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ORAL CONTROLLED DRUG ADMINISTRATION

Pharmacokinetic Considerations

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INTRODUCTION

Although the concept of sustained or controlled delivery of orally administered drugs has been with us for some time, there has been a remarkable increase in interest in this type of dosage form during the last decade. This has been due to the simultaneous maturation of various factors including the prohibitive cost of developing new drug entities, expiration of existing patents, and the discovery of novel polymer systems and devices suitable for controlled delivery of oral dosage forms.

During the early days of oral controlled drug release, the literature was replete with skepticisms, which were for the most part jusified (1,2). However, significant advances in formulation methodology, and also a better understanding of the advantages and limitations of controlled release dosage forms, have provided the necessary impetus for the rapid advances that are currently being made in this area.

The number of drug substances that are currently available in controlled release dosage form is illustrated in Table I. For many drugs or drug combinations, several commercial products are available, and the number of drug substances available in controlled release form is increasing almost daily.

Most of the oral controlled release products currently available are diuretic and cardiovascular drugs, respiratory agents, and CNS-acting compounds. Surprisingly, little attention has been paid to antimicrobial agents.

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TABLE I.

Some Substances Available in Controlled Release Form

Vitamins, Minerals, and Hormones

Ascorbic acid
Iron preparations
Methyltestosterone
Nicotinic acid
Potassium
Pyridoxine
Vitamin combinations

Diuretic and Cardiovascular Drugs

Acetazolamide
Ethaverine HCl
Isosorbide dinitrate
Nicotinyl alcohol
Nitroglycerin
Papaverine HCl
Pentaerythritol tetranitrate
Procainamide
Quinidine gluconate and sulfate
Reserpine

CNS Drugs

Amphetamine sulfate
Aspirin
Caffeine
Chlorpromazine
Dextroamphetamine sulfate
Diazepam
Diethylpropion HCl
Fluphenazine
Indomethacin
Lithium
Meprobamate
Methamphetamine HCl
Orphenadrine citrate
Pentobarbital
Pentylenetetrazole
Perphenazine
Phenmetrazine HCl
Phenobarbital
Phentermine HCl
Phenylpropanolamine HCl
Prochlorperazine

Respiratory Agents

Aminophylline
Brompheniramine maleate
Carbinoxamine maleate
Chlorpheniramine maleate
Combination, antitussive
Combination, expectorant
Combination, upper respiratory
Dexchlorpheniramine maleate
Dimethindene maleate
Diphenylpraline HCl
Dyphylline
Phenylpropanolamine HCl
Pseudoephedrine HCl and sulfate
Theophylline
Trimeprazine
Tripelennamine HCl
Xanthine combinations

Antimicrobial

Tetracycline

Gastrointestinal Drugs

Belladonna alkaloids
Hexocyclium methylsulfate
l-Hyoscyamine sulfate
Isopropamide iodide
Prochlorperazine maleate
Tridihexethyl chloride

Other

Pyridostigmine bromide

To the writer's knowledge, only one compound, tetracycline, is available in controlled release form, and this has been highly successful in the United Kingdom. Controlled release of those antimicrobial agents that have appropriate pharmacokinetic properties appears to represent an area of virtually untapped potential. However this situation may remain so until more infor-

mation is available regarding the temporal relationships between circulating drug levels and antibacterial effect (3).

ADVANTAGES OF CONTROLLED DRUG RELEASE

Controlled release dosage forms are invariably more expensive than conventional formulations, and they can be justified only when they offer one or more distinct therapeutic advantages. Some of the advantages that have been claimed are given in Table II. While each of these is important from one viewpoint to another, the only advantages relevant to this chapter are items 1, 2, 3, and 8. Item 1 can be achieved only if the controlled release formulation contains a fast release component, or if a fast release formulation is used to initiate therapy. Items 2 and 3 describe the essence of controlled drug release, i.e. to obtain prolonged circulating drug levels with less fluctuation compared to conventional dosage forms, and to achieve these with less frequent drug administration. Item 8, which is a primary goal of controlled release dosage, may be predicted from theoretical drug level-response relationships, but is difficult to prove experimentally. At the present time it appears that improved pharmacologic effect from controlled release compared to conventional dosage forms can generally be claimed only by inference from blood level data.

DISADVANTAGES OF CONTROLLED DRUG RELEASE

The major disadvantages of controlled drug release dosage forms are summarized in Table III. The first of these, the possibility of 'dose dumping', a term used to describe inadvertent rapid release of drug material due to faulty formulation, is theoretically important for potent drugs which have a narrow therapeutic index. However good manufacturing practice, and also the highly sophisticated dosage forms currently appearing on the market, make the possibility of this occurring unlikely.

Administering a fraction of a tablet or capsule in order to obtain fine dose adjustment is more difficult with some controlled release dosage forms than others. For example Theo-Dur® tablets (granules in a matrix) or Theo-dur

TABLE II.

Objectives and Possible Advantages of Controlled Release Dosage Forms

1. To achieve rapid onset and then maintain therapeutic drug levels.
2. To reduce dosing frequency.
3. To reduce fluctuations in drug levels.
4. To reduce total amount of drug used.
5. To reduce inconvenience to the patient, and increase compliance.
6. To reduce patient care time.
7. To avoid nightime dosing.
8. To obtain more uniform pharmacologic response.
9. To reduce GI irritation.
10. To reduce side effects.

TABLE III.

Disadvantages of Controlled Release Dosage Forms

1. Possibility of dose dumping.
2. Reduced potential for accurate dose adjustment.
3. Slow absorption may delay onset of activity.
4. Increased potential for first-pass metabolism.
5. Possible reduction in systemic availablility.
6. Drug release period restricted to residence time in GI tract.

Sprinkle® capsules (encapsulated granules) can readily be subdivided to obtain a fraction of the dose. On the other hand formulations such as repeat action tablets or osmotic pump devices lose their sustained release properties once the dosage form is fractured.

Slow absorption inevitably delays the onset of drug activity from an initial dose, but this is probably unimportant during a repeated dosage regimen. In fact, as indicated later in this chapter, the absence of a fast release component may be advantageous for controlled release formulations. Increased first-pass metabolism may occur for drugs that undergo extensive hepatic

clearance (4), but only if hepatic clearance is saturable following rapid drug absorption from conventional doses. If saturation does not occur, and if hepatic clearance is first-order in nature, then the same proportion of an oral dose will be cleared during the first pass through the liver regardless of the absorption rate. To the writer's knowledge no instances of increased first-pass clearance have been reported from controlled release compared to conventional dosage forms.

While reduced drug absorption due to first-pass metabolism may be unimportant, at least in the light of present knowledge, reduced and variable absorption of controlled release drugs from the GI tract has been documented. This type of problem is clearly demonstrated in Figures 1 and 2, which show a wide range in apparent absorption efficacy from commercial controlled release tablets and capsules of theophylline (5). Reduced systemic drug bioavailability has also been reported for some controlled release formulations of procainamide (6) and vitamin combinations (7). Many other studies, however, have reported no reduction in systemic drug availability from controlled release dosage forms (8-13).

Residence time within the GI tract is a major factor and a possible disadvantage associated with oral controlled release products, and distinguishes the oral from parenteral dosage routes. It is clear from other presentations in this Symposium and elsewhere that the actual time period available for an oral dosage form to effectively release drug for absorption is not well established and may vary among and between individuals. The residence time of the dosage form in the stomach is variable depending on the activity of the patient, the presence or absence of food in the stomach, and the direct or indirect action of other drugs (14). Once it leaves the stomach, the dosage form together with dissolved drug, passes into the optimal absorption region of the proximal small intestine. Distal to this region absorption becomes less efficient and the drug is furthermore exposed to the bacterial microflora. Because of the variable GI transit time, and also these other interfering factors, it is difficult to estimate the optimum release period for an oral controlled release dosage form. It is also speculative to assume that

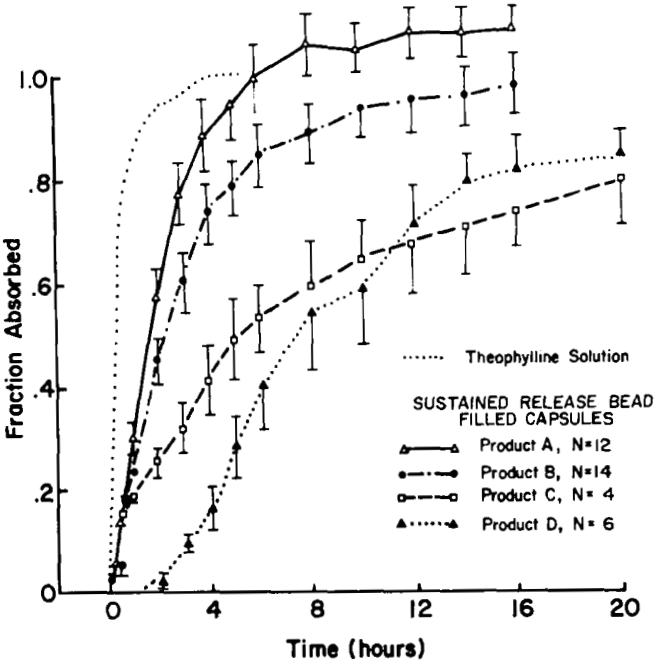


Figure 1

Cumulative absorption plots of theophylline from 4 commercial controlled release capsules, and from an aqueous solution. Error bars indicate one standard deviation. Reproduced by permission from reference 5.

absorption efficacy is constant throughout the entire period that drug is in the GI tract.

