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BIOPHARMACEUTIC AND PHARMACOKINETIC ASPECTS IN THE DESIGN OF CONTROLLED RELEASE PERORAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Present peroral controlled release drug delivery systems (CRDDS) are for a maximum of 24 hours clinical effectiveness. Such systems are primarily for drugs of short elimination half-life. However, also drugs of long half-life qualify if a reduction in steady state fluctuation is desired. The biopharmaceutic evaluation of a drug for potential use in CRDDS requires knowledge on the absorption mechanism of the drug from the G.I. tract, the general absorbability, the drug's molecular weight, pK_a, solubility at different pH and apparent partition coefficient. The pharmacokinetic evaluation requires knowledge on a drug's elimination half-life, total clearance, absolute bioavailability, possible first-pass effect, and the desired steady concentrations for peak and trough. Even if a drug's disposition after I.V and peroral fast release administration is best described by a two- or higher-compartment model, one can collapse these for all practical purposes to a one-compartment model for the design of a CRDDS if the release rate is much smaller than the intrinsic absorption rate and the distribution rates, and is the actual rate-limiting process. Two simple approaches for the pharmacokinetic design of required release characteristics and required maintenance dose to achieve desired steady state maximum and minimum concentrations are discussed, one for zero-order and one for first-order release.

INTRODUCTION

Controlled release drug delivery systems (CRDDS) are dosage forms from which the drug is released by a predetermined rate which is based on a desired therapeutic concentration (in either systemic circulation or a target site) and the drug's pharmacokinetic characteristics. Thus, CRDDS are not identical to sustained release dosage forms which merely prolong the release of the drug so that the drug is absorbed over a longer period of time. However, the materialistic principles and release patterns may be the same; the difference is in the predetermined controlled rate of drug release.

Also, along with the CRDDS a new term was introduced: drug delivery devices (DDD). A DDD is a prefabricated system that releases a predetermined volume or amount independent of the drug used. In other words a DDD would deliver for instance 0.05 $ml \cdot h^{-1}$ of a solution regardless which drug is contained in the solution (example: ALZET Osmotic Pump). However, an elementary osmotic pump in a tablet form where the release is among others a function of the drug's solubility, is a CRDDS (example: OROS) and not a device[1].

CRDDS and DDD are available or being investigated for various routes of administration and various times of extension of duration. The release time may extent from 12 hours to 1 year. In Fig. 1[2] types of CRDDS and DDD for various routes of administration and lengths of duration of action are shown. This paper is concerned with only one type of CRDDS: the P.O. dosage forms for up to 24 hours of duration of action.

REASONS FOR P.O. CONTROLLED RELEASE DRUG DELIVERY

Short Elimination Half-Life ($t_{1/2}$) and Minimum Effective Concentration (MEC) Required for Administration Every 12 or 24 Hours

The shorter the $t_{1/2}$ of a drug the larger will be the fluctuations between the maximum steady state concentration ($C_{ss\ max}$) and the minimum steady state concentration ($C_{ss\ min}$)

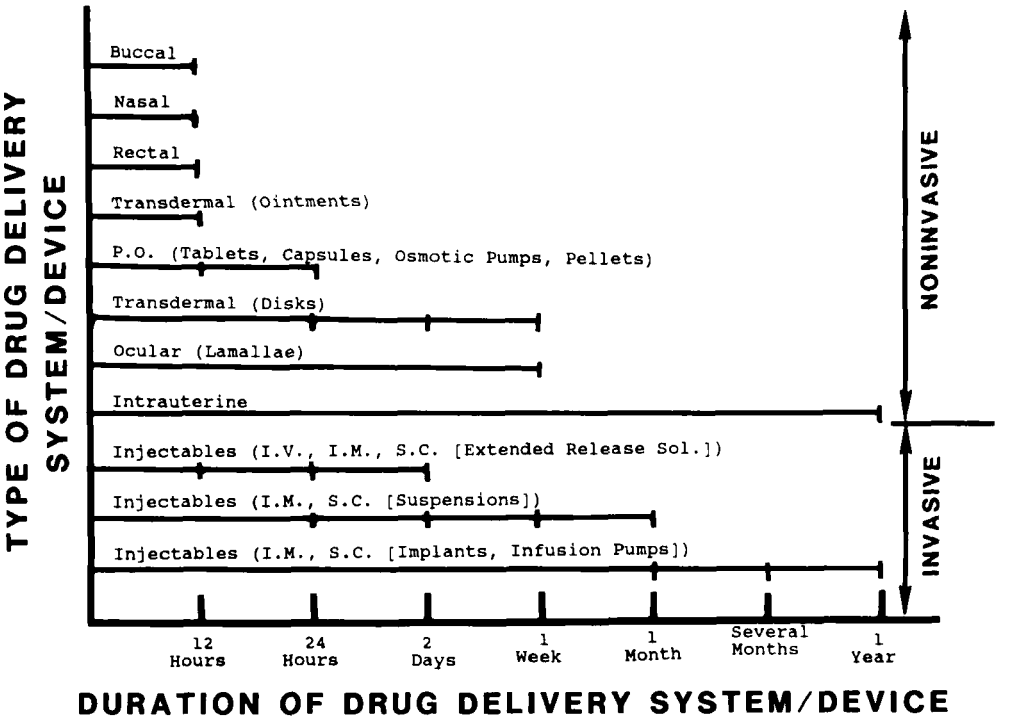

FIGURE 1

SCHEMATIC DIAGRAM OF TYPES OF CONTROLLED-RELEASE DELIVERY SYSTEMS/DEVICES AND ROUTE OF ADMINISTRATION, AND LENGTH OF DURATION OF ACTION. (WITH PERMISSION OF COPYRIGHT OWNER, REF. 2)

upon repetitive (multiple) dosing. Thus the drug product needs to be administered more frequently. If a minimum effective concentration, MEC, is therapeutically required, either frequent dosing of a conventional drug product is necessary or a controlled release preparation may be chosen. In Fig. 2^2 a schematic presentation is given for a drug having a $t_{1/2}$ of 3 hours. A conventional dosage form my have to be given every 3 hours to achieve and maintain a certain MEC (A in Fig. 2), or a CRDDS may be chosen for 6 or 12 hourly dosing intervals (B and C in Fig. 2).

