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Research Article

Computer-Aided Dosage Form Design. II. Methods for Defining a Zero-Order Sustained-Release Delivery System of Maximum Formulating Flexibility

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Classical methods employing pharmacokinetic data to calculate zero-order release rates for sustained release products require that a constant-rate drug delivery system must have a duration which is exactly equal to the desired dosage interval. This traditional approach fails to establish the minimum acceptable duration and also fails to provide any flexibility in the formulation goal. While it does calculate one pair of duration and dose values, there are infinite pairs of values capable of maintaining the desired plasma concentrations using the selected dosing interval. In the current method, computer simulations are used to establish the boundary conditions within which any pair of duration and dose values will maintain the desired levels when administered on the chosen dosing interval. By comparing the boundary conditions for every subject in a group, a single set of conditions which would work for the entire group can be selected. These final limits represent the broadest specifications for zero-order drug delivery system design for that particular drug combined with the plasma concentration goals and the desired dosing interval. The method is illustrated using theophylline pharmacokinetics.

KEY WORDS: zero-order delivery; drug delivery system; sustained release; computer simulation; dosage form design; theophylline; pharmacokinetics.

INTRODUCTION

Zero-order release is considerd ideal in developing sustained-release drug delivery systems (DDS). Previously published methods for calculating the required zero-order release rate (k_0) and dose size (D) are based on the maintenance of a single steady-state drug plasma concentration (1–10). This steady-state concentration is generally the midpoint of a known therapeutic window or the midpoint of the range encountered using the usual dosage regimen when a window has not been established. In this traditional approach, the total duration (T_R) during which a DDS releases drug must equal the dosing interval, τ (1,11). The total dose contained in the DDS is obtained by multiplying (plasma concentration) × (volume of distribution) × (elimination rate constant) × (duration). The hourly rate of release is then calculated from the time in hours to deliver the total dose:

$$k_o = D/T_R \quad (1)$$

which may also be written

$$(\%\ \text{released/hr}) = 100\%/T_R \quad (2)$$

For the most common goal, that of a twice-a-day (morning and night) regimen, the traditional approach dictates that a DDS must deliver 8.33% of the dose/hr over a 12-hr duration. Thus a single calculated duration and dose, based on a mean steady-state concentration, presents the most restrictive goal for the formulator. It may be possible to maintain acceptable concentrations using a 12-hr dosing interval and a DDS of a much shorter duration. In fact, there may be a wide range of combinations of doses and durations which will maintain multiple-dose steady-state concentrations within a selected range.

The present method employs pharmacokinetic data to define the widest possible range of doses and durations by employing computer simulations to reiteratively identify all of the zero-order dosage forms which will provide acceptable levels in each individual for whom pharmacokinetic data are available. The results for the entire group are then reviewed to establish the widest single range of DDS requirements which would successfully treat all members of the group. The method is general and can be applied to any drug using any desired dosing interval.

Reported theophylline data in children and adults have been employed to illustrate the application of this method. The results illustrate how the dose and duration ranges are interrelated in such a way that maximizing one will restrict the other. Therefore both the dose size and the duration range must be optimized for maximum formulating flexi-

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bility. The goal for dosage form development can be defined by optimizing these two variables. The method can be used to determine the broadest possible dose and duration ranges which will accommodate all of the individuals in the study or to examine how this target becomes even broader if some fraction of the total population can be excluded from candidacy for treatment with the new dosage form. These results can then be used to decide on the advisability of proceeding with product development activities.

EXPERIMENTAL

General Approach. Simulations of steady-state plasma concentrations from multiple dosing of zero-order formulations of drugs described by one- or two-compartment model disposition are based on the following schemes and their corresponding equations.