A 12-hour period has been selected for the pharmacokinetic simulations in this chapter to represent the maximum time that a controlled release oral dosage form has to release drug for absorption. This is a generalization that may or may not be suitable for particular drugs and dosage forms depending on the type of formulation, the susceptibility of released drug to bacterial degredation and absorption efficiency in different regions of the GI tract.

Using the 12-hour period it is clear that, unlike parenteral controlled release devices, any drug remaining in the dosage form after this time will either be voided in the feces or degraded by intestinal bacteria. This argument does not apply to those devices, some of which are described elsewhere in

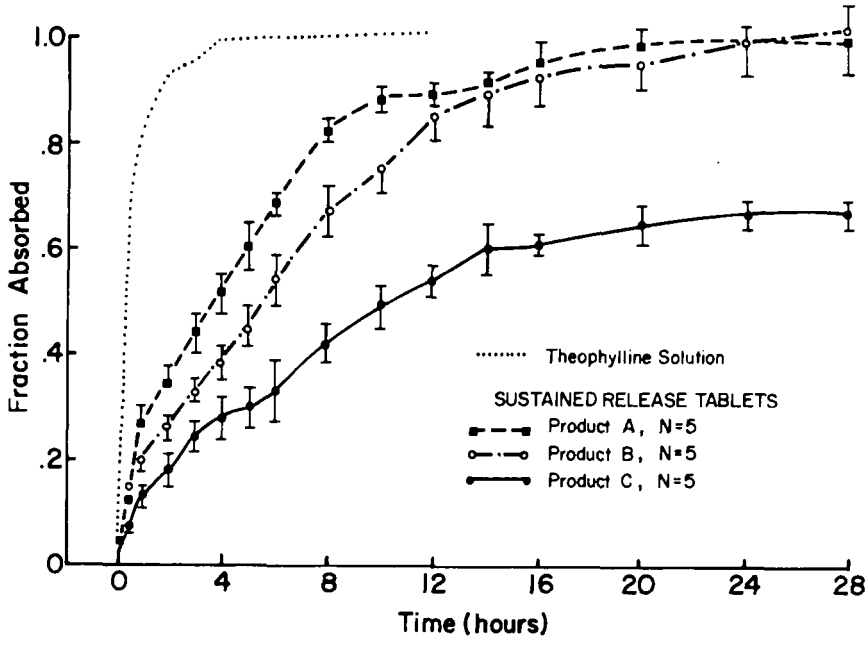


Figure 2

Cumulative absorption plots of theophylline from 3 commercial controlled release tablets and from an aqueous solution. Error bars indicate one standard deviation. Reproduced by permission from reference 5.

this Symposium, that are designed to stay in the GI tract for prolonged periods of time by means of flotation or adhesion to the GI epithelium.

DRUGS THAT ARE UNSUITED FOR CONTROLLED RELEASE

Apart from the above disadvantages, some drug types are inherently unsuited for controlled release formulations, and considerable time and effort may be wasted in their development. Some typical characteristics are described in Table IV. For drugs with a short biological half-life of less than 2 hours, or that are administered in large doses, a controlled release dosage form may need to contain a prohibitively large amount of drug. On the other hand, drugs with a long biological half-life of 8 hours or more are sufficiently sustained in the body from conventional doses, and prolonged release dosage forms are generally not necessary. Dose dumping of a potent compound,

TABLE IV.

Characteristics That May Make a Drug Unsuitable for Controlled Release Formulation.

1. Short biological half-life.
2. Long biological half-life.
3. Potent drug with narrow therapeutic index.
4. Large doses.
5. Poorly absorbed.
6. Low or slow solubility.
7. Active absorption.
8. Time course of circulating drug levels does not agree with pharmacologic effect.
9. Extensive first-pass clearance.

or of a drug with a narrow therapeutic index due to faulty formulation, may have disastrous consequences. However as indicated earlier the likelihood of this occurring with current technology and control methods is small.

Absorption of poorly water-soluble compounds is often limited by dissolution rate. Incorporation of such compounds into a controlled release formulation is therefore unnecessary, and is likely to reduce overall absorption efficiency. Administering drugs such as warfarin, whose pharmacological effect is considerably delayed relative to its blood profile, is of no clinical advantage. Similarly, incorporating compounds such as fluorouracil, amino acids, and perhaps some beta lactam antibiotics and thiazide diuretics that appear to exhibit reduced absorption efficacy at sites distal from the proximal small intestine, is likely to reduce absorption efficiency while achieving little or no prolongation of effect. As stated earlier, if a drug undergoes extensive first-pass clearance that is saturable with conventional fast-release dosages, then systemic availability may be decreased due to nonsaturation of the clearance mechanisms following a controlled release dosage form. However if hepatic clearance is not saturated with conventional doses, slower absorption of drug should not cause a reduction in systemic availability.

Although the characteristics described in Table IV are useful rules of thumb on which to base decisions whether or not to consider a controlled release dosage form for a particular drug, there are several exceptions. Nitroglycerin is reported to have a short biological half-life of < 0.5 hr. It is rapidly metabolized in the liver and is generally considered to be poorly absorbed orally. However a large number of controlled release oral nitroglycerin products are available, in addition to an increasing number of topical and transdermal preparations. The low circulating levels of nitroglycerin obtained from these products appear to provide adequate prophylaxis against anginal attacks, but would be inadequate to treat acute anginal episodes. At the other end of the scale, many of the drugs listed in Table I have biological half-lives in excess of 8 hours. Controlled release of these products may reduce toxic side effects by preventing the sharp peaks in circulating drug levels that may occur with conventional doses, but it is unlikely to provide more sustained blood levels nor prolonged therapeutic effect compared to conventional dosage forms.

The renewed interest in controlled drug release has given rise to a variety of new formulations. Products that are representative of well established and also some more novel categories are summarized in Table V. This list will increase further as more novel dosage forms are introduced. Microencapsulation and osmotic pressure systems will doubtless find more applications. Other products that prolong GI residence time, either by means of adhesion or by the use of low density hydrated gels have been introduced (Susadrin®, Valrelease®). These dosage forms may undergo extensive development for other drugs in the near future.

PHARMACOKINETICS OF CONTROLLED RELEASE

In vitro Considerations

Despite the large and expanding array of formulations devoted to oral controlled drug release, and despite the complex and varied physical properties involved in the release of drug from these formulations, the number of kinetic models that are necessary to describe the overall drug release phe-

TABLE V.

Categories of Oral Controlled Release Dosage Forms

Category	Product	Active Ingredient
1. Slow erosion with initial fast release dose	Tedral SA	Theophylline, ephedrine HCl, phenobarbital
2. Erosion core only	Tenuate Dospan	Diethylpropion HCl
3. Repeat action tablets	Chlor-Trimeton Repetabs	Pseudoephedrine sulfate, chlorpheniramine maleate
4. Pellets in capsules	Combid Spansule	Isopropamide iodide, Prochlorperazine maleate
5. Pellets in tablets	Theo-dur	Theophylline
6. Leaching	Desbutal Gradumet	Methamphetamine HCl, pentobarbital sodium
7. Ion-exchange resins	Biphetamine	Amphetamine, dextroamphetamine
8. Complexation	Rynatan	Chlorpheniramine, phenylephrine, and pyrilamine tannates
9. Microencapsulation	Nitrospan	Nitroglycerin
10. Flotation-diffusion	Valrelease	Diazepam
11. Osmotic pressure	Osmosin[1]	Indomethacin

[1] U.K. market.

nomena from existing dosage forms is relatively small. The major release patterns are summarized in simple graphical form in Figure 3.

The release patterns can be divided into two major categories, those that release drug at a slow zero-, or first-order rate, and those that provide an initial rapid dose, followed by slow zero-, or first-order release of the sustained component. The sustained nature of drug release from these dosage forms, even when a fast release component is also present, presents problems in in vitro dissolution testing.

In vitro dissolution is now widely accepted as a standard for drug release from conventional dosage forms, and the use of such tests to determine drug product bioavailability or bioequivalence has been emphasized by the

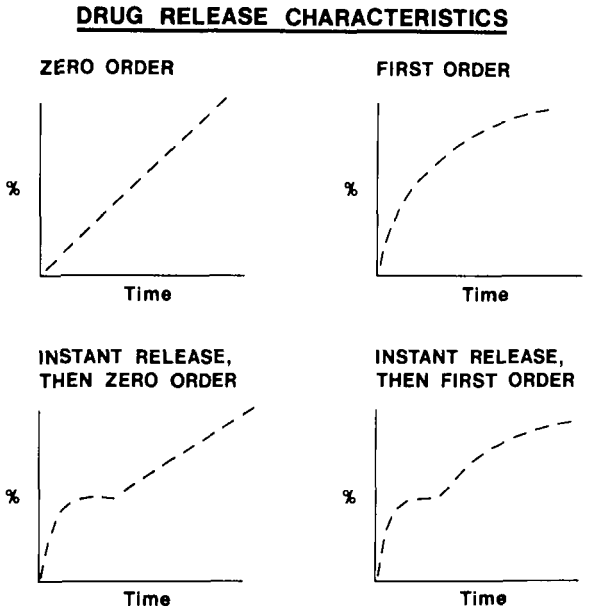


Figure 3

Drug release characteristics from oral controlled release dosage forms.

