat different. The relatively low concentration of polymer imparts a substantial increase in the bulk or "macroscopic" viscosity. The microscopic environment of a diffusion species, however, is largely solvent, and only infrequently does the diffusant encounter a polymer segment along its diffusion path. Thus, the Stokes–Einstein equation would not be expected to hold for diffusion in dilute polymer solutions.

Reports have appeared involving studies of diffusion in dilute polymer solutions. Florence *et al.* (4) measured the diffusion coefficients of sodium chloride and potassium chloride in aqueous solutions of polyethylene oxide (polyethylene glycol) and polyvinylpyrrolidone. Using these diffusion coefficients and the Stokes–Einstein equation, they calculated the "effective" or "microscopic" viscosities. These values were smaller than the corresponding relative bulk viscosities. Block and Lamy (5) also observed a difference between the bulk viscosity and that apparently experienced by a diffusant. Li and Gainer (6), working with organic solvents, developed equations relating the diffusivity in these systems to such parameters as heat of mixing, viscosity, and diffusivity (in the pure solvent). Taking another approach, Wang (7) developed an equation for the self-diffusion of water in protein solutions based on the physical obstruction by the protein and the hydration effect.

The self-diffusion of the counterion in dilute polyelectrolyte solutions was studied by Huizenga *et al.* (8) and Pefferkorn and Varoqui (9). They found that diffusion coefficients decrease as the degree of neutralization increases. Rinando *et al.* (10) also found that diffusivity decreases as the degree of substitution on carboxymethylcellulose increases. These results were explained in terms of electrostatic effects of the polyelectrolyte on the counterion.

The use of polyelectrolytes to enhance the absorption of drugs that are co-ions of the polymer was suggested by Higuchi *et al.* (11). The experimentally observed increased transport rate was attributed to the Donnan membrane effect. Diffusion properties in the solution were not considered.

The present studies were undertaken to determine the diffusional properties of drugs that are present as co-ions in polyelectrolyte solutions and the characteristics of their transport out of these solutions across a cellophane membrane. This article reports the results of the diffusion studies.

EXPERIMENTAL

The capillary method (12) was employed to determine the diffusion coefficient of salicylate in a solution of sodium carboxymethylcellulose. Briefly, this method is based on the diffusion of a radioactive tracer out of a capillary tube into a tracer sink, which has the

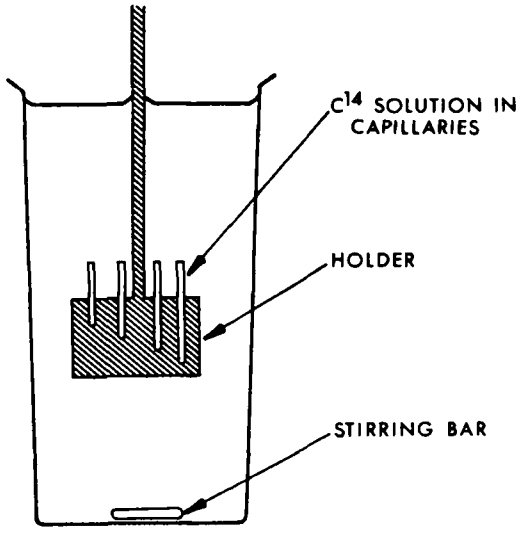

Figure 1—*A set of four capillaries in a tall beaker containing 250 ml. sink solution stirred by magnetic bar.*

Table I—Diffusion Coefficients of Salicylate (8 m*M*) in Sodium Carboxymethylcellulose Solutions (w/v %) and in Sodium Fluoride (1 *M*) at 37°, (Average ± *SD*) × 10^5 cm.²/sec.

