# Pharmacokinetic Determinants in the Design and Evaluation of Sustained-Release Dosage Forms

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**Abstract:** A new method employing the principle of superimposition was developed to aid in the formulation of sustained-release dosage forms. Independently absorbed components of a product, e. g., waxed pellets for an oral capsule, are administered separately and their plasma level-time profiles determined. Using a trial and error procedure, the ratios of pellets are varied to obtain a desired plasma level-time profile. The use of (*1*) time averaged plasma concentration-time data, (*2*) amount remaining to be absorbed (excreted) plots, and (*3*) cumulative amount absorbed (excreted) plots were all shown to be inappropriate for pharmacokinetic analyses in general, and evaluation of sustained-release products in particular. It was recommended that raw plasma concentration-time data be made available for sustained-released products, and that individual rate of absorption plots be used to assess absorption kinetics. It was concluded that much of the sustained-release pharmacokinetic data presently in the literature have been presented in such a manner, e. g. averaged data, as to be of limited value.

A sustained-release (SR) dosage form may be defined as a preparation from which drug is absorbed *in vivo* at a considerably slower rate than from an equivalent dose in a conventional dosage form (1). When intended for acute or intermittent administration, it is desirable to have an initial slug of drug rapidly absorbed followed by a slower "maintenance" component (2, 3). For chronic drug administration, a zero-order absorption rate is the theoretical goal, where the rate of systemic drug appearance, $R_{systemic}$, is given by:

$$R_{systemic} = F \cdot R = CL \cdot C \qquad \text{(Eq. 1)}$$

where F is the drug bioavailability, R is the rate of drug administration, CL is total plasma clearance and C is the target steady-state plasma concentration. The amount of drug contained in each unit dosage form, $D_{unit}$, is given by:

$$D_{unit} = CL \cdot C \cdot \tau / F \qquad \text{(Eq. 2)}$$

where $\tau$ is a constant dosing interval. In practice, very few (if any) SR dosage forms result in zero-order systemic drug appearance (1).

The fundamental dilemma encountered with any oral dosage form, but for SR dosage forms in particular, is the variety of unpredictable physiological factors and states which affect drug release and absorption. Intra- and inter-subject differences can exist in gastrointestinal pH, volume, blood flow, electrolyte concentration, motility, gastric emptying and residence times, microflora, adsorptive and absorptive capacities, morphology, secretions, cell metabolism, relative surface areas, enzyme activity, etc. The rate and/or extent of drug absorption for all oral dosage can be affected by these factors, but SR products are considerably more susceptible, since they are intended to render more precise delivery. A further complication is that these properties may not be independent. For example, anxiety can affect pH which can affect motility which can affect microflora which can affect . . . Pragmatically, controlled delivery can never be achieved – this would be a violation of Ashby's Law of Requisite Variety: control can be exercised only by a controller [dosage form] having at least as high a variety as the system [gut] to be controlled (4). Drug delivery failures invariably arise, since gut and dosage form behavioral constraints, be they imposed by physical, chemical, pharmacokinetic or other reductionist models, have consistently failed to adequately incorporate the full complexity of the modeled phenomena. There is little or no control in any meaningful sense of the word, and it is therefore best to refer to these products as sustained-release or prolonged release.

The fact that drug in a SR dosage form is not absorbed at a zero-order rate does not imply a faulty product. The goals of SR therapy can often be achieved with first-order absorption. Gibaldi and Perrier (5) have demonstrated that for many drugs, acceptable steady-state plasma level-time profiles may be obtained assuming absorption half-lives of about 3–4 hours. Their criterion of acceptability was a low $C_{av,max}/C_{av,min}$ quotient, where the plasma concentrations are the time averaged maximum and minimum steady-state values, respectively. Theeuwes and Bayne (6) have termed this ratio the "dosage form index" and used it successfully to compare acetazolamide SR dosage forms.

Sustained-release dosage forms may be of varying physical and chemical types – coated beads, multiple-layer tablets, ion exchange resins and osmotic pumps to mention a few. It is widely held that zero-order *in vivo* release is the intent, but this is incorrect – the ultimate goal is zero-order systemic drug appearance. Zero-order *in vivo* release will produce zero-order systemic absorption only if: (1) the gut behaves as a one compartment model, i. e., its various segments are homogeneous with respect to absorption; and/or (2) drug release rate is rate limiting for absorption. Adair *et al.* (7) successfully predicted plasma concentration-time profiles for drugs in oral SR dosage forms based on *in vitro* dissolution and *in vivo* oral solution absorption profiles. This implies that one or both of these assumptions may be mathematically valid in certain situations. Their basic assumptions are that *in vitro* dissolution

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is duplicated *in vivo,* and that once in solution, regardless of location in the gut, absorption is kinetically indistinguishable from that observed with an orally administered solution. Drug released and dissolved in the large intestine is treated as drug entering the stomach. This technique would not be expected to work for those compounds whose absorption appears limited to short, site-specific, gut segments, e. g., riboflavin (8) and isonicotinuric acid (9). Moreover, there is never any *a priori* assurance that *in vitro* release rates recur *in vivo* or that the gut behaves in any consistent manner with respect to absorption for its anatomically and physiologically distinct segments. This is not intended as a criticism of the Adair *et al.* (7) procedure, but rather is a caveat to its use.