United States Food and Drug Administration (15). While dissolution rate provides an excellent measure of product uniformity, it does not always accurately predict bioavailability (16,17,18).

Whereas for conventional oral drug products *in vitro* dissolution criteria are expressed in terms of the fastest possible dissolution rate, i.e. the absence of an upper limit, the situation is quite different for controlled release products. In the latter case, optimum dissolution rate is not the fastest that can be obtained but rather some intermediate value which will hopefully reflect prolonged release of drug in the GI tract. Thus for these products a dissolution window is required, and deviation from the optimum rate can be in terms of too fast or too slow.

Given the difficulty of establishing guidelines for these dosage forms, the large number of formulations (each perhaps requiring a different solvent for appropriate dissolution measurement), and the different release profiles as illustrated in Figure 3, it is not surprising that there are currently no official guidelines for *in vitro* dissolution tests of oral controlled release

dosage forms. There are also no clearly established relationships between *in vitro* drug release and *in vivo* bioavailability characteristics. The appropriateness of a controlled release formulation and also equivalence between different controlled release products or between controlled release and conventional products must currently be based on *in vivo* data.

In vivo Considerations

Successful development of a controlled release oral dosage form requires a thorough appreciation of the inherent opportunities and limitations characteristic of a particular drug-dosage form combination. A controlled release formulation that is suitable for one drug may be inappropriate for another. Zero-order release may be more important for some types of drugs than others. A fast release component may or may not be important. The tenuous rational for incorporating a fast component into chronically administered oral formulations is discussed later in this chapter.

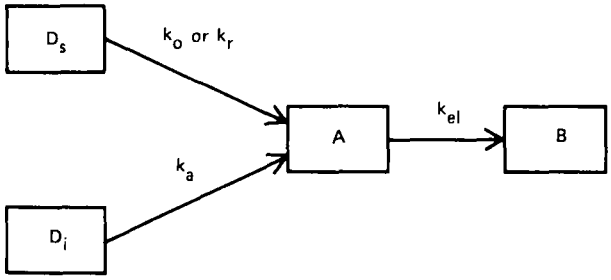
In the following sections, attention will be focused on the pharmacokinetics associated with the four major controlled release patterns shown in Figure 3, the types of blood-level profiles that may be achieved following single and repeated doses of these dosage forms, and how these profiles are influenced by GI transit time and by varying drug release and elimination rates.

Drugs may be shown to obey single- or multi-compartment pharmacokinetic models depending on their affinity, and also the rate at which they penetrate, various body organs and tissues. Multi-compartment characteristics are more readily identified following rapid drug administration compared to slow administration as the distribution phase is not obscured by absorption processes. For example after bolus intravenous injection it is frequently possible to describe drug profiles in terms of two- or three-compartment kinetic models, whereas profiles from the same drugs cannot be described in terms more complex than the simple one-compartment model after oral or intramuscular doses.

Slow absorption of drugs from controlled release formulations, be they oral or otherwise, generally precludes description of resulting drug profiles

by kinetic systems more complex than the simple one-compartment model. That basic approach will be used here. For ease of presentation the following additional simplifying assumptions are made: (i) drug absorption, metabolism, and excretion are all first-order processes, (ii) drug absorption and elimination are irreversible, (iii) drug that is released into the GI tract is completely absorbed in its unchanged form, and (iv) release of drug from the sustained release formulation is rate-limiting in the absorption process.

The model which is applicable to controlled release dosage forms is shown in Scheme I (19)[1]



Scheme I

D_s = Slowly released drug

D_i = Instantaneously released drug

A = Unchanged drug in the body

B = Cumulative amount of drug excreted in urine or metabolized

k_a = First-order rate constant for transfer of drug from the absorption site into the systemic circulation

k_o, k_r = Zero-order (k_o) or first-order (k_r) rate constants for release of drug from D_s

k_{el} = First-order rate constant for elimination of drug by combined urinary excretion, metabolism, etc.

[1] In the original model an additional step was incorporated for absorption of the slowly released component D_s. However as k_o or k_r are generally significantly smaller than k_a, deletion of that step does not significantly alter the resulting drug profiles (19).

I. FIRST-ORDER RELEASE

Single Dose

In this model the amount of drug in the body following a single dose is given by Equation 1, in which k_r is the sole rate constant governing absorption ($k_r << k_a$).

$$A = \frac{D_s k_r}{k_r - k_{el}} [e^{-k_{el}t} - e^{-k_r t}] \quad \text{(Eq. 1)}$$

Equation 1 can be converted to describe drug concentration, C, simply by adding the drug distribution volume, V, to the denominator, as shown in Equation 2.

$$C = \frac{D_s k_r}{V(k_r - k_{el})} [e^{-k_{el}t} - e^{-k_r t}] \quad \text{(Eq. 2)}$$

With this model, drug profiles can be influenced by both the absorption and elimination rate constants as shown in Figures 4 and 5. From Figure 4 it is clear that the drug profile is markedly influenced by its biological half-life ($t_{1/2} = \ln 2/k_{el}$), the peak level, A_{max}, and time of peak level, T_{max}, both increasing as the half-life becomes more prolonged. The curves generated with k_{el} = 0.3 hr^{-1} and 0.5 hr^{-1} have identical elimination slopes with values of 0.2 hr^{-1}. These are examples of the flip-flop model, where $k_{el} > k_r$ (20), and the apparent elimination slope is controlled by the rate at which drug is released from is formulation in the GI tract. This is not an uncommon situation with controlled release formulations.

From Figure 5 it is clear that for a given value of k_{el}, drug profiles are lowered and are more prolonged as k_r is reduced. In this case, however A_{max} is reduced while T_{max} is prolonged as the drug release rate constant is reduced.

The reduction in the value of A_{max} (or C_{max}) as a result of controlled release is of concern, particularly for drugs that have a well defined minimum effective concentration in the body. The controlled release dose, D_s, that is necessary in order to achieve the same A_{max} as its fast release counterpart is

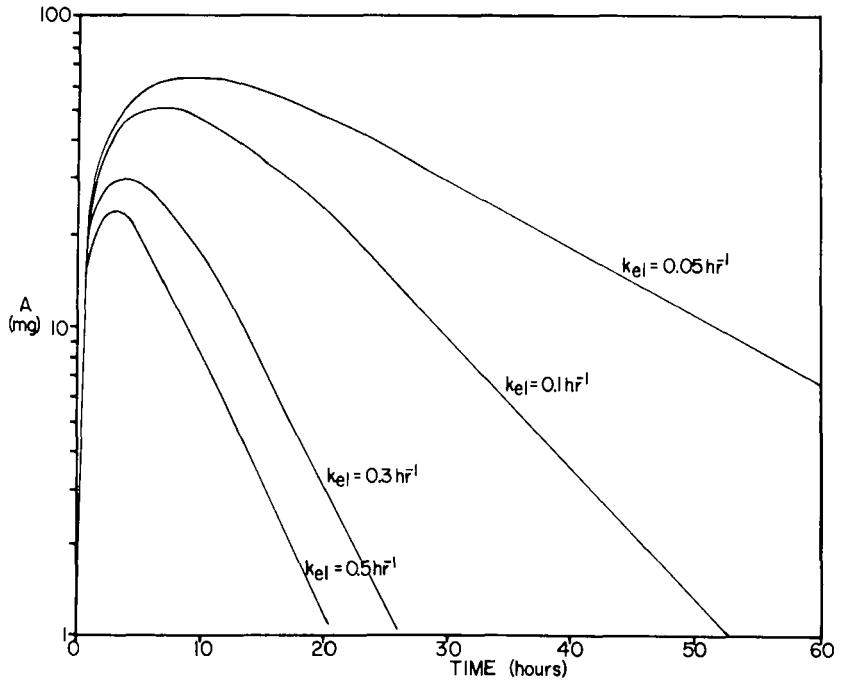


Figure 4

Drug levels following a single dose. Curves generated from Equation 1 with D_s = 100 mg, k_r = 0.2 hr^{-1}, and k_{el} = 0.05, 0.1, 0.3, and 0.5 hr^{-1} (adapted by permission from reference 19).

readily calculated by means of Equation 3 (19). For a drug which has an elimination

$$\frac{D_s}{D_i} = \left(\frac{k_a}{k_{el}}\right)^{\frac{k_{el}}{k_{el} - k_a}} \cdot \left(\frac{k_r}{k_{el}}\right)^{\frac{k_{el}}{k_r - k_{el}}} \qquad \text{(Eq 3)}$$

$t_{1/2}$ of 4 hr (k_{el} = 0.17 hr^{-1}) and a k_a of 1.0 hr^{-1}, and a controlled release rate constant k_r of 0.5 hr^{-1} (release $t_{1/2}$ = 1.4 hr), then a controlled release dose would have to be 1.2 times greater than the fast release dose to achieve the same value of A_{max}. If k_r were reduced further to 0.2 hr^{-1} (release $t_{1/2}$ = 3.5 hr) then the controlled release dose would have to be 1.8 times the fast release dose. A k_r of 0.1 hr^{-1}, which is practical only in cases of prolonged residence time in the GI tract, would necessitate a dose increase by a factor of 2.5.