The longer the extent of duration the larger the total dose per unit delivery system needs to be. Hence, there is a

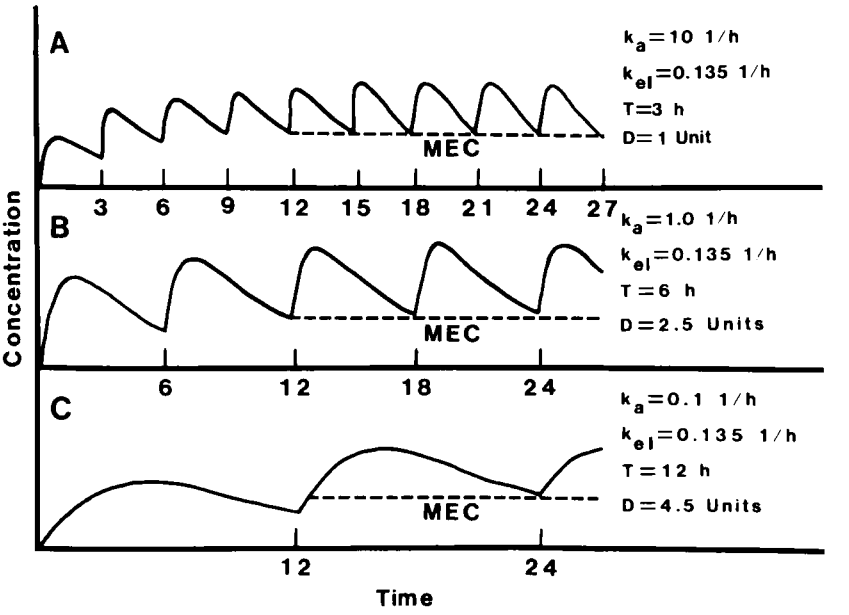

FIGURE 2

SCHEMATIC PRESENTATION OF A HYPOTHETICAL DRUG HAVING AN ELIMINATION HALF-LIFE, $T_{1/2}$, OF 5.13 HOURS AND AN INTRINSIC ABSORPTION RATE, K_A, OF 10 HR^{-1} (A) IN FORM OF A P.O. SOLUTION GIVEN EVERY 3 HOURS, AND IN FORM OF CONTROLLED RELEASE SYSTEMS FOR τ = 6 HOURS (B) AND τ = 12 HOURS (C) DOSING INTERVALS. MEC = MINIMUM EFFECTIVE CONCENTRATION.

limitation to the amount of drug that can be practically incorporated into such a system.

Relatively Long $t_{1/2}$, and Either Wide or Narrow Therapeutic Range or Small Fluctuation Desired at Steady State

It is the belief of some that neither a sustained nor a CRDDS is needed or useful for drugs having a $t_{1/2}$ of 12 hours or more. This is not so because there are two cases for which a 12 or 24 hour CRDDS seem to be indicated:

Two to Three Day Extension

A drug having a $t_{1/2}$ between 12 and 72 hours may be designed for a CRDDS permitting application every two to three days. The decline of the blood level-time curve after release of the drug from the system will depend on the drug's $t_{1/2}$. Naturally, fluctuations between $C_{ss\ max}$ and $C_{ss\ min}$ may accordingly be relatively large. In other words, one adds to the slow elimination process another 12 to 24 hours of slow release.

Narrow Therapeutic Range, Small Fluctuation

For some drugs, having a $t_{1/2}$ between 20 and 100 hours, and which are intended for long-term use, one may desire small fluctuations between peaks and troughs at steady state either to achieve a certain therapeutic effect or because the therapeutic range is narrow. The latter case has been suggested for lithium which has a $t_{1/2}$ of 19-22 hours[3], as shown in Fig. 3.

BIOPHARMACEUTIC ASPECTS

The goal of P.O. CRDDS is to achieve and maintain a rather flat, plateau-like drug concentration in blood at steady state within a dosing interval (τ) of 12 or 24 hours with minimal fluctuation between a maximum steady state concentration ($C_{ss\ max}$) and a minimum steady state concentration ($C_{ss\ min}$). Hence, a general prerequisite in the design is that there is an established relationship between the desired pharmacologic response, i.e. a well defined therapeutic range, and the pharmacokinetics of the drug. Only drugs for which such a relationship can be identified are *a priori* candidates for CRDDS.

Advantages of CRDDS

The main advantages are an increase in efficacy and decrease in side effects or toxicity by "flattening" the blood level concentration-time curve, and a less frequent administration of the drug. Furthermore, prescribed dosage regimens such as q6h are

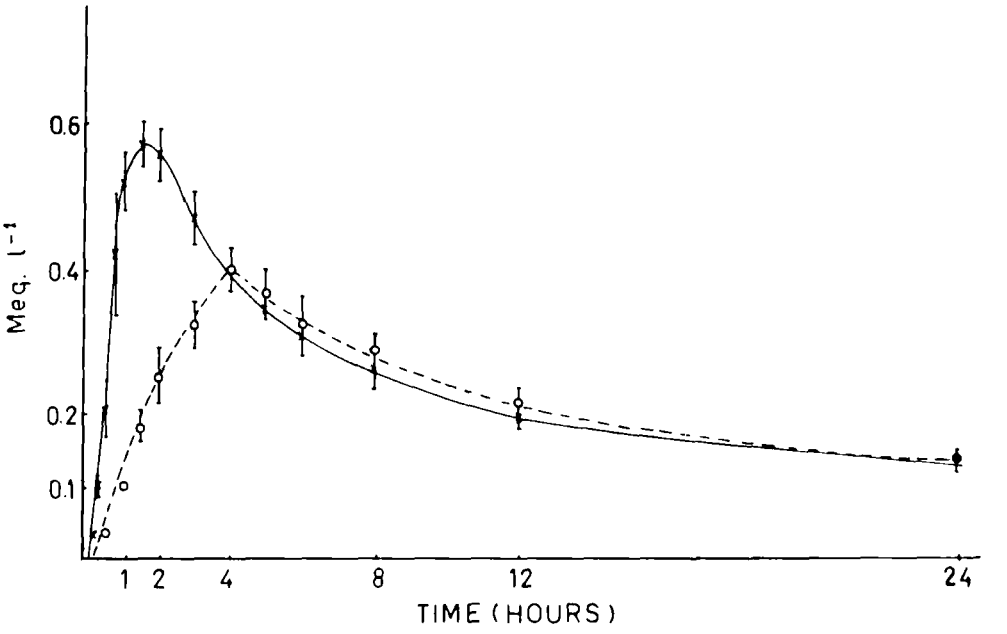

FIGURE 3

MEAN ± S.D. LITHIUM SERUM CONCENTRATION IN HUMANS (N = 8) FOLLOWING ADMINISTRATION OF TWO 300 MG LITHIUM CARBONATE CONVENTIONAL TABLETS (____) AND 500 MG OF CONTROLLED RELEASE FORMULATION (----). (WITH PERMISSION OF COPYRIGHT OWNER, REF. 3)

not followed by the majority of patients[4] and even in hospital settings q6h does not necessarily mean that the dose be given every 6 hours, but is simply viewed as four times per day, such as at 9:00, 12:00, 17:00 and 21:00[5]. The most important advantages are listed in Table 1.