A method of SR product design is presented here based on the superimposition postulate (overlaying principle) (5, 10) which does not inherit any of these potential difficulties. It too has its limitations, but these are of a different sort. Also discussed are methods for the evaluation and presentation of SR pharmacokinetic data. It will be demonstrated that certain methods of plotting and analyzing data are considerably more revealing than other more customary plots.

## Pharmacokinetic Design and Evaluation of Sustained-Release Products

### *Design of Products Based on the Superimposition Principle*

Most physical pharmacists working with SR dosage forms have a predilection for zero-order drug release. For certain drugs (*vide supra*), this may effectuate zero-order absorption, but for others it will not. In the design formulation of some dosage forms, therefore, it may be more logical to abandon hypothetical, esoteric and technological constructs (products arising from these constructs rarely abide by human judgments of their efficiencies) in favor of an empirical approach using established technologies. Here we apply the principle of the blunt ax – if it chopped down the tree, it was sharp enough.

Let us assume we have a hypothetical drug whose population pharmacokinetics are characterized by the parameters listed in Table 1. Note that the terminal disposition half-life is 3.0 hours, and that the steady-state hepatic extraction ratio is 0.05; the only first-pass effect is hepatic, and there are no active metabolites. We intend to administer our oral dosage form at 12 hour intervals and achieve a time-averaged plasma drug concentration, $C_{av}$, of 44.5 ng/ml. Assuming zero-order absorption, the amount of drug to be contained in each unit dosage form, given by eq. 2, is 12.0 mg. Fig. 1 illustrates an idealized plasma level-time curve, where absorption is zero-order between 0–12 hours and then abruptly ends. Technology exists in our hypothetical pharmaceutical company to make coated slow-release beads or pellets intended for hard gelatin capsules or embedded in an inert tablet matrix. Four types of beads are prepared (A, B, C and D) and placed separately in hard gelatin capsules at 12 mg doses. Alternatively, each of the types are individually and homogeneously embedded in the inert tablet matrix. The four dosage forms in 12 mg doses are administered to a panel of subjects under simulated clinical conditions. Typical smoothed plasma level-time profiles are constructed from the data on Cartesian coordinates, and these are illustrated in Fig. 1. Fig. 2 illustrates semilogarithmic plots of the same data. In this example, bioavailabilities are all 0.95, but this is not necessary for the method. We now assume that any combination of bead types mixed in the final dosage form will not interact, e. g., bead type A will give the same absorption profile regardless of how much B, C, and D are present (*vide infra*). Stage I entails a quasi-empirical mathematical mixing of different proportions of the 4 bead types to try and match the theoretical 12 hour zero-order absorption generated curve. The principle of superimposition is used to generate theoretical single dose curves, and a trial and error procedure is used to continue improving the fit (graphical iteration). At this point, one should not be overly preoccupied with finding a perfect match. The top segment of Fig. 3 illustrates the best fit obtained by the author after 4 hours of

**Table 1** Population pharmacokinetic parameters for a hypothetical drug. Abbreviations are those recommended by Rowland and Tucker (11).

| | |
|---|---|
| $t_{1/2}, \lambda_1$ | = 0.112 hrs |
| $t_{1/2}, \lambda_2$ | = $t_{1/2}, \lambda_z$ = 3.00 hrs |
| $k_{12}$ | = 4.0 hrs |
| $k_{21}$ | = 1.0 hrs |
| $k_{10}$ | = 1.43 hrs |
| $V_1$ | = 14.9 liters |
| $V_{ss}$ | = 74.4 liters |
| CL | = 21336 ml/hr |
| $CL_H$ | = 5334 ml/hr |
| $CL_R$ | = 16002 ml/hr |
| $C_b/C$ | = 1.0 |
| $Q_H$ | = 1778 ml/min |
| $E_H$ | = 0.05 |
| F | = 1 – $E_H$ = 0.95 |

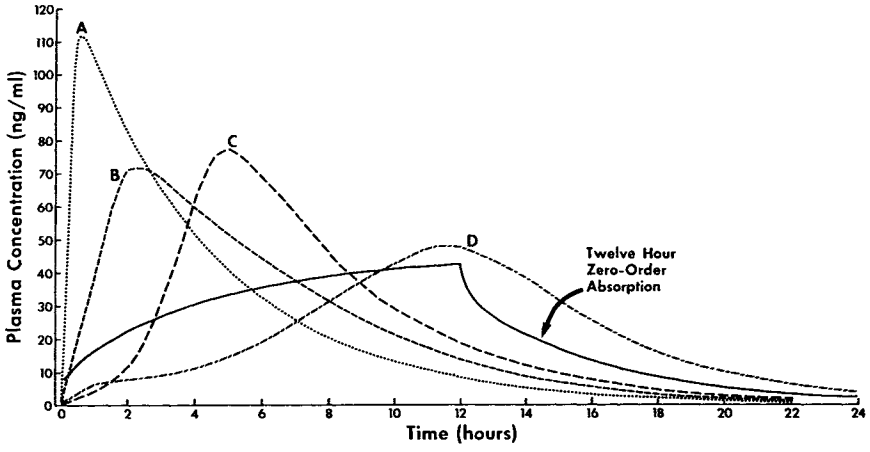


**Fig. 1** Smoothed plasma concentration-time curves resulting from administration of 4 bead types of a hypothetical drug (see Table 1) at 12 mg doses to a panel of subjects. Also illustrated is a theoretical curve for 12 hour zero-order absorption.