Medium		Concentration					
		0.5	0.75	1.25	1.5	2.0	2.5
Sodium carboxymethylcellulose (7MXF)	D[a]	1.10 ± 0.04	1.07 ± 0.04	1.12 ± 0.01	1.03 ± 0.04	1.09 ± 0.08	1.09 ± 0.09
	D'[b]	1.35 ± 0.02	1.35 ± 0.01	1.39 ± 0.02	1.44 ± 0.05	1.55 ± 0.01	1.55 ± 0.02
		0.5	0.75	1.0	1.25	1.5	2.0
Sodium carboxymethylcellulose (7M27SF)	D	1.11 ± 0.01	1.08 ± 0.06	1.11 ± 0.02	1.06 ± 0.03	1.09 ± 0.04	1.04 ± 0.08
	D'	1.33 ± 0.03	1.32 ± 0.06	1.42 ± 0.03	1.35 ± 0.05	1.42 ± 0.07	1.42 ± 0.02
		0.5	0.85	1.25	1.5	2.0	2.5
Sodium carboxymethylcellulose (12M8P)	D	1.04 ± 0.07	0.98 ± 0.03	1.03 ± 0.05	1.03 ± 0.09	1.01 ± 0.06	0.99 ± 0.04
	D'	1.23 ± 0.04	1.29 ± 0.06	1.42 ± 0.05	1.47 ± 0.06	1.48 + 0.01	1.48 ± 0.07
		1.0	2.0	3.0	4.0	5.0	6.0
Sodium carboxymethylcellulose (7LXF)	D	1.08 ± 0.06	1.03 ± 0.02	1.00 ± 0.03	0.94 ± 0.05	0.91 ± 0.03	0.86 ± 0.05
	D'	1.32 ± 0.03	1.42 ± 0.03	1.46 ± 0.03	1.49 ± 0.07	1.45 ± 0.02	1.27 ± 0.04
		0.01	0.02	0.04	0.1	0.2	0.4
Sodium fluoride	D	1.08 ± 0.03	1.18 ± 0.04	1.18 ± 0.04	1.15 ± 0.03	1.12 ± 0.03	1.09 ± 0.01
	D'	1.09 ± 0.06	1.18 ± 0.04	1.13 ± 0.02	1.17 ± 0.04	1.12 ± 0.12	1.11 ± 0.02

[a] Self-diffusion coefficient (see Case A in text). [b] Apparent diffusion coefficient (see Case B in text).

same chemical composition as the solution inside the capillary. The solution to Fick's second law corresponding to these boundary conditions is:

$$\frac{C}{C_0} = \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} \exp\left[-(2n+1)^2 \pi^2 \frac{Dt}{4l^2}\right] \quad \text{(Eq. 1)}$$

where C_0 and C are the tracer activities in the capillary initially and at time t (seconds), l is the length of the capillary in centimeters, and D is the self-diffusion coefficient in square centimeters per second. Four capillaries were used for each run; they had an inside diameter of 0.5 mm. and nominal lengths of 2.4, 2.7, 3.1, and 3.5 cm. The accurate length of each capillary was determined with a projection device[1], and the volume was calculated from the weight of mercury required to fill the capillary at a known temperature. The capillary holder was so constructed that each opening of the set of four capillaries was at about the same level below the surface in a 250-ml. tall beaker, which held the sink solution (Fig. 1). The effect of stirring at 100 r.p.m. on the diffusion path length was negligible (13, 14).

Sodium salicylate[2] solutions (8 m*M*) were prepared containing the appropriate amount of sodium carboxymethylcellulose[3]. An appropriate amount of neutralized ^{14}C-salicylic acid[4] was added to about 0.3 ml. of the solution to yield an initial activity of about 5000 counts/min./μl. The tracer solution was degassed and then put into the capillary with a 33-gauge needle. The precaution about temperature equilibrium and immersing effects was followed as suggested by Wang (13). After 96–120 hr. of diffusion, the remaining activity in each capillary was washed into a counting vial with water (0.2 0.3 ml.) from a syringe. Most of the water in the vial was evaporated by heating in an oven to increase the counting efficiency. The radioactivity was obtained using the standard preset ^{14}C window opening[5]. The external standard ratio-efficiency curve was constructed to correct the quenching effect; background was also corrected. The range of C/C_0 was about 0.1–0.4. The diffusion coefficients were calculated from Eq. 1, and the average values and standard deviations are listed in Table I.

RESULTS AND DISCUSSION

The effect of sodium carboxymethylcellulose on salicylate diffusion was studied in two cases: Case A, polymer was both inside and outside of the capillary; and Case B, polymer was inside the capillary only. In both cases, the initial sodium salicylate concentration of 8 m*M* was the same inside and outside the capillary; *i.e.*, there was no salicylate concentration difference. The diffusion coefficient D obtained in Case A is the true self-diffusion coefficient since there is no chemical potential gradient at the capillary opening. The diffusion coefficient obtained in Case B is not the true self-diffusion coefficient, even though it was evaluated through Eq. 1, because there is a polyelectrolyte concentration gradient at the boundary.

Case A: Self-Diffusion—The relative viscosity of bulk solution deduced from the manufacturer's data booklet (15) is listed in Table II. It is apparent that the Stokes–Einstein equation does not hold since the relative viscosity increases over 1000-fold while the diffusion coefficient decreases less than 10% (Table I).

