DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(14-16), 2177-2195 (1989)

A FLOW-THROUGH DISSOLUTION APPROACH TO IN VIVO/IN VITRO CORRELATION OF ADINAZOLAM RELEASE FROM SUSTAINED RELEASE FORMULATIONS

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SUMMARY

A Copley™ fraction collector and a Disotest™ flow-through system were coupled to provide an automatic discrete sampling flow-through dissolution system for use both in the "open-loop" and "closed-loop" mode. The system was used to investigate the release characteristics of adinazolam in sustained release formulations using a pH 1.2 simulated gastric fluid (without enzymes) dissolution medium (USP XXI). These experimental formulations are designed to provide relatively slow to rapid drug release. The dissolution effluent was analysed off-line by reverse phase HPLC to determine the adinazolam concentration at programmed timed intervals. The differential dissolution profiles produced when the system is used in the "open-loop" configuration are more discriminating in describing the release characteristics of the formulations according to the relative release rates than the "closed-loop" cumulative profiles. Using the characteristic

dissolution time parameter from the Weibull function, a better correlation with in vivo bioavailability data was achieved for the data from the system in the "open-loop" mode than when it was used in the "closed-loop" mode. In the "open-loop" mode the Weibull function characteristic dissolution time parameter yielded the best quantitative correlation with a correlation coefficient of 0.92 compared to a value of 0.85 for the "closed-loop" configuration.

INTRODUCTION

In vitro dissolution testing is commonly used in the design and evaluation of solid oral sustained release formulations. However, the conventional USP and BP rotating paddle and rotating basket techniques can only provide cumulative release data. Although this information indicates the time of completion of the dissolution process and the overall release rate of actives, it may not adequately describe the release characteristics of controlled release solid oral dosage forms. Since the development of commercial flow-through dissolution systems (1) there have been many reports on the use of the technique for evaluating sustained release formulations (2-4). In the "open-loop" mode (unlimited supply of dissolution fluid) sink conditions are maintained irrespective of drug solubility (5). The method also shows low variability over a wide range of hydrodynamic conditions (6). With appropriate sampling of the dissolution effluent, exact drug

concentration versus time profiles can be obtained directly without data manipulation. Since these differential profiles show variations in the in vitro drug release process more clearly, dose dumping and erratic drug release may be more obvious.

Linear systems analysis has been used to define in vivo input-response relationships (7) and for non-compartmental in vivo/in vitro correlations (8). With this technique the input function I(t), related to in vitro dissolution (which is a differential function for non-zero order slow release), combines with the weighting function W(t), representing the body system, to give the response function R(t). R(t) is related to in vivo plasma concentration-time profiles (Equation 1).

$$R(t) = I(t) * W(t) \qquad [1]$$

The input and weighting functions are combined by the process of convolution symbolised by the asterisk (8). The closer the in vivo and the in vitro curve parameters are related to the principles of linear systems analysis for input-response relationships, the better the parameters will be for correlation purposes (9). The similarity of differential dissolution profiles, obtained using the flow-through method in the "open-loop" mode, to the in vivo bioavailability profiles should therefore allow useful empirical in vivo/in vitro correlation of sustained release formulations.

The use of the Weibull function curve parameters for empirical non-compartmental correlation between *in vivo* and *in vitro* systems following the principles of linear systems analysis, has been discussed previously (10). The explicit form of the Weibull function (Equation 2), where F_t is the fraction dissolved at time t, requires four parameters to describe the dissolution curve, (F_∞, β, t_0 and T_d). F_∞ is the fraction dissolved at time t_∞, β is the shape parameter, t_0 is the lag time and T_d represents the characteristic dissolution time. Of these four parameters the

$$F_t = F_\infty - F_\infty \times exp\left\{ -\left[\frac{(t-t_0)}{T_d} \right]^\beta \right\} \qquad [2]$$

characteristic dissolution time T_d, which is the time for 63.2% to dissolve, appears to be the most appropriate for correlating dissolution data (10) since it consistently represents the time for release of a certain fraction of drug irrespective of the values of the other parameters.

In this study, the release characteristics of adinazolam from three experimental sustained release formulations are investigated using the flow-through dissolution method. The Weibull function characteristic dissolution time parameter is used to assess the relationship between the flow-through dissolution profiles and *in vivo* profiles from previous bioavailability studies.

MATERIALS

Dissolution studies were carried out on three batches of low strength (15 mg) and three batches of high strength (30 mg) adinazolam sustained release tablets manufactured by the Upjohn Company (Kalamazoo, USA). Tablets from the same batches were used for the bioavailability studies. The formulations are designed to provide relatively slow to rapid release characteristics. Reagents used in the dissolution tests were of analytical reagent grade and solvents for HPLC measurements were of HPLC grade (Fisons, UK).

