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CORRELATION OF DISSOLUTION-DIALYSIS RATES WITH BIOAVAILABILITY OF NITROFURANTOIN SOLID DOSAGE FORMS

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ABSTRACT

The correlation of in-vitro dissolution-dialysis rates of solid dosage forms with in-vivo bioavailability was investigated. Dissolution-dialysis measurements were made of 50mg and 100mg tablets and capsules of Nitrofurantoin commercial products. The samples used represented product lots whose bioavailability had been previously reported. The dissolution-dialysis medium used was pH 7.2 phosphate buffer. A cellulose dialysis membrane was used. A high degree of correlation was osbserved between apparent dialytic rate constant (K_{app}) of the drug and reported in-vivo bioavailability parameters for all 50mg tablets. But the 50mg capsule K_{app} value, measured under the same test conditions, was higher and did not correlate with the tablet data. However a value correlating with tablet data was obtained when the stirring speed was reduced from 100 RPM to 10 RPM. A satisfactory correlation was not obtained for the 100 mg dosage forms. This might be due to bladder drug saturation reported to occur at higher dose levels of Nitrofurantoin.

INTRODUCTION

The measurement of the dissolution rate of a drug from a dosage form is of significant interest for a number of reasons,

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the most significant being to seek indication of in-vivo bioavailability. Therefore, investigation of in-vitro test methods to evaluate if they would serve as indicators of product bioavailability is needed. The purpose of this study was to evaluate the applicability of a specific dissolution-dialysis procedure for the correlation of in-vitro measurements with in-vivo data of commercial 50mg and 100mg nitrofurantoin tablets and capsules.

The biological availability of nitrofurantoin is susceptible to the influence of formulation variation (1). However, attempts to correlate the in-vitro dissolution rate measurements of this drug with in-vivo bioavailability have met with only limited success (2-7). Disanto and associates reported that there was a need for development of tests capable of correlating in-vitro data with in-vivo bioavailability for controlling lot to lot uniformity of nitrofurantoin products (6). These authors indicated that such correlations must include tests other than those presently required. Bates and associates discussed the inconsistencies in the compendial dissolution tests specifications for nitrofurantoin and suggested that these should be modified (8,9).

The bioavailability of a drug depends on the rate of transfer of drug molecules across a membrane. However, the dissolution rate of the drug product is not necessarily an indication of the amount of drug available for permeation through a membrane. The need to test in-vitro drug bioavailability of different brands of a drug product by simultaneous dissolution-dialysis or by dissolution-permeation techniques has been pointed out in the literature (10,11).

EXPERIMENTAL

Materials

Potassium phosphate monobasic and sodium hydroxide pellets used for preparing the buffer solutions were analytical reagent grade materials. Nitrofurantoin micronized powder was used to

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prepare solutions for obtaining the Beer-Lambert plot for spectrophotometric analysis of the drug. The purity and identity of this sample was evaluated by measurements of molar absorbtivity and of an infrared spectrum and comparing these with corresponding values obtained from a USP reference standard of nitrofurantoin. The samples of nitrofurantoin solid dosage forms used were from lots of products for which the bioavailability had been previously investigated (7). The specific commercial products used are shown in Table I.

Dissolution-Dialysis Cell

Dissolution-dialysis experiments were carried out in a dialysis cell previously developed in our laboratories for the evaluation of nitrofurantoin suspensions (12). The rationale for the specific design of the cell was to provide a large surface area for dialysis, so that dialysis rate was dissolution dependent and not permeation dependent. A modification was found to be necessary to adapt this method for the evaluation of solid dosage forms. The modification consisted of using the USP dissolution basket assembly with a propeller installed above the basket. This was found to be necessary because the tablets could not be placed directly under the stirrer and capsules would float on the surface of the dissolution medium.