Scheme I represents the oral administration of a drug described by monoexponential disposition.

$$[\text{DDS}] \xrightarrow{k_0} [\text{DS}] \xrightarrow{k_a} [\text{A}] \xrightarrow{k}$$

Scheme I

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

Scheme II represents zero-order (k_0) release from an orally administered DDS, followed by first-order absorption (k_a) and biexponential disposition (k_{12}, k_{21}, and k_{10}).

$$[\text{DDS}] \xrightarrow{k_0} [\text{DS}] \xrightarrow{k_a} [\text{A1}] \xrightarrow{k_{10}}$$
$$\underset{k_{12}}{\downarrow\uparrow}\ \underset{k_{21}}{}$$
$$[\text{A2}]$$

Scheme II

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

The total time during which drug is released from the DDS may be calculated by rearranging Eq. (1) to give $T_R = D/k_0$. The drug plasma concentration time course equation following the administration of a zero-order DDS must accommodate two conditions: that during release and that following release. For Scheme I, the time course *after* the release of drug is complete ($t > T_R$) is given by

$$C = \left[\frac{k_a f D}{V T_R}\right]\left[\frac{(e^{k_a T_R} - 1)e^{-k_a t}}{k_a(k - k_a)} + \frac{(e^{kT_R} - 1)e^{-kt}}{k(k_a - k)}\right] \quad (3)$$

where f is the bioavailable fraction, C is the concentration in the body, and V is the volume of distribution. This may be used to describe the time course *during* the release of drug by substituting t for T_R in each of the two exponents ($k_a T_R$ and kT_R).

For Scheme II, the time course *after* the release of drug is complete is

$$C = \left[\frac{k_a f D}{V_1 T_R}\right]\left[\frac{(k_{21} - k_a)(e^{k_a T_R} - 1)e^{-k_a t}}{k_a(\alpha - k_a)(\beta - k_a)} + \frac{(k_{21} - \alpha)(e^{\alpha T_R} - 1)e^{-\alpha t}}{\alpha(k_a - \alpha)(\beta - \alpha)} + \frac{(k_{21} - \beta)(e^{\beta T_R} - 1)e^{-\beta t}}{\beta(k_a - \beta)(\alpha - \beta)}\right] \quad (4)$$

where C is the concentration in V_1, the volume of the central compartment, α and β are the two-compartment model disposition rate constants (11). This may also be used to describe the time course *during* the release of drug ($t < T_R$) by substituting t for T_R in each of the three exponents ($k_a T_R$, αT_R, and βT_R).

For any given set of pharmacokinetic values, the principle of superposition (12) can be applied to Eq. (3) or (4) to generate multiple-dose steady-state concentration time courses using any desired dosing interval. These steady-state values can be compared to a desired concentration range to determine the suitability of the duration and dosage size employed in the simulation. By using a computer, the simulations can be rapidly and repeatedly compared to the desired steady-state concentration range.

General Method of Computer Reiteration. Having selected a desirable concentration range and dosing interval, a zero-order DDS has two adjustable parameters, dosage size (D) and duration (T_R), which are interrelated by the release rate [Eqs. (1) and (2)]. For any chosen dosing interval, there are an infinite number of combinations of dose size and duration which will provide the desired steady-state concentrations. This method establishes the widest range of doses and durations which will accommodate all members in a group.

Although the pharmacokinetic basis for Fig. 1a has not yet been discussed, it is helpful to examine this typical product of the computer reiteration process while reading the following description of the procedure.

For a given set of pharmacokinetic values in Eq. (3) or (4), the values for the dosage form duration (T_R) and dose (D) are systematically altered. This effectively alters the release rate (D/T_R), which may also be considered as (% released/hour) = $100\%/T_R$. The resultant steady-state concentration time course is compared to the selected concentration range for each set of values for duration and dose.

The process is initiated by empirically selecting small values for duration and dose that fall below the minimum pair of values producing acceptable concentrations. The dose size is reiteratively increased while T_R is held constant, and each time the steady-state concentrations are compared to the desirable range. If the dose size is increased to a selected maximum, known to be impossibly large, without achieving the desirable range, then T_R is increased and again held constant while the process is repeated. Eventually, as D is increased at constant T_R, plasma concentrations will exceed the required minimum but stay within the acceptable range. This pair of values is part of curve A–B–D in Fig. 1a. The pair of T_R and D values is stored and the D value is again incremented, ultimately causing plasma concentrations to exceed the maximum allowable value. The last acceptable set of values is stored. This pair is part of curve G–F–D in Fig. 1a. Then T_R is increased and the process is repeated until all of the combinations of dose and duration which will provide the desired steady-state levels using the desired dosage interval are defined as shown by the shaded area in Fig. 1a. By examining these limits in a number of subjects, the largest ranges for the dose size and duration can be selected for the group. Figure 1 is discussed in detail as part of the following illustration.