METHODS

Dissolution Test

Dissolution studies were carried out at 37 ± 0.1 °C using an in-line discrete automatic sampling flow-through system, which comprises a Disotest CE6 thermostatted flow-cell unit, a Disopump CY6 (Sotax AG, Switzerland) and a Dissoette fraction collector (Copley, UK). When the system was configured in the "open-loop" mode, the dissolution effluent was sent to waste via the sampling unit and when in the "closed-loop" mode, the effluent was re-cycled. In the "open-loop" mode, a single reservoir containing 50 litres of dissolution fluid was used. For the "closed-loop" mode, a paddle apparatus (Caleva Model 6ST, UK) was used to provide the six reservoirs needed for the six flow cells. Each reservoir contained 500 ml of dissolution medium stirred at 100 rpm. The

dissolution fluids employed were pH 1.2 simulated gastric fluid without enzymes (USP XXI) and phosphate buffers at pH 4, pH 7 and pH 9. Dissolution tests were conducted using 22.6 mm diameter flow cells with flow rates of 8 ml/minute or 15 ml/minute for the "closed-loop" mode and 8 ml/minute for the "open-loop" mode. At timed intervals, the dissolution effluent was sampled by removal of 8 ml and 3 ml fractions for the "open-loop" and the "closed-loop" configurations respectively. Sampling in both cases was carried out over 960 minutes at intervals of 0.5 minute to 2 hours.

HPLC Analysis

The HPLC analyses to determine the levels of adinazolam in the fractions of dissolution effluent were performed using a Brownlee RP-8 column eluted with acetonitrile/tetrahydrofuran/(0.1 M) pH 3.6 phosphate buffer (20:5:75) mobile phase at 1.5 ml/min. Detection was by UV absorbance at 220 nm.

In Vivo Bioavailability Studies

Comparative bioavailability studies of adinazolam in healthy human volunteers, for the sustained release formulations, were performed by the Upjohn Company, Kalamazoo, USA.

Data Processing

Differential profiles obtained directly for the "open-loop" dissolution studies and the plasma concentration-time profiles from the bioavailability studies were converted to cumulative profiles

to obtain Weibull function curve parameters by trapezoidal integration. All transformations and evaluation of cumulative curve parameters were carried out on the raw data from the dissolution and bioavailability studies using an IBM-PC based program. The program uses a linear form of the Weibull function (Equation 3) and least squares fit to the converted data to evaluate β and T_d. A simplex optimisation routine is employed to find values for F_∞ and t_0 giving the best fit for the data to the Weibull function.

$$\ln(-\ln(F_\infty - F_t)) = \beta\ln(t-t_0) - \beta\ln T_d \qquad [3]$$

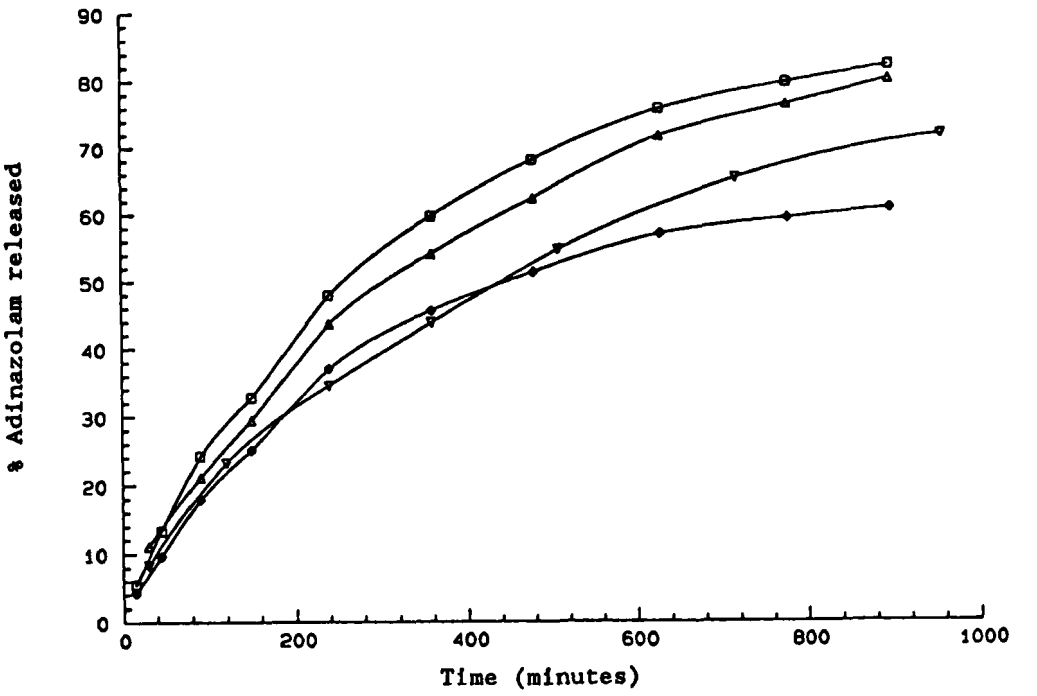

FIGURE 1
"Closed-Loop" Cumulative Dissolution Profiles for 15 mg Slow Release Formulation in pH 1.2 - 9.0 Dissolution Fluids. □ pH 1.2; △ pH 4.0; ▽ pH 7.0; ♦ pH 9.0.