Measurement Conditions

The measurements were made at 37°C in 0.1 M phosphate buffer (pH 7.2) as both the dissolution and the dialysis medium. The dissolution chamber contained 500 ml and the dialysis chamber contained 1100 ml of the dissolution-dialysis medium. For the purpose of the test, the tablet or capsule was placed in the basket and subsequently mounted on the stirrer. The sample was stirred at 100 rpm and 5 milliliter samples of the dialysis medium were withdrawn at specific time intervals. The sample volume was immediately replaced with an equal volume of fresh dialysis medium. The dialysis rate measurements were carried out for a period of five hours in order to obtain an adequate dialysis profile for the dosage form. The samples were analyzed

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Table I

Nitrofurantoin Commercial Products Investigated

Dosage Form	Dosage Form Code #	Manufacturer	Lot #	Strength mg.
T[a]	4	McKesson Lab.	2B039	100
T	13	Wolins Pharmacal.	24015	100
T	3	Ketchum Lab.	2011460	100
T	12	Lederle Lab.	286-104	100
T	6	Eaton Lab.	698627	100
T	5	Purepac Pharm.	1061460	100
C[b]	7	Eaton Lab.	697203	100
T	14	Wolins Pharmacal.	24732	50
T	11	McKesson Lab.	2J784	50
T	2	Lederle Lab.	286-108	50
T	9	Eaton Lab.	693775	50
T	1	Ketchum Lab.	204145	50
T	8	Purepac Pharm.	090009	50
C	10	Eaton Lab.	698613	50
C	16[c]	Eaton Lab.	719800	100
T	15[c]	Eaton Lab.	716887	50
C	17[c]	Eaton Lab.	808034	50

a = Tablet

b = Capsule

c = Additional Test Samples For Which Bioavailability Data Was Not Available

spectrophotometrically for nitrofurantoin concentration at a wave length of 380 nm. A cumulative correction was made for the previously removed sample following a procedure described in the literature (13).

The specific experimental procedure was selected on the basis of preliminary studies. In these studies, the effect of

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stirring rate on the dissolution dialysis rate of the drug from solid dosage forms was investigated at various stirring speeds. Based on these results, the stirring speed of 100 rpm was selected. This stirring speed was selected as this gave a drug dialysis rate that was feasible to measure. Furthermore, this is the agitation rate specified in the USP dissolution test method for this drug. At higher stirring speeds, vibration of the membrane occurred causing loss of stirring control.

The dissolution-dialysis medium was a phosphate buffer solution, pH 7.2. The reason for this selection was that this is the dissolution medium specified in the USP dissolution test for this drug. This is also the medium used in a number of dissolution rate studies on this drug reported in the literature. The reproducibility of the measurement of the drug dialysis rate was found to be in the range of $\pm$10%.

RESULTS AND DISCUSSIONS

Data Treatment

An apparent dialysis rate constant (K_{app}) was calculated utilizing the equation reported by Davis, et al, (14) as follows:

$$\text{Log}\left[V_o A_t - (V_o + V_i)\, A_o\right] = -\frac{V_o + V_i}{2.3\, V_o V_i} Kt + \text{Log}\,(A_t V_o) \qquad (1)$$

Where V_o is the volume of the test medium in the dialysis chamber, V_i is the volume of the test medium in the dissolution chamber, A_o is the amount of drug dialyzed into the dialysis chamber, A_t is the total amount of drug in the dosage form, t is the time in minutes and K_{app} the apparent dialytic rate constant. The term $\text{Log}\left[V_o A_t - (V_o + V_i)\, A_o\right]$ represents the amount of drug remaining in the dissolution chamber at any time. The plots of this quantity versus time were found to show an initial curvature indicating a lag time, after which the plots were linear indicating a steady state diffusion of the drug between the two compartments of the dialysis cell. Representative plots of this function are shown in Figure 1. In all instances, steady state diffusion