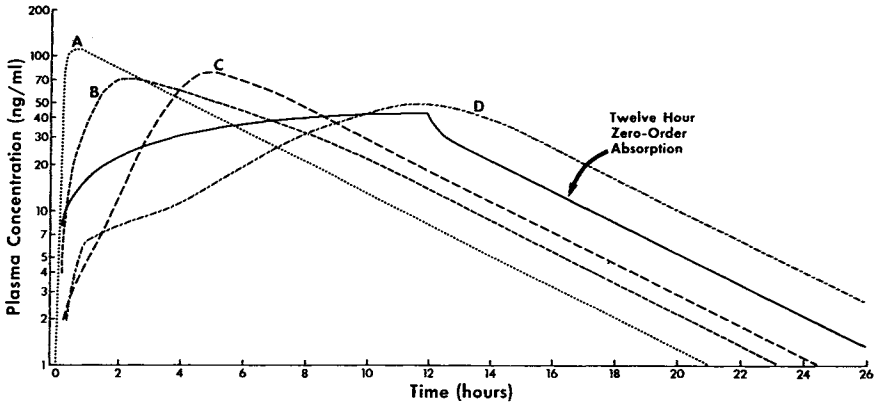


**Fig. 2** Semilogarithmic plot of the data illustrated in Figure 1.

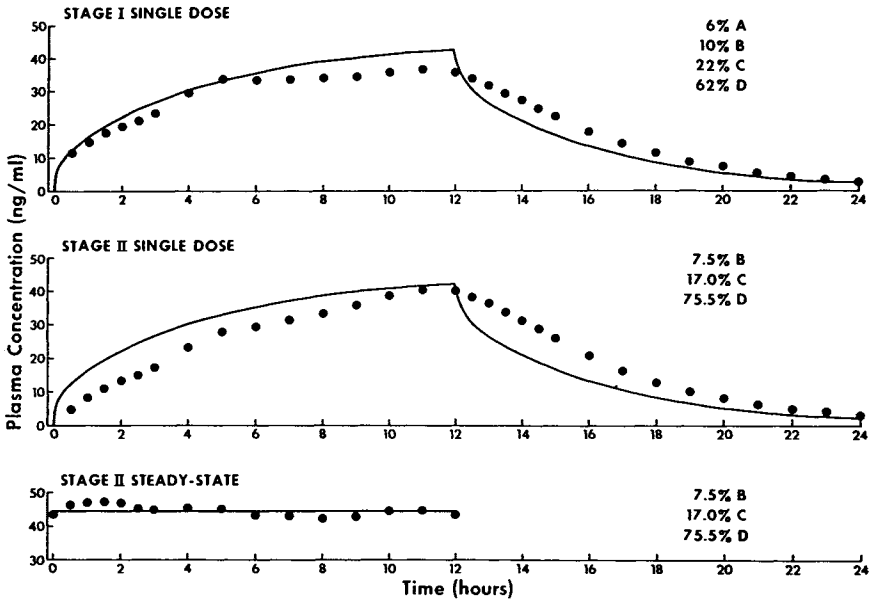


**Fig. 3** Stage I and II plasma level-time profiles for 12 mg doses of the hypothetical drug (Table 1). Solid lines represent theoretical curves for the perfect 12 hour zero-order absorption product. Data points are from mixtures of the indicated bead types. See text for discussion.

work. It contains 6, 10, 22 and 62%, respectively, of bead types A, B, C and D; the total dose is 12 mg, and the idealized and generated curves, although not superimposable, do have the same areas. Stage II utilizes the principle of superimposition to generate steady-state plasma level-time profiles. The mixture of beads is again varied by graphical iteration to fine-tune the dosage form so as to mimic a horizontal line of 44.5 ng/ml. The goodness of fit criterion is minimization of the dosage form index. The bottom segment of Fig. 3 illustrates the best steady-state profile that could be generated after an additional 4 hours of work. Note that bead type A was completely eliminated. The dosage form index is 1.11. A single-dose plasma concentration-time profile was generated for this bead ratio, and this is illustrated in the center portion of Fig. 3. Note that the superimposition generated single dose curve deviated more from the idealized 12 hour zero-order absorption curve than in phase I. This is irrelevant, since the drug is intended for chronic administration. The low plasma levels on the single dose curve between 0 to 12 hours, relative to the idealized curve, are counterbalanced by continued absorption and relatively high levels at later times. For many dosage forms the opposite will be true. An initial rapid burst of absorption may be needed to compensate for reduced absorption towards the end of the dosage interval. A Loo-Riegelman rate of absorption plot (12–15) from a single oral dose of the Stage II product is illustrated in Fig. 4; note that absorption does not

