Effect of Polymers on Dissolution from Drug Suspensions

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Abstract □ The effect of three viscosity grades of methylcellulose on the dissolution–dialysis rate of nitrofurantoin suspensions was investigated using a cell designed to provide a large surface area for dialysis. Apparent dialytic rate constants of drug dispersions and solutions were measured in 0.1 *N* HCl and in pH 7.4 buffer. Samples containing methylcellulose had lower rates of dialysis, with the lowest rate being observed for samples in which the polymer was used as the suspending agent. The reduced rate of dialysis of the drug suspension containing methylcellulose is thought to be due to complexation of the drug in solution with the polymer as well as formation of microscopic regions of high viscosity surrounding the undissolved drug particles leading to a reduction in the dissolution rate of the drug. An empirical relationship was obtained to enable the estimation of the effective drug concentration in the dissolution chamber for drug dispersions. The method is based on utilizing dialysis rate data of drug solutions. This relationship could be used for comparing suspension formulations in terms of the amount of drug available for dialysis.

Keyphrases □ Nitrofurantoin—suspensions, dissolution–dialysis rate, effect of three viscosity grades of methylcellulose □ Dissolution–dialysis rates—nitrofurantoin suspensions, effect of three viscosity grades of methylcellulose □ Methylcellulose—three viscosity grades, effect on dissolution–dialysis rates of nitrofurantoin suspensions □ Suspensions, drug—nitrofurantoin, dissolution–dialysis rates, effect of three viscosity grades of methylcellulose □ Viscosity—three grades, methylcellulose, effect on dissolution–dialysis rates of nitrofurantoin suspensions □ Antibacterial agents, urinary—nitrofurantoin suspensions, dissolution–dialysis rates

The dissolution rate of a drug from a suspension is generally assumed to be similar to that of its dispersion in water. However, lower cumulative excretion of nitrofurantoin was reported from a dispersion in 5% methylcellulose solution as compared to that of the drug dispersion in water (1). Other reports also indicated unsatisfactory bioavailability of drugs from suspensions (2–8). These findings suggest the possibility of drug–adjuvant interactions in suspension formulations that could affect drug dissolution and absorption. Therefore, there was a need for a systematic investigation of factors affecting the drug dissolution from suspension formulations.

This investigation was concerned with the effect of polymeric suspending agents on the dissolution rate of nitrofurantoin. Its dissolution rate was investigated by a dissolution–dialysis technique, because conventional dissolution rate measurement methods were not suitable for precise determination of dissolution behavior. A specially designed dissolution–dialysis technique was used.

EXPERIMENTAL

The model drug selected was nitrofurantoin[1]. Three viscosity grades of methylcellulose[2], 50, 400, and 4000 cps, were used as suspending agents. Dissolution–dialysis experiments were carried out at 37° using 0.1 *N* HCl and 0.1 *M* phosphate buffer (pH 7.4) as the dissolution and dialysis media. Rates of dialysis of the drug from dispersions of nitrofurantoin in deionized water and in polymer solutions were determined. In addition, dialysis rates were measured using solutions of the drug in deionized water and in the polymer solutions.

Dissolution–Dialysis Cell—A diagram of the dissolution–dialysis cell is shown in Fig. 1. The dissolution chamber consisted of a cylindrical Plexiglas frame made up of two Plexiglas disks (C and D) connected with three Plexiglas supports (F) onto which a cellulose dialysis tubing[3] was mounted. The dissolution chamber was placed in a 2-liter resin reaction kettle[4] which served as the recipient chamber.

The cell had provision for a sample introduction port (I) for the addition of the test sample to the dissolution chamber (B) and a port (J) for removing samples of the desorbing solution from the dialysis chamber (A). In a typical experiment, 50 ml of the dissolution medium was placed in the dissolution chamber and agitated at 70 rpm using a constant-speed mixer[5] and a three-blade stainless steel propeller. Eleven hundred milliliters of the desorbing solution (identical to the dissolution medium) was placed in the dialysis chamber and stirred at approximately 500 rpm with a controlled magnetic stirrer[6].

The cellulose dialysis tubing was obtained as a 150-mm flat width tubing, having an average pore diameter of 50 Å and a thickness of 3.25×10^{-2} mm when fully hydrated. A piece of tubing approximately 30 cm long was thoroughly washed several times in deionized water and soaked in deionized water for 24 hr in a refrigerator to achieve hydration. The hydrated dialysis tubing was then mounted on the Plexiglas frame (Fig. 1). The dissolution chamber was filled with 500 ml of deionized water and observed for at least 3 hr for possible leakage. The diameter of this chamber was about 90 mm and, when filled with 500 ml of the dissolution medium, the level of the medium rose to about 95 mm from the bottom of the dissolution chamber.