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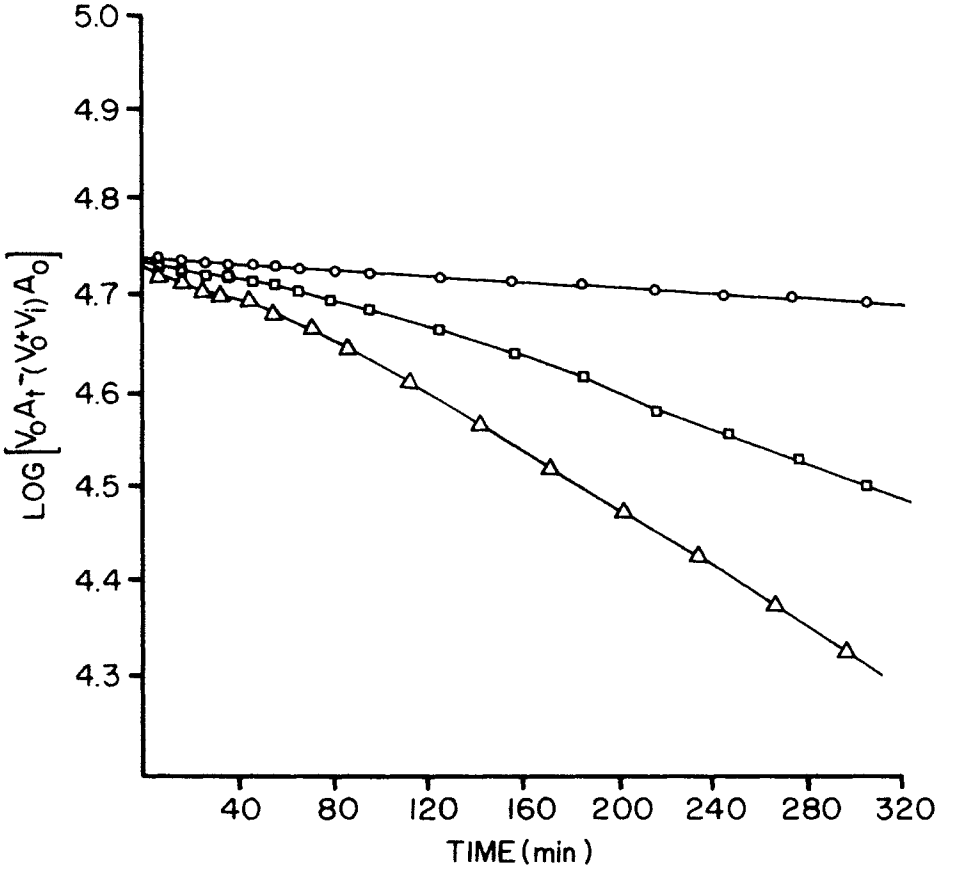

FIG. 1 Dialysis rate of 50 mg nitrofurantoin tablets:

⊙—⊙ Tablet # 14, ⊡—⊡ Tablet # 9, △—△ Tablet 8.

was reached in time period ranging from 30 to 90 minutes. The apparent dialytic rate constants for all samples were calculated from the slopes of the linear portion of the plots. These values and the corresponding in-vivo data from the study of Meyer, et al, are shown in Tables II and III (7). It should be noted that in some cases, the tablet products did not disintegrate in the dissolution medium during the time period of this study. Con-

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Table II

Apparent Dialytic Rate Constant K_{app} Values Obtained For 50 mg. Nitrofurantoin Tablets, and Corresponding In-Vivo Bioavailability Parameters[a]

Drug Product Code #	K_{app} $min.^{-1}$	Mean Cumulative Drug Excreted in 12 Hours, % of Total Dose	Duration (Hrs) For Maintaining Drug Concentration of 30 mcg/ml in Urine	Duration (Hrs) for Maintaining Drug Concentration of 75 mcg/ml in Urine
14	0.110	14.22	0.51	0.11
11	0.170	17.83	0.49	0.10
9	0.877	38.86	3.88	1.30
2	0.912	32.46	2.38	0.99
15[b]	1.187	-----	----	----
1	1.230	36.38	3.30	1.34
8	1.326	37.63	3.11	1.56

[a] From: M.C. Meyer, et al, J. Pharm. Sci. 63, 1693 (1974)

[b] Tablet From the Same Manufacturer As Product #9, But Of Different Lot Number.

sequently these products had the lowest values for the apparent dialytic rate constant.