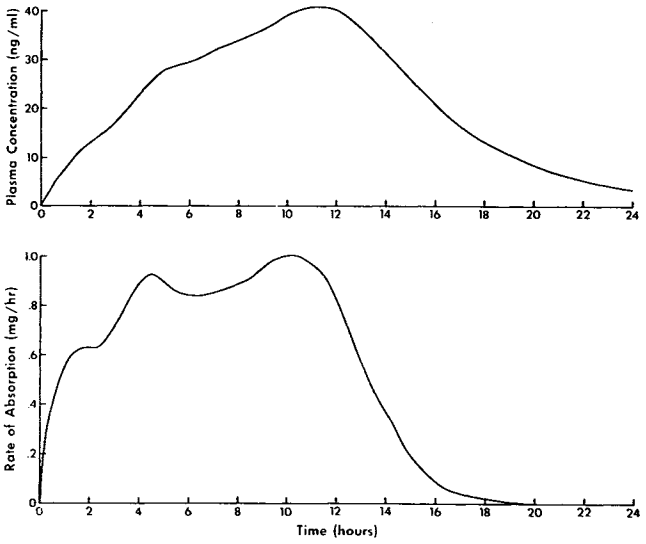


**Fig. 4** Theoretical plasma concentration and rate of absorption curves for a hypothetical drug (Table 1) administered as a single 12 mg oral dose of beads from the Phase II evaluative procedure. The mixture contains 7.5, 17.0 and 75.5%, respectively, of bead types B, C and D. Rate of absorption was determined by the Loo-Riegelman method (12–15).

appear zero-order. This is somewhat misleading, as there is dose-to-dose overlap in drug absorption with multiple dosing. At steady-state, the rate of absorption plot closely parallels the plasma levels illustrated in the bottom segment of Fig. 3. Once the principle of superimposition has identified a satisfactory theoretical combination of beads, clinical pharmacokinetic testing will be required for verification.

A potential technological limitation in utilizing the proposed method is the difficulty of manufacturing bead types with the same batch-to-batch drug releasing properties. Appropriate *in vitro-in vivo* correlations would be helpful in minimizing this variability. Another disadvantage of the approach is that it assumes bead components will not interact. If bead types A and B clump together and this affects release, an error is introduced. In practice, this is not likely to occur, since the same bead coatings are generally used but at different thicknesses. A proper perspective of this methodology subsumes the advantages and potential pitfalls in the overall context of dosage form objectives.

*Steady-State Evaluation of Sustained-Release Products*

Single dose studies may be used to evaluate SR products intended for chronic administration, and this is the basis for the method proposed. However, once single dose studies have been satisfactorily completed, multiple dose pharmacokinetic studies should be instituted with those patients for whom the product is intended. The dosage form index compiled from individual subject data is an excellent parameter when used properly. Improper usage would occur if insufficient data points were available or data were gathered at inappropriate times. Failure to compare data to an appropriate control, e. g., the conventional dosage form, may also impart misleading information. A dosage form index of 1.4 for a SR product is meaningless if the same value is obtained with conventional dosage form administration at the same interval.

The single most important strength and weakness of the dosage form index is that it measures behavioral extremes. A useful adjuvant, therefore, would be a parameter which measures mean deviation from some theoretical norm. Over a steady-state interval, what is the average deviation of actual plasma levels (C) from a horizontal $C_{av}$? One possible approach would be to calculate $\Sigma\ (C-C_{av})^2$. Squaring of the differences does alleviate problems arising from negative numbers, but it also introduces an unnecessary and confounding mathematical operation. A much better approach is to measure the absolute area above and below the horizontal $C_{av}$ over a dosage interval. This is illustrated in Fig. 5 for averaged data from 3 theophylline preparations (16). Initially, serum level data at the top and center segments were multiplied by suitable factors such that $C_{av}$ values were equivalent for all dosage forms (this method is not intended as a bioavailability assessment). The deviated areas (shaded areas) were measured and expressed relative to the elixir, which was arbitrarily set to 100. By definition, the absolute areas above and below $C_{av}$ are equal. SR product A (relative area = 68.8) is superior to the elixir (relative area = 100), and product B (relative area = 21.0) is superior to product A. The data illustrated in Fig. 5 represent time-averaged plasma concentration data and are used for illustrative purposes only. In an actual evaluative situation, it is important to calculate relative areas from individual subject data rather than from averaged plasma data. The use of averaged data almost always conceals intra- and inter-subject scatter, severely biasing the analysis (*vide infra*); this is also true for the dosage form index.

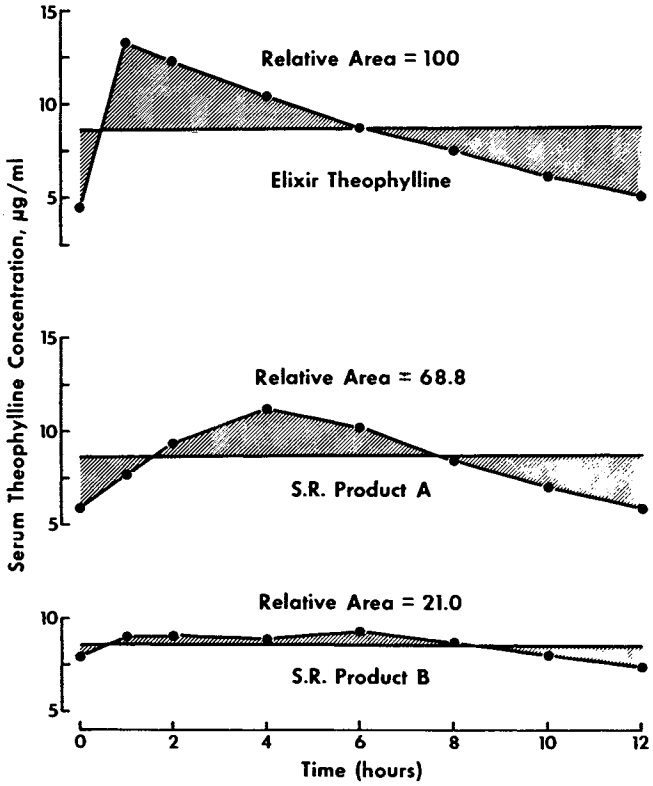


**Fig. 5** Averaged steady-state serum theophylline levels following 12 hourly oral administration of 3 dosage forms: Top – 250 mg elixir; Middle – 250 mg SR capsule; Bottom – 300 mg SR tablet. Serum levels in the top and center segments were multiplied by appropriate factors to produce values of $C_{av}$ equivalent to the bottom figure, i. e., 8.63 µg/ml. Shaded regions are area deviations from the horizontal ideal. Data from ref. (16).