Mackie and Meares (16) proposed the following equation to calculate the mobility of an ion, U, in a polymer matrix:

$$U = U_0 \left(\frac{1 - V_p}{1 + V_p}\right)^2 \quad \text{(Eq. 2)}$$

where U_0 is the mobility of the ion in water, and V_p is the volume fraction of polymer. Since the diffusion coefficient, D, is proportional to U, one can write (4):

$$D = D_0 \left(\frac{1 - V_p}{1 + V_p}\right)^2 \quad \text{(Eq. 3)}$$

Since the density of a 2% carboxymethylcellulose solution at 25° is 1.0068 g./cm.³ (15), assuming weight to volume concentration equal to volume to volume concentration, the diffusivity in the polymer solutions can be calculated with Eq. 3 if D_0 is known. The experimental value of the diffusion coefficient for salicylate (8 m*M*) in water at 37° was found to be 1.11 × 10^{-5} cm.²/sec. Others have reported values of 1.00 × 10^{-5} (17), 1.33 × 10^{-5} (18), and 0.925 × 10^{-5} cm.²/sec. (19), all determined under somewhat different experimental conditions. The experimentally determined diffusivities, shown as the ratio D/D_0, are given in Fig. 2 (Case A). The line generated from Eq. 3 is included and it can be seen that the agreement is rather good.

Taking a somewhat different approach, Wang (7) developed an equation for self-diffusion of water in a protein solution. Neglecting the hydration effect, *i.e.*, the association between polymer and diffusant, the proposed equation is:

$$D = D_0(1 - \alpha V_p) \quad \text{(Eq. 4)}$$

where α is the shape factor of protein. This equation predicts a linear dependence of D on the volume fraction. At low values of volume fraction, *i.e.*, in the range of the present study, it can be shown that Eq. 3 reduces to:

$$D = D_0(1 - 4V_p) \quad \text{(Eq. 5)}$$

Thus, at low concentrations of polymer, Eqs. 3 and 4 have the same functional relationship. The current data thus appear to obey either equation because of the low polymer concentration.

Data from the literature are available to evaluate these two equations further. By using two sets of diffusion coefficients reported by Florence *et al.* (4), one set given by Wang (7), and the set deter-

[1] Shadowgraph, Nippon Kogaku K. K. Japan.
[2] Sodium salicylate analytical reagent, Mallinckrodt Chemical Works, St. Louis, Mo.
[3] Cellulose gum, various types, Hercules Inc., Wilmington, Del.
[4] ^{14}C-Salicylic acid, Amersham/Searle Corp., Arlington Heights, Ill.
[5] Liquid scintillation system, LS-100, Beckman, Fullerton, Calif.

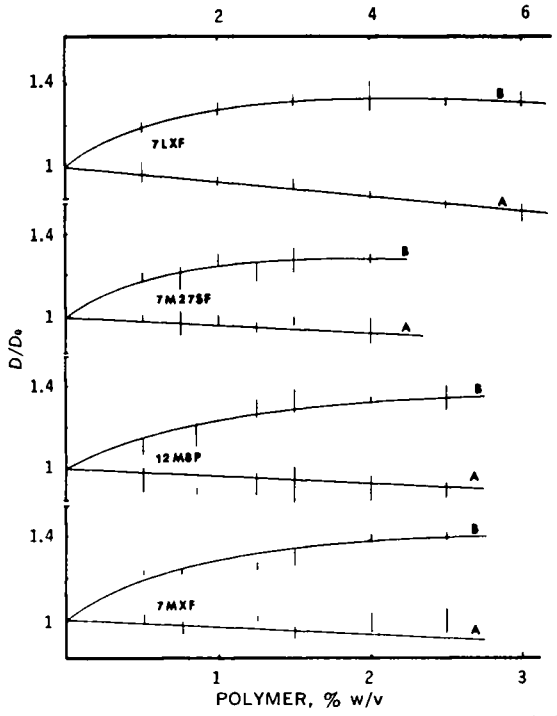

Figure 2—D/D_0 *of sodium salicylate* versus *concentration (w/v %) of sodium carboxymethylcellulose of various types: 7MXF, 12M8P, 7M27SF, and 7LXF. Upper scale is for 7LXF only. Case A = self-diffusion in polymer solution; Case B = diffusion* out of *polymer solution.*

mined for sodium carboxymethylcellulose (7LXF) in this work, the equations can be tested for higher concentrations of polymer. With these diffusion coefficients, V_p was calculated from Eq. 3 and plotted against polymer concentration (Fig. 3). By assuming the actual volume fraction of polymer to be directly proportional to the polymer concentration, if Eq. 3 is the correct equation, Fig. 3 should display linear relationships. It can be seen, however, that all data display positive curvature.