Procedure—Appropriate volumes of the dissolution medium and desorbing solution were placed in the dissolution–dialysis cell and allowed to equilibrate for 1 hr at 37°. The test sample was quantitatively transferred to the dissolution chamber. Five-milliliter samples of the desorbing solution were withdrawn at 2, 5, 10, 20, 30, 40, 50, 60, 75, 90, 120, 150, and 180 min, and the sample volume was immediately replaced with fresh desorbing solution.

The concentrations of nitrofurantoin in the samples were determined after appropriate dilutions by spectrophotometric analysis at 369 nm for 0.1 *N* HCl and at 380 nm for the pH 7.4 buffer. A cumulative correction for the amount of drug dialyzed was made for the previously removed sample using an equation described in the literature (9).

Test Systems—To analyze the specific effects of the polymer on the dissolution behavior of the drug from suspensions, five test systems were investigated. They were dispersions and solutions of the model drug in water and in methylcellulose solutions.

System A, for measuring the dialysis rate of drug dispersions with suspending agent, consisted of a dispersion of 40 mg of drug in 20 g of methylcellulose solution added to 480 ml of the dissolution medium.

System B, for measuring the dialysis rate of aqueous drug dispersions, consisted of a dispersion of 40 mg of drug in 20 g of deionized water added to 480 ml of the dissolution medium.

System C, for measuring the effect of methylcellulose present in the dissolution medium, consisted of an aqueous dispersion of 40 mg of drug in 20 g of deionized water added to the dissolution medium

[1] Nitrofurantoin, Lot 100C-1300, Sigma Chemical Co., St. Louis, Mo.
[2] Methocel, Dow Chemical Co., Midland, Mich.
[3] Cellulose dialysis tubing (150 mm flat width), Union Carbide Corp., Chicago, Ill.
[4] Pyrex, Fisher Catalog No. 110847C (1974), Fisher Scientific Co., Pittsburgh, Pa.
[5] Servodyn constant-speed and torque control unit, model 600-013, Cole-Parmer Instrument Co., Chicago, Ill.
[6] Micro-submersible magnetic stirrer, Tri-R Instrument, Inc., Rockville Center, N.Y.

Table I—Composition of Samples of Test System A Prepared for Dissolution–Dialysis Experiments

Polymer	Concentration of Stock Solution of Polymer, % w/w	Amount of Polymer Stock Solution in Test Sample, g	Amount of Deionized Water in Test Sample, g	Final Concentration of Polymer in Test Sample, % w/w
Methylcellulose, 50 cps	6.45	15.50	4.50	5.00
Methylcellulose, 400 cps	3.26	17.63	2.37	2.87
Methylcellulose, 4000 cps	1.96	18.13	1.87	1.77

containing the same amount of methylcellulose as would be present if a methylcellulose suspension of the drug were being tested.

System D, for measuring the dialysis rate of drug solutions containing methylcellulose, consisted of a solution of 40 mg of drug plus the same amount of methylcellulose as in a drug suspension in 500 g of total solution.

System E, for measuring the dialysis rate of aqueous drug solutions, consisted of drug solutions ranging from 8 to 53 mg of drug in 500 g of the dissolution medium.

Preparation of Test Samples—*Test System A*—Dispersions of Test System A were made using predetermined amounts of the drug, the polymer stock solution, and deionized water. The specific amounts used for the preparation of each sample of Test System A are shown in Table I. The predetermined amount of the drug was weighed into a 40-ml screw-capped vial, and then the predetermined amount of water and 5 g of the appropriate polymer stock solution were added.

The sample was mixed[7] and then dispersed by sonification for 6 min, using the microtip horn of the sonifier[8] at a power output of 40 w. The vial was immersed in an ice and water bath to keep it cool during sonification. The sample vial was closed with the screw cap, using an additional polyethylene liner to obtain a leakproof seal. The sample was equilibrated at 37° for 24 hr in a rotating-bottle apparatus.