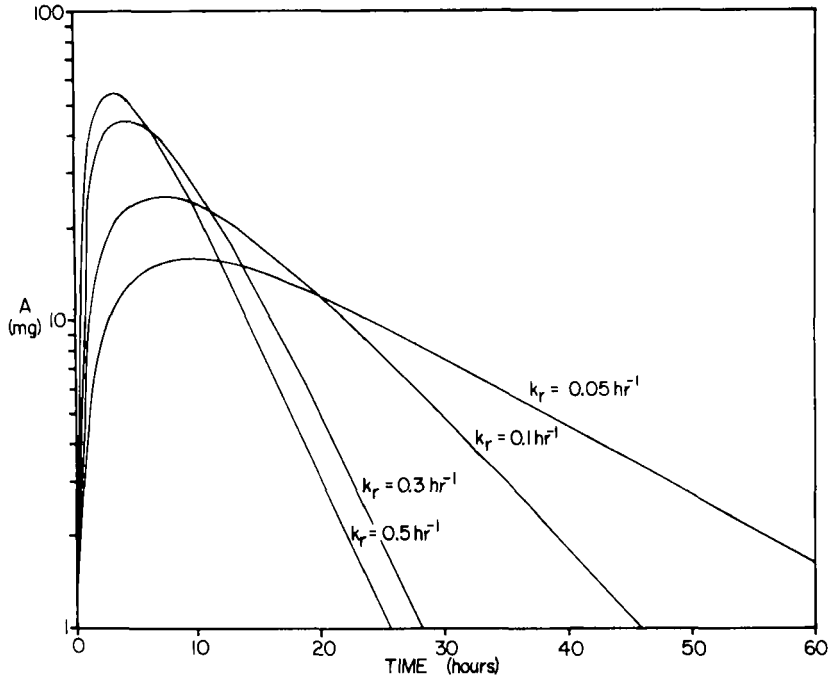


Figure 5

Drug levels following a single dose. Curves generated from Equation 1 with D_s = 100 mg, k_{el} = 0.2 hr^{-1}, and k_r = 0.05, 0.1, 0.3, and 0.5 hr^{-1} (adapted by permission from reference 19).

Repeated Dose

The same rules govern drug accumulation following repeated doses of both controlled release and conventional dosage forms. As long as the dosage interval τ is less than the time taken for all drug to be cleared from the body, accumulation will occur with each subsequent dose until steady-state is reached. The time taken to reach steady-state is controlled by the drug elimination rate and is independent of the absorption or drug release rate. Thus, prolonging the absorption of a drug by means of controlled release has no influence on its accumulation rate.

As it takes a fixed time period, 4.3 x $t_{1/2}$, to reach 95% of steady-state, the number of doses required to attain this condition depends upon the relationship between the dosage interval and the drug elimination half-life. Thus for a compound that is dosed once every half-life it will take between 4

and 5 doses to reach 95% of steady-state. If a controlled release dosage form permits dosage every second half-life, then 95% of steady-state will be achieved between 2 and 3 doses.

The major difference between controlled and conventional dosage forms is in the maximum A^{∞}_{max} and minimum A^{∞}_{min} values when steady-state is reached.

These values can be calculated from Equations 4 and 5, while the time of peak values, T^{∞}_{max} is given by Equation 6.

$$A^{\infty}_{max} = D_s \left[\frac{1}{1 - e^{-k_{el}\tau}}\right]\left[\frac{k_r(1 - e^{-k_{el}\tau})}{k_{el}(1 - e^{-k_r\tau})}\right]\frac{k_{el}}{k_{el} - k_r} \qquad \text{(Eq. 4)}$$

$$A^{\infty}_{min} = \frac{D_s k_r}{k_r - k_{el}}\left[\frac{e^{-k_{el}\tau}}{1 - e^{-k_{el}\tau}} - \frac{e^{-k_r\tau}}{1 - e^{-k_r\tau}}\right] \qquad \text{(Eq. 5)}$$

$$T^{\infty}_{max} = \frac{1}{k_r - k_{el}} \ln \left[\frac{k_r(1 - e^{-k_{el}\tau})}{k_{el}(1 - e^{-k_r\tau})}\right] \qquad \text{(Eq. 6)}$$

From Equation 6, the time of peak level increases as the release rate constant is decreased. For example, if $k_{el} = 0.17\ hr^{-1}$, and τ is 12 hr, then k_r values of 0.5, 0.2, and 0.1 hr^{-1} would result in T^{∞}_{max} values of 2.4, 3.9, and 4.4 hr, respectively, compared to 2 hr with a conventional formulation with a k_a of 1.0 hr^{-1}. Thus in this example a 10-fold decrease in the absorption rate constant results in only a 2.2-fold increase in the value of T^{∞}_{max}.

It is generally accepted, and indeed this is a major rationale for development of prolonged action dosage forms, that controlled release results in lower C^{∞}_{max} and higher C^{∞}_{min} values compared to conventional dosage forms, i.e. a flatter blood level curve is obtained. However this is not necessarily the case. Consider the situation in Figure 6. A conventional dosage form of a drug with a k_a of 1.0 hr^{-1} and k_{el} 0.1 hr^{-1}, administered 100 mg every 6 hr yields peak and trough amounts of drug in the body of 105 and 54 mg, respectively. A controlled release dose ($k_r = 0.5\ hr^{-1}$) administered 200 mg every

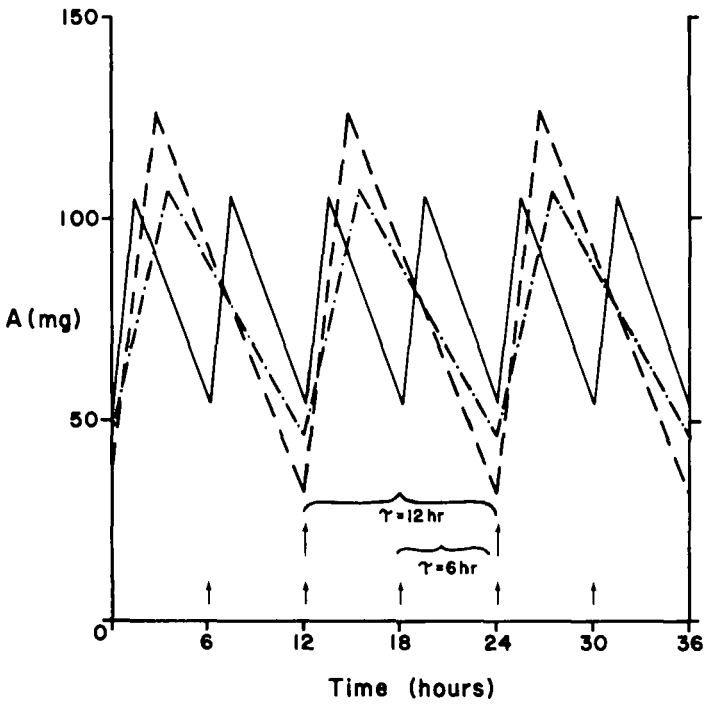


Figure 6

Drug levels at steady state during repeated doses, 400 mg per day in divided doses, of a conventional formulation with k_a = 1.0 hr^{-1} (——) and controlled release formulations with k_r = 0.5 hr^{-1} (---) and 0.25 hr^{-1} (-•-•), τ = 6 hr for the conventional formulation and 12 hr for the others, and k_{el} = 0.2 hr^{-1}. Data generated from Equations 3, 4, and 5.

12 hr results in increased peak and decreased trough levels. The value of k_r must be reduced to ca 0.25 hr^{-1} in order to obtain similar peak and trough levels to those from the conventional dosage form. Oscillations in drug levels will of course always decrease with decreasing absorption rate if the dose and interval are held constant, but this is not normally the objective with controlled release dosage forms.

II. ZERO-ORDER RELEASE

Single Dose

With this model the amount of drug in the body following a single dose is given by Equation 7, in which k_o is the sole rate constant governing absorption ($k_o \ll k_a$).

$$A = \frac{k_o}{k_{el}}[1 - e^{-k_{el}t}] \qquad \text{(Eq. 7)}$$

Equation 7 can be converted to describe drug concentrations by adding the distribution volume to the denominator, as in Equation 8.

$$C = \frac{k_o}{Vk_{el}}[1 - e^{-k_{el}t}] \qquad \text{(Eq. 8)}$$

As in the first-order absorption case, drug profiles from this type of dosage form are influenced by both the rate at which drug is released from the dosage form and also the elimination rate, as shown in Figures 7 and 8.