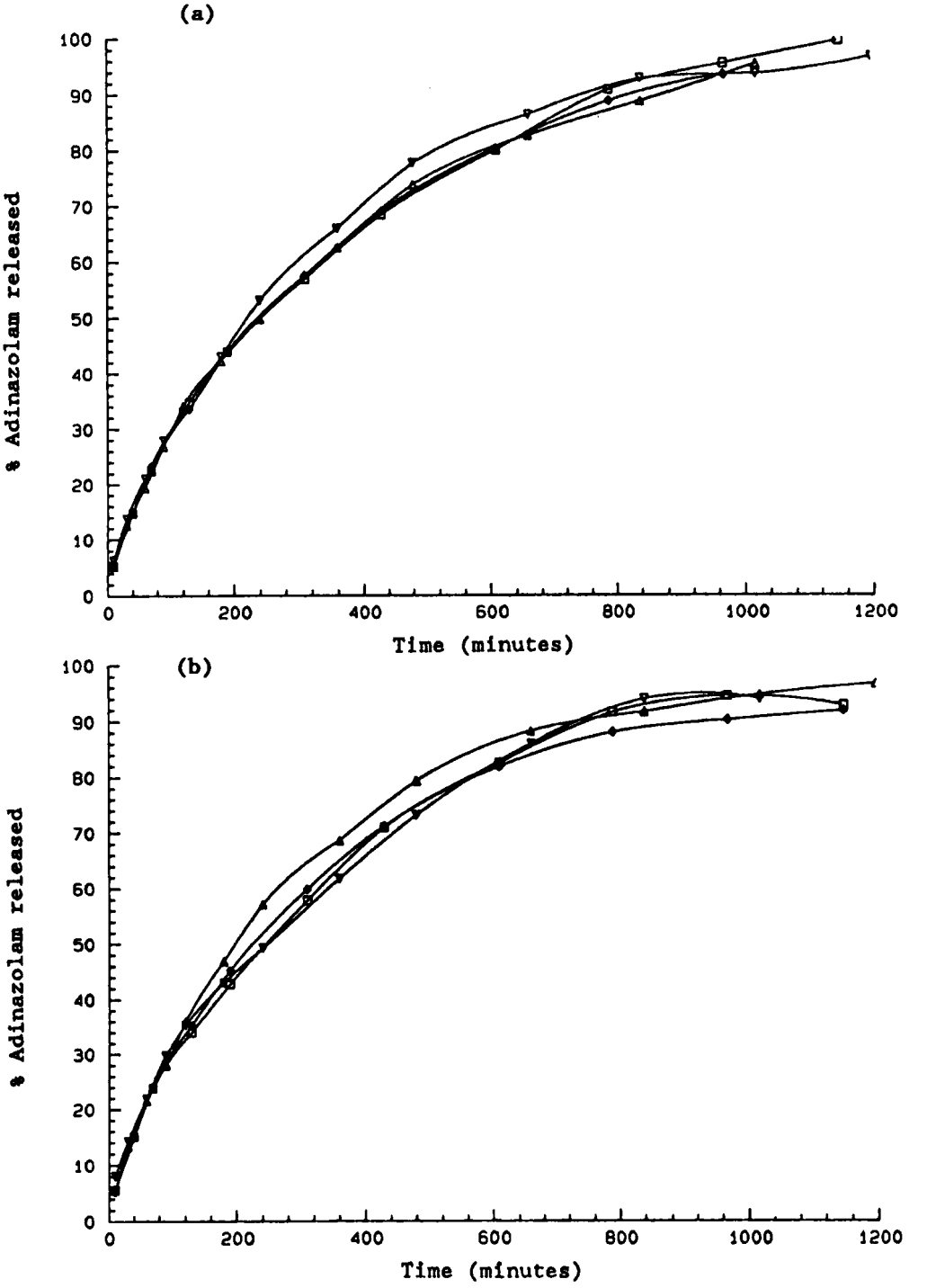

FIGURE 2 (a), (b) and (c)
"Closed-loop" Cumulative Dissolution Profiles of 15 mg and 30 mg (a) Slow (b) Moderate and (c) Rapid Release Formulations for 8 ml/min and 15 ml/min Flow Rates. □ 15 mg at 8 ml/min; ♦ 30 mg at 8 ml/min; ▽ 15 mg at 15 ml/min; △ 30 mg at 15 ml/min.