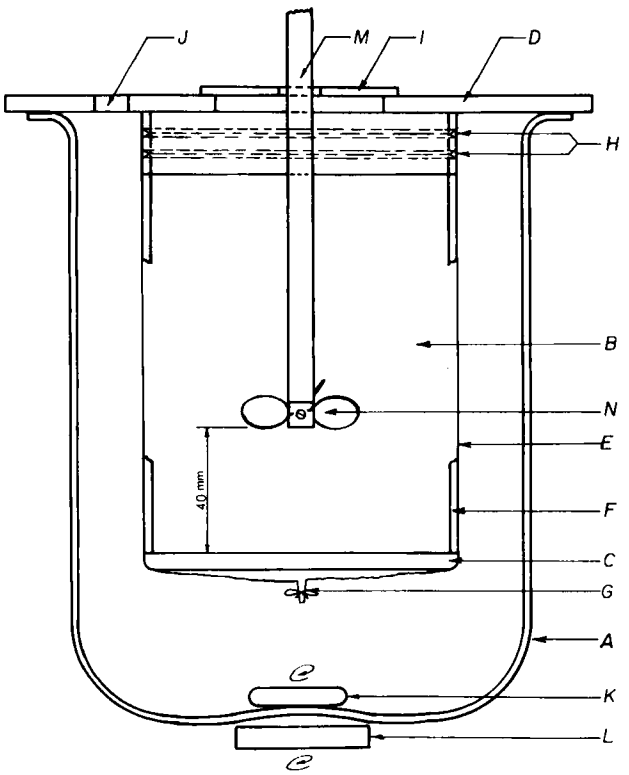

Figure 1—*Dissolution–dialysis cell. Key: A, 2-liter reaction kettle (dialysis chamber); B, dissolution chamber; C, Plexiglas disk (98 mm diameter, 5 mm thick); D, Plexiglas top (184 mm diameter, 5 mm thick); E, cellulose dialysis tubing (150 mm flat width); F, Plexiglas support (115 mm long, 10 mm wide, and 5 mm thick); G, lower end of dialysis membrane; H, heavy duty rubber bands; I, Plexiglas lid for sample introduction port (63 mm diameter); J, sample withdrawing port (10 mm diameter); K, magnetic spinning bar; L, microsubmersible magnetic stirrer; M, stirring shaft attached to a constant-speed motor; and N, stainless steel propeller.*

[7] S/P delux mixer, Scientific Products, Division of American Hospital Supply Corp., McGaw Park, Ill.

Test Systems B and C—The procedure outlined for preparing samples of Test System A was used for preparing samples of Test Systems B and C with some necessary changes. For Test System B, the drug was dispersed in 10 g of water initially and the dispersion was made up to 20 g with deionized water. Test System C was the same as Test System B, but the dissolution measurements were made using the dissolution medium as described earlier.

Test System D—The predetermined amount of the drug was weighed and transferred to a 500-ml volumetric flask. About 200 ml of dissolution medium was added to the flask, and the drug was dissolved with heat and mixing. The solution was allowed to cool to room temperature, and then the amount of the appropriate polymer stock solution was added to the contents of the flask necessary to obtain a polymer concentration in solution corresponding to that in System A. The solution was made up to 500 g with the dissolution medium. The test sample was then equilibrated at 37° for 24 hr in a water bath.

Test System E—The required amount of the drug as shown in Table II was dissolved in the appropriate test medium with the aid of heating and stirring. The samples were made up to 500 g with the appropriate test medium and were equilibrated at 37° for 24 hr prior to measurement.

The amount of nitrofurantoin to be used in the various test systems was such that, when all of the added drug had been dissolved, the final concentration was less than 20% of the equilibrium solubility of the drug in the dissolution–dialysis medium. The equilibrium solubility of nitrofurantoin at 37° was 143.8 μg/ml in 0.1 *N* HCl and 304.18 μg/ml in the pH 7.4 buffer solution.

The selection of each methylcellulose concentration was based on obtaining suspension vehicles with viscosity values in the range representative of commercial suspension products. The viscosity[9] values of four commercial suspensions at 60 rpm were 950–1250 cps. A solution of 50-cps methylcellulose, 5.0% (w/w), had a viscosity value of 1300 ± 100 cps. Therefore, this concentration was selected for 50-cps methylcellulose. Concentrations of the higher viscosity grades of methylcellulose were selected to give suspension vehicles of viscosities similar to the 5.0% (w/w) 50-cps methylcellulose solution. These concentrations were 2.78% (w/w) for 400-cps methylcellulose and 1.77% (w/w) for 4000-cps methylcellulose.

RESULTS AND DISCUSSION

Dissolution–Dialysis Cell—The rationale for the specific design of the dissolution–dialysis cell was to maintain dialysis conditions such that the dialysis rate measurements would reflect the dissolution behavior of the drug under sink conditions. The dialysis technique was employed in the past to maintain sink conditions in dissolution rate measurements of solid dosage forms (10, 11). However, reported dissolution–dialysis cells were unsuitable for the present investigation for two main reasons. First, the suspension formulations dissolved at a much faster rate than solid dosage forms. Second, the surface area for dialysis was quite small.

The net effect would be a rapid buildup of drug concentration in

[8] Sonifier cell disrupter model W185 with microtip, Heat Systems-Ultrasonics, Inc., Plainview, Long Island, N.Y.

[9] Brookfield Synchro-Lectric viscometer model LVT and No. 3 spindle, Brookfield, Stoughton, Mass.

Table II—Typical Amounts of Nitrofurantoin Used for Preparing Solutions of Various Concentrations for Test System E for Dialysis Experiments

Nitrofurantoin, mg	
0.1 *N* HCl	pH 7.4 Buffer
7.80	7.35
12.97	12.22
26.59	25.27
41.84	39.60
52.48	49.77

the dissolution medium, resulting in the loss of adequate sink conditions for drug dissolution. Therefore, the dialysis rate obtained by using small cells would not be an index of dissolution behavior because the rate-limiting factor would be the dialysis rate and not the dissolution rate. A cell was constructed to provide a large surface area for dialysis and thus prevent the concentration buildup in the dissolution chamber. The dialysis rate measurements under these conditions should reflect the dissolution behavior of drugs in suspensions.