In Figure 7, 4 different zero-order release rates are used, together with a k_{el} equivalent to a drug elimination half-life of 2.8 hr, i.e. at the short end of the 2-8 hr range generally considered suitable for controlled release formulations. It is clear from this figure that, while drug levels are directly proportional to the controlled release rate, the time course of accumulation during the single dose is independent of release rate, and is invariable for a given elimination rate constant. This is a well established property of zero-order release systems and is inherent in Equations 7 and 8. It is also clear from the figure that, even with a short drug elimination half-life of 2.8 hr, plateau drug levels are not achieved within the GI residence time of 12 hr. In order to achieve a plateau level it would be necessary to prolong the residence time to 20-24 hr. For drugs with longer elimination half-lives, there is little likelihood of achieving plateau drug levels from a single dose. For example a drug with a $t_{1/2}$ of 8 hr would have to be release continuously for 36 hr before steady-state levels were approached.

This argument is illustrated in Figure 8. Regardless of the zero-order release rate in this figure, a drug with a elimination $t_{1/2}$ of 1.7 hr (k_{el} = 0.4 hr^{-1}) will approach a steady-state level at 12 hr. On the other hand a drug with a $t_{1/2}$ of 7 hr (k_{el} = 0.1 hr^{-1}) will not achieved steady-state at 24 hr.

These examples highlight the misconception that it is possible to achieve plateau or steady state drug levels with a single dose of a zero-order release

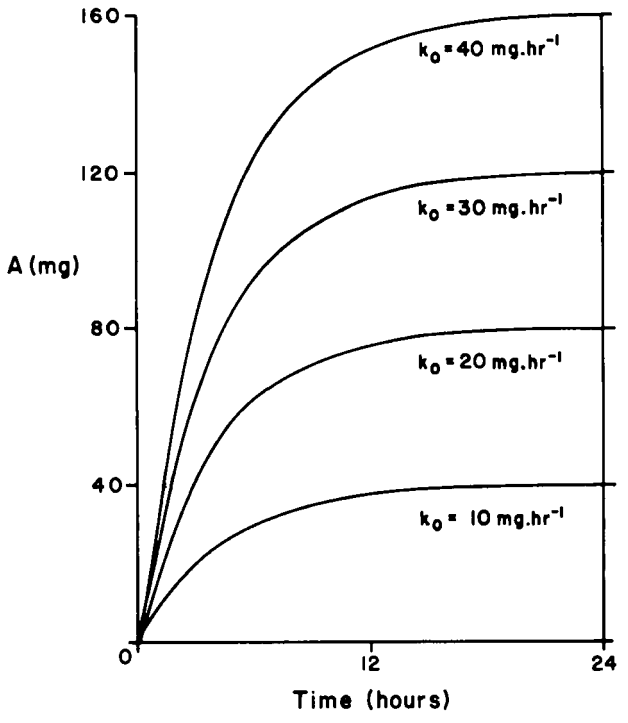


Figure 7

Accumulation of drug in the body from a single dose of a zero-order release dosage form with k_0 = 10, 20, 30, and 40 mg.hr^{-1} and k_{el} = 0.25 hr^{-1}. Data generated from Equation 6.

formulation. When a zero-order formulation has released all of its medication, or when the partially spent formulation is voided in the feces, drug levels in the body decline at a first-order rate regardless of whether or not steady-state levels have been reached. Typical profiles for drugs with elimination half-lives of 2 hr (k_{el} = 0.35 hr^{-1}) and 8 hr (k_{el} = 0.087 hr^{-1}) are shown in Figure 9.

Repeated Dose

Despite the discontinuous nature of drug levels from zero-order release formulations, as shown in Figure 9, the dependency of both the ascending and descending components of the curves on the drug elimination half-life lends itself, in theory at least, to sustained and controlled levels of medication

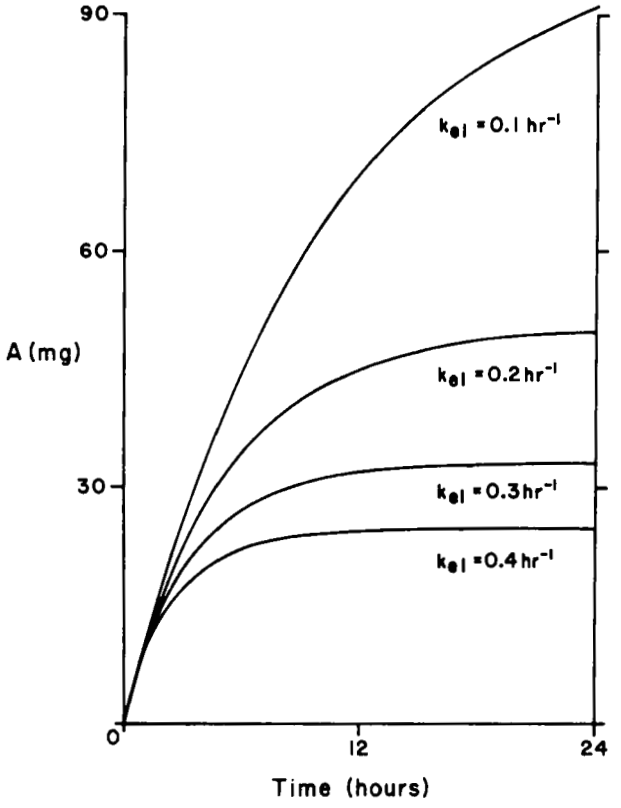


Figure 8

Accumulation of drug in the body from a single dose of a zero-order release dosage form with k_0 = 10 mg.hr^{-1} and k_{el} = 0.1-0.4 hr^{-1}. Data generated from Equation 6.

with repeated dosing. As with all other kinetic processes, steady-state occurs when the rate at which drug is delivered equals the rate at which it is eliminated.

Consider the 2 situations in Figure 9. If the drug with the shorter half-life is administered every 12 hr, as in Figure 10, then the descending portion of one dose and the ascending portion of the subsequent dose are mirror images of each other, and plateau drug levels are maintained with successive doses. If the drug with the longer half-life is given every 12 hr, then, as shown in Figure 11, accumulation will occur with successive doses until the steady-state level (k_0/k_{el}) is reached. Ninety-five percent of the steady-

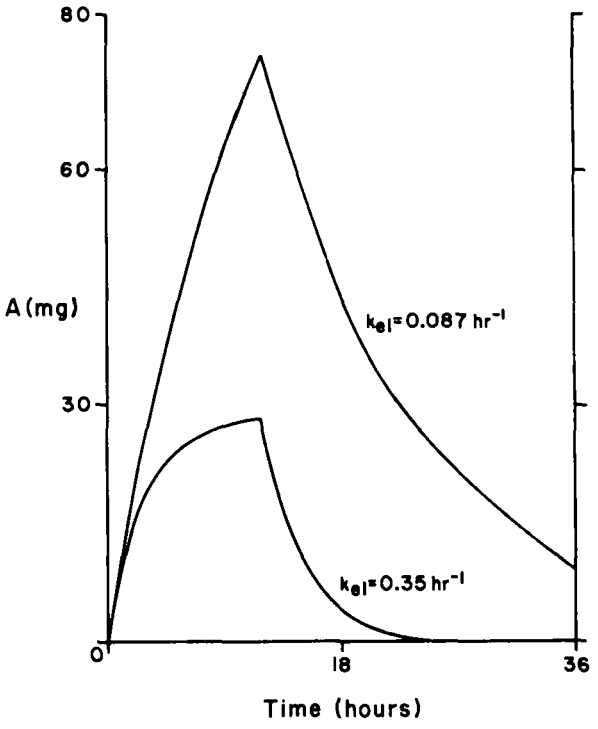


Figure 9

Drug levels during and after a single dose of a zero-order release dosage form with k_o = 10 mg.hr^{-1}, release time T = 12 hr, and k_{el} = 0.087 and 0.35 hr^{-1}.

state level will be reached at 4.3 x $t_{1/2}$ or some time between the 4th and 5th doses. Once steady-state is reached, whether it be during the initial dose or after a number of doses, plateau drug levels with minimal fluctuation can theoretically be obtained. Zero-order release formulations thus approach the ideal controlled release system, and several recently introduced products are based on this principle. However the actual curves obtained in vivo may depend not only on drug release rate from the dosage form but also on the stability of the drug and absorption efficacy from distal regions of the GI tract.