With the aid of conventional statistical criteria for distinguishing differences between products, relative area deviations from $C_{av}$ subsumed with bioavailability information and the Theeuwes-Bayne dosage form index (6) should provide a comprehensive steady-state profile of sustained release dosage form performance. This assumes the study has been properly designed and executed. Failure to obtain steady-state plasma samples at critical times will bias any study, regardless of the appropriateness of the calculated parameters and statistical tests. This could occur, for example, if samples were obtained only at time points where plasma levels were near $C_{av}$, as opposed to time points where these levels were also near $C_{av,min}$ and $C_{av,max}$. In this situation, both the relative area parameter and dosage form index would be misleadingly reduced.

A final thought on the interpretation of steady-state plasma level data is relevant. The fact that a drug delivery system produces a somewhat flat steady-state plasma level-time profile with a low dosage form index does not imply zero-order absorption. It is only when data points are randomly scattered in a time independent fashion above and below $C_{av}$ that rate plots confirm zero-order absorption. Fig. 6 illustrates a good example for a hypothetical drug having a terminal disposition half-life of 11.05 hours. The steady-state dosage form index is 1.26, indicating a moderately successful dosage form (if the drug were absorbed with a one hour half-life, the dosage form index would be 1.5). Note the steady-state plasma levels are

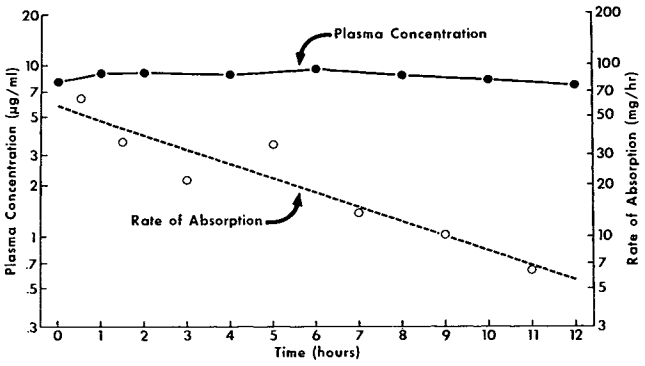


**Fig. 6** Steady-state plasma level-time profile and rate of absorption for a hypothetical drug administered in a SR dosage form at 300 mg every 12 hrs. Drug disposition parameters (standard abbreviations – ref. 11) are $k_{12} = 2.72\ hr^{-1}$, $k_{21} = 2.94\ hr^{-1}$, $k_{10} = .122\ hr^{-1}$, $V_1 = 22.8$ liters and $t_{1/2,z} = 11.05$ hrs. Rate of absorption was determined by the Loo-Riegelman method (12–15). The absorption half-life is approximately 3.6 hours; see text for discussion.

not randomly scattered about $C_{av}$, but tend to rise, peak and fall, be it ever so subtle. This is usually indicative of first-order absorption, and a Loo-Riegelman rate of absorption plot in the same figure indicates an absorption half-life of about 3.6 hours. The 11.05 hr disposition half-life buffers the plasma curve from abrupt declines. If absorption completely shut down for a full hour, the steady-state plasma level would only decline by about 6%. In contrast, if the disposition half-life was 3 hours, a one hour absorption shut-down would decay the steady-state plasma level by about 20%. Therefore, compounds with longer disposition half-lives (same $\tau$) will almost always have lower dosage form indices by virtue of disposition pharmacokinetics *per se*. The clinical situation was previously summarized by a paradigm (1): the degree of success one may expect clinically from a SR product is inversely proportional to the need for the product. Drugs for which SR dosage forms are not particularly needed perform the best.

*Averaged Data in Pharmacokinetics*

This author can think of no more disquieting practice in pharmacokinetics today than the use of averaged plasma level-time curves, especially when one has no access to the raw data (this author believes accessibility to raw data should be a precondition for publication). An ensconcing of intra- and inter-subject variability occurs in all cases, but it is particularly disturbing with SR data. Consider theoretical single dose plasma level-time curves A, B and C illustrated at the top of Fig. 7. These could be representative individuals or groups. Averaging the data results in the smoothed curve shown at the bottom (D). Note that the average curve bears little resemblance to any of the curves from which it was derived. Use of time averaged plasma concentration data following administration of SR products can and frequently does result in distortions of this sort. The degree of distortion will depend on the inter- and intra-subject variability, and the drawing-in of vertical standard deviation or standard error "bars" is no remedy. Moreover, the calculation of arithmetic mean and standard deviation values tacitly assumes a normal arithmetic distribution, a condition usually non-existent. Consider three monoexponential functions: $5.0e^{-1.0t}$; $5.0e^{-1.5t}$; and $5.0e^{-2.0t}$. Taking t as 0, 1 and 2, theoretical data points were generated and time averaged. Least squares analysis of these time-averaged data gave the function $4.89\ e^{-1.35\,t}$, which is obviously incorrect.