Data Treatment—For calculation of the apparent dialytic rate constant, the following equation, developed by Davis *et al.* (12), was used:

$$\log [V_0A_T - (V_0 + V_i)A_0] = -\left[\frac{V_0 + V_i}{2.3V_iV_0}\right]Kt + \log (V_0A_T) \quad \text{(Eq. 1)}$$

where V_0 = volume of the test medium in the dialysis chamber, V_i = volume of the test medium in the dissolution chamber, A_0 = amount of drug dialyzed into the dialysis chamber, A_T = total amount of drug in the test sample, t = time in minutes, and K = apparent dialytic rate constant.

The term $\log [V_0A_T - (V_0 + V_i)A_0]$ represents the amount of drug remaining in the dissolution chamber at time t. When $\log [V_0A_T - (V_0 + V_i)A_0]$ is plotted *versus* time, t, a straight line is obtained. The slope of the line is:

$$\text{slope} = -\left[\frac{V_0 + V_i}{2.3V_iV_0}\right]K \quad \text{(Eq. 2)}$$

Therefore, the apparent dialytic rate constant, K, can be evaluated as follows:

$$K \text{ min}^{-1} = \frac{-(\text{slope})(2.303)(V_iV_0)}{V_i + V_0} \quad \text{(Eq. 3)}$$

A representative plot of the log amount of drug remaining in the dissolution chamber as a function of time is shown in Fig. 2 for Test System C. The value of the apparent dialytic rate constant, K, for this system was evaluated using the slope of this plot, calculated by the method of least squares.

In the case of drug dispersions, Test Systems A, B, and C, the amount of drug in solution at zero time is not known. Therefore, the amount of drug added to the system was used as the value of A_T for the data treatment. Hence, the values of K for these samples represent apparent dialytic rate constants. Similarly, the extent, if any, of complexation between the drug and the polymer was not determined for Test System D. Hence, the values of the dialytic rate constant for this test system should also be considered as the apparent dialytic rate constant. With Test System E, however, K should be considered as representing the dialytic rate constant of the drug solution.

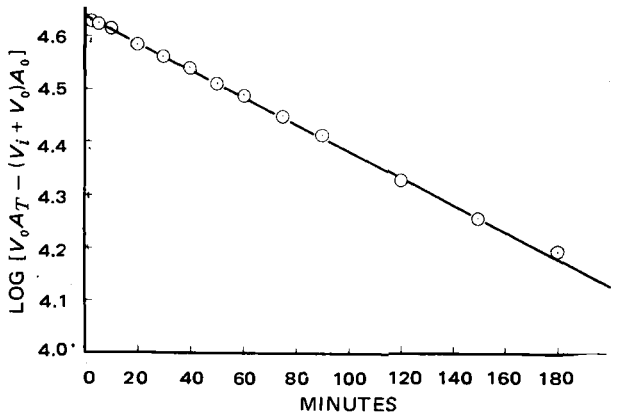

Figure 2—*Plot of logarithm of amount of drug remaining in the dissolution chamber* versus *time for Test System C of nitrofurantoin with 4000-cps methylcellulose as the suspending agent in 0.1* N *HCl.*

The rate of dialysis of dissolved drug is a function of the concentration of the dissolved drug, the diffusion coefficient of the drug, and the surface area of the dialyzing membrane. Therefore, with a suitable design of the dialysis cell, the rate of dialysis should serve as a more reliable index of the dissolution behavior of drug from the dosage formulation. Other investigators (13, 14) also indicated that the dissolution rate was an inadequate parameter for assessing the amount of drug available for absorption from a dosage form in the GI tract. They proposed that the rate of dialysis or the rate of permeation would be more appropriate.

Furthermore, conventional dissolution rate measurement methods involve filtration of the dissolution medium samples through a filter, usually a glass wool, a sintered-glass disk, or a membrane filter with an average pore diameter of 0.22 μm or larger. The finer particles of drugs could pass through the filter medium and continue to dissolve in the filtrate. A soluble drug–excipient complex could also be present in the filtrate and be measured as free drug if a nonspecific assay procedure is used for the analysis of the filtrate. Therefore, the dissolution–dialysis technique was used for the investigation of the dissolution of drugs from suspensions.

Dissolution–Dialysis of Nitrofurantoin in 0.1 *N* HCl—The apparent dialytic rate constants for the various samples of Test Systems A, B, C, and D in 0.1 *N* HCl are shown in Table III. Values for Test System E in this test medium are shown in Table IV.

As might be expected, the highest value of K was obtained for Test System E, the aqueous solution of the drug. The lowest value of K was obtained for Test System A, the suspension of the drug in methylcellulose solution. Essentially the same value of K was obtained for Test Systems B, C, and D; these values were intermediate between those for Test Systems A and E.

The values of K for drug suspensions would be expected to be lower than those for drug solutions since the drug concentration in the dissolution chamber should be dissolution controlled for these systems. The apparent dialytic rate constant values of Test System A were significantly lower than those of Test System B at the 90% confidence level using the F test.

