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Research Article

Computer-Aided Dosage Form Design. I. Methods for Defining a Long-Acting First-Order Delivery System of Maximum Formulating Flexibility

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The method provides an a priori assessment of the maximum allowable flexibility in the rate of release from a prolonged-release formulation. The clinical pharmacokinetic parameters describing the drug candidate are employed to calculate the ranges of rate constants and doses required for the formulation to provide a selected therapeutic duration. For a given patient, there may be an infinite number of combinations of release rate constants and dose sizes which will maintain steady-state plasma drug concentrations within a desired range when the formulation is administered at the selected dosing interval. Computer simulations of steady-state plasma concentrations are employed to establish the ranges for all of the acceptable rate constants and doses for each member of a group. The entire group is then examined to define the range of release rate constants and doses which would provide a useful formulation for every member in the group. Literature values for theophylline clinical pharmacokinetics in children and adults have been employed to illustrate the application of this method. The method is unique in that it provides an entire range of release rates on which to gauge the feasibility for success.

KEY WORDS: computer-designed formulation; prolonged-action dosage forms; drug delivery systems; long-acting formulations; theophylline delivery systems; pharmacokinetics.

INTRODUCTION

Compliance to a dosage regimen may be enhanced by reducing the number of times that a dose must be administered, i.e., from three or four times daily to once or twice a day. For some drugs, this can be achieved by replacing a conventional formulation with a prolonged-release dosage form.

Prior to initiating product development, two goals are commonly selected for a prolonged-release product:

(1) the desired dosing interval (often 12 hr for oral administration) and

(2) an acceptable maximum and minimum drug plasma concentration (generally a recognized therapeutic window or the concentrations which result from the use of a conventional formulation).

The release rate and dose size are then systematically altered in an empirical search for a combination that provides acceptable concentrations following administration using the desired dosing interval.

This trial and error approach is inefficient since there may be an infinite number of combinations of release rates and doses that will maintain acceptable concentrations, or conversely, there may be none at all. The present approach provides a method to assess the potential for success before the expenditure of time and money on formulation by predicting a priori whether or not the goals are achievable and, if so, which combinations of release rates and doses are required for success.

This approach is applicable to any drug and dosing interval provided that pharmacokinetic data are available for individual subjects within a representative group. The strength of this method derives from the fact that computer simulations of drug plasma concentration time courses, resulting from the administration of hypothetical formulations at the desired dosing interval, can rapidly identify all successful combinations of dose sizes and release rates for each of the subjects. By examining the entire range of acceptable release rates and doses for all of the subjects, a common set of ranges, which would accommodate the maximum number of people, can be established. This common set represents the maximum allowable formulation ranges for dose sizes and release rates. As such, it provides a basis to decide whether these ranges are easily achievable or too narrow to merit further investigation. The percentage of people in the group who are easily accommodated by a product with broad ranges also provides a preliminary indication of the potential for success.

This paper presents both the general approach and an illustrative example. The general methodology is presented for repetitive dosing of first-order prolonged-release formu-

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lations (1,2) containing drugs whose disposition is described by one- or two-compartment pharmacokinetic models. Subsequent papers will treat zero-order release, mixed-order release, and nonlinear disposition.

In order to illustrate how to apply the method, the reported pharmacokinetic values for theophylline in each member of a group of 10 children (3) and in a group of 7 adults (4) were employed to find the release rates and doses that would maintain theophylline steady-state levels between 10 and 20 mg/liter (5) when administered every 12 hr. This example illustrates why both the dose range and the release-rate range must be optimized to provide the maximum formulating flexibility. It also illustrates that a first-order prolonged-release theophylline formulation is impractical for a pediatric dosage form owing to narrow ranges which also fail to accommodate all of the children. However, the same methodology applied to the adult pharmacokinetic data provides a more promising prediction.

EXPERIMENTAL

General Approach. In this method, computer-simulated steady-state plasma concentrations from repetitive dosing of prolonged-release formulations are compared to the selected minimum and maximum concentrations. The computer thus identifies any formulation producing steady-state plasma concentrations within the selected range. In order to simulate drug plasma concentrations for the two first-order release cases presented here, two pharmacokinetic models and their corresponding repetitive-dosing steady-state plasma concentration time course equations are required.