Illustration of the Method Using Theophylline Data. The method is applicable to any drug wherein the

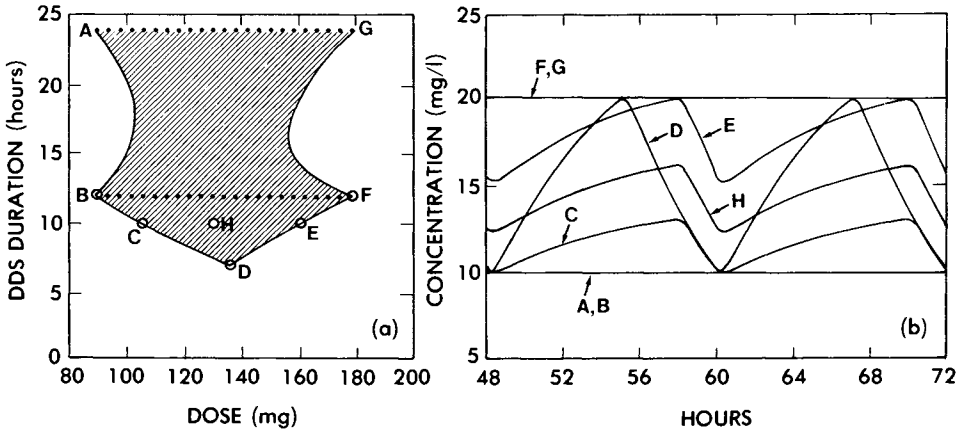

Fig. 1. (a) Zero-order release duration–dose boundary conditions for subject MG in Table I. Any DDS combining a dose and duration within the shaded area will maintain multiple-dose steady-state theophylline concentrations between 10 and 20 mg/liter when administered every 12 hr as shown in b, where the curves represent the corresponding labeled combination in a.

pharmacokinetic parameter values are available for each individual in a group. It requires only the selection of a dosage interval and acceptable range for the steady-state drug plasma concentration. These two requirements are not unique to this approach but are prerequisite to any method for calculating sustained-release DDS characteristics.

Theophylline has been selected to show how to apply this theory to a practical problem. A discussion of theophylline and its limitations as a choice has been previously presented (13). Values for theophylline pharmacokinetic parameters (k_{12}, k_{21}, and V_1) for each of 10 children (14) and for each of 7 adults (15) were employed together with a first-order absorption rate constant of 2.6 hr^{-1} for children (16,17) and 2.9 hr^{-1} for adults (17,18) with a bioavailable fraction of unity (11). The selected goal was to maintain steady-state theophylline plasma concentrations within a 10- to 20-mg/liter range using a 12-hr dosage interval (11).

RESULTS AND DISCUSSION

Maximum Dosage and Duration Ranges in a Single Subject. The shapes of the curves defining the ranges of acceptable durations and doses are highly dependent upon the disposition rate constants in Schemes I and II. Figure 1 is based on theophylline pharmacokinetic data in subject MG in Table I. Any DDS combining a dose size and duration in the shaded area in Fig. 1a will provide steady-state theophylline plasma concentrations between 10 and 20 mg/liter when administered every 12 hr to this child. Any combination of dose and duration falling on curve A–B–D will provide a steady-state minimum concentration equal to the lower limit of 10 mg/liter as shown by curves A, B, C, and D in Fig. 1b. Any combination on curve D–F–G will provide a steady-state maximum concentration equal to the upper limit of 20 mg/liter as shown by curves D, E, F, and G in Fig. 1b. The systems which lie inside the boundary of A–B–D–F–G in Fig. 1a will provide steady-state concentrations which fail to reach either the upper or the lower limit in Fig. 1b as illustrated by example H. Furthermore, the DDS at position D produces a concentration time course which traverses the entire range from 10 to 20 mg/liter since it lies on

Table I. Individual 12-hr Maintenance Dosage Ranges for an Oral Theophylline DDS: The Selected DDS Represents One Potential Unit Size