Disadvantages of CRDDS

The question of patient compliance is only relative and relates to dosing within a day. However, if a CRDDS administration is missed once or twice, the reduction or loss in effect may be greater than that found after conventional dosage forms. If for an unknown reason the CRDDS would not release the proper

TABLE 1:
Important Advantages of P.O. CRDDS

- Avoidance of undesirably high peaks (toxicity)
- Avoidance of undesirably low troughs (subtherapeutic)
- Limited fluctuation within therapeutic range (increased safety and efficacy)
- Approach constant rate infusion blood levels (improved therapeutic precision)
- Maintenance of therapeutic concentration also during the night (therapeutic protection during night)
- Decreased dosing frequency (improved patient compliance)
- Drugs of short elimination half-life do not depend on strict frequent dosing (convenience and compliance)

amount, therapeutic failure would result. On the other hand, if the CRDDS would release the drug instantly (mechanical failure, chewing, masticating), the total drug content may become available (which is greater than in a conventional dosage form) for absorption and toxicity may result. If a CRDDS becomes lodged in a segment of the G.I. tract a high drug concentration may be obtained locally, possibly irritating or damaging the G.I. mucosa. Drugs with extensive first-pass metabolism are poor candidates for CRDDS unless their metabolites are also pharmacologically effective, such as propranolol and procainamide. Also, CRDDS are not suitable for drugs with extremely short or extremely long elimination half-lives if they have a low therapeutic index or narrow therapeutic range, are not stable throughout the gastrointestinal tract or have a poor P.O. bioavailability. Some of the important disadvantages are listed in Table 2.

TABLE 2:
Important Disadvantages of P.O. CRDDS

- Loss of efficacy by missing one or two doses (patient compliance)
- Loss of effect due to failure in release
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake)
- Local irritation or damage of epithelal lining (lodging of dosage forms)
- Loss of effect due to diarrhea (too fast transit time)
- Poor dosage form for drugs with
    - extensive first-pass metabolism (except metabolites are also effective)
    - extremely short elimination half-life (low therapeutic index)
    - extremely long elimination half-life (narrow therapeutic range)
    - bioavailability problems
    - instability in G.I. environment

Desired Biopharmaceutic Characteristics of Drug to Qualify for Candidacy for CRDDS

Molecular Weight/Size

Small molecules may pass through pores of a membrane by convective transport. This applies to both, the drug release from the dosage form and the transport across a biologic membrane. Convective transport is available to molecules with diameters smaller than that of the pore. For biological membranes the limit may be a MW of 150 for spherical molecules and a MW of about 400 for chain-like compounds.

Solubility

Except for the limited case of pinocytosis, a subgroup of endocytosis, for all other mechanisms of absorption the drug must be present at the site of absorption in form of a solution.

During the preformulation phase it is necessary not only to determine a drug's solubility in water but also at various pH values. The physiologic pH range in the G.I. tract is between pH 1 and pH 7.8. If the solubility is less than 0.1 $\mu g \cdot ml^{-1}$ (particularly in acidic environment), one may expect variable and reduced bioavailability. If the solubility is less than 0.01 $\mu g \cdot ml^{-1}$ absorption and availability most likely become dissolution-limited. Hence, driving force for diffusion may be inadequate.

It seems that drugs are well absorbed by passive diffusion from the small intestine upon P.O. administration if at least 0.1 to 1 % is in nonionized form, and from the rectum upon administration if 1-5 % is in nonionized form[6].

In drug delivery design it is important to calculate the degree of ionization and the % of drug nonionized to obtain an indication whether absorption from a particular site or transport can be assumed to be unrestricted in case of passive diffusion.

Apparent Partition Coefficient (APC)

Drugs being absorbed by passive diffusion must have a certain minimal APC. The higher the APC in an n-octanol/buffer system the higher is the flux across a membrane for many drugs. The APC should be determined for the entire pH range in the G.I. tract. The APC must also be applied for partitioning of the drug between CRDDS and the biological fluid. For instance, the partitioning (release) of a drug of high APC from a fat-based CRDDS or lipophilic matrix may be slow and incomplete. On the other hand, this very principle is the basis of several such systems.

General Absorbability/Absorption Mechanism

For a drug to be a viable candidate for a P.O. CRDDS, its absorption mechanism must be by diffusion throughout the entire G.I. tract. The term diffusion here refers to the dual pathway of absorption either by partitioning into the lipid membrane (across the cell) or by passing through water-filled channels (between cells). The other transport mechanisms, particularly active, carrier-mediated transport, are not available in all segments of

Table 3:
Absorption Rate of Allopurinol from Different Segments of the Rat G.I. Tract (Modified after ref. 22)

SEGMENT OF G.I. TRACT	NORMAL SEGMENT DIMENSION IN ADULT RATS Area/Unit Length ± SD [cm^2/cm]	ALLOPURINOL ABSORPTION RATE ± SD [$\mu g/min/cm$]	NORMALIZED RATE ± SD [$\mu g/min/cm^2$]	RELATIVE RATE [%]
Duodenum	8.2 ± 0.8	0.559 ± 0.10	0.068 ± 0.01	100.0
Midgut	6.3 ± 0.7	0.478 ± 0.12	0.070 ± 0.01	85.3
Ileum	4.4 ± 0.8	0.325 ± 0.14	0.071 ± 0.04	58.1
Upper Colon	2.2	0.027 ± 0.06	0.012 ± 0.03	4.9
Lower Colon	2.2	0.056 ± 0.08	0.025 ± 0.05	9.9

the G.I. tract[7]. Therefore, a test to determine the absorption mechanism, such as the guinea pig isolated ileum sac method should be performed[8,9].

It is also important that absorption occurs from all segments of the G.I. tract which may depend on the drug's pK_a, the pH in the segment, binding of drug to mucus, blood flow rate, etc. The general absorbability is usually tested in the in situ rat intestinal perfusion model. In principle there are four commonly used techniques: 1) Single-pass perfusion[10-13], 2) Recirculating perfusion[14-17], 3) Oscillating perfusion[18], and 4) Closed-loop method[19-20]. In a recent study the four methods were compared and constant values for absorption and similar coefficients of variation were obtained with the first three methods listed above[21]. The absorption process seems to be highly dependent on the hydrodynamics in the G.I. lumen.

In another recent study the closed-loop method was used to study allopurinol absorption from different sites of the intestine[22]. The results are listed in Table 3[22]. As seen from Table 3, allopurinol is well absorbed from the small intestine but

Table 4:
Gastrointestinal Transit Times in Minutes ± SEM of Pellets and Intact Tablets in Humans (With permission, ref. 23)

FORMULATION	GASTRIC EMPTYING TIME [min]	SMALL INTESTINE TRANSIT TIME [min]	COLONIC ARRIVAL TIME [min]
Pellets*	79 ± 20	277 ± 82	305 ± 100
Tablets	164 ± 92	188 ± 23	265 ± 59

*For pellets the transit time is for 50 % of the particles to leave or arrive at the particular site.

poorly absorbed from the large intestine. Hence, a P.O. CRDDS with a release time exceeding the transit time of the small intestine would not be feasible.

