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DISSOLUTION KINETICS OF HYDROCORTISONE INTO DILUTE POLYMER SOLUTIONS

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ABSTRACT

Dissolution rates for hydrocortisone alcohol were determined using a stationary disk/rotating fluid system, with dilute concentrations of polymers present in the dissolution media. Independent measurements of drug solubility, drug diffusion coefficient, and viscosity were made. Drug diffusion coefficients were found to decrease with increasing bulk viscosity, although the product of the diffusion coeffecient and kinematic viscosity was found not to be constant.

The polymers studied are commonly used in steroid otic/ophthalmic or rectal suspension formulations, and were

found to measurably decrease the dissolution rate of hydrocortisone relative to its rate in water. For most polymer systems studied, the decrease in dissolution rate was comparable to a solution of sucrose having similar bulk kinematic viscosity. Dissolution rates were analyzed using an equation which relates the drug dissolution rate with drug solubility, drug diffusion coefficient, bulk kinematic viscosity, and stirring rate. All systems having sucrose or hydroxypropyl methyl cellulose, and polyvinyl pyrrolidone were well represented by this relationship, while the system having the polyethylene oxide was less well characterized. From this analysis, it is suggested that bulk viscosity effects are primarily communicated to the dissolution process through decreased diffusivity.

INTRODUCTION

One of the major concerns of clinical and pharmaceutical investigators during the last decade has been the evaluation of the relative therapeutic effectiveness of drug products (1). The problem of bioinequivalence is of potential importance in steroidal suspensions because of the extremely low solubility of the drug and the addition of stabilizing agents, such as polymers, to the formulation.

Studies of the effect of polymers on the transport properties of drugs appear in the pharmaceutical, chemical and chemical engineering literature (2-11). It is

significant that most of the studies demonstrate substantial effects of commonly used polymers on the diffusion coefficient and dissolution rate of drugs. One of the primary objectives of this research was to evaluate the effect of commonly used polymers on the dissolution rate of a relatively insoluble steroid via independent experimental determination of physicochemical parameters, such as the solubility and diffusion coefficient of drugs in dilute polymeric media, and the density and viscosity of these media. Low concentrations of polymers, similar to those found in steroid suspension formulations, were selected and utilized.

The dissolution apparatus used in this study was the stationary disk/rotating fluid device. This dissolution device is economical, relatively simple, convenient to operate and flexible for use under a variety of test conditions(12).

BACKGROUND

The effect of polymers on the transport properties of drugs or chemicals has been generally found to decrease the dissolution rate of drugs (2-11). Whereas most of the studies lack a mechanistic evaluation of the effects of polymers on the dissolution rate, several different mechanisms have been proposed. Howard et al. (3,4) found that commonly used polymers such as carboxymethyl cellulose

and hydroxypropyl methyl cellulose may decrease the dissolution rate of prednisolone acetate suspensions. It was shown that these polymers acted by altering particle size distribution, and possibly by serving as a diffusion barrier.

Recently, Nelson and Shah (5) evaluated the influence of fluid flow and viscosity on the dissolution rate of ethyl-p-aminobenzoate using a specially designed cell. The dissolution rate was found to be relatively unchanged under fixed flow conditions as the viscosity of aqueous solutions of hydroxypropyl cellulose increased. This finding was attributed to the relationship between fluid flow and the rate of shear using a laminar flow cell as a dissolution device.

Several empirical equations, which show the dissolution rate to be a function of the viscosity, have been proposed (7). The influence of viscosity of polymeric solutions on the dissolution rate of soluble inorganic salts was studied (8). Sarisuta and Parrott (9) studied the influence of viscosity on the dissolution rate of benzoic acid in aqueous solution of methylcellulose, hydroxypropyl cellulose, and guar gum. They proposed an equation which related the dissolution rate of benzoic acid to solubility, diffusion coefficient and viscosity. The equation included electrical effects in the case of an ionizable polymer. Other factors, such as the dependence of the dissolution rate on the radius

of the dissolving tablet, the stirring rate, flow patterns and the hydrodynamics of the dissolution testing system were not taken into consideration. In a recent study, Bogardus (10) investigated the effect of viscosity on the dissolution rate of cholesterol. He indicated that there is a marked effect of viscosity on the decrease of the dissolution rate of drugs.