The value obtained for Test System A indicated the effect of

Table III—Values of Apparent Dialytic Rate Constant, K, in 0.1 *N* HCl Test Medium for Systems Containing Nitrofurantoin

Test System	Methylcellulose[a]			
	None	50 cps	400 cps	4000 cps
A	—	1.67 (1.58–1.78)	1.64 (1.52–1.71)	1.66 (1.60–1.72)
B	1.98 (1.84–2.05)	—	—	—
C	—	2.02 (1.87–2.21)	1.83 (1.81–1.84)	1.95 (1.92–1.98)
D	—	1.97 (2.07–1.87)	1.93 (1.86–1.98)	2.05 (2.00–2.10)

[a] Average value (K, min^{-1}) of three experiments; range given in parentheses.

Table IV—Values of Dialytic Rate Constant, K, and Coefficient of Variation of K for Test System E Containing Nitrofurantoin

Test Medium	K[a], min^{-1}	Coefficient of Variation of K
0.1 N HCl	2.36	6.25
pH 7.4 buffer	2.21	3.82

[a] Average of five values obtained for each of five test samples of Test System E.

methylcellulose in retarding drug dissolution. This effect could be due to entrapment of the drug in the polymer chain or adsorption of polymer on the drug particles, forming a weak drug–polymer adsorbate. One example of such an interaction, the adsorption of a hydrophilic polymer on barium sulfate particles in barium meal preparations, was reported previously (15). The formation of a drug–polymer adsorbate or the entrapment of the drug in the polymer chain would prevent easy access of the solvent to the drug particles. Such a possibility was proposed (1) for nitrofurantoin suspensions with methylcellulose as the suspending agent.

Also possible is the formation in the dissolution medium of regions of high viscosity due to the hydrated polymer surrounding drug particles in the sample. The dissolved drug molecules in these regions would encounter a high resistance in the diffusion process. This resistance would be reflected as a slow concentration buildup of dissolved drug in the dissolution medium, which would then be reflected as a slower dialysis rate when compared to aqueous dispersions of the drug (Test System B) under similar conditions.

The combined effect of these phenomena is named "dissolution-controlled dialysis" in this investigation. The dialysis of dissolved drug from drug suspensions in polymer solutions could also be affected by possible complex formation of drug in solution with polymer and the effect of increased bulk viscosity of the dissolution medium due to the polymer.

The apparent dialytic rate constant of Test System C, containing the same total amount of polymer in the dissolution chamber as Test System A, was similar to that of Test System B. This finding indicates that the presence of methylcellulose in the dissolution medium did not appreciably affect drug dissolution behavior as was noted for Test System A, where the same amount of polymer was present but as a suspending agent in the drug suspension. This finding is consistent with the observations of Braun and Parrott (16). They found that when methylcellulose was present in the dissolution medium, a substantial increase in the relative viscosity was necessary to decrease the dissolution rate of benzoic acid. At the polymer concentrations used in this study, a high relative viscosity might occur in a microscopic region surrounding drug particles in Test System A but not in Test System C.

The values of K for Test System D were significantly lower ($p < 0.1$) than those for Test System E, both of which were solutions. The lower value of K might be due to formation of drug–polymer complex or to the effect of bulk viscosity of the dissolution medium due to the presence of polymer. The amount of polymer in each test system was 0.2% for the 50-cps, 0.115% for the 400-cps, and 0.071% for the 4000-cps methylcellulose, which increased the bulk viscosity of the dissolution medium approximately 1.6 times.

Table VI—Values of the Dialytic Rate Constant, K, and the Apparent Dialytic Rate Constant, K_f, for Test System E: Nitrofurantoin in 0.1 N HCl and pH 7.4

Test Medium	Amount of Nitrofurantoin in Test System, A_T, mg[a]	K, min^{-1}	K_f, min^{-1}
0.1 N HCl	7.80	2.18	0.35
	12.97	2.32	0.62
	26.59	2.28	1.32
	41.48	2.53	2.86
	52.48	2.50	3.71
pH 7.4 buffer	7.35	2.25	0.33
	12.22	2.14	0.55
	25.27	2.34	1.55
	39.60	2.15	2.11
	49.77	2.17	3.10

[a] Data from Table II.

Reduced dialysis rates as a result of an increase in the relative viscosity were reported previously (17–19), with the effect being evident at relative viscosities of approximately 4.0 or higher. Hence, a relative viscosity value of 1.6 would not be expected to affect substantially the dialysis rate of dissolved drug from the dissolution chamber. Moreover, the same apparent rate constant was observed for Test Systems B and C. Therefore, the reduced dialysis rate observed for Test System D probably was due to complex formation between the drug and the polymer, as suggested by Seager (1).