Dose range		Selected DDS[b]		Dose range		Selected DDS[d]	
Child (No.)[a]	mg	mg	Units	Adult No.[c]	mg	mg	Units
AP (1)	88–140	120	1	1	364–612	500	1
MG (2)	105–161	120	1	2	371–631	500	1
DN (3)	150–190	180	1.5	3	500–867	750	1.5
JM (4)	164–233	180	1.5	4	499–815	750	1.5
EC (5)	167–230	180	1.5	5	575–933	750	1.5
JC (6)	196–253	240	2	6	629–973	750	1.5
GF (7)	235–244	240	2	7	1161–1630	1500	3
MA (8)	213–306	240	2				
JL (9)	339–375	360	3				
GL (10)	363–432	360	3				

[a] Numbers refer to Fig. 3a; initials refer to Ref. 14.
[b] Unit dose size = 120 mg/DDS.
[c] Numbers refer to Fig. 3b and Ref. 15.
[d] Unit dose size = 500 mg/DDS.

the intersection of curves A–B–D (for the minimum) and D–F–G (for the maximum).

At any given duration (T_R) in Fig. 1a, the percentage released per hour is constant at $100\%/T_R$, although the rate in milligrams per hour increases with the dose; $k_0 = D/T_R$. Those systems located on dotted lines A–G or B–F all have a single duration equal to an integer multiple of the dosing interval [$T_R = n\tau = n$(12 hr)]. These maintain constant steady-state concentrations as illustrated by curves A, B and G, F in Fig. 1b. In fact the profile in Fig. 1a is repetitive when extended to higher durations, where the identical maximum dosage ranges of A–G and B–F repeat at every integer multiple of the dosage interval, i.e., 12, 24, 36, 48 hr, etc. However, durations beyond 24 hr are impractical for oral administration unless the gastrointestinal transit time can be extended by bioadhesives, gastric entrapment, etc. In the current paper, the duration obtained by classical methods, $T_R = \tau = 12$ hr, is regarded as the maximum acceptable duration and discovering shorter successful durations will be regarded as advantageous.

Selection of Duration and Dosage Ranges: Theory. There are two considerations in defining the DDS requirements: (1) the duration (which determines the percentage release rate [Eq. (2)], and (2) the dosage range (which governs the final product sizes and therefore controls the dosing flexibility). If the maximum dosage range represented by B–F (Fig. 1a) is chosen as a goal, then the maximum flexibility in product size is obtained but the DDS must release its contents uniformly over the exact dosage interval ($T_R = \tau = 12$ hr). Conversely, if the widest range for the duration is selected, then the acceptable dosage range is minimized. Therefore, a compromise must be reached between these two conflicting limitations to provide flexibility in both formulation and dosage.

The selection of a dosage size and duration for a twice-a-day DDS is illustrated using Fig. 2. If the maximum dose range is selected as shown by the dashed line in plot a, the DDS must uniformly deliver its contents over a period of 12 hr as shown in b. Although maximum flexibility in dosage is obtained, this restricted release pattern makes formulation difficult. The dashed line in profile c shows the widest range for duration. This allows a uniform release pattern within 6 to 12 hr as shown by the shaded area in d. But a narrow dosage range results since a 6-hr duration requires a 140-mg dose with no flexibility as shown in c. Some compromise must be made to minimize these limitations on the duration and dose range. One set of choices is illustrated in e and f. Here, a DDS which can uniformly release its contents within 8 to 11 hr (shaded area in f) provides reasonable flexibility in both the release patern and the dosage range (shaded area in e).

Thus, to provide the broadest target for DDS design, the duration and dosage range must be optimized. Neither of the extreme cases, i.e., the widest dosage or duration range, represents the most flexible target since maximizing one restricts the other. Figure 1a represents the duration–dose boundary for a DDS which will accommodate one of the children. An ideal DDS should provide the necessary flexibility to accommodate all of the patients. The selection of the ranges for product duration and dose size for the entire group is based on an examination of the boundary conditions for each member of a group as illustrated next.

Theophylline DDS: Duration and Dosage Ranges for the Entire Group. The duration–dose profiles for each child are shown in Fig. 3a. A profile defined using the mean pharmacokinetic values would not represent the range of individual dosage requirements for the group. The same is true for the seven adults shown in Fig. 3b.