Hansford and Litt (11) studied the dissolution rate of benzoic acid and naphthol from rotating disks into highly concentrated non-Newtonian solutions of carboxymethyl cellulose and polyethylene oxide. Mass transfer expressions were developed based on the convective theory and the hydrodynamics of the system.

It is significant that the studies cited above demonstrate real effects of commonly used polymers on the diffusion coefficient and dissolution rate of drugs. One objective for this study was to evaluate the effect of dilute solutions of polymers on the dissolution rate of a drug having limited solubility, such as hydrocortisone. The polymers tested are commonly used as viscosity inducing agents in otic/ophthalmic and rectal suspension formulations. Another objective was to relate the dissolution rates to bulk kinematic viscosity, υ, drug diffusion coefficient, D, drug solubility, Cs, and stirring rate, ω.

MATERIALS AND METHODS

Preparation of Tablets for the Dissolution Studies:

Hydrocortisone tablets (The Upjohn Company, Kalamazoo, Michigan, Lot #471JR) were made in the following manner. Two hundred mg of the powder was weighed and transferred to a stainless steel die having an 0.55 cm radius. A flat plate was used as a lower punch so that the tablet surface was flush with the die surface. The powder was compressed at 600 Kg pressure for twenty seconds using a Carver laboratory press (Carver Laboratory Press, Model K, Fred S. Carver, Inc., Hydraulic Equipment, Summit, New Jersey). The tablet was visually inspected to confirm that the tablet surface was flush with the surface of the die and free from lamination and capping.

All tablets were made twenty four hours prior to the dissolution run, and kept under a clean inverted 25 ml beaker until the time of the run. This procedure ensured the consistency of the tablets and was found to improve the reproducibility of the dissolution data.

Polymer Solution Preparation

Table 1 gives a list of the different polymers and the concentrations of the polymer solutions used in this study. Glass distilled water was used as a solvent.

Since the polymer solutions used in this study were all very dilute, the Ubbelohde capillary viscometer was chosen

for the viscosity determinations, due to its sensitivity to low viscosity solutions. All viscosity measurements were done at twenty five degrees Centigrade, and glass distilled water was used to calibrate the viscometer.

Dissolution Testing

a. Apparatus

The dissolution apparatus used in this study was previously described (12). It consists of a 200 ml jacketed flask, with two side openings that facilitate sample withdrawal and replacement. Samples were withdrawn and replaced by the use of the two separate three ml pipettes. The tablet die was introduced into the dissolution medium through the neck opening of the flask. The contents of the flask were maintained at twenty five degrees Centigrade by the use of a circulatory water bath (Messgerate-Werk Lauda, West Germany, type RM35) and stirring was achieved by the use of a magnetic stirrer (Nuova II Stirrer, Sybron) and a magnetic stir bar. Care was taken to place the dissolution flask on the magnetic stirrer in exactly the same position for every dissolution run in order to maintain consistency and reproducibility among runs. The 3 cm stir bar used had a smooth surface and was especially designed to provide smooth, consistent stirring. A strobe lamp (Grass Medical Instruments Co., Quincy, Massachusetts) was used to calibrate

stirring speeds, and the speeds were checked from time to time by using a strobe light.

b. Dissolution Testing Procedure for Hydrocortisone Tablets

Prior to dissolution testing, tablet surfaces were pre-wetted for two minutes in a separate flask containing glass distilled water held at twenty five degrees Centigrade. This conditioning procedures was necessary to minimize tablet flaws such as rough edges. This step also ensured the dissolution of any loose powder on the surface of the tablet or die prior to dissolution testing. It also helped to prevent air bubble formation on the tablet surface during the dissolution study. The tablet surface was then allowed to air dry for five minutes. Pre-wetting tablets prior to dissolution testing was found to improve the reproducibility of the dissolution rates.