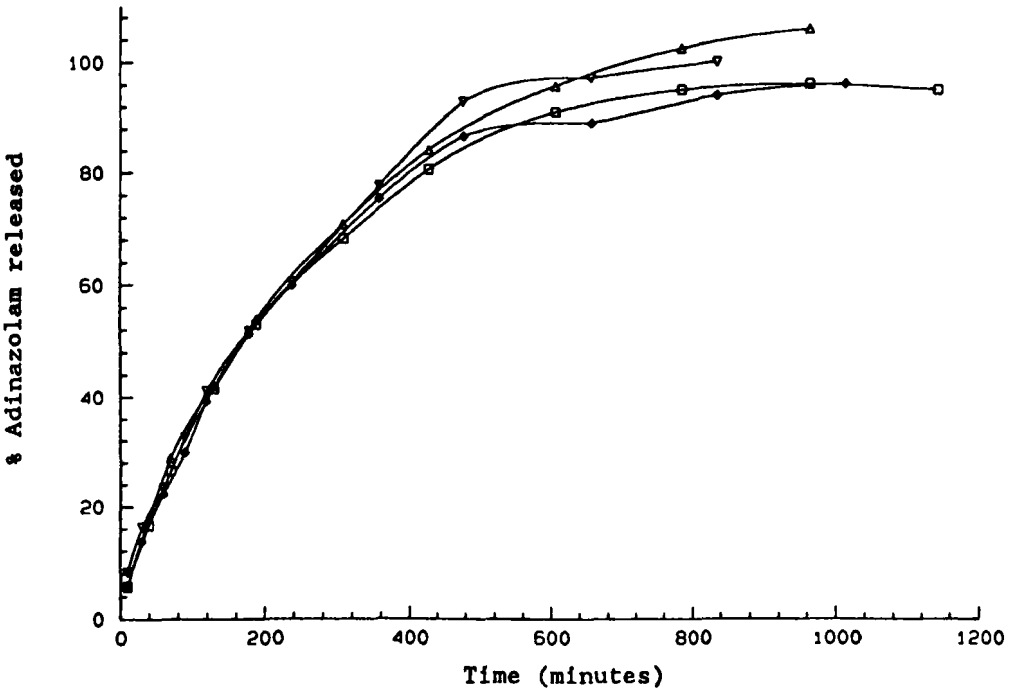

FIGURE 2 (c)

RESULTS AND DISCUSSION

Six batches of the adinazolam sustained release tablets at 15 mg and 30 mg strengths designed for slow, moderate and rapid release were examined using the flow-through dissolution system in both the "open-loop" and "closed-loop" modes. The results for the "closed-loop" mode with the 15 mg formulations (Figure 1), show an increase in the overall release rate of adinazolam on decreasing the pH of the medium from 9.0 to 1.2. Since sink conditions are maintained throughout the pH range, then the changes in the release profiles observed may be due to the effects on the excipients used

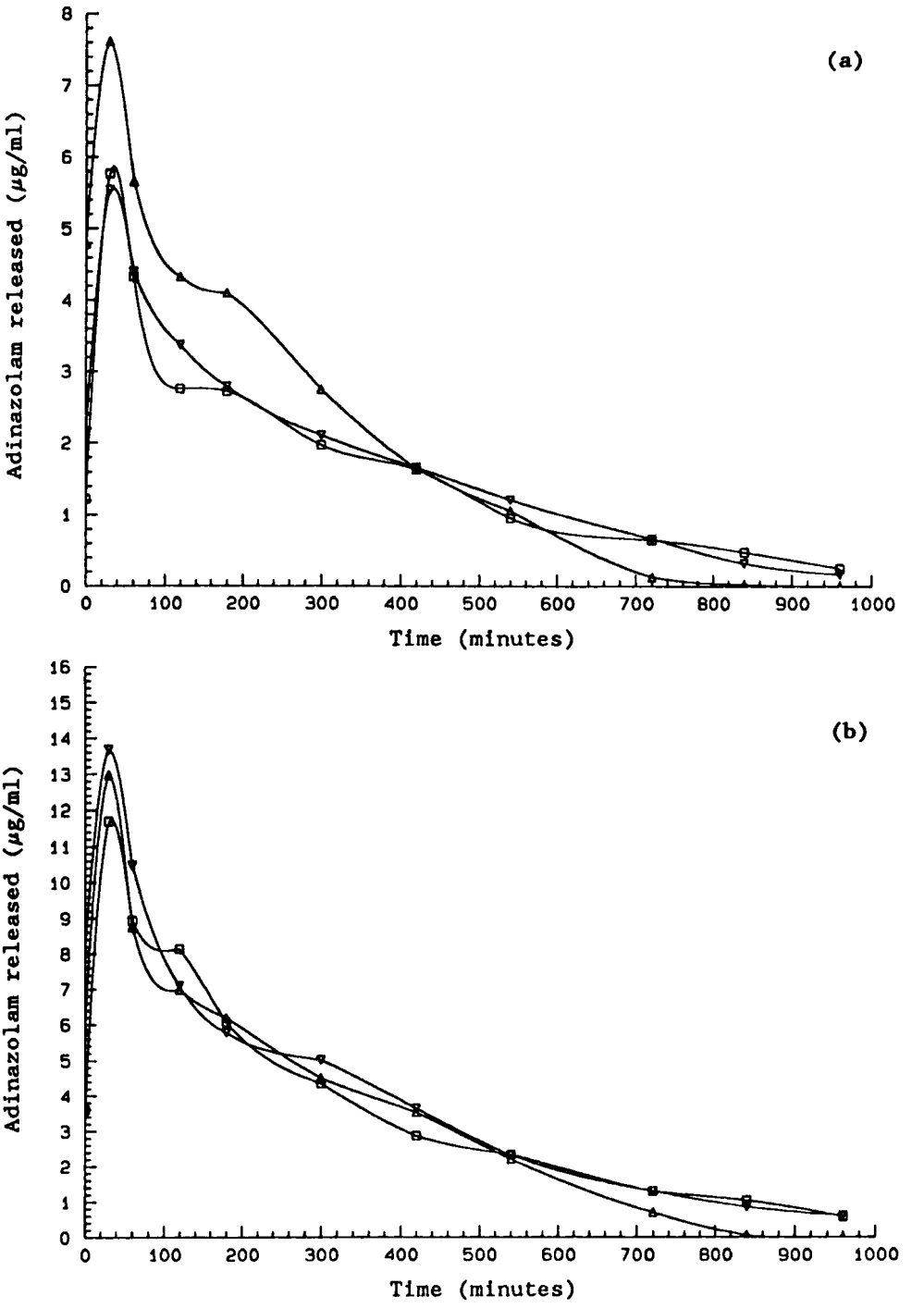

FIGURE 3

"Open-Loop" Differential Dissolution Profiles for (a) 15 mg and (b) 30 mg Formulations. △ Rapid release; ▽ Moderate release; □ Slow release.