Scheme I represents first-order (k_1) release from an orally administered drug delivery system (DDS), followed by first-order absorption (k_a) and biexponential disposition (k_{12}, k_{21}, and k_{10}).

$$\begin{array}{ccccc} & \overset{k_1}{} & & \overset{k_a}{} & \overset{k_{10}}{} \\ [\mathrm{DDS}] & \rightarrow & [\mathrm{DS}] & \rightarrow [A1] & \rightarrow \\ & & & k_{12} \downarrow \uparrow k_{21} & \\ & & & [A2] & \end{array}$$

Scheme I

The amount contained in each phase as a function of time is designated: [DDS] = drug in the DDS; [DS] = drug in solution in the gastrointestinal tract; [A1] = drug in the central compartment; and [A2] = drug in the peripheral compartment.

Scheme II represents the oral administration of a drug described by one-compartment model disposition.

$$[\mathrm{DDS}] \xrightarrow{k_1} [\mathrm{DS}] \xrightarrow{k_a} [A] \xrightarrow{k}$$

Scheme II

[A] is the amount of drug in the body and k is the elimination rate constant.

Solving the differential equations for the concentration in plasma in Scheme I, applying the multiple dosing factor (5), and setting $n = \infty$ provide

$$C^{ss} = \left[\frac{k_1 k_a fD}{V_1}\right]\left[\frac{(k_{21} - k_1)}{(k_a - k_1)(\alpha - k_1)(\beta - k_1)(1 - e^{-k_1\tau})} e^{-k_1 t'} + \frac{(k_{21} - k_a)}{(k_1 - k_a)(\alpha - k_a)(\beta - k_a)(1 - e^{-k_a\tau})} e^{-k_a t'} + \frac{(k_{21} - \alpha)}{(k_1 - \alpha)(k_a - \alpha)(\beta - \alpha)(1 - e^{-\alpha\tau})} e^{-\alpha t'} + \frac{(k_{21} - \beta)}{(k_1 - \beta)(k_a - \beta)(\alpha - \beta)(1 - e^{-\beta\tau})} e^{-\beta t'}\right] \quad (1)$$

where C^{ss} is the steady-state concentration in V_1, the volume of the central compartment, α and β are the apparent disposition constants (5), fD is the bioavailable dose, and t' is the time during each dosing interval, $0 \leq t' \leq \tau$. Applying the same treatment to Scheme II yields

$$C^{ss} = \left[\frac{k_1 k_a fD}{V}\right]\left[\frac{1}{(k_a - k_1)(k - k_1)(1 - e^{-k_1\tau})} e^{-k_1 t'} + \frac{1}{(k_1 - k_a)(k - k_a)(1 - e^{-k_a\tau})} e^{-k_a t'} + \frac{1}{(k_1 - k)(k_a - k)(1 - e^{-k\tau})} e^{-kt'}\right] \quad (2)$$

where C^{ss} is the steady-state concentration in the body and V is the volume of distribution.

Thus, steady-state concentrations obtained by repetitively dosing a two-compartment model drug with a formulation having a release rate constant of k_1 are given by Eq. (1), and those for a one-compartment model drug by Eq. (2). In each equation, the values for all of the pharmacokinetic parameters, with the exception of the release rate constant and dose, must be known. By selecting a dose and rate constant, one can simulate the resultant steady-state concentration time course and compare it to the desired limits. By repeating this process, all of the combinations of k_1 and D which provide C^{ss} values within any selected range can be determined. Thus, one can define the entire range of acceptable values using the computer to search reiteratively for all of these combinations, as discussed next.

General Method of Computer Reiteration. Having selected a drug, a desirable concentration range, and a dosing interval, an infinite number of combinations of dose sizes and release rate constants may be able to maintain acceptable steady-state concentrations in accordance with Eq. (1) or (2). By systematically changing the values for k_1 and D, the entire range of successful combinations can be found using computer reiteration as follows.