The tablet was kept in the die, and mounted directly on a glass holder. The dissolution run was started by gently lowering the tablet and holding it four cm above the bottom of the dissolution flask which contained 180 ml of glass distilled water, maintained at twenty five degrees Centigrade by the use of a circulatory water bath and stirred by a magnetic stirrer and a magnetic stir bar. Care was taken to place the tablet accurately in the same position inside the dissolution flask for every dissolution run. The surface of

the tablet was checked to ensure that no air bubbles formed on the tablet surface throughout the experiment.

A concentration jump technique (13) was used in order to avoid tablet to tablet variation. An initial dissolution rate in glass distilled water was determined by withdrawing 3 ml samples at five minute intervals for the first thirty minutes. Each volume of sample removed was immediately replaced by an equal volume of fresh solvent kept at twenty five degrees Centigrade. After the first thirty minutes of the dissolution run, 50 ml of the solvent were withdrawn using a syringe fitted with a long needle and 50 ml of the polymer solution were immediately added to the dissolution flask, the final concentration is that shown in Table 1. Since the volume withdrawn at any one time did not exceed 50 ml, the tablet surface was never exposed to air after the dissolution was started.

Tablet preparation provided a smooth surface for dissolution. Observation of tablet surfaced before and after a dissolution run showed no signs of erosion or striations indicative of stirring-induced stress on the surface.

Preliminary dissolution experiments showed that the data obtained in the first sixty minutes of the dissolution run was adequate to represent the dissolution rate of flat faced tablets using the dissolution apparatus described in this study. Three ml samples were withdrawn every five minutes

TABLE 1

POLYMER SOLUTIONS

Polymer	Concentration of Solution % W/V
1. HPMC[a]	0.1%
2. HPMC	0.2%
3. HPMC	0.5%
4. PVP[b]	0.2%
5. PEO[c]	0.15%
6. Sucrose[d]	18.0%
7. HPMC[e]	0.2%

a. Hydroxypropyl Methyl Cellulose, Methocel 60 HG, 50 CPS, Dow Chemicals Lot #QP-262324A.

b. Polyvinyl Pyrrolidone, Fisher Scientific Company (ave M.W. 40,000)

c. Polyethylene Oxide, Polyox WSR 205.

d. Sucrose, Fisher Scientific Company, Lot #765399.

e. Hydroxypropyl Methyl Cellulose, Methocel E4M Premium, Dow Chemical, Lot #QP-1061504.

for thirty minutes after the addition of the polymer solution. All samples were immediately assayed on the Perkin Elmer Hitachi (Double Beam, Coleman 124 Hitachi Ltd., Tokyo, Japan) spectrophotometer at 248 nm. and the absorbances were converted into concentration units by using a standard curve. Polymer content did not contribute to the absorbance values of the hydrocortisone alcohol at 248 nm. The volume of samples withdrawn was noted and subsequently taken into consideration when calculating the total amount

dissolved. The dissolution curves were subsequently corrected for the cumulative amount of the drug lost through sampling. The dissolution rate was obtained from the slope of the cumulative amount of drug dissolved versus time curves.

The temperature of the dissolution medium was intermittently checked using a laboratory thermometer and was found to be 25° ± 0.2 degrees Centigrade. After the dissolution run was completed, the tablet was visually inspected for capping or erosion. The tablet and dissolution medium were then discarded and fresh tablets and polymer solutions used for every run.

c. Diffusion Coefficient Determination

Diffusion coefficients were determined using a non-steady state method described by Fawcett and Caton (14) and characterized for pharmaceutical solutes by Stout et al. (15).

d. Equilibrium Solubility Studies

Equilibrium solubility values were determined at 25 degrees Centigrade using the method described by Paruta et al. (16).