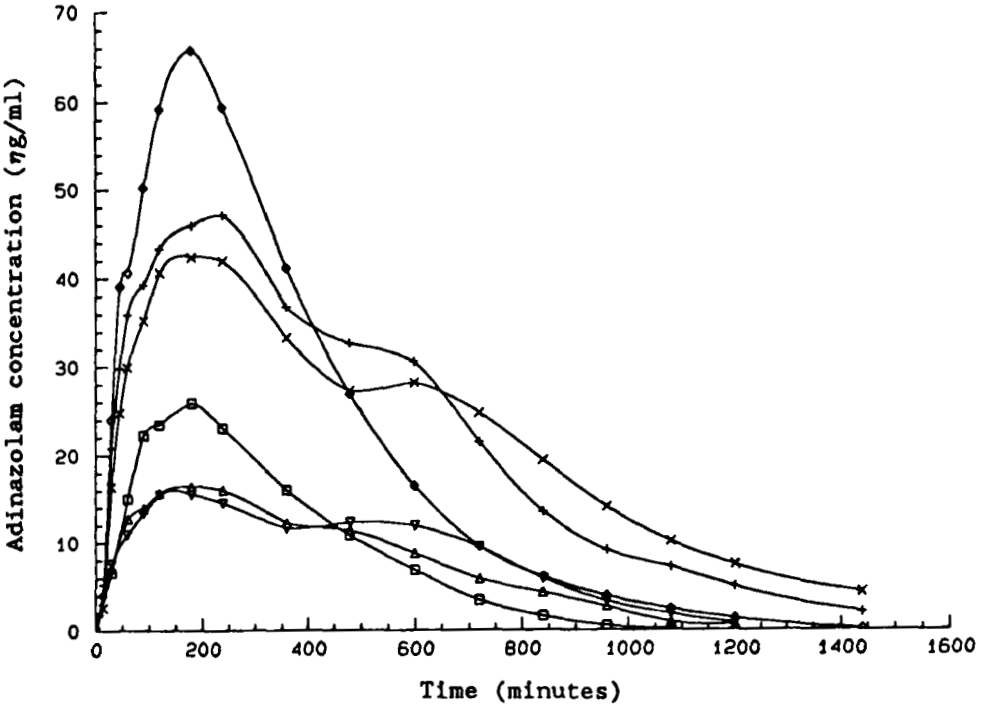

FIGURE 4
Plasma Concentration-Time Profiles for the Three Formulations at 15 mg and 30 mg dose. ♦ 30 mg Rapid release; + 30 mg Moderate release; x 30 mg Slow release; □ 15 mg Rapid release; △ 15 mg Moderate release; ▽ 15 mg Slow release.

in the formulations. The cumulative release profiles (Figures 2a and 2b) for the three formulations obtained for flow rates of 8 and 15 ml/minute show no significant difference in the release rates of adinazolam from the slow and moderate formulations. The profiles for the rapid release formulation begin to show small deviations in the release rates in the terminal regions of the profiles (Figure 2c). The differential dissolution profiles for the three formulations tested in simulated gastric fluid without enzymes

using the "open-loop" system (Figure 3), show resemblance to the in vivo profiles (Figure 4). The curves indicate slight variability in the release rates of the formulations during the dissolution process. This behaviour is not so evident in the cumulative profiles obtained using the dissolution system in the "closed-loop" mode (Figure 5). Although more data points are needed to describe the drug release process more accurately, the "open-loop" configuration shows the potential for illustrating variations the release profiles. The relative release rates for the three formulations (slow, moderate and rapid release) are also apparent from these differential dissolution profiles for both high and low strength tablets, showing consistency with the in vivo plasma concentration-time profiles.

Transformation of the in vivo and the in vitro differential profiles to generate curves fitted to the Weibull function, illustrated in Figure 6, was performed directly on the raw data from the bioavailability and the "open-loop" flow-through dissolution studies. Values for the curve shape parameter, β, for the in vivo curves (Table 1) are all significantly greater than 1 (consistent with a sigmoidal curve), which indicates a slow initial release of adinazolam followed by an accelerated approach to the final plateau (10). On the other hand, the values for the shape parameter for the "open-loop" dissolution data (Table 2), are approximately 1 or slightly less than 1, which is indicative of a fast initial in vitro release approaching the plateau at a rate consistent with a simple first order exponential curve. The Weibull