For a given set of values for pharmacokinetic parameters and the desired dosage interval, the corresponding equation is initialized with small values for the dose and release rate constant. The steady-state concentrations are simulated as a function of time and compared to the desired limits. Those which produce concentrations within the limits are considered potentially useful combinations. For each release rate constant, the dose size is reiteratively increased and the levels are tested until all successful dose sizes are found. Then the release rate constant value is increased and the process repeated. Thus for each k_1 value, the entire range of doses capable of providing the selected plasma concentration range using the desired dosing interval is identi-

fied by the computer. For each successful k_1 value there exists a minimum and maximum useful dose. By establishing all of the successful k_1 values, a continuous function for the minimum and maximum dose boundaries is established. When the minimum and maximum dose continuum is displayed on a plot of k_1 versus dosage, a triangular boundary results. Any formulation having a dose size and release rate within this boundary will maintain steady-state concentrations within the selected range as illustrated next using theophylline.

Illustration of the Method Using Theophylline Data. Several papers have reported linear biexponential disposition for theophylline in children and adults (3–8). Although nonlinear elimination has also been observed (9), there is insufficient documentation of V_{max} and K_m values in individual patients at this time. Wagner (9) reviewed reports of both linear and nonlinear theophylline kinetics within the therapeutic dosing range and concluded that the reason for this discrepancy is obscure. Although the requisite renal and metabolic data were not available, Wagner employed published metabolic data to approximate pooled V_{max} and K_m values (9). Using these estimates, the application of Michaelis–Menten kinetics, instead of assuming first-order elimination, had only a modest effect within the therapeutic dosage range which included all formulations from 150 to 1500 mg. Wagner warns that high doses, such as those experienced during dose-dumping from 24-hr formulations, would prolong theophylline plasma concentrations beyond that expected from first-order kinetics.

Linear pharmacokinetics adequately described theophylline disposition within the population employed in this example (3,4). These data are used solely to illustrate the methodology. This same approach can be applied to nonlinear kinetics using the equations published by Wagner (9) to simulate theophylline serum time courses if individual K_m and V_{max} values are available for a group of patients.

Values for theophylline pharmacokinetic parameters (k_{12}, k_{21}, k_{10}, and V_1) for each of 10 children, 1 to 5 years old, reported by Loughnan *et al.* (3) and those for each of 7 adults determined by Kaumeier *et al.* (4) were used to illustrate how this method is applied. The approach can be applied to any drug or reapplied to theophylline using parameter values which differ from those used here.

The oral absorption of theophylline in solution is known to be rapid and complete in children and adults (10). Reported estimates for k_a (hr^{-1}) in adults range from 2.9 to 8.9 hr^{-1} (11). A mean k_a value of 2.6 hr^{-1} was reported by Bolme *et al.* (12) following the oral administration of an aqueous solution of choline theophylline in six children (0.6 to 4.5 years old). The k_a values used in this example are 2.6 hr^{-1} (children) and 2.9 hr^{-1} (adults) and the bioavailable factor (f) value is one.

Equation (1) was used to simulate the oral administration of one prolonged-release theophylline formulation to each of the 10 children and 7 adults every 12 hr. The selected goal was to maintain steady-state plasma theophylline concentrations (C^{ss}) within the range 10 to 20 mg/liter (5). The final selection of a release rate and dosage size is carried out by considering each of the individuals in a group and attempting to define a single formulation which will accommodate the greatest number yet provide maximum flexibility for the formulator.

RESULTS AND DISCUSSION

The release rate constant and dose size for an acceptable long-acting first-order formulation can be defined a priori using the pharmacokinetic properties of the drug in a number of subjects. While each drug presents unique pharmacokinetic values, the approach is general.

Dosage Form Requirements in One Subject. The results for subject MG in Table I illustrate the relationship between the release rate constant versus dose boundary conditions (E–A–F in Fig. 1A) and some corresponding steady-state plasma concentration time courses (Fig. 1B). The oral administration of any theophylline formulation having a release rate constant and dose size within the boundary E–A–F (Fig. 1A) will maintain steady-state concentrations between 10 and 20 mg/liter when administered every 12 hr. Any combination of dose and release rate on boundary E–A (Fig. 1A) results in minimum steady-state concentrations of 10 mg/liter as shown in Fig. 1B (curves A and B). Any combination on A–F results in maximum values of 20 mg/liter (curves A and D). Since point A represents the intersection of these limits, a dosage form based on this combination transverses the entire range as seen in Fig. 1B. Any combination within the boundary E–A–F will provide plasma concentrations above the minimum yet below the maximum as illustrated by curve C in Fig. 1B for point C in Fig. 1A.