RESULTS AND DISCUSSIONS

Basic objectives for this study included the evaluation of the effect of commonly used polymers on the dissolution rate of steroids in a hydrodynamically controlled system. A

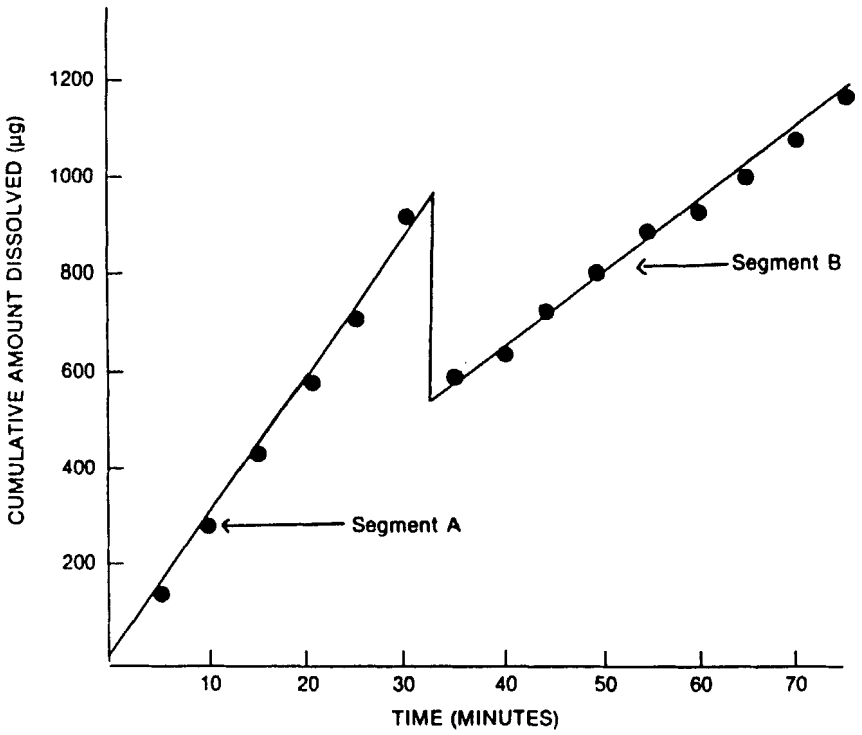

Figure 1: Dissolution Profile for Hydrocortisone Using Concentration Jump Technique (Segment A, Pure Water; Segment B, 0.5% HPMC)

variety of dilute polymer solutions were utilized. Physicochemical properties of the drug in each polymer dissolution medium were independently determined.

A representative dissolution profile of hydrocortisone alcohol into dilute polymer solutions, in this case hydroxpropyl methyl cellulose (HPMC), is shown in Figure 1. The drop in concentration of the drug at thirty minutes is due to the dilution effect of the concentration jump technique (16). The abscissa represents time in minutes and

the ordinate represents the cumulative amount of the drug dissolved in micrograms. Each point represents an average of two independent dissolution runs. In all the dissolution rate studies, the dissolution rate was determined from the slope of the least squares line. Linearity was excellent as demonstrated by the data in Figure 1. This indicates that the variation of the dissolution rate of each tablet from time to time was small. The slope of segment "A" (Figure 1), which represents the dissolution rate of hydrocortisone alcohol in glass distilled water, was 0.458 μg/s as determined by the least squares method, while that of segment "B", which represents the dissolution rate of hydrocortisone alcohol in 0.5% weight by volume hydroxypropyl methyl cellulose, was 0.235 μg/s. It was evident from this representative plot that the addition of commonly used polymers, such as HPMC, even in concentrations as low as 0.5% weight by volume, reduced the dissolution rate by approximately fifty percent. Similar results were observed by using several other polymers in varying concentrations. Table 2 gives a list of the polymers used and the corresponding dissolution rates of hydrocortisone alcohol tablets at twenty five degrees Centigrade. The viscosities of the different polymeric media are given in Table 3. By referring to the dissolution rate data in Table 2, and the viscosity values in Table 3, it was evident that the

TABLE 2

DISSOLUTION RATES OF HYDROCORTISONE ALCOHOL IN VARIOUS POLYMERIC MEDIA AT 25°c at 200 RPM USING DISKS OF 0.55 CM

MEDIUM (% weight by volume)	DISSOLUTION RATE (μg/sec)
1. Water	0.458(0.0272)[a]
2. 0.2% PVP[b]	0.395
3. 0.1% HPMC[c]	0.363
4. 0.2% HPMC	0.327
5. 0.5% HPMC	0.235
6. 0.15% PEO[d]	0.360
7. 0.2% HPMC[e]	0.205
8. 18% Sucrose	0.290

a. The number given in parenthesis for the dissolution rate in water is the standard deviation for 10 dissolution runs.