The pharmacokinetic values for each subject result in unique boundary conditions each having an individual min-

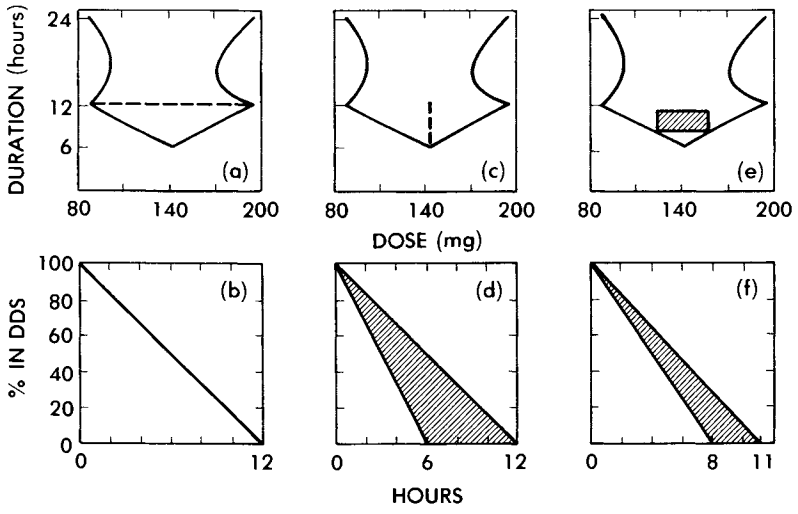

Fig. 2. Selection of a dosage range and release rate range for a zero-order DDS for administration every 12 hr. In a, the maximum dosage range is represented by the dashed line. This requires that the duration equals the dosing interval ($T_R = \tau$) resulting in the single 12-hr constant release rate pattern shown in b. In c, the maximum duration range has been selected (dashed line), thus providing the widest possible release pattern shown in d. The compromise shown in e provides a range of acceptable values for both the dose and the release rate pattern as shown in f.

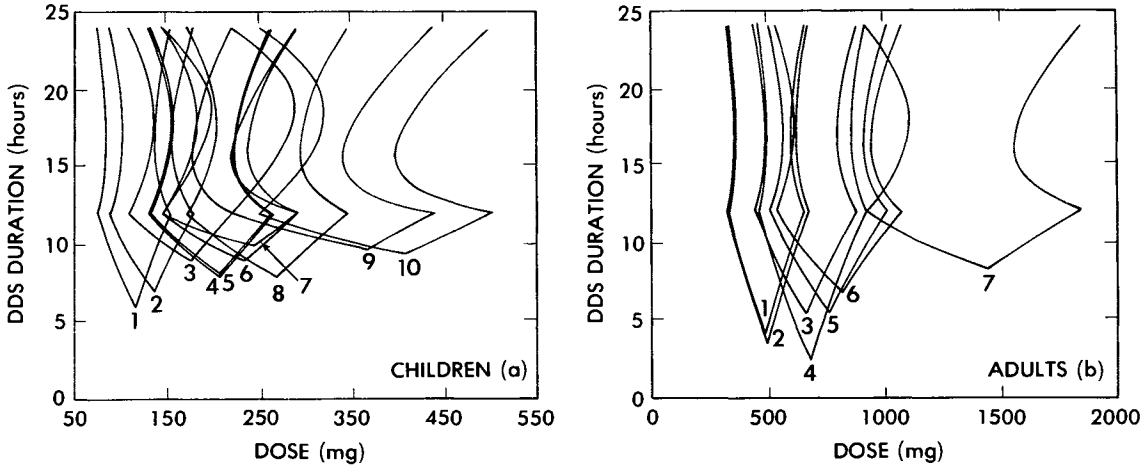

Fig. 3. Duration–dose boundary conditions for a zero-order DDS administered every 12 hr. Combining a dose and duration within each boundary will maintain theophylline steady-state concentrations between 10 and 20 mg/liter in the corresponding subject, where a represents the 10 children and b the seven adults in Table I.

imum required duration and effective dose range owing primarily to intersubject variability in clearance. Consequently, the design of a DDS must allow for individualized theophylline dosing for each patient (11). The duration–dose boundaries are used to optimize both DDS parameters: duration and dose size. Once these two values are selected, the release rate is fixed at $100\%/T_R$.

Defining a DDS to Accommodate an Entire Group: Theory. Since intersubject variability in clearance is generally expected, an ideal DDS should provide the necessary flexibility to accommodate all the patients, In lieu of the unpredictability of gastrointestinal transit time, the upper limit for an acceptable DDS duration range is set at the classical value of $T_R = \tau = 12$ hr in this paper. The lower limit for the DDS duration range is set equal to that of the patient whose minimum required duration is the longest of the group.