With both the first-order and zero-order release systems described above it is clear that, whether considering single dose or multiple dose concepts, the time taken to achieve desired therapeutic levels in the body is a function of the elimination rate constant. The slower the elimination, the more time

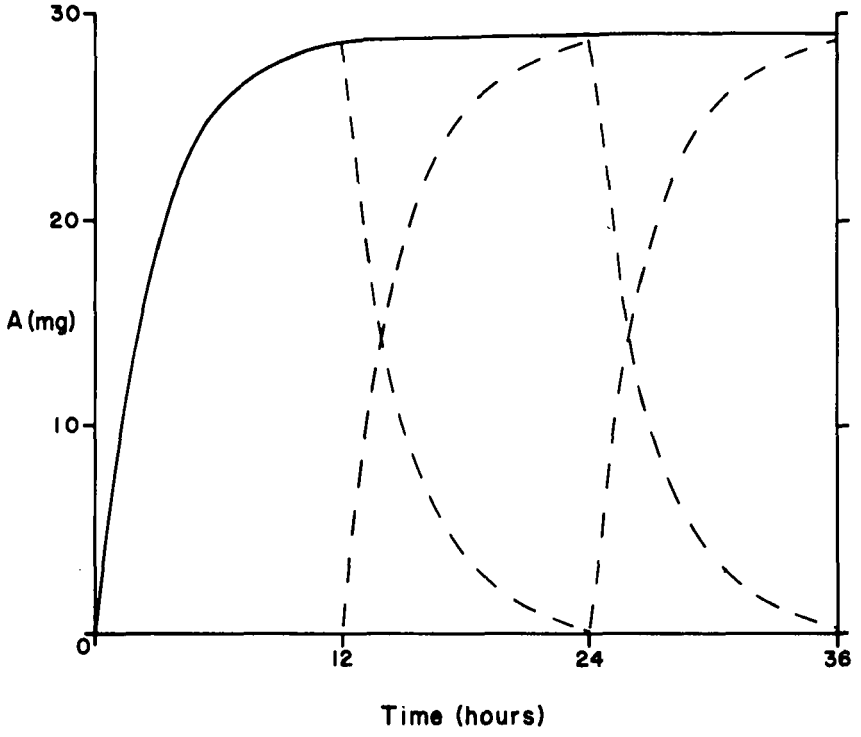


Figure 10

Drug levels during 12 hourly repeated doses of the rapidly eliminated dosage form from Figure 9. In this and subsequent figures, solid lines indicate total drug levels while dashed lines indicate the individual levels of successive doses or from separate dose components.

is required to reach steady-state. For multiple doses the problem is similar, and can be resolved in similar fashion, for both conventional and controlled release formulations. Methods for calculating appropriate loading doses under a variety of situations are well documented (21), and will not be discussed here.

For single doses, the problem of slow accumulation is unique to the controlled release dosage form, and a number of formulations have been designed incorporating a fast release drug component in addition to a controlled release component. While such formulations may be useful when administered as single doses, or as widely spaced intermittent doses, their usefulness when

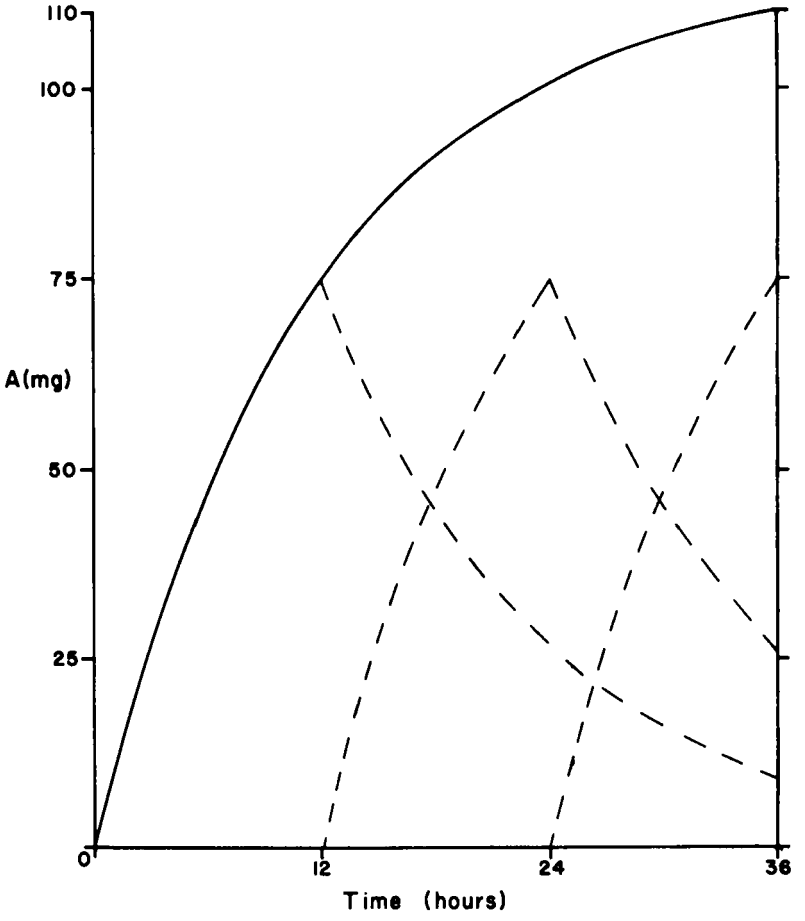


Figure 11

Drug levels during 12 hourly repeated doses of the slowly eliminated dosage form from Figure 9.

administered chronically in order to maintain drug levels in the body is less certain. The following sections will consider some of the advantages and disadvantages of this type of dosage form.

III. ZERO-ORDER RELEASE WITH A FAST RELEASE COMPONENT

Single Dose

Incorporation of a fast release component into a formulation is intended to rapidly obtain a desired drug level in the body, and then to maintain this level by means of the slow release component.

The pharmacokinetics associated with this type of drug release are more complex than those for the simple slow release models because of the additive contributions of both the fast and slow release components. Although the temporal relationship between release of the two components may vary with particular formulations, discussion of this model will assume the simple case where release of both components starts simultaneously.

For this type of formulation, and again assuming $k_o << k_a$, the amount of drug in the body following a single dose is given by Equation 9.

$$A = \frac{D_i k_a}{k_a - k_{el}}\left[e^{-k_{el}t} - e^{-k_a t}\right] + \frac{k_o}{k_{el}}\left[1 - e^{-k_{el}t}\right] \qquad \text{(Eq. 9)}$$

The first and second portions of the right hand side of this equation represent the contributions of the fast and slow release components, respectively. The first portion is similar in form to Equation 1, i.e., release by first-order process, while the second portion is identical to Equation 7, i.e. zero-order release. The amount of drug in the controlled release component, D_s, is given by $k_o T$, where T is the duration of drug release. The drug profile obtained from a single dose of this type of controlled release formulation is a composite of a rapidly increasing and then declining component and of a slowly increasing component that may or may not achieve steady-state depending on the drug elimination half-life. This dosage form is of course ideally suited for drugs with relatively long biological half-lives that would not achieve steady-state if a fast release component were not included.

A controlling factor for drug profiles obtained with this dosage form is that both the rate of decline in drug levels from the fast-release component and the rate of increase in levels from the zero-order release component are controlled by the drug elimination rate constant k_{el} (Equation 9).

Several methods have been described to calculate the optimal proportions and amounts of drug in D_i and D_s to rapidly achieve and then maintain required therapeutic drug levels (22,23,24,25). The most recent of these is based on the simple assumption that the fast release component should provide the same quantity of drug as the amount of drug in the body that would yield the desired therapeutic response at steady-state, A_{ss} as in Equation 10 (25).

$$D_i = A_{ss} = \frac{k_o}{k_{el}} \qquad \text{(Eq. 10)}$$

This approach ignores the possible additive effect of drug levels resulting from the fast and slow release components at early times after dosing, and may therefore result in drug levels slightly higher than the desired steady-state levels shortly after dosing. However this effect is likely to be slight, and the method is both simple and practical considering the various factors that influence drug release and pharmacokinetics in individual patients.

Application of the method can be demonstrated for theophylline. Theophylline has a biological $t_{1/2}$ of approximately 4 hr (k_{el} = 0.17 hr^{-1}) and a distribution volume of 32 liters (26). A steady-state level of 5 µg/ml is thus equivalent to $A_{ss} = D_i$ = 160 mg, and k_o = 160 x 0.17 = 27.2 mg/hr (Eq. 10). Substituting these values into Equation 9 and assigning k_a = 1.3 hr^{-1} (26) and a zero-order release time of 12 hr, yields the drug levels in Figure 12. The required level of 5 µg/ml is approached at 1 hr, achieved at 2 hr, and maintained through 12 hr, after which time the zero-order component is exhausted of drug, and levels then fall at an exponential rate determined by k_{el}.