Correlation of 50 milligram tablets

It was found that plots of the K_{app} versus cumulative drug excreted in urine for 12 hours was linear. A similar plot of K_{app} versus duration of drug level of 75 mcg/ml in urine was also found to be linear. These plots are shown in Figures 2 and 3. A linear plot was also obtained when the duration of drug level of 30 mcg/ml in urine was plotted against K_{app}. These relationships can be expressed by the following equation:

$$P = A K_{app} + B \qquad (2)$$

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Table III

Values of K_{app} Obtained for 100 mg Nitrofurantoin Tablets, and Corresponding In-Vivo Bioavailability Parameters

Drug Product Code #	K_{app} $Min.^{-1}$	Mean Cumulative Drug Excreted in 12 Hours, % of Total Dose	Duration (Hrs) For Maintaining Drug Concentration of 30 mcg/ml in Urine	Duration (Hrs) for Maintaining Drug Concentration of 75 mcg/ml in Urine
4	0.085	31.84	5.27	1.82
13	0.112	31.20	4.77	2.23
3	0.311	29.65	4.93	2.48
12	0.925	29.69	4.87	2.20
6	1.768	33.08	5.50	2.32
5	1.960	37.99	4.79	2.60

[a] From: M.C. Meyer, et al, J. Pharm. Sci. 63, 1693 (1974)

Where P is the in-vivo parameter, A and B are constants and K_{app} is the same as in equation 1. The values of A and B obtained are shown in Table IV. The correlation coefficients for this relationship are also shown in Table IV. As can be seen, a high degree of correlation was found between the bioavailability parameters and the apparent dialytic rate constant measured by the procedure of this study.

Correlation of 50 mg capsules

The in-vivo data reported for the capsule products indicated that these products were less bioavailable than the tablets (7). This might be expected since the particular capsule products are

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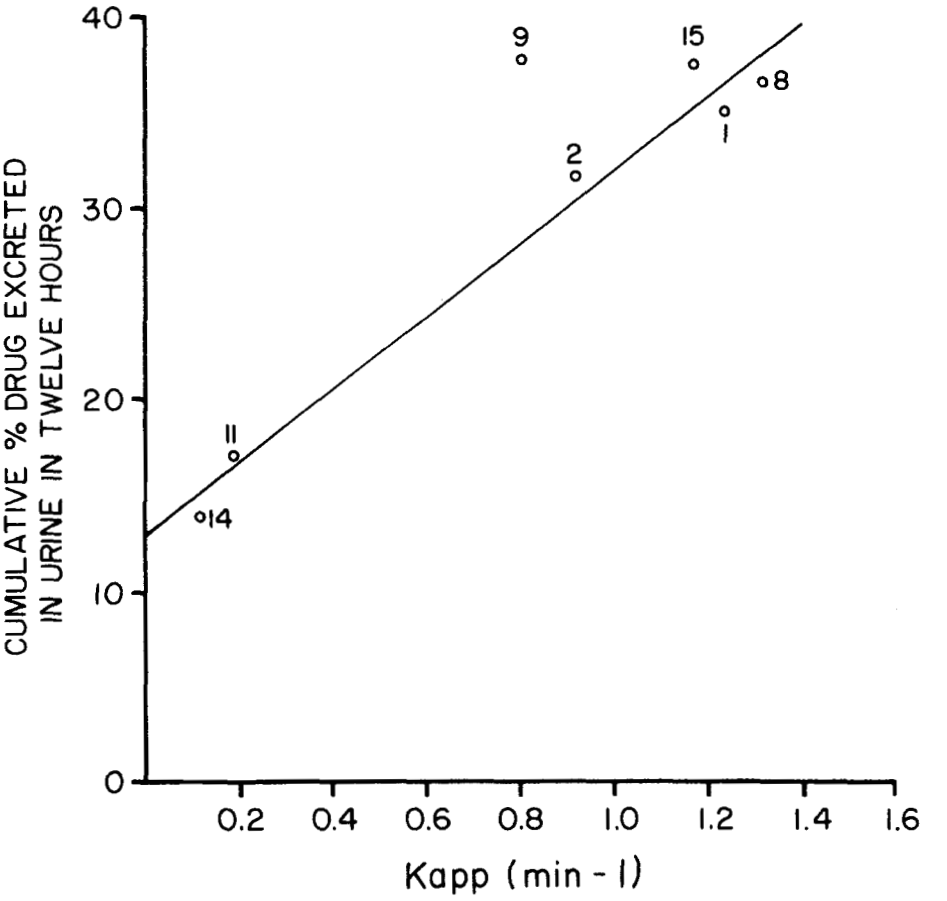