b. Polyvinyl pyrrolidone

c. Hydroxypropyl methyl cellulose 60 HG, 50 CPS

d. Polyethylene oxide, Polyox

e. Hydroxypropyl methyl cellulose. Methocel E4M

TABLE 3

SOLUBILITY AND DIFFUSION COEFFICIENT DATA FOR HYDROCORTISONE ALCOHOL IN VARIOUS MEDIA AND KINEMATIC VISCOSITY VALUES FOR EACH MEDIUM AT 25° C

	MEDIUM	SOLUBILITY (μg/ml)	DIFFUSION COEFFICIENT X10^6 cm^2/sec	KINEMATIC VISCOSITY X10^2 cm^2/sec	$D\upsilon$ x10^8
1.	Water	327. (8.42)[b]	4.50 (0.106)[a]	0.874 (0.00040)[b]	3.93
2.	0.2% PVP	340. (1.50)	3.90 (0.283)	0.894 (0.0040)	3.49
3.	0.1% HPMC[c]	330. (14.7)	2.98 (0.199)	0.999 (0.0021)	2.98
4.	0.2% HPMC	335. (0.00)	2.63 (0.480)	1.24 (0.0027)	3.26
5.	0.5% HPMC	339. (16.8)	2.02 (0.190)	2.18 (0.0025)	4.40
6.	0.15% PEO	336. (1.50)	2.28 (0.430)	1.24 (0.0067)	2.83
7.	0.2% HPMC[d]	334. (1.57)	1.89 (0.069)	3.72 (0.0094)	7.03
8.	18% Sucrose	363. (0.00)	2.29 (0.570)	1.24 (0.0047)	2.84

a. Range of two experimental values

b. Standard deviation of three experimental values

c. Hydroxypropyl methyl cellulose, 60 HG, 50 CPS

d. Hydroxypropyl methyl cellulose, Methocel, E4M

dissolution rate decreases as the bulk viscosity of the dissolution medium increases.

Several polymers with different chemical structures were selected for this study to provide information on whether chemical effects or physical barrier effects influence drug transport. Hydroxypropyl methyl cellulose was chosen because it is commonly used in pharmaceutical suspensions, and for the possibility of it forming hydrogen bonding with steroids. Three concentrations of this polymer were used, and, as expected, it was found that there was an increase of the solution viscosity with increasing polymer concentration. Two different HPMC polymers were utilized in this study since these polymers had the same structures but different molecular weights. Thus, it was possible to vary the viscosity of the dissolution medium without changing the polymer or the concentration used. Sucrose was selected to provide the viscosity effect of a non-polymeric solution. Polyethylene oxide exists in linear chains and causes a substantial increase in viscosity even when used in very small quantities, while a 0.2% solution of polyvinyl pyrrolidone has little effect on the viscosity of the medium.

Table 3 gives a summary of the physicochemical data for hydrocortisone alcohol in various polymer solutions. All values were determined at 25 degrees Centigrade. It was evident that the presence of non-ionic polymers did not

influence the solubility of the hydrocortisone alcohol remarkably when compared with its solubility in distilled water. However, sucrose promoted the solubility by 11%.

The diffusion coefficient data in Table 3 show that diffusivity consistently decreases with increasing bulk viscosity, regardless of the chemical structure of the viscosity inducing agent. Sucrose solutions were included to compare the effect of a small molecular weight viscosity inducing agent with other polymers. An 18% sucrose solution was found to decrease diffusivity to about the same extent as polymers with similar bulk viscosity. The range of viscosities measured was limited to about four times that of water, and should be representative of the viscosities for various otic/ophthalmic, rectal and parenteral steroid formulations. The corresponding decrease in measured diffusion coefficients varied between 12 and 60% for this viscosity range when compared with diffusion and viscosity data for water.

