In Vitro and *in Vivo* Evaluation of Whole and Half Tablets of Sustained-Release Adinazolam Mesylate

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The mechanism of release from sustained-release adinazolam mesylate tablets was assessed by the Higuchi equation and by analysis of drug release profiles through 60% released using the Peppas equation. Computed values of the diffusional exponent, n, ranged from 0.59 to 0.66. Values of n in this range are consistent with a mixed mechanism of release, with diffusion of drug through the hydrated polymer matrix and relaxation of this matrix being the principal processes controlling release. The rate of *in vitro* drug release was increased for half tablets relative to whole tablets and is attributed to an increase in the surface to volume ratio of half tablets of about 16%. This increase in surface-to-volume ratio of half tablets was reflected by an increase in the constant, k, from the Peppas equation of 20–23% and by an increase in the slope of Higuchi plots of 12–18% for four lots of tablets. *In vivo/in vitro* relationships from two bioavailability studies were thoroughly evaluated. Using either a linear or a quadratic relationship, an *in vivo/in vitro* correlation exists for sustained-release adinazolam mesylate tablets.

KEY WORDS: adinazolam mesylate; oral sustained release; matrix sustained release; mechanism; *in vivo/in vitro* correlation; bioavailability; absorption.

INTRODUCTION

Adinazolam mesylate is a novel triazolobenzodiazepine which, in preclinical screens (1) and clinical trials (2,3), appears to have antidepressant activity. Adinazolam has also exhibited clinical efficacy in the treatment of panic disorder and anxiety (4,5). In man, adinazolam is converted to *N*-desmethyladinazolam via first-pass metabolism in the liver; the absolute bioavailability of adinazolam is approximately 40% (6). To investigate the feasibility of an oral sustained-release dosage form of adinazolam, Wagner *et al.* varied the dose rate of an oral solution of adinazolam between 1 and 3 $mg \cdot hr^{-1}$ and demonstrated that the relative bioavailability was not markedly affected (7). This observation, along with adinazolam's relatively short biological half-life (≈2–3 hr) (8), suggests that adinazolam is a suitable candidate for an oral sustained-release dosage form.

In the present investigation, several matrix sustained-release formulations of adinazolam mesylate are evaluated *in vitro* and *in vivo*. A hydrophilic polymer, hydroxypropylmethylcellulose (HPMC), is used to control the rate of drug release. The use of cellulose ethers for matrix sustained-release dosage forms has been studied extensively (9–12) and recently reviewed (13–16). The mechanism of release from such dosage forms is not completely understood, but in general terms, upon exposure of the tablet matrix to aqueous medium, the hydrophilic polymer (HPMC) hydrates and swells to form a viscous gel phase which acts as a barrier to drug release. For swellable polymers such as HPMC, the mechanism has been described as a coupling of diffusion and macromolecular relaxation processes, with the release kinetics dependent on the relative ratio of diffusion to relaxation (17,18).

The principal objectives of this work were twofold. First, the *in vitro* drug release profiles of sustained-release adinazolam mesylate tablets were determined and the release mechanism was inferred by application of the Higuchi equation (30) and the simplified equation of Peppas (17,18). Second, the bioavailability and pharmacokinetics of sustained-release adinazolam mesylate tablets were evaluated in two separate studies and the relationship between *in vitro* drug release and *in vivo* drug absorption was evaluated and compared across the two clinical studies. For each of these objectives, both whole and half tablets of sustained release adinazolam mesylate were evaluated. The results of these studies are of interest because only a few studies directly comparing whole- and half-tablet performance have appeared in the literature (19–21).

MATERIALS AND METHODS

Formulations

A sustained-release formulation for twice-daily administration of adinazolam mesylate was desired. Three prototype formulations were developed using a hydrophilic polymer (hydroxypropylmethylcellulose; HPMC 2208 USP) to control the rate of drug release. These formulations, each containing 15 mg of drug per tablet, were designed to have a range of *in vitro* drug release rates using a strategy similar to that described in Ref. 22. The three prototype formulations were evaluated *in vivo* in the first bioavailability study and are referred to as the Slow, Medium, and Fast formulations. The Slow formulation was selected for further evaluation; 15- and 30-mg strengths were utilized in the second bioavailability study.