FIG. 2 Correlation of K_{app} and cumulative percent drug excreted in urine in twelve hours.

designed to contain the drug in a macrocrystalline form to reduce gastric irritation (15). However, when the dialysis rates of these products was measured under the same test conditions as for the tablets, the values of K_{app} obtained were much higher than would be predicted by the correlation of Equation 2. This may be due

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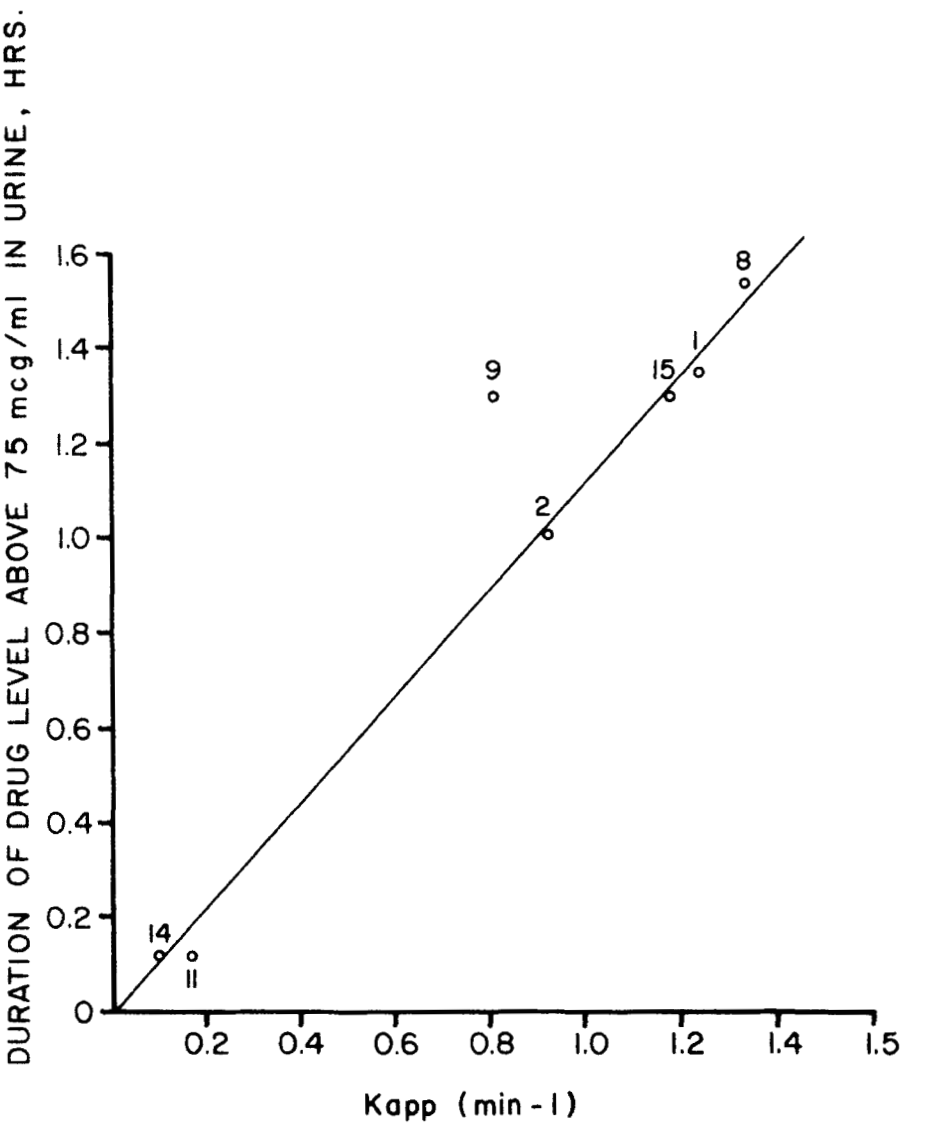

FIG. 3 Correlation of K_{app} and duration of drug level above 75 mcg/ml in urine.