Dissolution rates were evaluated for hydrocortisone alcohol in each polymer solution by using the following relationship (12)

$$R \alpha \omega^{1/2} \qquad (1).$$

According to equation 1, the dissolution rate is proportional to the stirring rate raised to the one-half power. In order to test this relationship, dissolution rates

TABLE 4

DISSOLUTION RATES (μg/s) OF HYDROCORTISONE ALCOHOL IN DISTILLED WATER, 0.2% HPMC AND 0.15% PEO AT THREE STIRRING SPEEDS AND 25°C USING DISKS OF 0.550 cm RADIUS

Stirring Speed rpm	MEDIUM 0.2% HPMC[a]	0.15% PEO[b]
100	0.155 (.037)[c]	0.253 (.020)
200	0.205 (.022)	0.360 (.015)
300	0.258 (.016)	0.458 (.012)

a. Hydroxypropyl methyl cellulose, Methocel 4EM.

b. Polyethylene oxide, Polyox.

c. Range of data

were measured at 100, 200, and 300 revolutions per minute for two of the polymer solutions (Table 4). The relationship given in equation 1 was tested by determining the slope of a plot of the natural logarithm of the dissolution rate versus the natural logarithm of stirring rate, where the slope is an estimate of the numerical coefficient of interest. In the case of 0.2% HPMC (Methocel, EM4), the numerical coefficient was found to be 0.461, which is within about 8% of the model based value of 0.5. In the case of 0.15% PEO, a value of 0.518 was found for the numerical coefficient, which is

within about 4% of the expected value. The reasonable agreement between calculated and expected values for the numerical coefficient suggests that the relationship between stirring rate and the rheological behavior of the dilute polymer solutions tested follows that predicted by equation 1. Other authors have mentioned that unusual viscosity effects are not expected for dilute polymer solutions, except at low stirring rates of < ten revolutions per minute where viscosity varies with shear rate (9). When R is plotted versus stirring rate to the one-half power, the confidence interval for the y intercept includes zero for the HPMC and PEO systems. Thus, the data can be interpreted as predicting dissolution under nonstirred conditions.

A relationship given by equation 2 has been found to be useful in evaluating dissolution rates which are determined in stirred vessels (12,17). With constant stirring rate and disk radius, a linear relationship between the dissolution rate, R, and the physiocochemical variables of interest (Cs, D, and υ) is expected according to

$$R \alpha (Cs\ D^{2/3}\ \upsilon^{-1/6}) \qquad (2)$$

or

$$R = MX$$

where $X = (Cs\ D^{2/3}\ \upsilon^{-1/6})$ and M is the slope. To test this relationship experimental values for R were used as the dependent variable and experimental values for Cs, D, and υ

were used to calculate the quantity in parenthesis as the independent variable. Since both the dependent and independant variables are subject to error, the straight line for the data set was fitted using the method of Bartlett (18). Both the dependent and corresponding independent variables were placed in an ordered array R1, R2, R3,.....R8 and X1, X2, X3,...X8. The slope was calculated according to

$$M = [(R8 + R7 + R6) - (R3 + R2 + R1]/[(X8 + X7 + X6) - (X3 + X2 + X1)]$$

The data in Table 5 were used to generate the following equation for the relationship between R and X

$$R = 2.36X - 0.00840.$$

Calculated values for R were determined and are shown in Table 5. Equation 2 predicts R reasonably well for the aqueous system, for the sucrose system, and most of the polymer systems, with the PEO system giving poorest agreement. It should also be noted that the 95% confidence interval for the y intercept includes a value of zero as expected from the model.