A similar test can be made for Eq. 4. Because of the constant factor α, the quantity αV_p calculated from Eq. 4 is plotted against polymer concentration (Fig. 4). Again, if the equation truly describes the phenomenon, this plot should be linear. It can be seen that Fig. 4 displays much better linear relationships than Fig. 3.

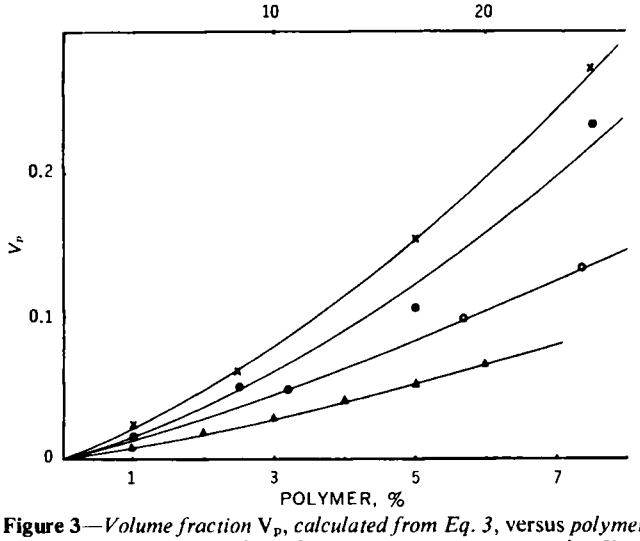

Figure 3—*Volume fraction* V_p, *calculated from Eq. 3,* versus *polymer concentration. Upper scale is for water-protein system only. Key:* ●, *sodium chloride-polyethylene glycol 6000* (Reference 4); ×, *potassium chloride-polyethylene glycol 6000* (Reference 4); ○, *water-protein* (Reference 7); *and* △, *sodium salicylate-sodium carboxymethylcellulose 7LXF (this work).*

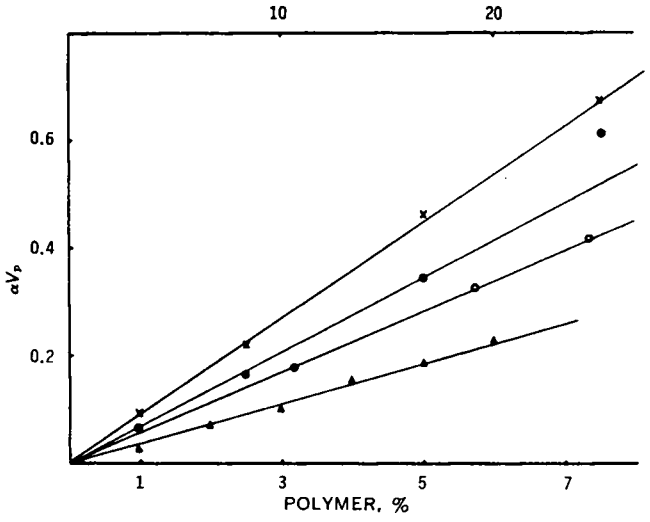

Figure 4—αV_p, *calculated from Eq. 4,* versus *polymer concentration. Upper scale is for water-protein system only. Key:* ●, *sodium chloride-polyethylene glycol 6000* (Reference 4); ×, *potassium chloride-polyethylene glycol 6000* (Reference 4); ○, *water-protein* (Reference 7); *and* △, *sodium salicylate-sodium carboxymethylcellulose 7LXF (this work).*

Therefore, Eq. 4 appears to be a better representation for the experimental data at higher polymer concentrations.

A practical consideration based on this information is that the diffusive transport of a drug in a dilute polymer solution is dependent on αV_p. One can define $\overline{\alpha V_p}$ as the value of αV_p per unit concentration, so $\overline{\alpha V_p}$ can be evaluated experimentally. The slopes of the lines in Fig. 4 were $\overline{\alpha V_p}$ in units of volume fraction per percent. Their values are listed along with the standard errors in Table III, and these factors are different for different polymers. A polymer having a relatively large $\overline{\alpha V_p}$ decreases diffusive transport more than one having a small $\overline{\alpha V_p}$. This factor $\overline{\alpha V_p}$ may be a more useful term than viscosity to characterize a polymer relative to its effect on the diffusive properties of small molecules in dilute solutions of the polymer.