Regarding intestinal transit time in man the data listed in Table 4 can be used as guideline[23].

This brings us to a very important consideration regarding P.O. CRDDS. If it takes only about 5 hours for pellets or tablets to arrive in the colon, considerable absorption must be expected from the colon. Assuming that defecation in man occurs once or twice daily, the mean total G.I. transit time may be limited to about 16 hours. Hence, even for a 24 hour duration CRDDS, the time available for release might be limited to 16 hours, and the remaining 8 hours of duration of effect will then be dictated by the elimination kinetics of the drug. For drugs with a short elimination half-life a 24 hour system might not be a good one. The ideal characteristics are summarized in Table 5.

Table 5:
Desired Biopharmaceutic Characteristics of Drugs to be used in P.O. CRDDS

- Molecular weight/size: < 1000
- Solubility: > 0.1 $\mu g \cdot ml^{-1}$ for pH 1 to pH 7.8
- pK_a: nonionized moiety > 0.1 % to 1 % at pH 1 to pH 7.8
- Apparent partition coefficient: high
- Absorption mechanism: diffusion
- General absorbability: from all G.I. segments
- Release should not be influenzed by pH and enzymes

Type of Dosage Form

Two different types of P.O. CRDDS have been described in the literature such as:

- Single units (capsules, coated tablets, osmotic pumps, insoluble matrix tablets, soluble matrix, degradable matrix, ion-exchange resins)
- Multiple units (granules, microcapsules, beads, ion-exchange resins)

These types are operated by various mechanisms:

- diffusion through inert matrix
- diffusion across hydrophilic matrix
- diffusion-erosion
- diffusion-degradation
- ion-exchange
- osmosis
- combinations

The release rates from such systems are usually by:

- zero-order
- first-order
- square root of time

Even though that first-order and square root of time release can result in highly effective delivery systems[24] it is widely believed that the ultimate goal is a zero-order release profile. One must keep in mind that zero-order in vitro release will produce zero-order in vivo release and zero-order (in vivo) absorption only if: (1) the entire GI tract behaves as a one-compartment model, i.e. the various segments throughout the GI tract are homogeneous with respect to absorption, and (2) drug release rate is the rate-limiting step in the absorption process[25].

Constant delivery rate over some period of time is not universally applicable to all drugs. For instance, it is believed that constant rate of delivery of nitroglycerin is undesirable because blood vessels loose their capability of constriction/dilation, or, gonadotropin releasing hormone, GRH, administered in spaced intervals stimulates ovaries and testes, whereas when given continuously the opposite effect is obtained: the functions of ovaries and testes are inhibited (chemical sterilization).

With first-order release, on the other hand, smaller and smaller amounts are released per unit of time with increasing time. Assuming that the rate of absorption gets slower past the small intestine due to increased viscosity, decreased mixing (peristalis) and decreased intestinal surface area, less drug is absorbed, when in fact the opposite should occur, namely larger amounts should be released toward the latter part of the duration of the delivery system.

In any case, the drug release from the CRDDS should not be influenced by pH changes within the G.I. tract, by enzymes present in the lumen, peristalsis, etc.

PHARMACOKINETIC CHARACTERIZATION OF DRUG FOR DESIGN OF CRDDS

For CRDDS, the general absorbability must be established. The intrinsic rate of absorption is of minor importance, because the apparent rate of absorption will be dictated by the delivery system. In other words, ideally the liberation or drug release

rate (therefore the term: controlled-release delivery system) is the rate-limiting step for the absorption process. CRDDS are multiple dose systems designed to result in steady state concentrations, C_{ss}. The magnitude of C_{ss} depends on the dose rate, D/τ, (amount drug per unit of time), and the total clearance, Cl_{tot}, (loss of drug from the volume of distribution per unit of time) of the drug. To understand the design and evaluation of CRDDS, some basic principles are discussed here.

Compartment Model

In the case of CRDDS the absorption is not completed instantly as with an I.V. push (rapid I.V. injection), it is pertinent to discuss here only the concentration-time curves as they are observed upon extravascular or infusion administration.

Assuming first-order elimination, which is the case for most drugs, and plotting the concentration-time data semilogarithmically, the terminal slope is the elimination phase, characterized by a straight line.

One can now back-extrapolate this terminal phase to the ordinate. We will find three possibilities as shown in Fig. 4[2]:

1. If the drug is rapidly absorbed and rapidly distributed between systemic circulation (including organs of instant equilibrium) and those tissues to which the drug eventually goes, the peak will be below the back-extrapolated, terminal line (A in Fig. 4).

2. If the drug is rapidly absorbed but slowly distributed between systemic circulation (including organs of instant equilibrium = central compartment) and those tissues to which the drug eventually goes (peripheral compartment), the peak will be above the back-extrapolated, terminal line (B in Fig. 4).

3. If the drug is slowly absorbed but rapidly distributed between central and peripheral compartment, the peak will be below the back-extrapolated, terminal line (C in Fig. 4).

The insets on the right hand side in Fig. 4 symbolize the compartment models. A in Fig. 4 is a one-compartment model, B and C are two-compartment models.

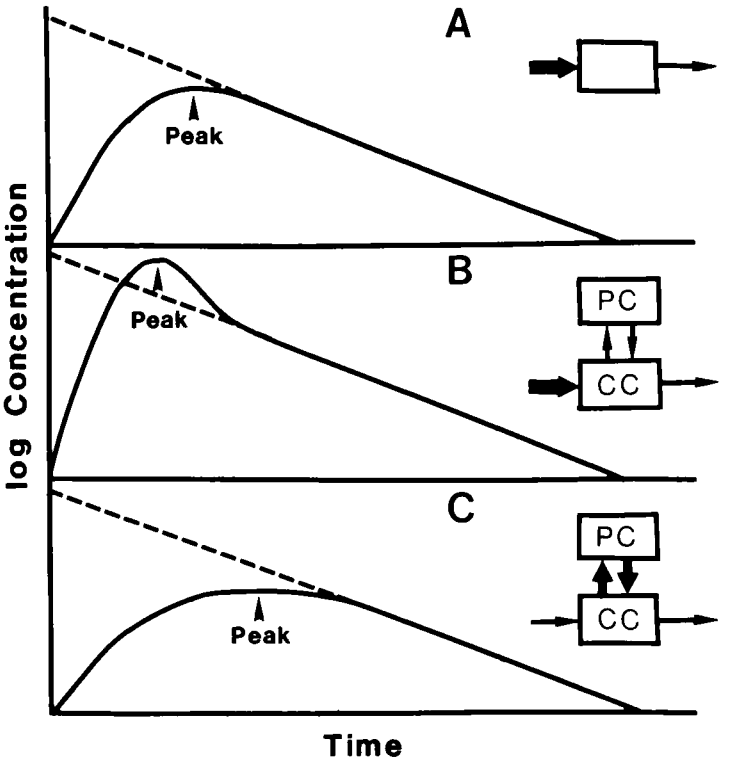

FIGURE 4

SCHEMATIC BLOOD CONCENTRATION-TIME CURVES AFTER EXTRAVASCULAR ADMINISTRATION. FOR EXPLANATION SEE TEXT. THE THICKNESS OF THE ARROWS INDICATES THE RELATIVE MAGNITUDE OF THE CORRESPONDING RATE OF THE PROCESS. (WITH PERMISSION OF COPYRIGHT OWNER, REF. 2)