Although the above method clearly works very well in rapidly achieving a desired drug level, the level reached is only one-half the usually accepted minimum therapeutic theophylline concentration of 10 µg/ml. This is intentional, and illustrates two common problems with controlled release formulations. The first of these is dosage size. In order to obtain and maintain a theophylline level of 5 µg/ml during a 12 hr period requires a total of 160 + 27.2 x 12 = 486.4 ≃ 500 mg. This is probably the upper size limit for a single oral dosage unit. A theophylline level of 10 µg/ml under the same conditions would require a total dose of 1000 mg (320 as D_i and the balance as D_s released during 12 hr) and this is too large for a single dosage unit. This level can be obtained however by giving 2 controlled release dosage units. Similarly 15 µg/ml and 20 µg/ml levels are achieved with 3 and 4 dosage units, respectively. Thus, whatever the dosage size for a particular drug, multiples of a minimum drug level are achieved simply by taking the appropriate number

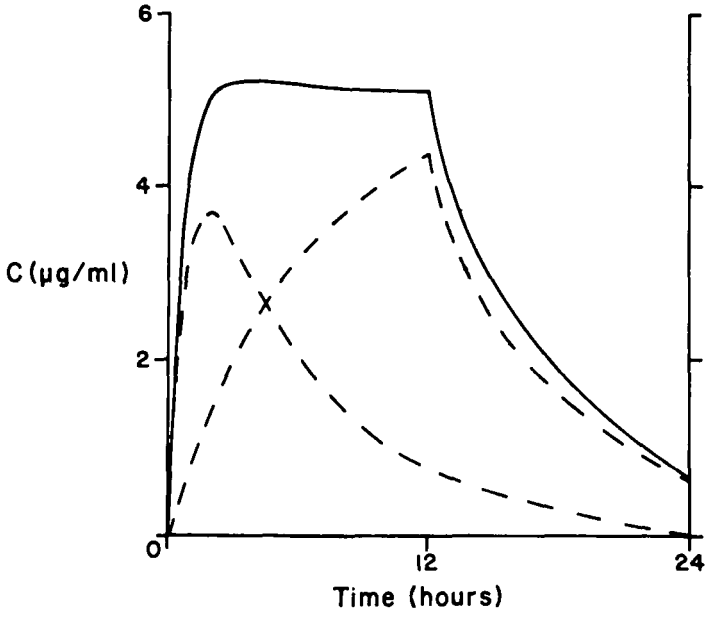


Figure 12

Predicted plasma theophylline concentration profile from a single dose of an oral formulation containing 160 mg as a fast-release component and a slow component releasing 27.2 $mg.hr^{-1}$ during 12 hr. The curves are calculated to achieve steady-state levels of 5 μg/ml by Equation 9, with k_a = 1.3 hr^{-1}, k_{el} = 0.17 hr^{-1}, and V = 32L (27).

of tablets. While this process is elegantly simple, the reverse is not. Due to their complex structure, and the nature of drug release, it is usually not possible to break most controlled release formulations in order to achieve a smaller dose. Thus it makes good sense to prepare controlled release dosage forms in the smallest practical dosage units in order to obtain maximum flexibility in dosing.

Repeated Dose

With this model, even more so than with Models I and II, the objective with repeated doses is not so much to achieve increasing drug levels until a plateau level is eventually achieved, but rather to maintain the plateau levels that were obtained with the initial dose. It is at this point that the

argument for a fast release component in an oral controlled release dosage form tends to fall apart.

It was previously demonstrated that for formulations that release all of the drug at a slow, zero-order rate, repeated doses at intervals equal to the total release time of each dose will yield continuous drug levels with no peaks or troughs (Figures 10 and 11). However, no matter how the formulation is prepared, this type of drug level pattern cannot be achieved when a fast release component is added.

Consider the fast and slow combination of theophylline again. If this formulation were taken every 12 hr then, unlike the situation in Figure 11, there would be considerable increases in drug levels with each successive dose, and undue accumulation may occur if drug levels have not returned to the required C_{ss} level at the end of each dosing interval. This is demonstrated in Figure 13 using the same pharmacokinetic values as those for Figure 12, and a dosing interval of 12 hr. Although a plateau level of ca 5 μg/ml is rapidly obtained with the initial dose, levels are transiently increased to 8.7 and 9.2 μg/ml shortly following the second and third doses, respectively, i.e. levels almost double those following the initial dose. The implications for possible toxic side effects shortly after dosing with this type of formulation are obvious.

What can be done to prevent transient fluctuations in drug levels with this type of formulation? Several approaches are possible, and these have been described in detail elsewhere (19). One can minimize the transient increase in drug levels by decreasing the loading dose in all doses subsequent to the first, or by administering the dosages at time intervals greater than the zero-order drug release period. While these approaches may appear attractive in theory they are either impractical from a formulation viewpoint or cumbersome with respect to drug administration. A most realistic solution is not to include a fast-release component at all, but rather to administer a conventional fast-release dosage form initially, in order to obtain therapeutic levels, and then to administer repeated doses of a zero-order controlled release dosage form as in Model II to maintain constant levels with minimum fluctuation.

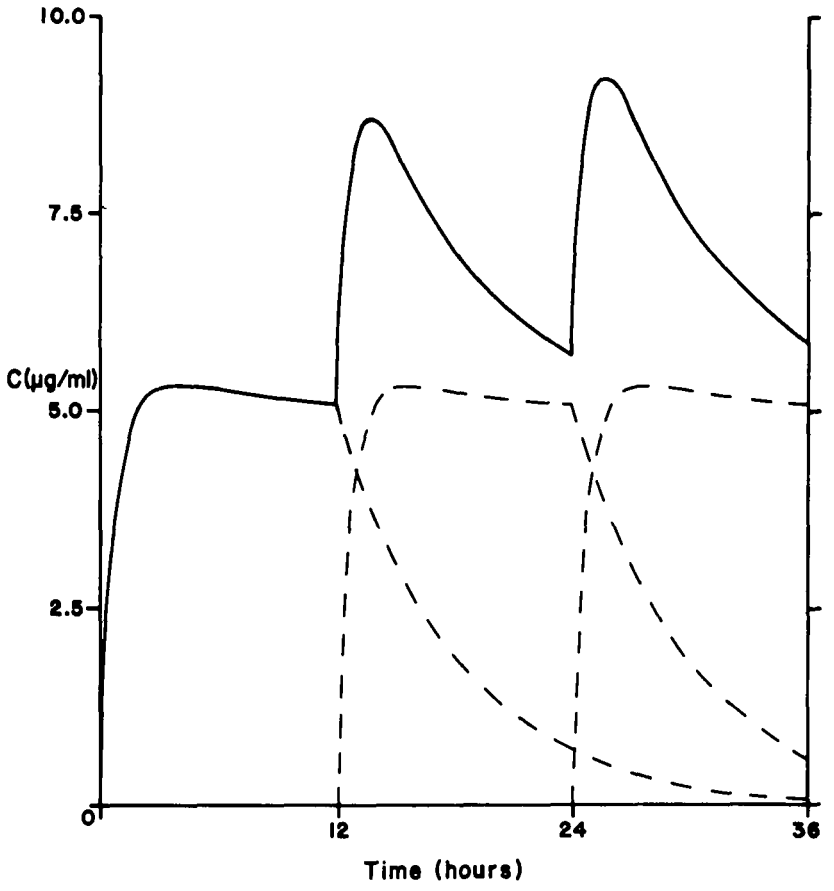


Figure 13

Predicted plasma theophylline concentration profile from 3 successive doses of the formulation in Figure 12. Pharmacokinetic parameters are the same as in the previous figure, and the dosage interval is 12 hr.

For our theophylline example, an initial fast release dose of (say) 300 mg together with a zero-order release formulation that releases 600-650 mg during 12 hr, with subsequent 12-hourly doses of the zero-order release formulation alone, would serve to rapidly achieve and maintain a plasma level of ca 10 µg/ml.

IV. FIRST-ORDER RELEASE WITH A FAST-RELEASE COMPONENT

Single Dose

Unlike the situation in Model III, both the fast and slow components of this dosage form release drug at a first-order rate; and again applying the

simplifying assumption that $k_a >> k_r$, if release of both components starts simultaneously, then drug levels are described by Equation 12.

$$A = \frac{D_i k_a}{k_a - k_{el}}[e^{-k_{el}t} - e^{-k_a t}] + \frac{D_s k_r}{k_r - k_{el}}[e^{-k_{el}t} - e^{-k_r t}] \qquad \text{(Eq. 12)}$$

This equation is simply the sum of two separate but simultaneous first-order absorption and elimination profiles, with different apparent absorption rate constants k_a and k_r.

With this pattern of drug release, which is probably more common than that represented by Model III, a strong argument can be made for delaying the initiation of release of the slow component until some time later compared to the fast component. Consider the examples in Figure 14. In this case the slow release component is 3-fold greater than the fast release component and the slow first-order release constant k_r is varied from one-tenth to one-half the intrinsic absorption rate constant k_a. The curve obtained when all of the dose is in the fast-release form, i.e., a conventional dosage form, is included for comparison. It is clear that when $k_r = 0.5k_a$ there is negligible sustained effect. Levels are not significantly prolonged until k_r is reduced to $0.1k_a$. Unfortunately in this situation a large fraction, somewhere between 25 and 50% of the slow release proportion of the dose, may not be absorbed at all due to the limited GI residence time, and the sustained effect during 8-24 hr, or 12-24 hr would be lost.