Reference formulations consisted of a 1 mg/ml aqueous solution of adinazolam and an immediate-release compressed tablet. These formulations provide similar plasma adinazolam concentration–time profiles *in vivo* in man (23).

In Vitro Drug Release

The USP apparatus I (rotating basket, Hanson Research Inc., Model 72) with a rotation speed of 100 rpm was used for drug release testing. Unless otherwise noted, the dissolution medium consisted of 500 ml of 0.05 *M* phosphate buffer adjusted to pH 7.0 (ionic strength = 0.11 *M*). A Hanson dis-

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soette (Model 27-6A) was used to sample automatically about 3 ml of dissolution medium at time intervals of 0.5, 1, 3, 5, 9, 12, and 18 hr. The samples were filtered by placing Gelman Acrodisc 5.0-μm filters in-line with the dissoette. Adinazolam mesylate concentrations were determined by an HPLC procedure. To assess the effect of tablet breaking on release rate, Slow release tablets were manually broken, and unless otherwise specified, 2 tablet halves were placed in each of four baskets and 2 whole tablets were placed in the other two baskets. This procedure yielded equivalent results to placing individual tablet halves in separate baskets and summing the fractions dissolved from the appropriate tablet halves.

Data Analysis. Two empirical mathematical models, the Weibull function (24) and the Peppas equation (17,18), were used in this work. Equation (1) gives the Weibull function,

$$M_t = M_\infty \cdot \left\{1 - \exp\left[-\left(\frac{t - t_{lag}}{T_d}\right)^\beta\right]\right\} \quad (1)$$

where M_t is the percentage dissolved at time t, M_∞ is the percentage dissolved at infinite time, t_{lag} is a lag time, T_d is a reciprocal rate constant, and β is a curve-shaped parameter. T_d is sometimes referred to as the characteristic dissolution time and is indicative of the relative rate of dissolution. Equation (2) gives the simple equation proposed by Peppas for analyzing the release mechanism from swellable and nonswellable controlled-release systems (17,18),

$$\frac{M_t}{M_\infty} = kt^n \quad (2)$$

where k is a constant that incorporates characteristics of the polymer network and the drug, and n is the diffusional exponent indicative of the drug release mechanism. Peppas has reported values of n for different dosage form geometries and related them to the mechanism of release. For cylindrical geometry, values of n less than 0.45 have been shown to correspond to a purely Fickian diffusion mechanism, values of n greater than 0.89 indicate a relaxation controlled-release mechanism (Case II transport), and n values between 0.45 and 0.89 exhibit an anomalous (non-Fickian) diffusional mechanism (17,18). Equation (2) is applicable only for data up to 60% of dose release (17,18).

A custom nonlinear regression program was used to fit Eqs. (1) and (2) to *in vitro* drug release data. Four parameters (M_∞, t_0, T_d, and β) were included in the nonlinear regression for the Weibull function and two parameters (k and n) were included for the Peppas equation. During this work it was discovered that the computed values of k and n are dependent on the data range included in the fit. However, due to a discrete number of time points in the dissolution profile, it was not possible to apply Eq. (2) to fit the dissolution data over a constant fraction released (i.e., 60%). Accordingly, Eq. (2) was used to fit the predicted dissolution profiles generated from the parameters obtained from fitting the raw dissolution data to the Weibull function. This interpolation approach allowed each dissolution profile to be fit to a constant fraction dissolved (60%) and provided a more realistic comparison of k and n values for whole and half tablets.

Pharmacokinetic Studies

Study Subjects. Healthy male subjects between 18 and 40 years of age and with body weights ranging from 53.6 to 96.8 kg were recruited for these studies. Subjects provided written informed consent prior to enrollment in the studies, which were approved by the local Institutional Review Board. Normal results from physical examination and clinical chemistry screens as well as negative results from a urine drug screen were also required prior to enrollment.