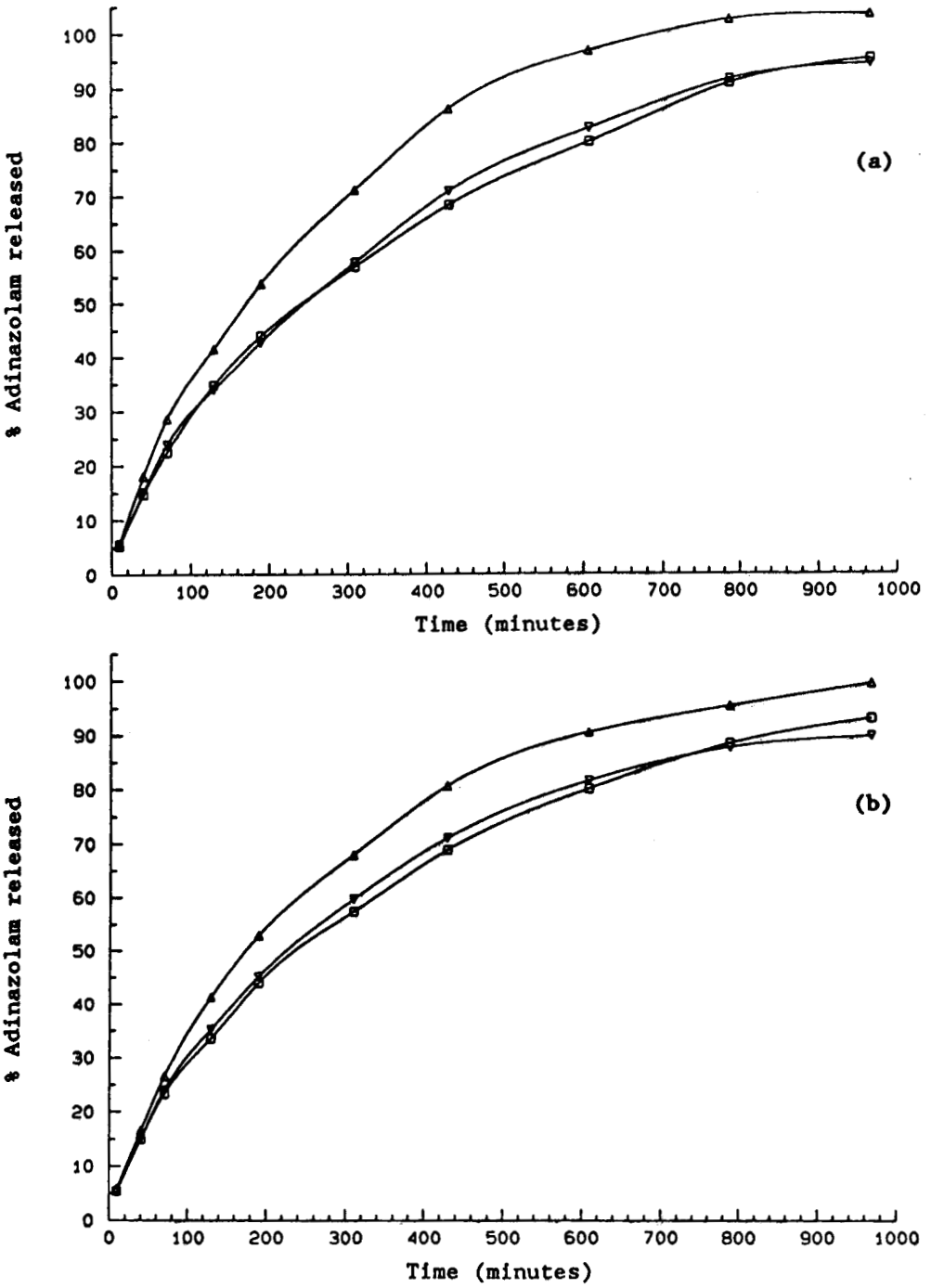

FIGURE 5

"Closed-Loop" Cumulative Dissolution Profiles for (a) 15 mg and (b) 30 mg Formulations. △ Rapid release; ▽ Moderate release; □ Slow release.