Preferably, several graphs utilizing representative subjects can be presented. It is hoped authors will avoid the temptation of showing only their better data.

*Pitfalls in the Plotting and Evaluation of Sustained-Release Data*

It is a fundamental precept and *sine qua non* of all conventional least squares analyses that data points be statistically independent (17). In cumulative amount absorbed (excreted) and amount remaining to be absorbed (excreted) plots, the error associated with each data point includes the errors associated with all previous points; error cumulation can and frequently does produce artifacts, thereby nullifying results obtained by least squares analysis (18). These plots are also extreme smoothing devices which minimize fluctuations. Some phar-

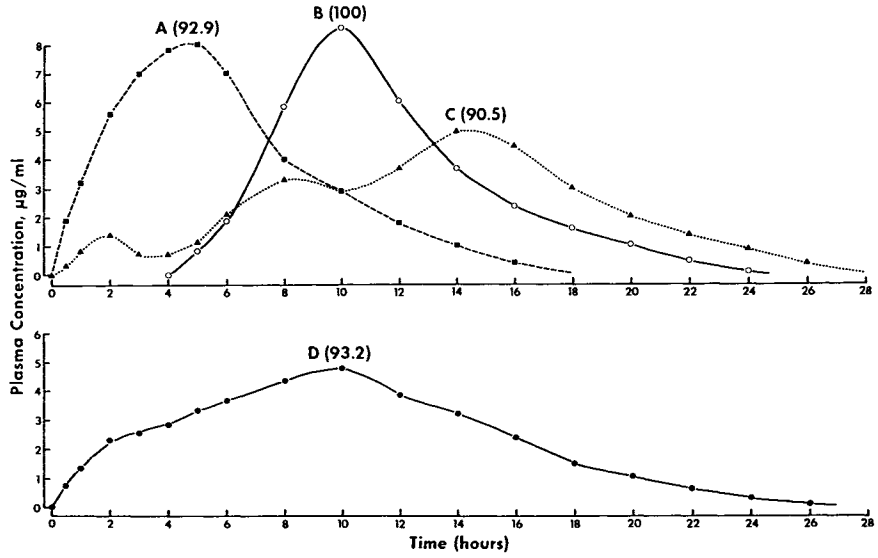


**Fig. 7** Plasma level-time curves (hypothetical) A, B and C (top) represent distinct individuals or groups. Curve D (bottom) is the time averaged result from curves A, B, and C. The numbers in parentheses represent relative AUCs.

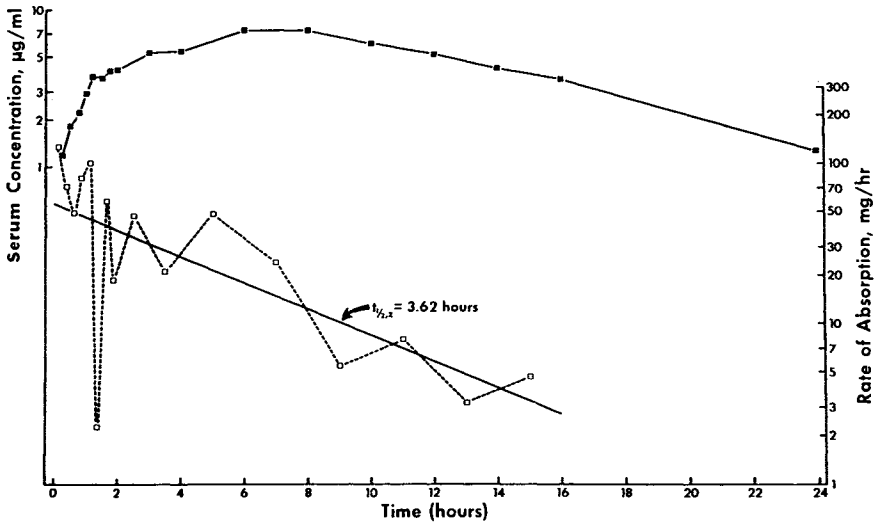


**Fig. 8** Single dose, theophylline serum level-time profile following oral administration of 400 mg of a SR product to a healthy human subject. Data is from Subject A, ref. 21. Rate of absorption was determined by the Wagner-Nelson method (23); see text for assumptions. Note the non-randomness of scatter of data points (0–1.5 hours) about the fitted, first-order rate of absorption line (half-life, $t_{½,z}$, of 3.62 hours). This denotes first-order absorption is inconsistent with the data (18). See text for discussion.

maceutical scientists argue these plots merely reduce "noise", this being desirable since the correct answer (usually a rate constant) is obtained. (In the present context, noise refers to any unwanted perturbations or disturbances in the dependent variables which interfere with or otherwise hinder proper interpretation of the data.) Such reasoning is fallacious on at least 2 scores. First, it represents a *hysteron proteron,* i. e., it initially assumes that which it purports to establish. Analyses by Wagner (19) and Martin (20) using "amount remaining to be excreted plots" clearly reveal that artifacts can arise. Secondly, the assertion that the smoothing effect of these plots is noise squelching, presupposes that most data point fluctuations are noise and not signal. A true noise squelching device preferentially depresses extraneous noise – these plots squelch everything, willy-nilly.