Study Design. In study 1, 12 subjects received the following treatments according to a four-way Latin square crossover design: Slow adinazolam mesylate SR 15-mg tablets, Fast SR 15-mg tablets, Intermediate SR 15-mg tablets, and 3 × 5-mg immediate-release tablets. In a separate phase at the end of the study, all subjects received 15 ml of a 1 mg/ml solution of adinazolam mesylate. In study 2, 24 subjects received the following treatments according to a four-way crossover design: one Slow adinazolam mesylate SR 15-mg tablet, one 15-mg SR tablet broken at the score and both halves administered, one 30-mg Slow SR tablet, and one 30-mg SR tablet broken at the score and both halves administered. In a separate phase, each subject received one 30-mg immediate-release adinazolam mesylate tablet. Seven days separated study periods in each study.

Study Procedures. Each drug treatment was administered after an overnight fast; drug was administered with 180 ml water. Subjects fasted until 4 hr after drug administration. Serial blood samples were collected over a 24-hr period after dosing; plasma was harvested and frozen at −20°C. Plasma adinazolam concentration was determined by HPLC (25). The limit of quantitation of this procedure was 2.0 ng/ml and the coefficient of variation was less than 7.2%.

In Vivo/In Vitro Correlations

Fractions absorbed *in vivo* for the SR tablets were determined using either the Wagner–Nelson method (26) or the "Exact Loo Riegelman" approach (27). One- or two-compartment models with first-order absorption were fit to adinazolam concentration–time data obtained after the administration of adinazolam oral solution (study 1) or immediate-release tablet (study 2) using nonlinear least-squares regression. Model selection criteria were the goodness of fit as assessed by residual analysis, examination of the standard deviation of the parameter estimates, and the Akaike information criterion (28). Microscopic rate constants from two compartment fits were calculated as described in Ref. 27. The fractions absorbed at each time were calculated for the SR tablet treatments using Eqs. (3) and (4), respectively, depending on whether the oral solution data for the subject were best described by a one- or two-compartment model (26,27),

$$F_{abs} = \frac{C_T + k_{10}\int_0^T C_t dt}{k_{10}\int_0^\infty C_t dt} \quad (3)$$

$$F_{abs} = \frac{C_T + k_{10}\int_0^T C_t dt + k_{12}e^{-k_{21}T}\int_0^T C_t e^{k_{21}t} dt}{k_{10}\int_0^\infty C_t dt} \quad (4)$$

where C_t and C_T are the plasma concentration at a given time, k_{10} is the elimination rate constant from the central compartment, and k_{12} and k_{21} are first-order rate constants for distribution between the central and the peripheral compartments (27).

In vivo/in vitro relationships were developed by least-squares regression of fractions absorbed versus percentage dissolved. The data for percentage dissolved for these relationships were computed at each *in vivo* sampling time using the parameters obtained from a fit of the raw dissolution data to the Weibull function. To avoid extrapolation errors, only data between the time interval of the drug release experiment (0.5–18 hr) were used. This is a reasonable approach given the excellent fit provided by the Weibull function (see Figs. 1 and 2A and B) and the much greater variability in the *in vivo* data.

RESULTS AND DISCUSSION

In Vitro Drug Release

Drug release profiles of the Slow, Medium, and Fast formulations are included in Fig. 1 for conditions of phosphate buffer (pH 7.0) (A) and simulated gastric fluid (B). It can be seen that the release rate is significantly faster in acidic media and that slightly better discrimination among the profiles is achieved in phosphate buffer at pH 7.0. Accordingly, all other experiments were conducted using the pH 7.0 medium. Figures 2A and B show a comparison of whole- and half-tablet release profiles for 15- and 30-mg SR tablets, respectively. The release rate of half tablets is significantly faster than that of intact tablets. The relative increase in the percentage dissolved for half tablets is greatest at the early time points (25–35% at 0.5 to 1 hr) and monotonically decreases to about 3–6% at 18 hr.

In Figs. 1 and 2A and B, the error bars represent 95% confidence intervals about the mean and the smooth curve is the fitted data using the Weibull function [Eq. (1)]. The

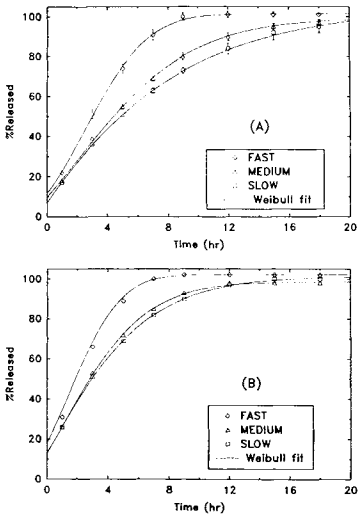

Fig. 1. Drug release profiles for the Slow, Medium, and Fast formulations of sustained-release adinazolam mesylate 15-mg tablets using the 100-rpm rotating basket with (A) pH 7.0 phosphate buffer and (B) pH 1.2 simulated gastric fluid as media.