Evaluation of the data in the context of equation 2 shows that dissolution rates decrease with increasing viscosity. However, the relationship between R and υ is a weak one given by $R \alpha \upsilon^{-1/6}$. The effect of viscosity is

TABLE 5

EXPERIMENTAL CALCULATED DISSOLUTION RATE VALUES OF HYDROCORTISONE ALCOHOL IN EACH MEDIUM AT 25°C

MEDIUM	EXPERIMENTAL DISSOLUTION RATE μg/s	($C_s D^{2/3} \upsilon^{-1/6}$)	CALCULATED DISSOLUTION RATE[a] μg/s
Water	0.458	0.196	0.455
0.2% PVP	0.395	0.185	0.429
0.1% HPMC[a]	0.363	0.147	0.339
0.15% PEO	0.360	0.121	0.278
0.2% HPMC	0.327	0.133	0.306
18% Sucrose	0.290	0.131	0.301
0.5% HPMC	0.235	0.103	0.235
0.2% HPMC[b]	0.205	0.0884	0.201

a. Hydroxypropyl methyl cellulose, 60HG, 50 cps

b. Hydroxypropyl methyl cellulose, E4M

primarily communicated to the dissolution process through decreased diffusivity, which is in keeping with findings from previous research (19).

According to Levich (20), as kinematic viscosity increases the diffusion coefficient decreases according to

$$D\upsilon = \text{constant} \qquad (3).$$

The methodology for this research was not designed to test the form of the relationship between D and υ in order to apply convective diffusion principles. However, the data in

Table 3 show that the product of D and υ do not yield a constant. Instead, the diffusion coefficient tends to decrease more rapidly than expected from equation 3 for a given viscosity, except for 0.5% HPMC and Methocel E4M. However, reasonable agreement between calculated and experimental dissolution rates (Table 5) suggest that Equation 3 is not a requirement for the relationship given by equation 2. This finding is consistent with that of Flynn et al. (19).

In summary, the effect of dilute polymers, in concentrations commonly used in otic/ophthalmic or rectal steroid suspension formulations, is to reduce the dissolution rate of hydrocortisone alcohol via decreased diffusivity. Formulation effects of these dilute polymer solutions on dissolution rates were evaluated using a rotating fluid/stationary disk where complicating factors relating to particle size, particle shape and changing surface area are not present.

REFERENCES

1. J.J. Lima, J. Giller, J.J. MacKiechan and W.J. Jusko, American Journal Gastroenterology., 73, 232-236 (1980).

2. A.R. Cooper, Jr. and W.D. Kingery, Journal Phys. Chem., 66, 665-668 (1962).

3. S. Howard, J. Mauger and L. Phusanti, J. Pharm. Sci., 66, 557-562 (1977).

4. S. Howard, J. Mauger, J. Hsieh and K. Amin. Ibid., 68, 1475-1479 (1979).

5. K.G. Nelson and A.C. Shah, Ibid., 76, 799-802 (1987).

6. E. Roehl, C.V. King, and S. Kipness, Chem. Soc., 61, 2290-2295 (1939).

7. C. Wagner, Journal Phys. Chem., 53, 1030-1037 (1949).

8. A.T. Florence, P.H. Elworthy and A. Rahman, Journal Pharm Pharmacol. 25, 779-784 (1973).

9. N. Sarisuta and E. Parrot, J. Pharm. Sci. 71, 1375-1380 (1982).

10. J.D. Bogardus, Ibid., 73, 96-102 (1984).

11. G.S. Hansford and M. Litt, Chem. Eng. Sci., 23, 849-857 (1968).

12. N. Khoury, J. Mauger and S. Howard, Pharmaceutical Research. 5, 495-500 (1988).

13. T. Higuchi, S. Dayal and Ian H. Pitman, J. Pharm. Sci. 61, 695-699 (1972).

14. N.C. Fawcett and R. Caton, Journal Analytical Chem., 48, 600-604 (1979).

15. P.J. Stout, N. Khoury, J. Mauger and S. Howard, J. Pharm. Sci., 75, 65-67 (1986).

16. A. Paruta, B. Sciarrone and N. Lordi, Ibid., 58, 216-219 (1969).

17. K.P. Smith and C.K. Colton, AIChE J., 18(5), 958-967, 1961.

18. Bartlett, M.S., Biometrics, 5, 207-212 (1949).

19. G.L. Flynn, A.B. French, N.F.H. Ho, W.I. Higuchi, E.A. Ostafin, C.H. Warbasse, G.E. Amidon and E. Williams, Journal of Membrane Science, 19, 289-294 (1984).

20. V.G. Levich, Physicochemical Hydrodynamics, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1962, p. 53.