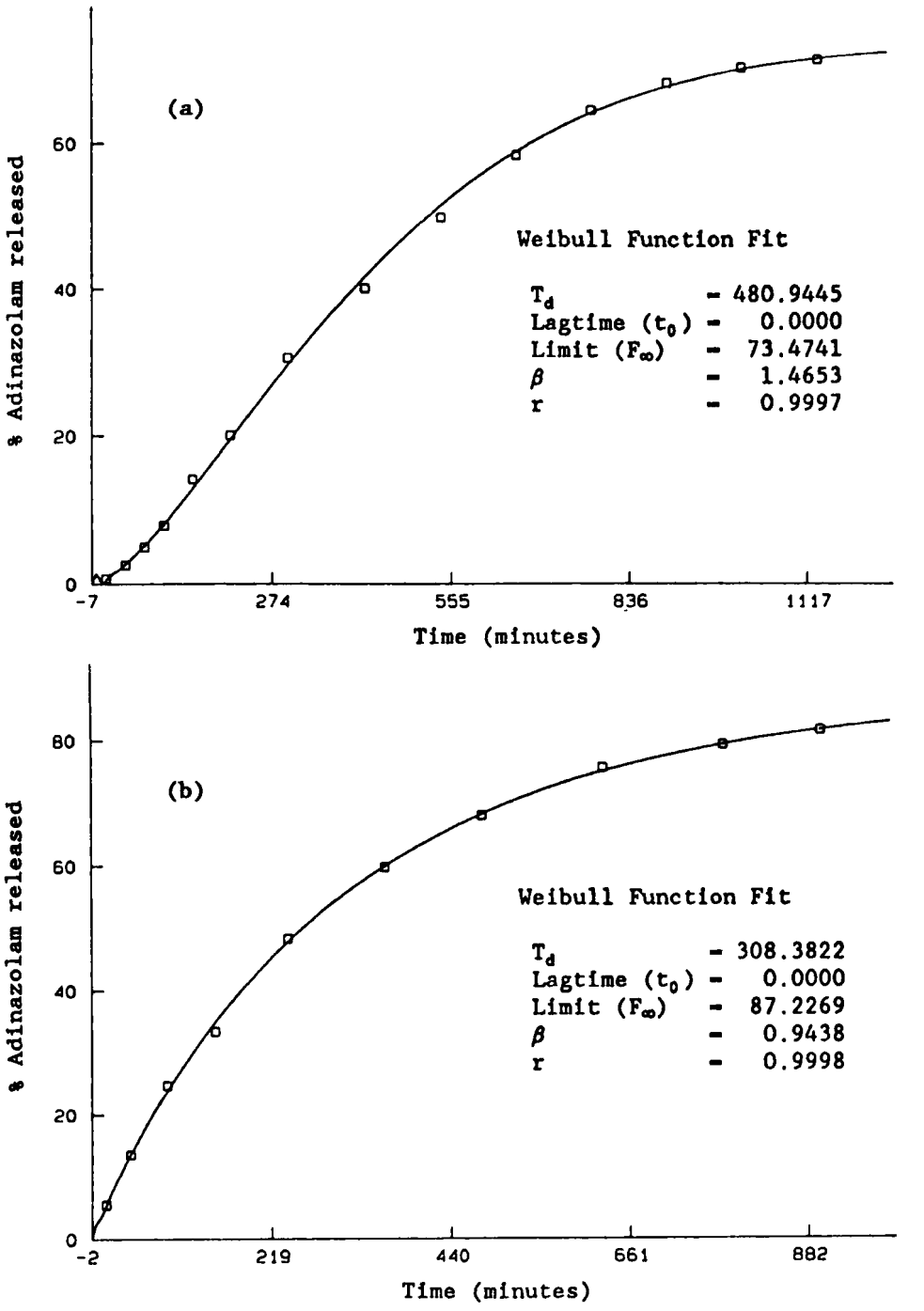

FIGURE 6
Cumulative Profiles Fitted to the Weibull Function.
(a) Bioavailability Data for 15 mg Slow release formulation;
(b) "Open-loop" dissolution data for 15 mg Slow release formulation

TABLE 1

Weibull function curve parameters for bioavailability data. T_d is the Weibull function characteristic dissolution time, which is the time taken for 63.2% of the drug to be released; β is the curve shape parameter.

Tablet Batch	Bioavailability Curve Parameters	
	T_d	β
A	480.94	1.47
B	317.34	1.61
C	415.62	1.46
D	529.82	1.47
E	351.76	1.51
F	465.86	1.47

TABLE 2

Weibull function curve parameters for dissolution data. T_d is the Weibull function characteristic dissolution time, which is the time taken for 63.2% of the drug to dissolve; β is the curve shape parameter; (a) is the 8.0 ml/min data, (b) is the 15.0 ml/min data.

Tablet Batch	T_d Open-Loop	T_d Closed-Loop (a)	T_d Closed-Loop (b)	β Open-Loop	β Closed-Loop (a)	β Closed-Loop (b)
A	316.89	489.50	456.43	0.91	0.78	0.79
B	221.44	294.90	266.15	1.17	0.87	1.07
C	289.08	432.42	628.01	1.00	0.80	0.73
D	301.64	489.49	334.51	0.92	0.78	0.91
E	247.50	298.64	251.84	1.13	0.89	0.99
F	308.07	349.42	349.10	0.93	0.83	0.92