However, this represents only 1 member of the group of 10 children. The acceptable release rate constant–dose size ranges will become significantly restricted when the entire group is considered, as illustrated next.

Dosage Form Requirements for the Entire Group. The release rate constant–dose size boundaries for the individuals in each group are shown in Fig. 2a (children) and Fig. 2b (adults). There is considerable interpatient variation in dosage requirements owing to the difference in clearance values.

Since the mathematical solution for the time required for 100% release from a first-order system is infinity, it is necessary to select a practical limit to avoid excretion of unreleased drug. If 12 hr were selected as the maximum time

Table I. Individual 12-Hour Maintenance Dosage Ranges for an Oral First-Order Theophylline Drug Delivery System (DDS) in Children (the Selected DDS Represents a Unit Size of 120 mg)

Patient (No.)[a]	Dose range (mg): $T90$ = 12 hr, k_1 = 0.19 hr^{-1}	Dose range (mg): $T90$ = 18 hr, k_1 = 0.13 hr^{-1}	Selected DDS: mg	Selected DDS: Units
AP (1)	99–135	92–140	120	1
MG (2)	120–153	110–160	120	1
DN (3)	(175)[b]	153–186	180	1.5
JM (4)	191–219	170–231	180	1.5
EC (5)	194–220	173–233	180	1.5
JC (6)	(233)[b]	204–247	240	2
GF (7)	(230)[b]	230	240	2
MA (8)	249–288	222–301	240	2
JL (9)	(350)[b]	335–359	360	3
GL (10)	(399)[b]	367–417	360	3

[a] Numbers refer to Fig. 2a; initials refer to Ref. 3.
[b] Taken from the dose at peak k_1 value.

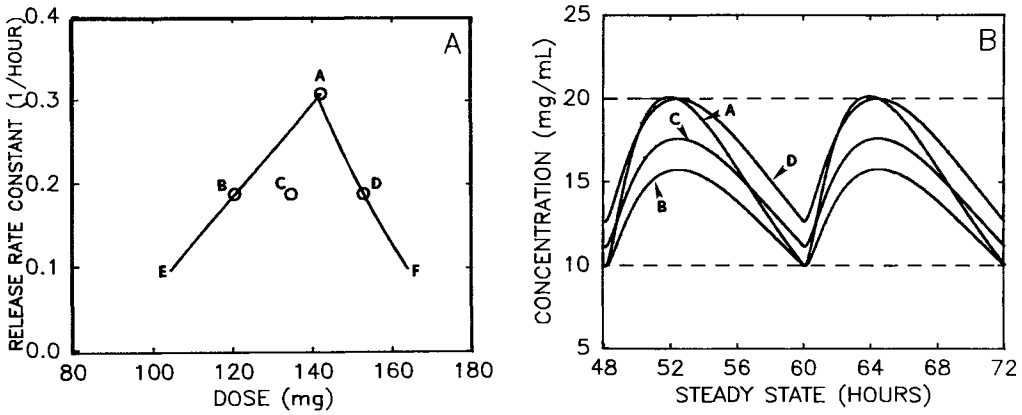

Fig. 1. (A) Release rate constant versus dose boundaries (E–A–F) for subject MG in Table I. Any combination of dose and release rate constant within these boundaries will maintain steady-state theophylline concentrations between 10 and 20 mg/liter when given every 12 hr as illustrated in B, where the curves correspond to the labeled combinations in A.

for 90% delivery, $T90$, the corresponding release rate constant value would be 0.192 hr^{-1}. This value is indicated by the dashed lines in Figs. 2a and b. Since the boundaries for children Nos. 3, 6, 7, 9, and 10 lie below this line, only 5 of the 10 children would be maintained within the chosen plasma concentration range (10–20 mg/liter) when properly dosed every 12 hr with this formulation. In contrast, all seven adults would exhibit satisfactory concentrations taking the appropriate dose of a formulation with k_1 = 0.192 hr^{-1} every 12 hr. Similar results were obtained using individual data for 16 adults reported by Mitenko and Ogilvie (8) but these subjects could not be used to determine dosage form sizes owing to the lack of reported body weights.