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Table IV

Values of Constants A and B of Equation 2 for 50 mg Tablet Products

In-Vivo Parameter	B	A	Correlation Coefficient
Mean Cumulative % Drug Excreted in 12 Hours	14.580	19.432	0.937
Duration, Hours of Maintaining Urine Drug Concentration of 75 mcg/ml	-0.030	1.206	0.975
Duration, Hours of Maintaining Urine Drug Concentration of 30 mcg/ml	0.357	2.491	0.887

to the fact that tablets and capsules do not behave similarly during the dissolution-dialysis measurements. With tablets, dissolution would involve a two stage process: dissolution of the drug in the tablet or granule matrix and diffusion of the dissolved drug from the matrix to the dissolution medium. In the case of the capsule products, dissolution would in effect be similar to that of a powder once the gelatin shell was disintegrated. Therefore, modifications of the test conditions were investigated for the measurement of K_{app} capsule products to seek measurement conditions that would give K_{app} values of the magnitude predicted by the tablet data. This was done by making dialysis rate measurements at various lower stirring speeds. The effect of stirring rate on K_{app} is shown in Figure 4. It was found that reduction of the stirring rate from 100 rpm to 10 rpm gave K_{app} values for capsule products that were consistent with the correlation obtained for the 50 mg tablets. These results would indicate that different dosage forms would require different measurement conditions in order to obtain in-vivo - in-vitro correlation. The studies on

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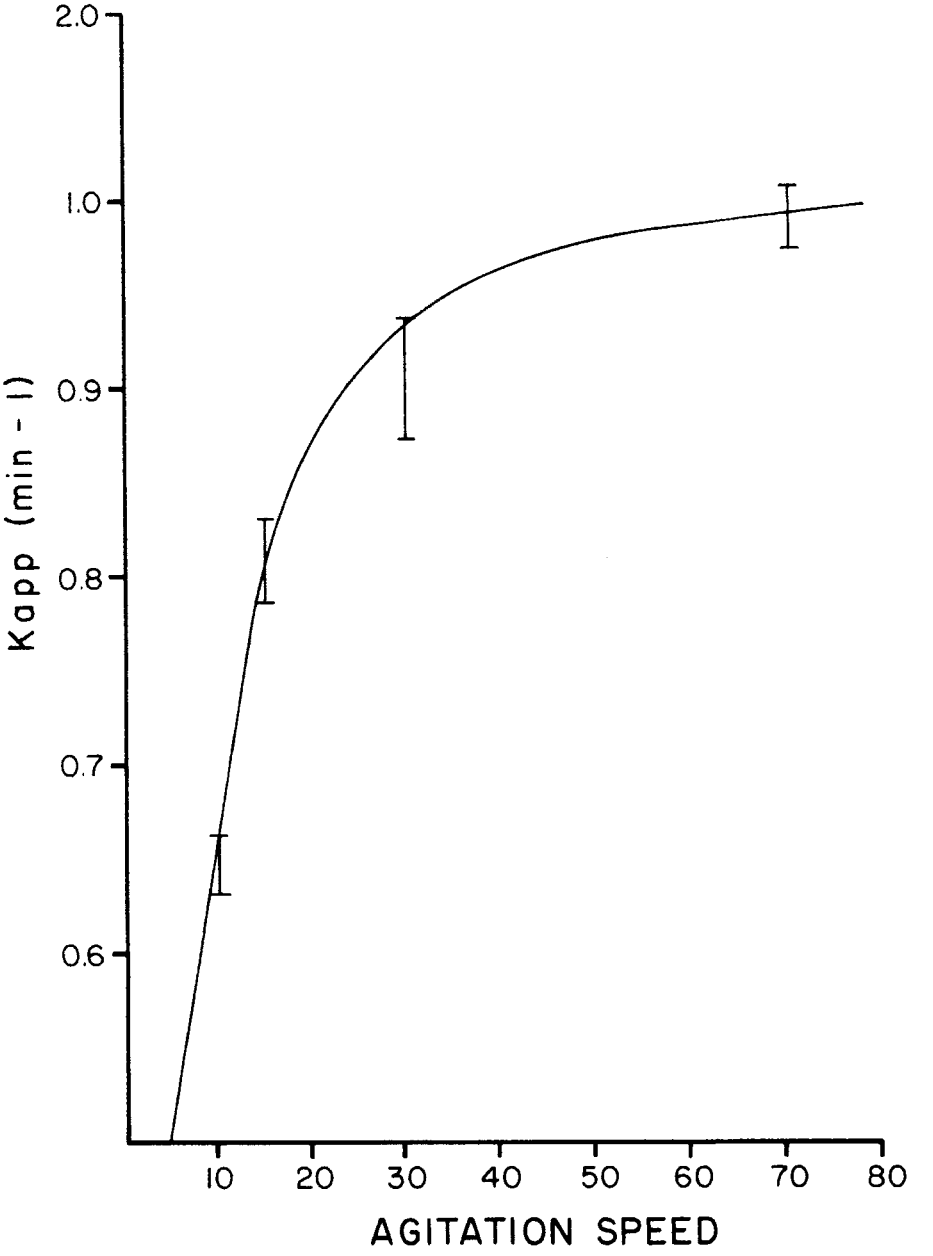