Figure 4a represents a hypothetical case wherein patients A, B, and C have increasing clearance values, thus providing three different duration–dose profiles. A DDS with a minimum duration set by C would have an acceptable duration range of 10 to 12 hr (Fig. 4b), thus exceeding the required minimum duration for all three patients. Patient A would require a dose size of 69–102 mg; patient B, 150–196 mg; and patient C, 245–286 mg. A DDS could be designed to accommodate these ranges by changing the number of units administered. For example, a 90-mg product of 10- to 12-hr duration would provide successful therapy for all three patients by administering 1, 2, or 3 units every 12 hr.

DDS Duration: Application to Theophylline. As shown above, it is necessary to establish the minimum duration required by each subject in order to select the range for the DDS duration. The minimum values for each individual can be observed in the duration–dose profiles in Fig. 3. The ideal duration should exceed the minimum observed value for all of the subjects. Figure 5 shows the relationship between the DDS duration and the percentage of the subjects in each group which would receive satisfactory therapy by combining this duration with an appropriate dose size. As seen in this histogram, the minimum required duration to accommodate all of the adults is 9 hr, and that for children is 10 hr. This calculated duration for the adult DDS agrees with the 9.2-hr duration for a commercially successful zero-order DDS reported by Spangler *et al.* (19).

Figure 6 shows the required DDS release rate profiles for both children and adults. A maximum duration of 12 hr has been chosen as the upper limit owing to the unpredictability of gastrointestinal transit time. The approach is not limited to this value; a user may select any value. Figure 6 shows a wide range of acceptable release rates for children and a wider range for adults. It also demonstrates why zero-order, rather than first-order, technology is more likely to succeed since a reasonable range exists in the release pattern. The application of this method to first-order DDS in children provided a single pattern having 90% release of

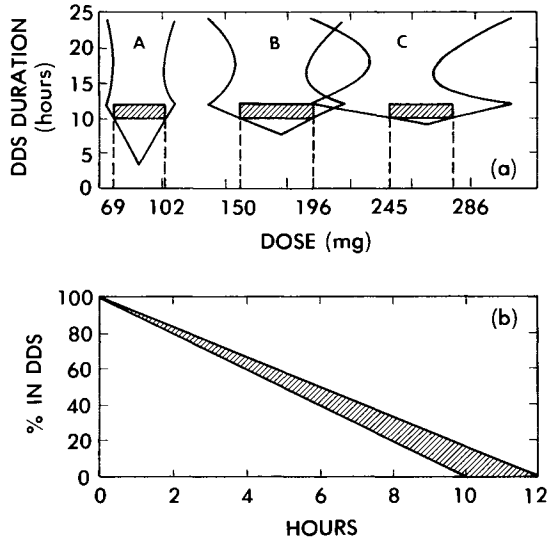

Fig. 4. (a) Hypothetical duration–dose boundaries wherein patients A, B, and C have increasing clearance values. A 90-mg zero-order DDS with the 10- to 12-hr release pattern shown in b would accommodate all three patients using regimens of 1 (for A), 2 (for B), or 3 (for C) units every 12 hr.

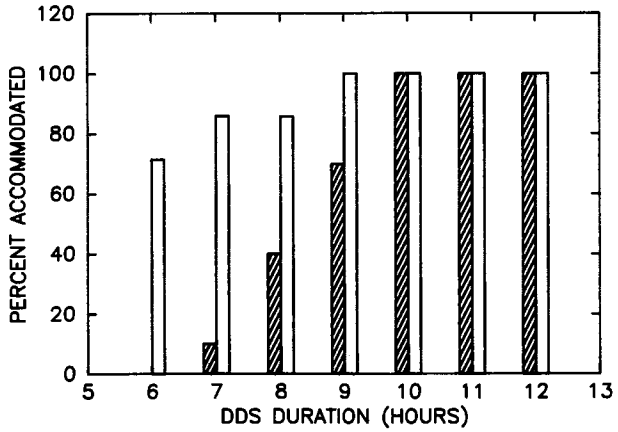

Fig. 5. The influence of the duration of a zero-order DDS on the percentage of subjects experiencing theophylline steady-state plasma concentrations between 10 and 20 mg/liter following oral administration every 12 hr: shaded bars are children (N = 10); open bars are adults (N = 7).

drug over 18 hr (13). The broader the acceptable range for release rate, the greater is the likelihood for success in developing a controlled-release device.