Samples of Test System D were equilibrated for 24 hr at 37° prior to measurement, thus allowing enough time for the formation of possible complexes. Since Test Systems B and C have essentially similar K values, the possible effect of complex formation is not evident in the samples of Test System C. This result might be due to the relatively rapid dialysis rate of the drug from the dissolution chamber not permitting sufficient time for a complexation equilibrium to be achieved in the dissolution chamber.

Dissolution–Dialysis of Nitrofurantoin in pH 7.4 Buffer—The apparent dialytic rate constants for Test Systems A, B, C, and D are shown in Table V, and those for Test System E are shown in Table VI.

Forty milligrams of nitrofurantoin was used for preparing samples of the various test systems with 50-cps methylcellulose as the suspending agent; twice that amount, 80 mg, was used for test samples with 400- and 4000-cps methylcellulose as suspending agents.

The results indicate that the effect of the polymer on the dissolution behavior of the drug in pH 7.4 buffer was essentially the same as its effect on drug dissolution in 0.1 N HCl for samples of the test systems with 400- and 4000-cps methylcellulose as suspending agents. The apparent dialytic rate constants for all samples with 50-cps methylcellulose were similar. A measurable difference between samples of Test System A and Test Systems B, C, and D was not detected in this case. This result was probably due to the lower amount of drug used and to the higher dissolution rate of the drug in the pH 7.4 buffer system because of its higher solubility in this medium.

Table V—Values of Apparent Dialytic Rate Constant, K, in pH 7.4 Buffer for Systems Containing Nitrofurantoin

Test System	Methylcellulose[a] None	50 cps[b]	400 cps[c]	4000 cps[c]
A	—	1.99[a] (1.96–2.03)	1.57[d] (1.54–1.61)	1.62[d] (1.61–1.63)
B	2.10[a] (2.04–2.17) 1.97[a,c] (1.87–2.07)	—	—	—
C	—	2.01[a] (1.91–2.11)	2.00[d] (1.95–2.05)	1.82[d] (1.79–1.85)
D	—	1.98[a] (1.85–2.11)	1.93[d] (1.92–1.95)	2.00[d] (1.94–2.05)

[a] Average value (K, min^{-1}) of three experiments; range given in parentheses. [b] Amount of nitrofurantoin used was approximately 40 mg. [c] Amount of nitrofurantoin used was approximately 80 mg. [d] Average value of two experiments; range given in parentheses.

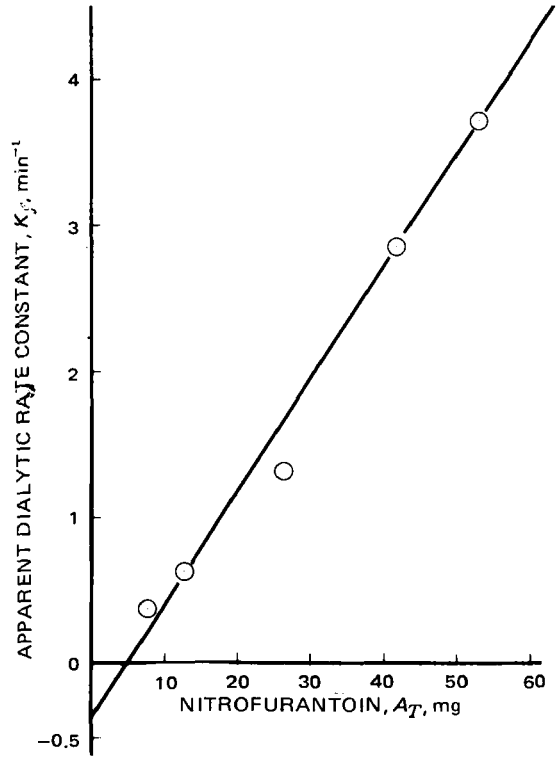

Figure 3—*Plot of the apparent dialytic rate constant,* K_f, *versus the amount of nitrofurantoin,* A_T, *in the dissolution chamber for 0.1 N HCl.*

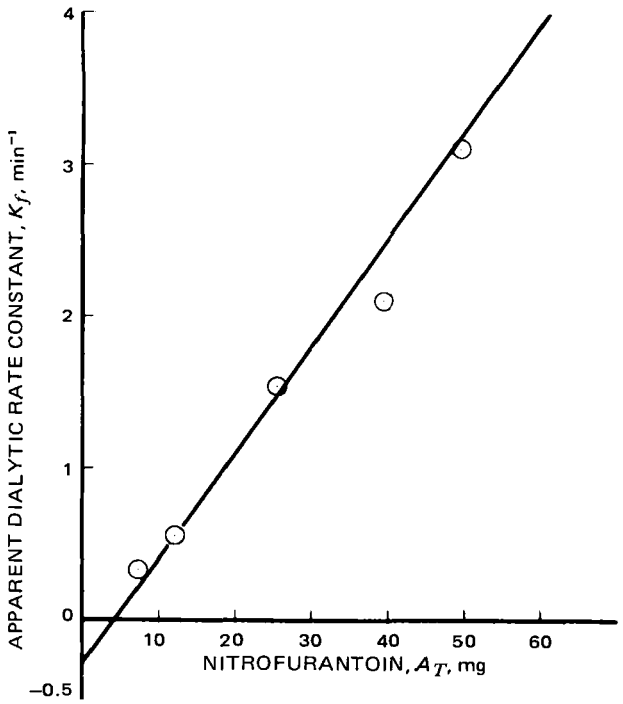

Figure 4—*Plot of the apparent dialytic rate constant,* K_f, *versus the amount of nitrofurantoin,* A_T, *in the dissolution chamber for pH 7.4 buffer.*