The concentration-time profile in C of Fig. 4 having the peak below the terminal line, looks similar to that in A of the figure. The distribution phase in two-compartment models may vary between a few minutes to a few hours. Since in controlled drug delivery systems the drug liberation is usually over a longer period of time than the duration of the distribution phase, we can "collapse" the two-compartment model into a one-compartment model.

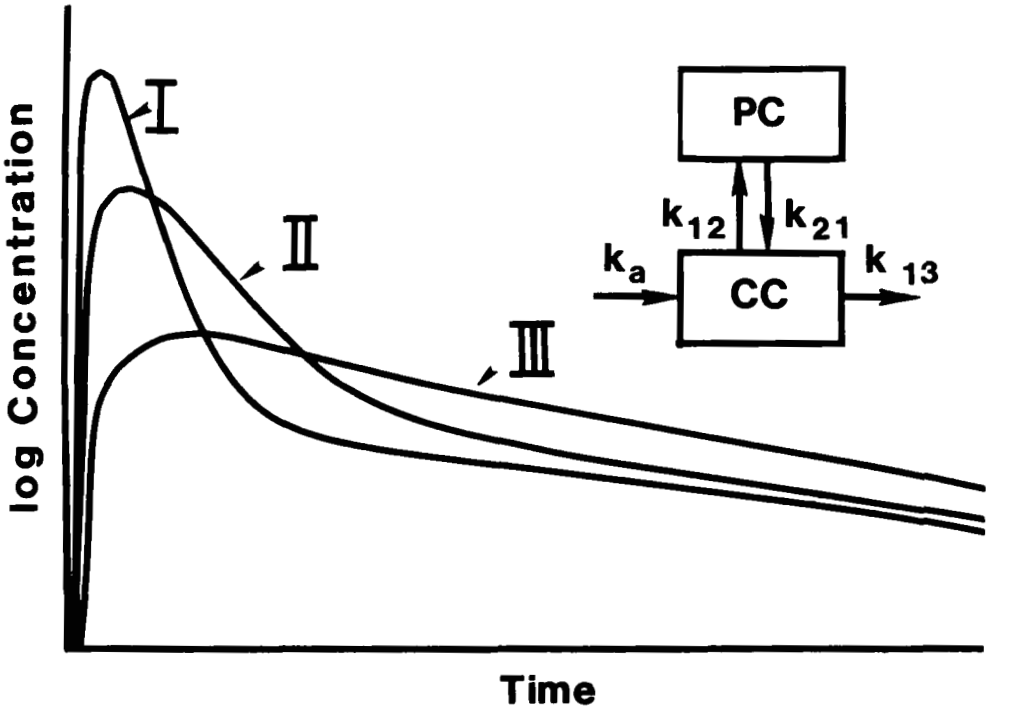

FIGURE 5

SCHEMATIC DIAGRAM TO DEMONSTRATE COLLAPSING OF A TWO-COMPARTMENT MODEL TO A ONE-COMPARTMENT MODEL. K_{12} = 0.8 H^{-1}; K_{21} = 0.25 H^{-1}; K_{13} = 0.2 H^{-1}. ONLY K_A IS CHANGED: FOR I = 5.0 H^{-1}; FOR II ⊟ 1.25 H^{-1}; FOR III ⊟ 0.7 H^{-1}. K_A = ABSORPTION RATE CONSTANT; K_{12} AND K_{21} = DISTRIBUTION RATE CONSTANTS; K_{13} = ELIMINATION RATE CONSTANT; CC = CENTRAL COMPARTMENT; PC ⊟ PERIPHERAL COMPARTMENT. (WITH PERMISSION OF COPYRIGHT OWNER, REF. 2)

However, one has to be aware that treating C in Fig. 4 as a one-compartment model, the apparent absorption rate constant is overlapped by and approaches the distribution rate constant. Nevertheless, the one-compartment model is quite suitable and applicable for the design of drug delivery systems.

In Fig. 5[2] the collapsing of a two-compartment model to an "apparent" one-compartment model is shown as a function of the absorption rate constant k_a.

For all practicality, the one-compartment open model is quite suitable to design CRDDS for most drugs.

Pharmacokinetic Parameters

To evaluate whether or not a drug is a viable candidate for the design of a CRDDS, one has to consider several pharmacokinetic drug parameters.

Elimination Half-Life ($t_{1/2}$)

Drugs having a $t_{1/2}$ between 1 and 8 hours are ideally suited for CRDDS. If the $t_{1/2}$ is less than 1 hour, the dose size required for a 12 or 24-hour duration dosage form may be too large to be incorporated into a dose unit. If the $t_{1/2}$ is only a few minutes, the drug is not a good candidate, because of a steep fall in blood level concentration once the release is terminated. In other words, large fluctuations of blood levels can be expected. If the $t_{1/2}$ is very long (> 24) there is usually no need for a CRDDS, unless it is simply intended for a reduction in fluctuation of steady state blood levels.

Total Clearance (CL)

The CL is a measure of the volume of distribution cleared of drug per unit of time. It is the key parameter in estimating the required dose rate for CRDDS, and for predicting the steady state concentration.

Terminal Disposition Rate Constant (λ_z)

The terminal disposition or elimination rate constant can be obtained from the $t_{1/2}$:

$$\lambda_z = 0.693/t_{1/2}$$

and is required to predict a blood level-time profile.

Apparent Volume of Distribution (V_z)

The V_z is the hypothetical volume a drug would occupy if it were dissolved at the same concentration as that found in blood. It is the proportionality constant relating the amount of drug in the body to the measured concentration in blood.

Among the triad Cl, V_z and $t_{1/2}$, the former two parameters (CL, V_z) are the independent variables and the last one ($t_{1/2}$) is the dependent variable:

$$CL = 0.693 \cdot V_z / t_{1/2}$$

The V_z or CL are required to predict the concentration-time profile.

Absolute Bioavailability (F)

The absolute bioavailability is the percentage of drug taken up into systemic circulation upon extravascular administration. For drugs to be suitable for CRDDS one wants an F value to be close to 100 %. An F value lower than about 0.75 (fraction), or which shows wide variation, should generally disqualify a drug for a CRDDS.