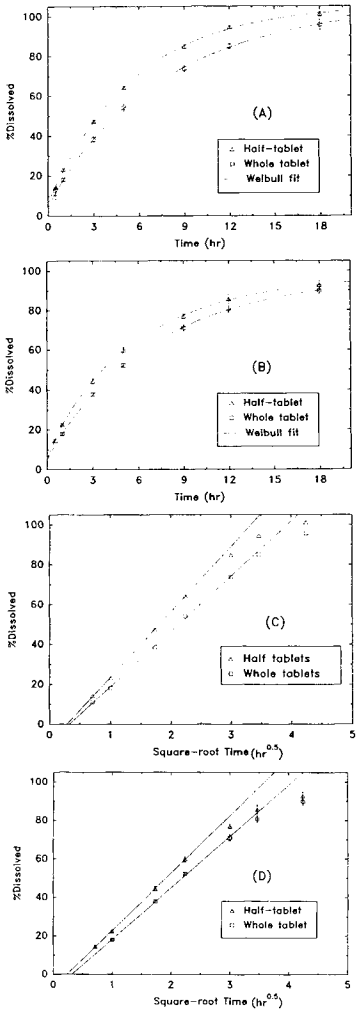

Fig. 2. Whole- and half-tablet drug release profiles for sustained-release adinazolam mesylate tablets: (A) 15 mg; (B) 30 mg. Error bars represent the 95% confidence interval about the mean percentage dissolved. C and D are the corresponding Higuchi plots (% dissolved vs square root of time) for the data in A and B, respectively.

Weibull function provided excellent fits to the data, with R^2 greater than 0.9901.

Mechanism of Release. The mechanism of release was inferred by evaluation of the linearity of Higuchi plots (% dissolved vs $t^{1/2}$) and by the value of the diffusional exponent, n, obtained by fitting Eq. (2) to the drug release data. Higuchi and Higuchi (29,30) derived simplified relationships based on Fick's laws of diffusion to describe the release of soluble and insoluble drugs from various matrices. Equation (5) gives the Higuchi equation as adapted by Lapidus and Lordi (9) for the release of drugs from swellable hydrophilic matrices,

$$M_t = 2M_\infty\left(\frac{S}{V}\right)\cdot\left(\frac{D't}{\pi}\right)^{1/2} \qquad (5)$$

in which S is the effective surface area for diffusion, V is the volume of the hydrated matrix, and D' is the effective drug diffusion coefficient in the hydrated matrix. This simple re-

lationship is frequently used to analyze the drug release mechanism from swellable hydrophilic matrices in terms of diffusion (9,10,14–16).

Figures 2C and D show plots of the percentage dissolved vs the square root of time for the whole and half 15- and 30-mg SR tablet data shown in Figs. 2A and B, respectively; linear least-squares regression results of these data and two additional 15-mg SR tablet lots are summarized in Table I. There are three main points to be made regarding these data. First, each plot shows a significant negative intercept. This has been observed previously (9–11) and is attributed to the time lag required to form the viscous gel layer. The data in Table I show a general trend of a shorter lag time (computed from the abscissa intercept of the square root of time plots) for half tablets relative to whole tablets. Second, the slopes for half tablets in these plots are significantly greater than those for whole tablets (see discussion below). Third, the data appear linear up to about 70–80% dissolved ($R^2 > 0.989$) and then taper off. The extended linearity of these data seems to indicate that diffusion is a predominant release mechanism.