Prediction of Effective Drug Concentration—The rate of dialysis of drug in dissolution–dialysis measurements depends upon its effective concentration in the dissolution chamber at any given time. The effective concentration is the drug concentration in solution available for dialysis that would be the concentration of free drug in solution (3). This concentration was not known for the drug dispersion samples of this study. Therefore, the total quantity of drug in the dispersion was used for the term A_T in Eq. 1 in calculating apparent dialytic rate constants for these samples.

However, an estimate of the effective drug concentration, A_e, for these samples can be obtained by applying a modification of Eq. 1 to the dialysis rate data of drug solutions (Test System E). For the term A_T in Eq. 1, the total amount of drug in the dispersion sample of interest is used in place of the known initial concentration of the drug in solution:

$$\log [V_0A_f - (V_0 + V_i)A_0] = -\left[\frac{V_0 + V_i}{2.3V_iV_0}\right] K_f t + \log (V_0A_f) \quad \text{(Eq. 4)}$$

where A_f replaces the term A_T in Eq. 1 and represents the total amount of drug in the dispersion sample of interest being evaluated. The term K_f is the apparent dialytic rate constant corresponding to the value of A_f used in applying Eq. 4. The rest of the terms are the same as in Eq. 1.

The solution dialysis studies (Test System E) utilized drug solutions at five concentrations (Table II). Values of K_f were calculated from dialysis rate data of these samples by means of Eq. 4, using 40 mg for the value of A_f for dispersion samples tested in 0.1 *N* HCl and 80 mg for samples tested in pH 7.4 buffer. The values of K_f, the apparent dialytic rate constant per Eq. 4 thus calculated, are shown in Table VI along with the values of K, the dialytic rate constant calculated per Eq. 1, for the same samples. A linear relationship was obtained when K_f was plotted as a function of A_T, the initial concentration of the drug solutions of Test System E, as shown in Figs. 3 and 4. This relationship can be expressed as:

$$K_f = \alpha A_T + \beta \quad \text{(Eq. 5)}$$

where α and β are constants characteristic of the specific value of A_f used for the calculation of K_f values. The values of α and β obtained and their correlation coefficients are shown in Table VII.

For evaluating the effective concentration in the dissolution–dialysis measurement of drug dispersions, the term A_T in Eq. 5 is replaced by the term A_e, the effective drug concentration in the dissolution chamber, and the term K_f is replaced by K, the apparent dialytic rate constant of the dispersion obtained using Eq. 1 to obtain:

$$K = \alpha A_e + \beta \quad \text{(Eq. 6)}$$

where α and β are the same as in Eq. 5, and K is the apparent dialytic rate constant of test samples as shown in Tables III and V. The effective drug concentration in the dissolution chamber for a given drug dispersion sample corresponding to its measured apparent dialytic rate constant can be obtained as follows:

$$A_e = \frac{K - \beta}{\alpha} \quad \text{(Eq. 7)}$$

Tables VIII and IX show A_e values calculated for the dispersion test systems of nitrofurantoin in 0.1 *N* HCl and pH 7.4 buffer.

It is thought that this procedure provides a useful method of opti-

Table VII—Regression Analysis Data for Nitrofurantoin

Test Medium	α^a	β^a	r^b
0.1 *N* HCl	0.0768	−0.4004	0.9915
pH 7.4 buffer	0.0636	−0.2556	0.9892

[a] The α and β are coefficients of Eq. 6. [b] Coefficient of correlation.

Table VIII—A_e Values[a] for Systems Containing Nitrofurantoin in 0.1 *N* HCl

Test System	Methylcellulose			
	None	50 cps	400 cps	4000 cps
A	—	26.93	26.54	26.80
B	30.96	—	—	—
C	—	31.48	29.00	30.57
D	—	28.94	30.31	30.56

[a] Average value (milligrams) of three experiments. Values were obtained using Eq. 7 and the K values from Table III.

Table IX—A_e Values[a] for Systems Containing Nitrofurantoin in pH 7.4 Buffer

Test System	Methylcellulose			
	None	50 cps[b]	400 cps[c]	4000 cps[c]
A	—	35.30[d]	57.80[e]	59.39[e]
B	37.03[d] 40.47[d,b]	—	—	—
C	—	35.62[d]	71.42[e,c]	65.72[e,c]
D	—	35.39[d]	69.20[e]	71.42[e]

[a] Values (milligrams) were obtained using Eq. 7 and the K values from Table V. [b] Amount of nitrofurantoin used was 40.0 mg. [c] Amount of nitrofurantoin used was 80.0 mg. [d] Average value of three experiments. [e] Average value of two experiments.

mum design of suspension formulations by enabling comparisons of the formulations in terms of equivalent drug solutions.