DDS Size: Application to Theophylline. Theophylline pharmacokinetics show a high degree of intersubject variability. Each patient presents a unique dosing problem (11). As shown by the duration–dose boundaries for these patients (Fig. 3), each subject has an individual required dose range. An ideal theophylline DDS must allow dosage adjustment to provide appropriate plasma levels for each patient. Table I summarizes the observed individual maintenance dose ranges for children and adults using a 12-hr dosing interval and a 10- to 12-hr zero-order release DDS. A 120-mg unit provides sufficient flexibility to dose all of the children in this study. A 500-mg unit would accommodate the seven adults. The number of units to be given every 12 hr to each patient for acceptable individualization is listed in Table I.

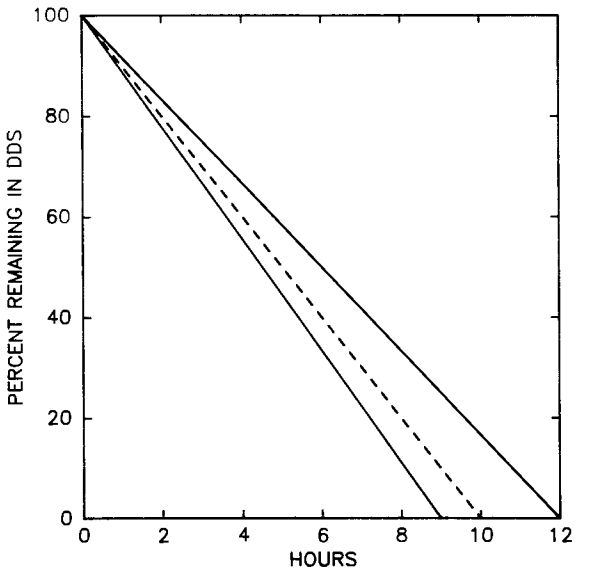

Fig. 6. The range of acceptable zero-order DDS release patterns which will accommodate all 10 children and 7 adults. The 12-hr duration has been selected as a maximum for both groups and the minimum of 9 hr (solid line) is observed for adults and 10 hr (dashed line) for children in Fig. 5.

Some of the calculated adult doses appear high relative to the suggested 300-mg maximum 12-hr maintenance dose (without serum monitoring) for body weights from 35 to 70 kg and 450 mg for body weights greater than 70 kg (20). However, they are reasonable since some patients require doses as high as 1600 mg (21). The reported steady-state trough and peak levels during a multiple-dose study with a commercially available zero-order theophylline sustained-release product (19) were used to calculate the doses assuming body weights of 70 kg and linear kinetics. In agreement with Table I, those adults would require doses ranging from 280 to 1400 mg every 12 hr to provide steady-state plasma time courses within the range of 10 to 20 mg/liter.

Adults usually require smaller doses than children when normalized according to total body weight (11). In this study, the range for children is 6.8 to 39.3 mg/kg, while that for adults is 4.4 to 24.9 mg/kg. However, it is necessary to design two sizes of delivery systems since the total dosage requirements for these two groups do not overlap (see selected DDS ranges). Adults require a larger unit DDS. This is due to the differences in the total body weights. In addition, the product release rates for the adult DDS exhibit a broader acceptable range (Fig. 6). This is due to the longer biological half-life and reduced theophylline clearance in adults relative to children. By selecting the 10- to 12-hr duration in Fig. 6, one DDS can be developed for both groups, with unit sizes representing the only differences.

An ideal drug candidate for prolonged-release formulations should be rapidly and completely absorbed following oral administration in order that absorption is truly controlled by the delivery rate (11). If this criterion is satisfied, k_a in Eqs. (3) and (4) will not influence the duration–dose profiles. This can be evaluated by substituting an extremely large value for k_a and comparing the profiles to the original results such as those shown in Fig. 3. In the theophylline example, the results are unchanged by this test. This test provides an additional advantage of this simulation approach since various estimates for k_a values can be examined for their potential influence.

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