Case B—To study further the effect of the polyelectrolyte on the diffusive transport of a drug as co-ion of the polymer, release rates *out of* the polyelectrolyte solutions were determined. Experiments similar to those of Case A were performed, except that the polyelectrolyte was present only inside the capillary and not in the sink. Thus, the diffusion coefficient calculated from the data by Eq. 1 is not the true self-diffusion coefficient because of the existence of a polyelectrolyte gradient at the boundary. However, the calculated apparent diffusion coefficient, D', does give an indication of the polyelectrolyte effect on the co-ion transport. The D' values are reported in Table I and, for comparison with Case A, the results are presented in Fig. 2 (Case B) as a ratio of D' to D_0. It can be seen that the radioactive salicylate ion is released faster than in Case A.

The polymer contains a net ionic charge, although it does not correspond exactly to the degree of substitution. These concentrated charges create a rather strong electric field which influences the distribution of ions around the polymer. Since the polyelectrolyte is present inside the capillary only, the electrochemical potential of the co-ion is changed relative to that outside the capillary. In addition to the Brownian diffusive transport, this electric field gradient gives another driving force for the salicylate transport. This additional driving force increases the apparent diffusion coefficient.

The increase in D' may also arise from other sources. The polymer diffusion out of the capillary may carry with it some salicylate ion. However, this probably would be small because the diffusion coefficient of a high molecular weight polymer is relatively small. Also, the osmotic pressure arising from the polyelectrolyte may induce water to flow into the capillary, forcing out the salicylate ion. Experiments were performed using the strong electrolyte sodium fluoride in place of the polyelectrolyte to establish an osmotic pressure difference. Using sodium fluoride up to a concentration of 0.4 M inside the capillary did not change D' significantly from D,

Table II—Relative Viscosity of Various Types of Sodium Carboxymethylcellulose Solutions (15)

Type of Polymer	Degree of Substitution	Concentration (% by Weight) 1.0	1.5	2.0	2.5	3.0	4.0	5.0	6.0
7MXF, 12M8P	0.7, 1.2	50	1.8×10^2	4.5×10^2	1.2×10^3	—	—	—	—
7M27SF	0.7	1.6×10^2	6×10^2	1.5×10^3	3×10^3	—	—	—	—
7LXF	0.7	11	—	20	—	1×10^2	3×10^2	8×10^2	2×10^3

Table III—Factor $\overline{\alpha V_p}$ for Various Polymer Systems

Polymer System	$(\overline{\alpha V_p} \pm SE) \times 10^2$, Volume Fraction/%	Reference
Sodium chloride–polyethylene glycol 6000	8.31 ± 0.73	4
Potassium chloride–polyethylene glycol 6000	9.08 ± 0.20	4
Sodium chloride–polyvinylpyrrolidone	48.1 ± 0.42	4
Water–protein	1.73 ± 0.03	7
Sodium salicylate–sodium carboxymethylcellulose (7LXF)	3.80 ± 0.12	This work

which was determined with sodium fluoride present both inside the capillary and the sink (Table I). Therefore, it can be inferred that the osmotic effect of the polymer is negligible.

From a practical point of view, the release rate of a medication from a preparation is an important factor to be considered by the formulator. The present work shows that high molecular weight polymers commonly used to increase the viscosity in liquid preparations decrease the diffusion of drugs *within* the solution only slightly (Eq. 4). Also, if the drug is present as a co-ion of the polyelectrolyte, it will be transported *out of* the polymer solution faster than if the polymer were not present. Increases of up to 40% were observed (Fig. 2).

The use of polyelectrolytes to enhance drug absorption was suggested by Higuchi *et al.* (11) nearly 2 decades ago. The present work substantiates this proposal by means of a different experimental approach and sheds light on the diffusive transport properties of small molecules in these dilute polymer solutions.

For sodium carboxymethylcellulose (degree of substitution 0.7), the release of co-ion increases as the concentration of polyelectrolyte increases initially and then levels off at about 2–3% (w/v), regardless of the molecular weight of sodium carboxymethylcellulose. Thus, when using this polyelectrolyte, the viscosity needed determines the molecular weight of the polymer, whereas the optimum polymer concentration for the drug release is in the range of 2–3%.

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▲ To whom inquiries should be directed.