In order to characterize the release mechanism further, Eq. (2) was fit to the dissolution data after adjustment of each sampling time to account for the lag time (10). Table I presents the fitted results for several lots of whole and half tablets of 15 and 30 mg sustained-release adinazolam mesylate. The values obtained for the diffusional exponent, n, range from 0.59 to 0.66, with half tablet values somewhat smaller than those of whole tablets. Values of the diffusional exponent in this range are indicative of a coupling of diffusional and macromolecular relaxation release mechanisms [so-called anomalous diffusion (18)]. These results are similar to those obtained by Ford (10), who reported values of n that ranged from 0.64 to 0.71 for release of soluble drugs from matrices containing HPMC with a viscosity of 15,000 cps. In addition, these results indicate that the extended linearity of the square root of time plots (Figs. 2C and D) noted above is somewhat deceiving, because examination of these plots alone may lead one to conclude that *in vitro* release is controlled by simple Fickian diffusion. Factors not accounted for in the mathematical derivation of Eq. (5), such as diffusion of solvent into and subsequent hydration and swelling of the polymeric matrix, erosion of the swollen matrix which causes a change in the diffusional path length (12), and diffusion in three dimensions, may combine to give the observed linearity of the square root of time plots.

Relationship to Surface Area. Upon breaking a dry SR adinazolam mesylate tablet along the score, two additional surfaces are exposed for dissolution. Based on the geometry of the tablet die and on measurements of the dry tablet thickness, an increase in the surface area-to-volume ratio of about 16% was computed for half tablets relative to whole tablets. Table I shows that this increase in surface area-to-volume ratio of half tablets is reflected by increases in the slopes of the Higuchi plots of 12 to 18% and the parameter k obtained from fits of the data to Eq. (2) of 20 to 23%. This can be rationalized by comparison of Eqs. (2) and (5). A purely Fickian diffusion mechanism would be characterized by linear plots of the percentage dissolved vs the square root of time and n from Eq. (2) equal to 0.5. For this case, k has physical meaning as shown in Eq. (6).

$$k = 2\left(\frac{S}{V}\right) \cdot \left(\frac{D'}{\pi}\right)^{1/2} \tag{6}$$

Thus, an increase in the surface-to-volume ratio of the swollen matrix should result in a proportionate increase in k and the slope of Higuchi plots. Although neither the increase in k nor the increase in Higuchi slope agrees with the true increase in surface to volume of 16%, the latter exhibits a range which encompasses it. These data provide additional support for the conclusion that diffusion is an important release-controlling mechanism for SR adinazolam mesylate tablets. However, as noted above, it is not simple Fickian diffusion but, rather, should be considered anomalous in nature.

Correlation of *in Vitro* Dissolution to *in Vivo* Bioavailability

It is well recognized that it is desirable from both a quality-control and a regulatory standpoint to establish an *in vivo/in vitro* correlation for a solid oral dosage form (32–34).

Table I. Comparison of Computed Parameters for Drug Release Data Fit to the Higuchi (Square Root of Time Law) and Peppas Equations

	Higuchi equation (linear regression of % dissolved vs $t^{1/2}$)							Peppas equation,[a] $M_t/M_\infty = k \cdot t^n$				
	Whole tablets			Half tablets				Whole tablets		Half tablets		
Lot[b]	t_{lag} (min)[c]	Slope[d] (% D $hr^{-1/2}$)	R^2	t_{lag} (min)[c]	Slope[d] (% D $hr^{-1/2}$)	R^2	% increase in slope[e]	k (hr^{-n})	n	k (hr^{-n})	n	% increase in k[e]
A	6.7	27.8	0.995	5.0	32.8	0.998	18.0	19.5	0.64	24.0	0.63	23
C	8.7	28.1	0.994	5.0	32.0	0.994	13.9	18.5	0.66	22.8	0.64	23
D	7.2	28.0	0.994	6.0	32.5	0.999	16.1	19.6	0.64	23.8	0.61	21
B	6.0	26.7	0.989	3.2	29.8	0.991	11.6	19.4	0.62	23.3	0.59	20

[a] The lag time was subtracted from each dissolution time value and the Weibull function was used to fit these data. Using the parameters from this fit, synthetic dissolution data were generated and fit to Eq. (2) over the time range corresponding to 60% dissolved.
[b] Lots A, C, and D are 15-mg strength; lot B is 30-mg strength. Lots A and B were included in the second bioavailability study.
[c] The lag time was computed as the square of the abscissa intercept of plots of percentage dissolved vs $t^{1/2}$.
[d] Whole tablets were fit over 9 hr, while half tablets were fit over 5 hr.
[e] Relative to whole tablets.