SUMMARY

The effect of selected suspending agents on the dissolution behavior of nitrofurantoin from suspension formulations was investigated utilizing the dissolution–dialysis technique. A dissolution–dialysis cell of special design was developed to provide a large surface area for dialysis to minimize concentration buildup in the dissolution chamber. Three viscosity grades of methylcellulose, 50, 400, and 4000 cps, were used as suspending agents.

The measurement procedure used was to determine the dialysis rate of the dissolved drug after addition of the test sample, drug dispersion or drug solution, to the dissolution chamber of the cell. The dissolution–dialysis measurements were carried out using 0.1 N HCl and pH 7.4 buffer. The dissolution behavior of the drug was evaluated in terms of the apparent dialytic rate constants of the test samples.

Methylcellulose caused a reduction in the dialysis rate of nitrofurantoin from both the drug solution and drug suspension. However, the maximum retardation effect was observed when methylcellulose was used as a suspending agent in preparing drug dispersions. The dialysis rate of the drug suspension in the methylcellulose solution was significantly less than that of the drug dispersion in water. The dialysis rates of (*a*) the drug dispersion in water, (*b*) the drug dispersion in water with an equivalent amount of polymer added to the test medium, and (*c*) the drug solution in the test medium containing the equivalent amount of polymer were similar but significantly less than the dialytic rate of the drug solution.

The reduction in the dialysis rate of the drug solution containing the polymer is thought to be due to the possible formation of a drug–polymer complex. The greater effect observed with the drug suspension in polymer solution is thought to be due to complex formation as well as to the formation of microscopic regions of high viscosity surrounding the drug particles, leading to the possible formation of a diffusion layer of high viscosity.

An empirical relationship was developed from solution dialysis rate data to estimate the amount of free drug available for dialysis when a fixed amount of drug was added to the dissolution chamber. This relationship permits consideration of suspensions in terms of equivalent drug solutions. Therefore, it could find application in the *in vitro* evaluation of test products in the development of suspension formulations.

REFERENCES

(1) H. Seager, *J. Pharm. Pharmacol.*, **20**, 968(1968).

(2) K. H. Harper and A. N. Wordan, *Toxicol. Appl. Pharmacol.*, **8**, 325(1966).

(3) C. Davison, J. L. Guy, M. Levitt, and P. R. Smith, *J. Pharmacol. Exp. Ther.*, **134**, 176(1961).

(4) M. H. Malone, R. D. Gibson, and T. S. Miya, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 529(1960).

(5) G. Levy and W. J. Jusko, *J. Pharm. Sci.*, **54**, 219(1965).

(6) R. R. Hewitt and G. Levy, *ibid.*, **60**, 784(1971).

(7) J. J. Ashley and G. Levy, *ibid.*, **62**, 688(1973).

(8) A. Berlin, B. Siwers, S. Agurell, A. Hiort, F. Sjoqvist, and S. Strom, *Clin. Pharmacol. Ther.*, **13**, 733(1972).

(9) D. E. Wurster and P. W. Taylor, Jr., *J. Pharm. Sci.*, **54**, 670(1965).

(10) E. Marlowe and R. F. Shangraw, *ibid.*, **56**, 498(1967).

(11) P. C. Sheen, Ph.D. thesis, University of Iowa, Iowa City, Iowa, 1971.

(12) R. E. Davis, C. W. Hartman, and J. H. Fincher, *J. Pharm. Sci.*, **60**, 429(1971).

(13) R. E. Northern, J. L. Lach, and J. H. Fincher, *Am. J. Hosp. Pharm.*, **30**, 622(1973).

(14) E. G. Lovering and K. B. McRae, *J. Pharm. Sci.*, **62**, 971(1973).

(15) A. M. James and G. H. Goddard, *Pharm. Acta Helv.*, **47**, 244(1972).

(16) R. J. Braun and E. L. Parrott, *J. Pharm. Sci.*, **61**, 175(1972).

(17) G. D. Redman, J. E. Christian, and G. J. Sperandio, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 98(1960).

(18) L. H. Block and P. P. Lamy, *Pharm. Acta Helv.*, **44**, 44(1969).

(19) P. P. Lamy, *ibid.*, **44**, 79(1969).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 10, 1975, from the *Division of Drug Product Technology, College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, TN 38163*

Accepted for publication January 15, 1976.

Presented at the Industrial Pharmaceutical Technology Section, APhA Academy of Pharmaceutical Sciences, New Orleans meeting, November 1974.

Abstracted in part from a dissertation submitted by N. B. Shah to the University of Tennessee Center for the Health Sciences in partial fulfillment of the Doctor of Philosophy degree requirements.

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