As an illustration, a representative single-dose serum level-time profile is illustrated in Fig. 8 following administration of 400 mg of SR theophylline to a human subject (21). For simplicity sake, let us assume: (*1*) even though theophylline disposition kinetics are best described by Michaelis-Menten kinetics (22), linear kinetics prevail; (*2*) a one-compartment open model characterizes disposition; (*3*) bioavailability is unity; (*4*) drug assays are error-free; and (*5*) absorption is complete at 16 hours. These assumptions need not be true for purposes of illustration, although they do discourage physical interpretation of the data. A Wagner-Nelson rate of absorption plot (23) is shown below the serum curve. The fluctuations in absorption rate represent both real variability as well as system noise. It is not only desirable but obligatory to reveal these fluctuations. It matters not whether they arise from system deviations or failures, random noise, or assay deficiencies. Fitting a monoexponential equation to the absorption data by least squares assumes a first-order process and gives a 3.62 hour half-life. Note the non-randomness of scatter of data points about the fitted curve between 0 and 1.5 hours. First-order absorption is therefore inconsistent (18), i. e., it is not supported by the data. If a simple function was used to characterize the data, perhaps a biexponential function would be appropriate.

Fig. 9 illustrates semilogarithmic plots of amount remaining to be absorbed and cumulative amount absorbed. As discussed previously (18), rate plots are preferable in pharmacokinetic analyses and can be used as a standard to evaluate cumulative

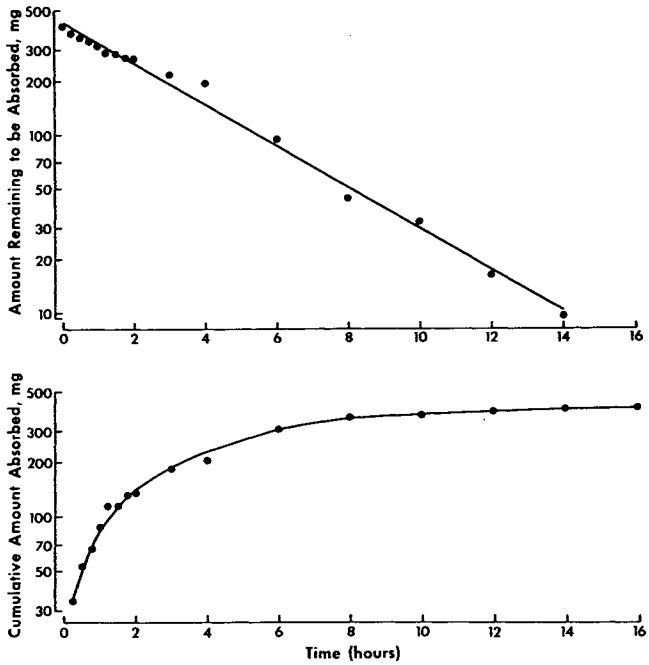


**Fig. 9** Semilogarithmic plots of amount remaining to be absorbed and cumulative amount absorbed for theophylline following single dose oral administration from a SR product. Data is the same as from Fig. 8. Lines were drawn by eye. The half-life in the top segment is 2.6 hours; note the non-randomness of scatter at early time points. See text for discussion.

and amount remaining to be absorbed (excreted) plots. The extreme scatter observed in the absorption rate plots is no longer revealed. Quite the contrary, the cumulative plot looks almost too perfect. The reader will notice the similarity in shape to *in vitro* cumulative dissolution curves – these too can be specious. On the amount remaining to be absorbed plot, a premonitory non-randomness of scatter between 0–1.5 hours is observed, but it doesn't look as bad as before. This is, *per se,* sufficient reason to invalidate the analysis (18); unfortunately, this criterion is often overlooked. The straight line function drawn by eye (least squares analysis is invalid – *vide supra*) indicates a half-life of about 2.6 hours. This is, of course,

incorrect. Absorption is not first-order (see Fig. 8), but even if it were, a 3.6 hour half-life would be more befitting. Errors in asymptote estimation (amount absorbed at infinity) were not present in this analysis, but provide yet another source of error (19, 20). Fig. 10 shows the same smoothed plots as in Fig. 9 but on Cartesian coordinates. Between 0-6 hours, the novice could mistakenly assume zero-order absorption was occurring. In some laboratories, it would be common practice to use only these 0–6 hour data, dismissing the latter time points as asymptotic and therefore unreliable. Another pharmacokinetic chimera might view zero-order absorption occurring, preceeded by a small initial absorption burst (indicated by the zero-time intercepts not intersecting 400 mg (dose) or 0 mg (amount in body at zero time).