Intrinsic Absorption Rate Constant (k_a)

The intrinsic absorption rate constant of the drug administered P.O. in form of a solution should be high, generally by an order of magnitude higher than the desired release rate constant of the drug from the dosage form, in order to insure that the release process is the rate-controlling step.

Therapeutic Concentrations (C_{ss})

The therapeutic concentrations are the desired or target steady state peak concentration ($C_{ss\ max}$), the desired or target minimum steady state concentration ($C_{ss\ min}$) and the mean steady state concentration ($C_{ss\ av}$). The difference between $C_{ss\ max}$ and $C_{ss\ min}$ is the fluctuation. The smaller the desired fluctuation the greater must be the precision of the dosage form performance.

The lower C_{ss}, the smaller V_z, the longer $t_{1/2}$, and the higher F, the less amount of drug is required to be incorporated into a CRDDS.

A summary of the pharmacokinetic parameter to be considered is given in Table 6.

SIMPLE PHARMACOKINETIC DESIGN FOR A ZERO-ORDER AND FIRST-ORDER CRDDS

The use of pharmacokinetic concepts as a tool in the development of CRDDS has been discussed widely. However, only few

Table 6:
Pharmacokinetic Characteristics of Drugs to be Used in P.O. CRDDS

- Elimination half-life, $t_{1/2}$: preferably between 0.5 and 8 hours.
- Total clearance, CL: should not be dose-dependent.
- Elimination rate constant, λ_z = required for design.
- Apparent volume of distribution, V_z: the larger V_z and MEC, the larger will be the required dose size. The maximum dose to be incorporated into a P.O. CRDDS is about 500 mg. The smaller V_z, the easier the incorporation of drug into dosage form.
- Absolute bioavailability, F: should be 75 % or more.
- Intrinsic absorption rate, $k_{a\ intr.}$: must be >>> release rate.
- Therapeutic concentration, $C_{ss\ av}$: the lower $C_{ss\ av}$ and the smaller V_z, the less amount of drug required.
- Toxic concentration, C_{tox} and minimum effective concentration, MEC: the further apart these two values are the "safer" the dosage form. Also suitable for drugs with very short $t_{1/2}$.

papers have discussed a step-wise, prospective approach for the design of CRDDS based on pharmacokinetic principles[25-28].

The two methods presented here[2,29,30] differ somewhat in the approach taken by others. The first difference is that we believe the actual release time should be shorter than the dosing interval for reasons already discussed previously (see section on General Absorbability). Secondly, we believe that collapsing a two- or higher compartmental model to a simple one-compartment model is justificable under the assumption that the release rate constant << intrinsic absorption and distribution rate constant. Thirdly, that the superposition method is a simple method to use in predicting steady state in absence of dose dependency or saturation kinetics.

Intermittent Zero-Order Release CRDDS

The CRDDS envisioned shall release the drug at zero-order rate (R°) for a period of time (t_{del}) shorter than the selected dosing interval (τ). After termination of release, the drug concentration in blood decays according to the drug's elimination rate constant (λ_z). The blood level-time profile mimics an I.V. constant rate infusion.

The step-wise design procedure is as follows:

Step 1:

Retrieve from the literature the following mean population pharmacokinetic parameters:

V_z in $ml \cdot g^{-1}$	(apparent volume of distribution)
λ_z in h^{-1}	(terminal disposition rate constant)
F	(fraction of P.O. bioavailability)
$k_{a\ intrin}$ in h^{-1}	(intrinsic absorption rate constant)
$DM_{convent}$	(conventional dose size which results in therapeutic effectiveness)
$C_{ss\ av\ des}$ in $mcg \cdot ml^{-1}$	(desired mean steady state "target" concentration)
C_{tox} in $mcg \cdot ml^{-1}$	(toxic concentration)
MEC in $mcg \cdot ml^{-1}$	(minimum effective concentration)

Step 2:

Decide on length of dosing interval to be either 12 or 24 hours:

τ in h

Based on $C_{ss\ av\ des}$, C_{tox} and MEC set limits for acceptable steady state fluctuation:

$C_{ss\ max\ des}$ in $mcg \cdot ml^{-1}$	(desired steady state peak concentration)
$C_{ss\ min\ des}$ in $mcg \cdot ml^{-1}$	(desired steady state trough concentration)

Step 3:

Estimate time for elimination (t_{elim}), i.e. time from termination of release to time of next dosing:

$$t_{elim} = \frac{\ln C_{ss\ max\ des} - \ln C_{ss\ min\ des}}{\lambda_z}$$

Step 4:

Estimate time span (t_{del}) for delivery of dose by zero-order mechanism:

$$t_{del} = \tau - t_{elim}$$

Step 5:

Estimate a reasonable, preliminary maintenance dose size (DM_{test}), based on a conventional dose size ($DM_{convent}$):

$$DM_{test} = \frac{DM_{convent} \cdot 0.693 \cdot \tau}{t_{1/2}}$$

Step 6:

Estimate preliminary zero-order release rate ($R°_{prelim}$). Assume that the system releases 90 % of drug (then the "driving force" is exhausted), P = 0.9 during t_{del} within each dosing interval τ. The preliminary zero-order release rate is:

$$R°_{prelim} = \frac{DM_{test} \cdot F \cdot P}{t_{del}}$$

Step 7:

Calculate some theoretical blood concentrations to be expected after administration of the <u>first</u> DM_{test}.

It is suggested at least to calculate two concentrations (C(t)) at about 1/3 and 2/3 of t_{del}, using the following equation:

$$C(t) = \frac{R°_{prelim}}{V_z \cdot \lambda_z} \cdot (1 - e^{-\lambda_z \cdot t})$$

where t is either $t_{del} \cdot 0.33$ or $t_{del} \cdot 0.66$.

Then the peak (C_{max1}) and the trough (C_{min1}) after the first DM_{test} are calculated:

$$C_{max1} = \frac{R°_{prelim} \cdot (1-e^{-\lambda_z \cdot t_{del}})}{V_z \cdot \lambda_z}$$

$$C_{min1} = C_{max1} \cdot (e^{-\lambda_z \cdot (\tau - t_{del})})$$

Step 8:

The superposition method is used to estimate accumulation to steady state.

For this purpose the concentrations expected, C(x), from the first DM_{test} to occur during subsequent dosing intervals are calculated for the times corresponding to the sampling times during the first dosing interval. The expected concentrations are generated until they reach a value of ≤ 1 % of C_{max1}:

$$C(x) = C_{min1} \cdot e^{-\lambda_z \cdot t}$$

For t use:
1. $t_{del} \cdot 0.33$
2. $t_{del} \cdot 0.66$
3. t_{del}
4. τ

Step 9:

An accumulation table is constructed as shown in Table 7.