FIG. 4 Effect of agitation speed on K_{app} value for 50 mg nitrofurantoin capsule products.

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the effect of stirring rate were done using samples of nitrofurantoin capsules of lots other than those for which bioavailability was reported.

Correlation of 100 mg tablets

Plots of the in-vivo parameters versus K_{app} values were evaluated in a manner similar to the procedure used for the 50 mg dosage forms. However, in this case, the in-vitro measurements for the 100 mg dosage forms did not correlate with the in-vivo parameters. It was noted that the values of the in-vivo parameters reported in the bioavailability study of Meyer, et al, fell within a relatively narrow range for all 100 mg products (7). A review of the literature suggested that this lack of correlation might be due to biological factors specific to the drug. Conklin and Hollyfield have reported that in-vivo saturation of the nitrofurantoin transfer system may occur at high drug concentrations (16). It is of interest to note that the studies reported in the literature indicating that in-vitro dissolution of the nitrofurantoin from solid dosage forms did not correlate with in-vivo parameters were also done with 100 mg dosage forms (2-7).

Evaluation of Test Procedure

A number of observations concerning the utility of this procedure for in-vitro - in-vivo correlations can be noted. It is apparent from the results of these studies that a high degree of correlation was obtained between the K_{app} and the reported in-vivo bioavailability parameters for the 50 mg tablet products. However, the same measurement conditions were found not to be suitable for the 50 mg capsule products. These results suggest that a single measurement procedure would not be suitable for in-vitro - in-vivo correlation of different dosage forms of the same drug. Rather, measurement conditions would have to be modified according to the dosage form.

The K_{app} were calculated in this study using dialysis rate data obtained over a period of 5 hours. However, in all cases, steady state diffusion was reached in a time period of 90 minutes or less. Therefore, it would be feasible to reduce the measure-

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ment time of this test procedure to three hours and still obtain K_{app} values from steady state diffusion. It is therefore felt that this procedure could be suitable for quality control monitoring of lot to lot variation of products using a time period of three hours for the measurement, to simplify the procedure.

CONCLUSIONS

A specific dissolution-dialysis technique was evaluated for correlation of in-vitro dissolution-dialysis rates with in-vivo bioavailability parameters using nitrofurantoin solid dosage forms for which the bioavailability data had been previously reported in the literature. This procedure was found to provide a high degree of in-vitro - in-vivo correlation for products that were of the same strength and dosage form, 50 mg tablets. The correlation model obtained for 50 mg tablets did not apply to 50 mg capsules under the same measurement conditions. However, from the tablet model it was possible to develop appropriate measurement conditions for the correlation of the capsule dosage form according to a similar model. Therefore, the results suggest that a single procedure would not be suitable for in-vivo - in-vitro correlation of various dosage forms of the same drug. Rather, test conditions would have to be modified according to the dosage form. The in-vitro data for the 100 mg products did not correlate with in-vivo bioavailability parameters. It is suggested that this specific procedure, modified to reduce the time of measurement to three hours, would be useful to monitor the lot to lot variation in dissolution rate of solid dosage forms.

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providing samples of the nitrofurantoin dosage forms used in this study.

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