Choosing a Release Rate Constant. Figure 3 summarizes the relationship between the percentage of subjects having acceptable steady-state theophylline concentrations and the $T90$ value for the formulation. The minimum $T90$ value required to accommodate all 7 adults is 8 hr (k_1 = 0.288 hr^{-1}), whereas that required for all 10 children is 18 hr (k_1 = 0.128 hr^{-1}). A formulation with a $T90$ value of 18 hr would deliver only 79% of the dose during a 12-hr period. This would predispose the product to bioavailability problems since the gastrointestinal transit time may not be sufficiently long to allow adequate delivery.

Although $T90$ = 12 hr accommodated only half the children, simulations that combine this release rate constant with the dose corresponding to each peak in Fig. 2a provided steady-state concentrations within or close to the selected range in all subjects. The greatest deviation was observed for patient GF (Fig. 2a, No. 7), where the observed steady-state range was 8.2 to 22.9 mg/liter. Therefore, $T90$ = 12 hr represents a more practical compromise than setting $T90$ = 18 hr since the observed deviation from the desired range is small. However, individualization of the dose would become difficult for at least half the subjects owing to the relatively narrow dose range as seen next.

Choosing a Dose Size. In addition to the selection of an adequate release rate constant, the unit dose size must also be determined. The acceptable dosage ranges associated with the release rate constant indicated by the dashed lines in Fig. 2 are listed for each subject in Tables I and II. Although the pediatric dosage ranges representing $T90$ = 12 hr and 18 hr differ (Table I), a 120-mg unit size would accommodate all of the children using either criterion. A 500-mg

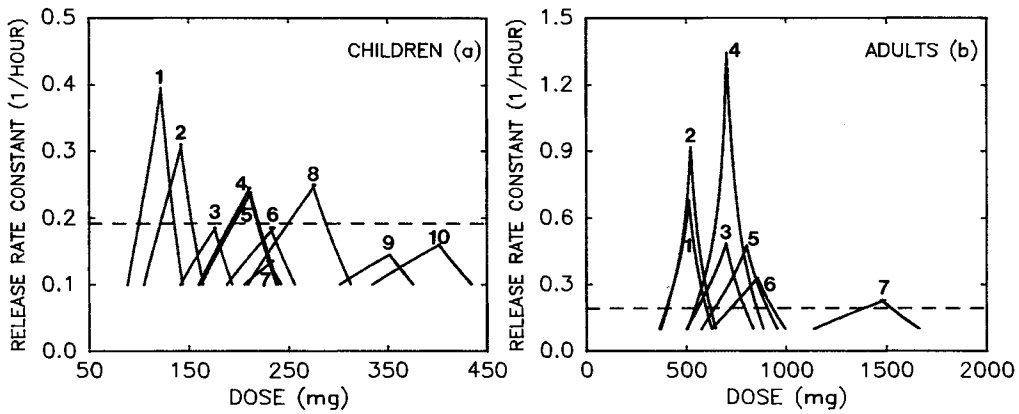

Fig. 2. Release rate constant versus dose boundaries for a first-order formulation administered orally every 12 hr to maintain theophylline steady-state concentrations between 10 and 20 mg/liter in the corresponding subjects, where (a) represents the 10 children in Table I and (b) the 7 adults in Table II.

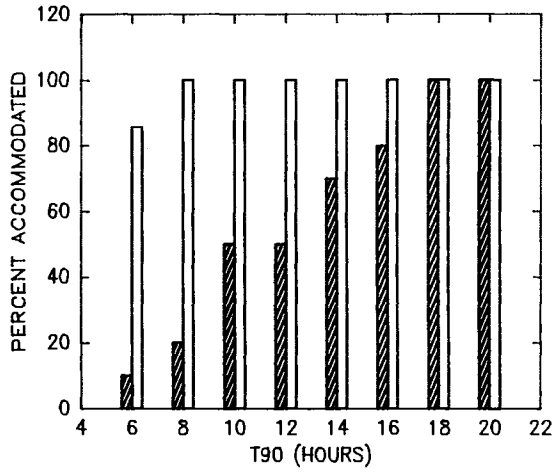

Fig. 3. The influence of the time required for a first-order formulation to deliver 90% of the dose ($T90$) on the percentage of subjects experiencing theophylline steady-state concentrations between 10 and 20 mg/liter following oral administration every 12 hr; shaded bars represent 10 children (Table I) and open bars represent 7 adults (Table II).