The concentration data from column DM_{test1} are repeated for DM_{test2}, DM_{test3}, etc., starting after 1, 2, 3, etc. dosing intervals, respectively. The last column is the sum of the values in each row listed under DM_{test1} through DM_{test5}. Read from Table 7 the steady state peak concentration for accumulation of the DM_{test} ($C_{ss\ max\ test}$).

Step 10:

The data obtained in the last column (Accumulation) of Table 7 are plotted numerically versus time (first column) as shown in Fig. 6.

Step 11:

The required amount of drug for the final CRDDS (DM_{final}), in order to achieve a desired peak steady state concentration (C_{ss}

Table 7
Accumulation to Steady State for a Zero-Order CRDDS According to the Superposition Method

Time [h]	Concentration in mcg·ml^{-1} for					
	DM_{test1}	DM_{test2}	DM_{test3}	DM_{test4}	DM_{test5}	Accumulation
0	0					0
$t_{del}\cdot 0.33$						
$t_{del}\cdot 0.66$						
t_{del}						
τ		0				
$\tau+t_{del}\cdot 0.33$						
$\tau+t_{del}\cdot 0.66$						
$\tau+t_{del}$						
2τ			0			
$2\tau+t_{del}\cdot 0.33$						
$2\tau+t_{del}\cdot 0.66$						
$2\tau+t_{del}$						
3τ				0		
$3\tau+t_{del}\cdot 0.33$						
$3\tau+t_{del}\cdot 0.66$						
$3\tau+t_{del}$						
4τ					0	
$4\tau+t_{del}\cdot 0.33$						
$4\tau+t_{del}\cdot 0.66$						
$4\tau+t_{del}$						
5τ						

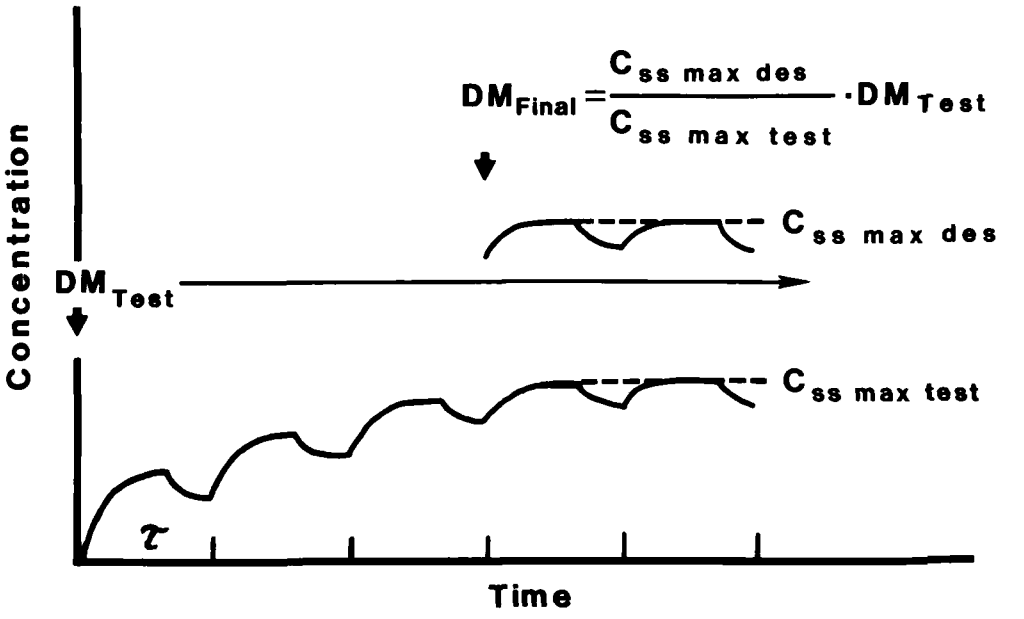

FIGURE 6

SCHEMATIC DIAGRAM FOR ACCUMULATION OF DRUG CONCENTRATION FROM A THEORETICAL TEST DOSE (DM_{TEST}) WITH ZERO-ORDER RELEASE TO STEADY STATE. USING THE SUPERPOSITION METHOD, THE EXPECTED STEADY STATE CONCENTRATION-TIME PROFILE FOR THE TEST-DOSE UPON MULTIPLE DOSING IS GENERATED. THE FINAL DOSE REQUIRED, DM_{FINAL}, IS CALCULATED FROM THE RATIO OF C_{SS} MAX DESIRED AND C_{SS} MAX TEST. τ IS THE CHOSEN DOSING INTERVAL. (WITH PERMISSION OF COPYRIGHT OWNER, REF. 2)

max des), is calculated:

$$DM_{final} = \frac{C_{ss\ max\ des}}{C_{ss\ max\ test}} \cdot DM_{test}$$

Step 12:

Calculate the final release rate ($R°_{final}$):

$$R°_{final} = \frac{DM_{final}}{t_{del}}$$

Intermittent First-Order Release CRDDS

The CRDDS shall release the drug at first-order rate (k_r^1) for a period of time (t_{del}) shorter than the selected dosing interval (τ). After termination of release, the drug concentration in blood decays according to the drug's elimination rate constant (λ_z). The blood level-time profile is typical for a one-compartment open model with a very slow input, hence, is a flip-flop model.

The step-wise design procedure is as follows:

Step 1: same as listed in 5.1.

Step 2: same as listed in 5.1.

Step 3:

Estimate time for elimination (t_{elim}), i.e. time from termination of release to time of next dosing. We assume that the terminal phase starts at a concentration of about 80 % of the peak concentration. Note: this value is arbitrarily set at 0.8, based on experience, but may be changed to another value between 0.6 and 0.9.

$$t_{elim} = \frac{\ln (C_{ss\ max\ des} \cdot 0.8) - \ln C_{ss\ min\ des}}{\lambda_z}$$

Step 4: same as listed in 5.1.

Step 5: same as listed in 5.1.

Step 6:

Estimate required first-order in vitro release rate constant (k_r^1). We assume that about 90 % of the drug is actually released during the delivery time. The reminder of drug may not be available. Hence, at time t=0, 100 % of the drug is unreleased, and at time $t=t_{del}$, 10 % is unreleased:

$$k_r^1 = \frac{\ln 100 - \ln 10}{t_{del}} = \frac{2.3}{t_{del}}$$

Step 7:

Calculate some theoretical blood concentrations to be expected after administration of the first DM_{test}.