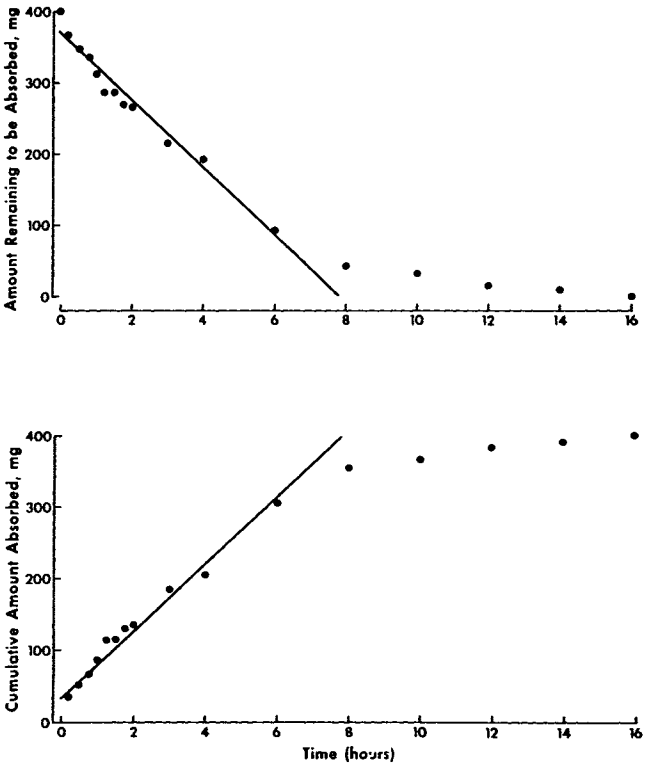


**Fig. 10** Cartesian plots of amount remaining to be absorbed and cumulative amount absorbed for theophylline following single dose oral administration of a SR product. Data is the same as in Figs. 8 and 9. Lines were drawn by eye. See text for discussion.

On the basis of the foregoing discussions, it is concluded: (*1*) time averaged concentration data should not be used in pharmacokinetics, unless some established theoretical basis for their application can be established; and (*2*) amount remaining to be absorbed (excreted) and cumulative amount absorbed (excreted) should not be employed, unless a rate plot is viewed simultaneously. The use of time averaged concentration data in pharmacokinetics is most frustrating and makes it virtually impossible to properly evaluate most SR product literature. In those cases where raw data were available to the author, distortions of intra- and inter-subject variability, as well as curve shape, have been egregious.

In treating individual subject data, rate plots are always preferred. Occasionally one hears of a urinary excretion study in which urine was collected at long intervals relative to the elimination half-life. It is noted that the delta approximation of the differential is invalid. Assuming monoexponential decay, a correct half-life will ensue provided $\Delta t$ is constant, regardless of half-life. When $\Delta t$ is large and highly erratic, difficulties do arise, and it may be best to discard the data. Use of amount remaining to be excreted plots may provide a sense of equanimity, but too often at the sacrifice of accuracy.

**Acknowledgements**

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## References

(1) Boxenbaum, H. (1982) Drug Develop. Indust. Pharm. 8, 1–25.
(2) Rowland, M., Beckett, A. H. (1964) J. Pharm. Pharmacol. 16, 156T–162T.
(3) Robinson, J. R., Eriksen, S. P. (1966) J. Pharm. Sci. 55, 1254–1263.
(4) Ashby, R. (1952) Design for a Brain, Chapman & Hall, London.
(5) Gibaldi, M., Perrier, D. (1982) Pharmacokinetics, 2nd ed., pp. 188–198, 451–457, Marcel Dekker, Inc., N. Y.
(6) Theeuwes, F., Bayne, W. (1977) J. Pharm. Sci. 66, 1388–1392.
(7) Adair, D. Personal communication.
(8) Levy, G., Jusko, W. J. (1966) J. Pharm. Sci. 55, 285–289.
(9) Boxenbaum, H. G., Jodhka, G. S., Ferguson, A. C., Riegelman, S., MacGregor, T. R. (1974) J. Pharmacokin. Biopharm. 2, 211–237.
(10) Wagner, J. G. (1975) Fundamentals of Clinical Pharmacokinetics, pp. 136–145, Drug Intelligence Publications, Inc., Hamilton, Ill.
(11) Rowland, M., Tucker, G. (1980) J. Pharmacokin. Biopharm. 8, 497–507.
(12) Loo, J. C. K., Riegelman, S. (1968) J. Pharm. Sci. 57, 918–928.
(13) Till, A. E., Benet, L. Z., Kwan, K. C. (1974) J. Pharmacokin. Biopharm. 2, 525–544.
(14) Till, A. E., Benet, L. Z., Kwan, K. C. (1975) J. Pharmacokin. Biopharm. 3, 291.
(15) Boxenbaum, H. G., Kaplan, S. A. (1975) J. Pharmacokin. Biopharm. 3, 257–264.
(16) Straughn, A. B., North, L. J. Presented at the 14th annual mid-year clinical meeting, American Society of Hospital Pharmacists, Dec. 2–6, 1979, Las Vegas, Nevada (Data on file, Key Pharmaceuticals, Inc., Miami, Fla.).
(17) Daniel, C., Wood, F. S. (1971) Fitting Equations to Data, Wiley-Interscience, N. Y.
(18) Boxenbaum, H. G., Riegelman, S., Elashoff, R. M. (1974) J. Pharmacokin. Biopharm. 2, 123–148.
(19) Wagner, J. G. (1963) J. Pharm. Sci. 52, 1097–1101.
(20) Martin, B. K. (1967) Brit. J. Pharmacol. Chemother. 29, 181-193.
(21) Simons, K. J., Frith, E. M., Simons, F. E. R. (1982) J. Pharm. Sci. 71, 505–511.
(22) Tang-Liu, D. D., Williams, R. L., Riegelman, S. (1982) Clin. Pharmacol. Therap. 31, 358–369.
(23) Wagner, J., Nelson, E. (1964) J. Pharm. Sci. 53, 1392–1403.