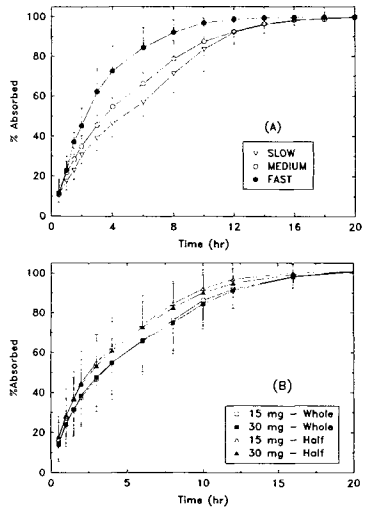

Fig. 3. Percentage of adinazolam absorbed *in vivo* computed using either the Wagner–Nelson or the Loo–Riegelman method for (A) the formulations used in the first bioavailability study (Slow, Medium, and Fast formulations) and (B) the formulations used in the second bioavailability study (15- and 30-mg Slow tablets). Error bars represent one standard deviation about the mean.

The principal utility of a correlation, where one can be shown to exist, is for setting drug release specifications that provide assurance of lot-to-lot consistency of *in vivo* product performance (32,33). Comparison of the data for *in vitro* drug release (Figs. 1B and 2A) and *in vivo* fractions absorbed (Fig. 3) for sustained-release adinazolam mesylate tablets reveals an excellent rank order correlation.

In vivo/in vitro relationships were evaluated for the individual treatments (tablet lots) included in the two bioavailability studies and for the pooled data sets from each study. In general, a quadratic regression model was found to fit the data significantly better than a linear model. Table II presents the regression results for the mean percentage absorbed *in vivo* vs the mean percentage dissolved *in vitro* using a quadratic model. The P value presented in the last column in Table II indicates whether the regression equation for a pooled data set is statistically equivalent to the regression equations of the individual data sets (31). Note that the Fast and Medium 15-mg SR formulations from the first bioavailability study pool ($P = 0.1108$), but the Slow and Medium formulations do not pool ($P = 0.0022$). Comparison of the regression equations (Table II) shows that the Fast and Medium formulations were fit best by a quadratic model (significant curvature in plots of percentage absorbed vs percentage dissolved), while the Slow formulation was fit best by a linear model. The differences observed are due in part to the differences in formulation composition utilized to vary the drug release rates. However, the statistical differences between these regression relationships are small, particularly in relation to the greater variability inherent in the *in vivo* data (cf. Figs. 1A and 3). A similar argument applies to the relationships developed in the second bioavailability study, where the 15-mg whole- and half-tablet data pool, the 30-mg whole- and half-tablet data pool, but the 15- and 30-mg data together do not pool (Table II).

Finally, comparison of the regression equations in Table II shows reasonable agreement across the two bioavailability studies. It is appropriate to pool these data given the relatively small differences among the regression equations. The combined data from each bioavailability study better define the *in vivo/in vitro* correlation by including additional product batches and a larger patient population. Figure 4 presents a plot of these data and shows the fitted regression line for the pooled data sets. The quadratic regression relationship for the data plotted in Fig. 4 is presented below:

$$Y = -1.2\ (\pm 1.5) + 1.36\ (\pm 0.06) \cdot X - 3.42\ (\pm 0.52)10^{-3} \cdot X^2,\ R^2 = 0.9912$$

This equation is the most accurate representation of the *in vivo/in vitro* correlation for sustained-release adinazolam mesylate tablets because data were included from two inde-

Table II. Summary of *in Vivo/in Vitro* Relationships[a] for Sustained-Release Adinazolam Mesylate Tablets