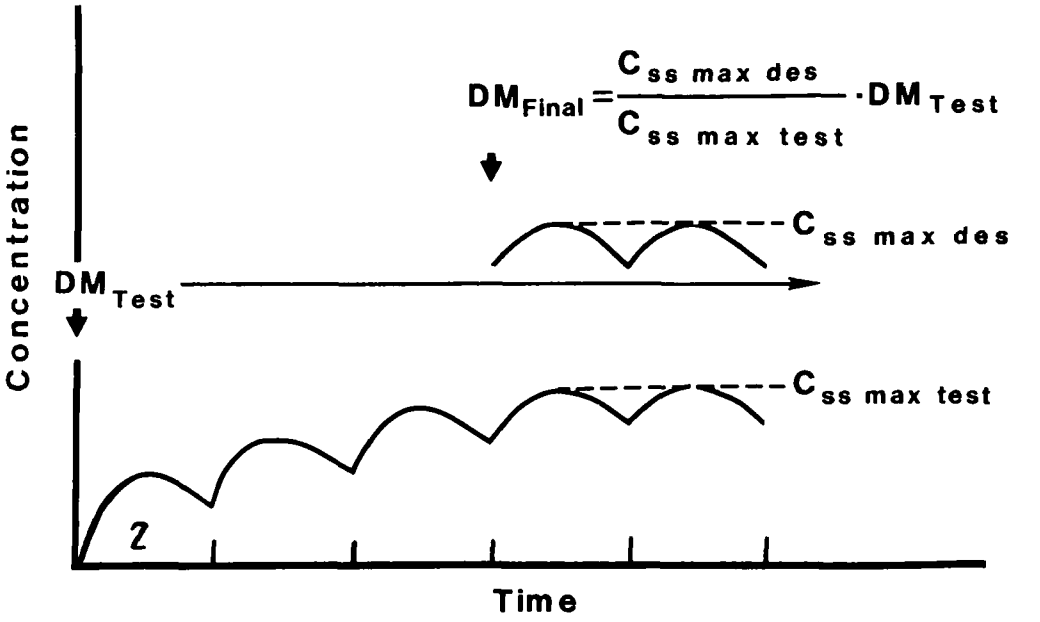

FIGURE 7

SCHEMATIC DIAGRAM FOR ACCUMULATION OF DRUG CONCENTRATION FROM A THEORETICAL TEST DOSE (DM_{TEST}) WITH FIRST-ORDER RELEASE TO STEADY STATE. USING THE SUPERPOSITION METHOD, THE EXPECTED STEADY STATE CONCENTRATION-TIME PROFILE FOR THE TEST DOSE UPON MULTIPLE DOSING IS GENERATED. THE FINAL DOSE REQUIRED, DM_{FINAL}, IS CALCULATED FROM THE RATIO OF $C_{SS\ MAX\ DESIRED}$ AND $C_{SS\ MAX\ TEST}$. τ IS THE CHOSEN DOSING INTERVAL.

First, the expected peak time (t_{max}) needs to be estimated:

$$t_{max} = \frac{\ln\left[k_r^1 \cdot (1-e^{-\lambda_z \cdot \tau})/\lambda_z \cdot (1-e^{-k_r^1 \cdot \tau})\right]}{k_r^1 - \lambda_z}$$

It is suggested at least to calculate two concentrations (C(t)) at about 1/3 and 2/3 of t_{max1}, then at t_{max}, at t_{del} and at

Table 8
Accumulation to Steady State for a First-Order CRDDS According to the Superposition Method

Time [h]	Concentration in mcg·ml^{-1} for DM_{test1}	DM_{test2}	DM_{test3}	DM_{test4}	DM_{test5}	Accumulation
0	0					0
t_{max}·0.33						
t_{max}·0.66						
t_{max}						
t_{del}						
τ		0				
$\tau+t_{max}$·0.33						
$\tau+t_{max}$·0.66						
$\tau+t_{max}$						
$\tau+t_{del}$						
2τ			0			
$2\tau+t_{max}$·0.33						
$2\tau+t_{max}$·0.66						
$2\tau+t_{max}$						
$2\tau+t_{del}$						
3τ				0		
$3\tau+t_{max}$·0.33						
$3\tau+t_{max}$·0.66						
$3\tau+t_{max}$						
$3\tau+t_{del}$						
4τ					0	
$4\tau+t_{max}$·0.33						
$4\tau+t_{max}$·0.66						
$4\tau+t_{max}$						
$4\tau+t_{del}$						
5τ						

τ, using the following equation:

$$C(t) = \frac{DM_{test} \cdot F \cdot k_r^1 \cdot k_a}{V_z \cdot (k_a - \lambda_z)} \cdot \left[\frac{e^{-k_r^1 \cdot t}}{(k_a - k_r^1) \cdot (\lambda_z - k_r^1)} + \frac{e^{-k_a \cdot t}}{(k_r^1 - k_a) \cdot (\lambda_z - k_a)} + \frac{e^{-\lambda_z \cdot t}}{(k_r^1 - \lambda_z) \cdot (k_a - \lambda_z)} \right]$$

where t is either $t_{max} \cdot 0.33$ or $t_{max} \cdot 0.66$, t_{max}, t_{del} or τ.

Step 8: same as listed in 5.1., except:

For t use:
1. $t_{max} \cdot 0.33$
2. $t_{max} \cdot 0.66$
3. t_{max}
4. t_{del}
5. τ

Step 9:

An accumulation table is constructed as shown in Table 8. Otherwise, see 5.1.

Step 10:

The data obtained in the last column (Accumulation) of Table 7 are plotted numerically versus time (first column) as shown in Fig. 7.

Step 11: same as listed in 5.1.

CONCLUSION

- The difference between P.O. Controlled Release and Sustained Release Drug Delivery Systems is, that the former ones are designed having a predetermined release rate, based on a desired therapeutic concentration for the pharmacologic effect and the drug's pharmacokinetic parameters, whereas the latter ones merely prolong the release of the drug to extend the time for absorption.

- Controlled Release Drug Delivery Systems (CRDDS) are designed for a specific drug, or they may utilize a Drug Delivery Device which releases a solution (containing the drug) at a predetermined rate.
- P.O. CRDDS are usually designed for a 12 h or 24 h duration of pharmacologic effect.
- P.O. CRDDS are either for drugs having a short $t_{1/2}$ or a long $t_{1/2}$. In the latter case it is for the purpose to "flatten" the steady state concentration and to avoid high peaks.
- Before designing a P.O. CRDDS the advantages and disadvantages of the systems have to be considered.
- Biopharmaceutic characteristics of a drug to be considered a viable candidate for a P.O. CRDDS include: molecular weight/size, pH dependent aqueous solubility, pK_a, apparent partition coefficient, absorption mechanism by diffusion, and general absorbability throughout the G.I. tract, including stability.
- The desirable release rate is of zero-order. However, also systems having first-order or square root of time release pattern are acceptable.
- For practical reasons the design of a P.O. CRDDS may be based on one-compartment open model for most drugs (in absence of dose dependency and saturation kinetics) because the release rate is usually << disposition rate.
- Pharmacokinetic characteristics of a drug to be considered a viable candidate for a P.O. CRDDS with zero-order or first-order release are discussed.

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