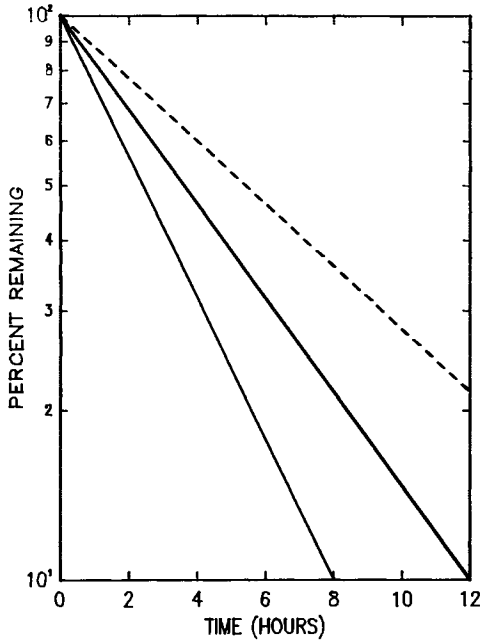

Fig. 4. Semilogarithmic plot of the percentage drug remaining in the drug delivery system (DDS) versus time. Solid lines represent the range of acceptable release patterns in adults, where the upper limit has been chosen to deliver 90% in 12 hr and the lower limit ($T90$ = 8 hr) is specified in Fig. 3. The dashed line ($T90$ = 18 hr) represents the minimum observed release rate to accommodate all 10 children (Fig. 3).

unit size works for all of the adults (Table II). Individualization of regimens, which is required for theophylline, could be achieved by monitoring theophylline serum concentrations to adjust the dose to 1 to 3 units every 12 hr as shown in the tables.

Assessment of the Predicted Requirements. The clinical pharmacokinetic properties have been used to describe theophylline formulations for 12-hr administration to children and adults. Although adults usually require less theophylline per kilogram of body weight than children (5), adults require a larger dose size owing to the differences in total body weights. In addition, the adult formulation exhibits a broader acceptable range of first-order release patterns. This is due to the longer biological half-life and reduced theophylline clearance in adults relative to children.

Although theophylline simulations using first-order delivery appear potentially successful in children and adults, the pediatric formulation requires 18 hr for 90% release to accommodate all 10 children. In these circumstances, bioavailability would become a significant concern owing to the unpredictability of gastrointestinal transit time. Figure 4 shows the required first-order release rate profiles for children and adults. An upper limit of 12 hr has been chosen as the time required to deliver 90% in adults. The approach is not limited to this value; a user may select any value. Figure 4 illustrates why first-order technology is more likely to succeed in adults than in children. The first-order release rate profiles which will accommodate all seven adults using the appropriate doses show a wide pattern, providing 90% delivery in 8 to 12 hr (solid lines). The minimum acceptable release rate to accommodate all 10 children is shown by the dashed line, which delivers only 79% in 12 hr. The pediatric first-order system is therefore ill advised owing to its potential for bioavailability problems and its narrow specification for product development. Zero-order release provides wider specifications for both children and adults as illustrated in a subsequent paper.

Table II. Individual 12-Hour Maintenance Dosage Ranges for an Oral First-Order Theophylline Drug Delivery System (DDS) in Adults (the Selected DDS Represents a Unit Size of 500 mg)

Patient No.[a]	Dosage range (mg), ($T90$ = 12 hr, k_1 = 0.19 hr^{-1})	Selected DDS	
		mg	Units
1	399–598	500	1
2	403–620	500	1
3	540–852	750	1.5
4	555–791	750	1.5
5	639–906	750	1.5
6	719–932	750	1.5
7	1378–1525	1500	3

[a] Numbers refer to Fig. 2b and Ref. 4.

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