Row	Data set	β_0 (±SD) (% Abs)	β_1 (±SD) (% Abs/% Dis)	β_2 (±SD) · 10^3 (% Abs/% Dis^2)	MSE$^{1/2}$ (% Abs)	R^2	N pts	P value[b]
			Lots from bioequivalence study 1					
1	Fast release	−6.8 (4.9)	1.61 (.18)	−5.69 (1.37)	2.47	0.9935	12	
2	Medium release	3.0 (2.3)	1.16 (.09)	−1.85 (0.79)	1.46	0.9979	12	0.1108[1,2]
3	Slow release	0.4 (3.5)	1.04 (.15)	0.23 (1.27)	2.31	0.9955	12	0.0022[2,3]
4	Pooled data	−3.3 (2.7)	1.38 (.11)	−3.52 (0.87)	3.02	0.9897	36	0.0002[1–3]
			Lots from bioequivalence study 2					
5	15-mg whole tablets	3.5 (1.9)	1.17 (.09)	−1.60 (0.84)	1.56	0.9976	11	
6	15-mg half tablets	0.5 (2.6)	1.26 (.10)	−2.66 (0.90)	1.81	0.9969	11	0.0701[5,6]
8	30-mg whole tablets	2.4 (2.6)	1.22 (.12)	−1.65 (1.23)	1.98	0.9961	11	
9	30-mg half tablets	1.8 (2.0)	1.22 (.09)	−1.64 (0.79)	1.30	0.9983	11	0.8253[7,8]
11	Pooled data	1.1 (1.4)	1.28 (.06)	−2.59 (0.58)	2.18	0.9940	44	0.0014[5–8]

[a] A quadratic ($y = \beta_0 + \beta_1 \cdot x + \beta_2 \cdot x^2$) regression model was used to fit data for % absorbed *in vivo* (y) (% Abs) versus % dissolved *in vitro* (x) (% Dis).

[b] A general linear test (29) was used to determine whether or not data from two or more data sets can be pooled. The superscript numbers indicate the row numbers of the data sets that were pooled. If the P value is less than 0.05, then it can be concluded with >95% confidence that there is a significant difference between the pooled regression equation and the individual regression equations from each data set.

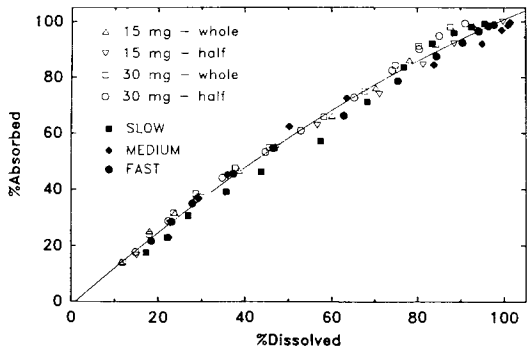

Fig. 4. Pooled *in vivo/in vitro* relationship for sustained-release adinazolam mesylate tablets. See text for regression relationship.

pendent bioavailability studies, four different lots, whole and half tablets, and two dosage strengths.

CONCLUSIONS

The *in vitro* drug release profiles of whole and half tablets of sustained-release adinazolam mesylate were fit well by the Weibull function and the mechanism of release was assessed using the Higuchi equation and by analysis of drug release profiles through 60% released using the Peppas equation. Higuchi plots of the drug release data are linear up to about 70–80% dissolved, indicating that diffusion is a predominant release mechanism. Computed values of the diffusional exponent (n = 0.59 to 0.66) from the Peppas equation are indicative of a mixed mechanism of release, with diffusion of drug through the hydrated matrix and relaxation of this matrix being principal processes which determine the observed kinetics of release. These data are consistent with results reported in the literature for the release of soluble drugs from hydrophilic matrix tablets. The increase in the release rate of half tablets relative to whole tablets is attributed to an increase in the surface area-to-volume ratio for half tablets of about 16%. The slope of Higuchi plots and a parameter, k, from the Peppas equation are proportional to this increase in surface-to-volume ratio. Taken together, the extended linearity of Higuchi plots and the proportionality between drug release rate and surface area to volume ratio indicate that Fickian diffusion is the predominant release controlling mechanism for sustained-release adinazolam mesylate tablets. However, the Peppas exponent indicates a coupling of diffusional and relaxational release mechanisms, termed anomalous diffusion by Peppas (17,18). Studies are underway in our laboratories to determine the relative contribution of each of these processes to the overall kinetics of release.

The *in vivo/in vitro* relationships from two bioavailability studies were thoroughly evaluated and found to be best described by a quadratic function.

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