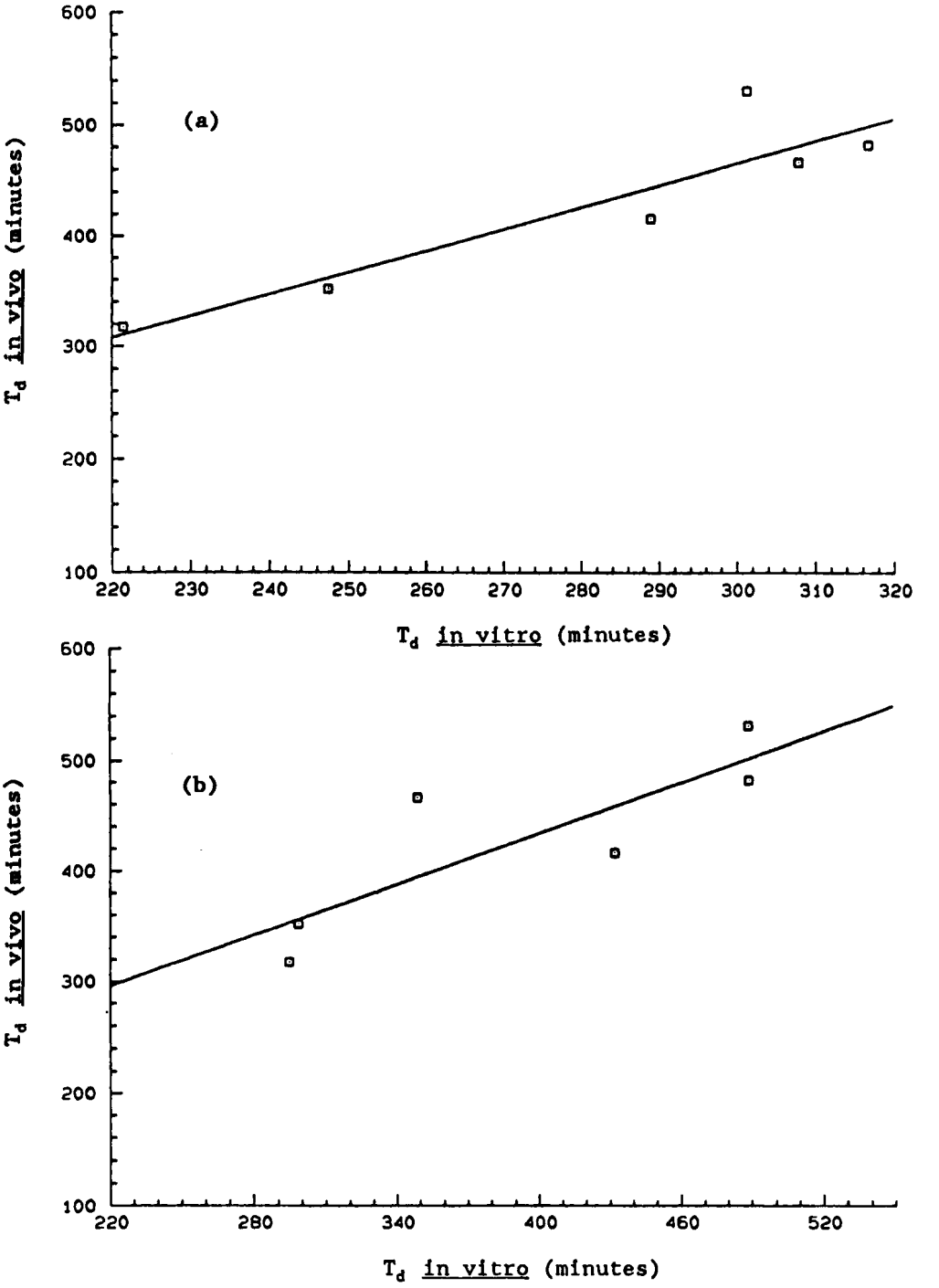

FIGURE 7

Plots of Weibull function T_d Parameters for Bioavailability data versus (a) "Open-Loop" Dissolution Data (correlation coefficient r = 0.92) and (b) "Closed-Loop" Dissolution Data (correlation coefficient r = 0.85).

function curve shape parameter values for the "closed-loop" dissolution data are in the range 0.73 to 1.07 (Table 2) which further support the notion of a faster initial in vitro release compared to the initial in vivo release. Additionally, the curve shape parameter values for the "closed-loop" configuration appear to be only marginally affected by changing the flow rate of the dissolution fluid from 8 ml/minute to 15 ml/minute.

Quantitative correlation of the flow-through dissolution results for the system in both the "open-loop" and the "closed-loop" mode with the bioavailability data for the three sustained release adinazolam formulations was attempted. This was done by use of the Weibull function curve parameter T_d (values listed in Tables 1 and 2). An association between the in vivo bioavailability and in vitro dissolution data was established for the system operating in both the "open-loop" and "closed-loop" mode, at a flow rate of 8 ml/minute (Figure 7). The correlation coefficient for the plot of T_d (in vivo) versus T_d (in vitro) was marginally better when the system was used in the "open-loop" mode ($r = 0.92$) than when it was used in the "closed-loop" mode ($r = 0.85$).

CONCLUSION

The "open-loop" flow-through dissolution differential profiles provide more information about the release characteristics of the sustained release formulations than the "closed-loop" cumulative

profiles. The differential dissolution curves indicate the changing rate of the in vivo input more clearly. They show a resemblance to curves for the bioavailability studies. The more discriminating nature of the differential dissolution profiles serves to reveal slight variations in the release characteristics of the sustained release formulations. The similarity of the "open-loop" differential profiles to the in vivo concentration-time profiles appears to allow marginally better in vivo/in vitro correlation than do the cumulative "closed-loop" profiles.

ACKNOWLEDGEMENTS

The authors are grateful to all Upjohn personnel involved in the bioavailability studies performed and in particular, M.T. Borin and H.S.H Lau, for allowing the inclusion of extracted data from their works. We would like to thank J.W. Skoug for providing the tablets and information essential for this study. Further, we would like to thank K.D. Cromie for her assistance in the preparation of this document.

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