The alternative approach to achieve prolonged circulating drug levels with this dosage form is to delay release of the second drug component so that it will provide a second input at a suitable time interval after the release of the fast component. Once this concept is accepted, then arguments can be made for either fast or slow release of the second drug component. The former of these, a repeat action effect, is similar to administering repeated doses of a conventional dosage form except that the second portion is released lower in the GI tract. The second component will thus be less susceptible to gastric degradation, but more susceptible to inefficient absorption from distal

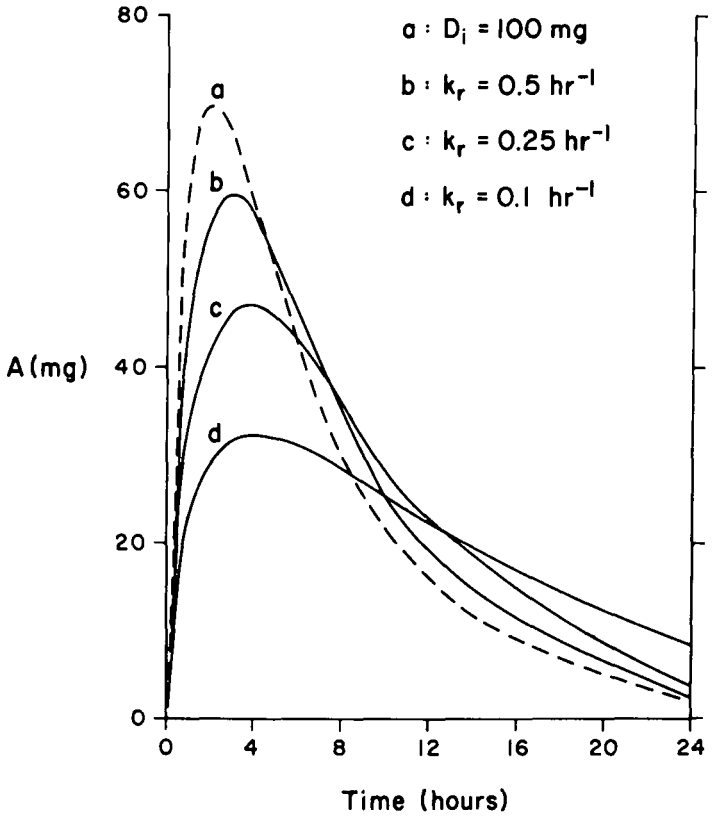


Figure 14

Drug levels following single oral doses of a dosage form containing fast and slow first-order release components, released simultaneously. Curves generated from Equation 12 with D_i = 25 mg, D_s = 75 mg, k_a = 1.0 hr^{-1}, k_{el} = 0.17 hr^{-1} ($t_{1/2}$ = 4 hr), and k_r = 0.1, 0.25, and 0.5 hr^{-1}. Note that the flip-flop model obtains when $k_r < k_{el}$ (20). The curve obtained from D_i = 100 mg and D_s = 0 is also shown.

regions of the intestine, bacterial metabolism, and also the possibility of poor absorption due to limited GI transit time. Apart from these practical and real problems, which are in part drug specific, the general pharmacokinetic treatment for 2- or 3-step fast release formulation does not differ conceptually from repeated doses of conventional dosage forms, and will not be discussed further here.

The alternative approach of having a delayed, controlled first-order release component is a viable method to maintain drug levels. The primary questions in this approach are: when should the second drug portion be released, and what are the relative proportions of drug in the fast and slow release components for optimal effect? These questions are interrelated, and the relative merits of different approaches are discussed in detail elsewhere (19). Two possible approaches are (i) to initiate release of the second component when levels from the first component are at a maximum, or (ii) to delay release of the second component until essentially all of the first component has been released (24).

The first approach is based on the argument that if the slow first-order release component can be designed so as to approximate zero-order release, then initiating the second component at the time when the drug levels from the fast component are at a peak should yield a plateau effect similar to that achieved with Model III. While this approach may be attractive in theory, it does not work well in practice. First-order release only approximates zero-order release when the amount of substance to be released is large and the first-order rate constant for release is small. This is illustrated using the theophylline example in Figure 15. An ideal plateau effect is approached only when D_s is 6-fold greater than D_i and k_r is reduced to 0.016 hr^{-1}. This is wasteful as only 20% of the slowly released dose would be absorbed from the GI tract during a 12 hr period, and only 30% during 24 hr. If drug release were restricted to a normal GI transit time of 12 hr, then at that time the rate of decline in drug levels would increase and would be controlled by the elimination rate constant k_{el}.

The second approach, that of initiating release of the slow component when most of the fast component has been released is more realistic. If the delay period is equal to the time when D_i is essentially completely released, then drug level curves similar to that shown in Figure 16 can be obtained. In this example the slow release component is released 4 hr, or 7.5 absorption half-lives, later than the fast component. Despite the fluctuation in the drug level profile, reasonably sustained levels are obtained using a relative-

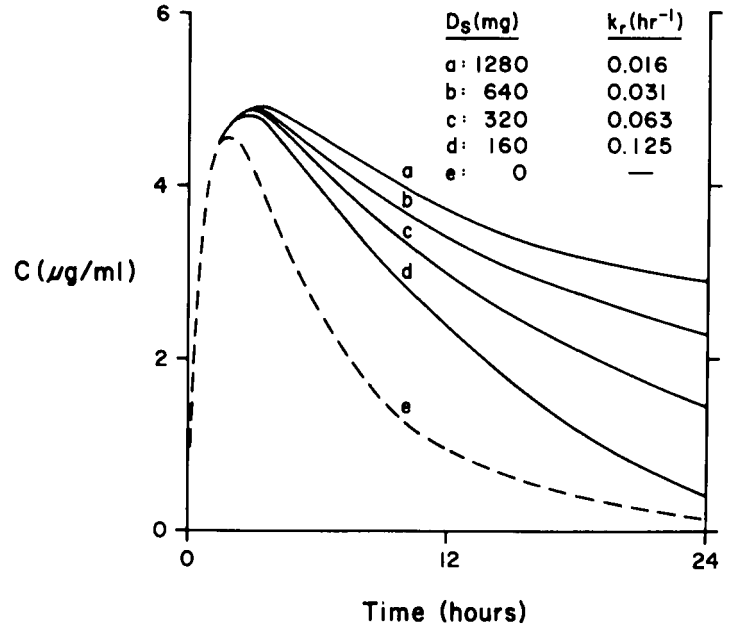


Figure 15

Predicted plasma theophylline concentration profiles from a single dose of an oral formulation in which first-order release of the slow component is initiated when plasma levels from the fast release component are at a maximum. The curves are calculated from Equation 12 with the value of t for the slow component reduced by T_{max} = 1.8 hr. Other constants are k_a = 1.3 hr^{-1}, k_{el} - 0.17 hr^{-1}, V = 32L, D_i = 200 mg, and D_S 160 mg (k_r = 0.125 hr^{-1}), 320 mg (k_r = 0.063 hr^{-1}), 640 mg (k_r = 0.031 hr^{-1}) and 1280 mg (k_r = 0.016 hr^{-1}).

ly small maintenance dose. This type of formulation is also efficient. In this example approximately 80% of the sustained dose would be absorbed by 12 hr and absorption would be quantitative in 24 hr if the dosage form were retained in the gut for that period of time.

Repeated Dose

A dosage form that contains a fast and slow first-order release component presents the same problems for multiple dosing regimens as those described for

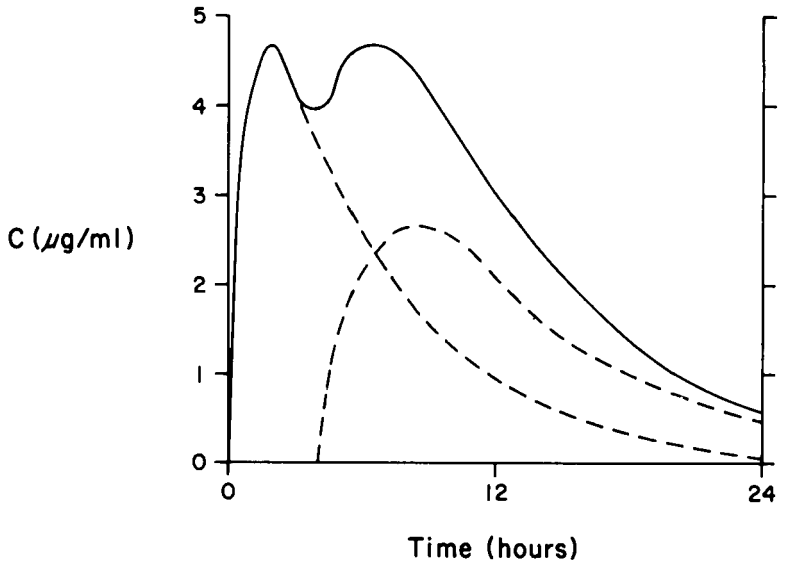


Figure 16

Predicted plasma theophylline concentration profile from a single dose of an oral formulation in which first-order release of the slow component is initiated when release of the fast component is 99% complete. The curve is generated from Equation 12 with D_i = 200 mg, D_s = 180 mg, k_a = 1.3 hr^{-1}, k_{el} = 0.17 hr^{-1}, and k_r = 0.3 hr^{-1}, and delay time for the slow component is 4 hr.

Model III. For that model it was shown that more satisfactory multiple dose drug profiles are obtained when the fast release component is absent. The situation is not so clear-cut in the present case, and a variety of multiple dose profiles can be obtained by judicious selection of drug quantities and release rates (19).

As an example consider the formulation from Figure 16. Multiple doses of this formulation could be given with the sustained and fast drug components unchanged, or with D_i reduced to compensate for drug remaining from the previous dose. Typical profiles are shown in Figures 17 and 18.

The profile in Figure 17 indicates that, as in Model III, repeated dosing of a formulation containing a fast release component that yields the required therapeutic level (or a suitable subfraction of the therapeutic dose as in this case) with the initial dose will lead to marked oscillation, a high pos-

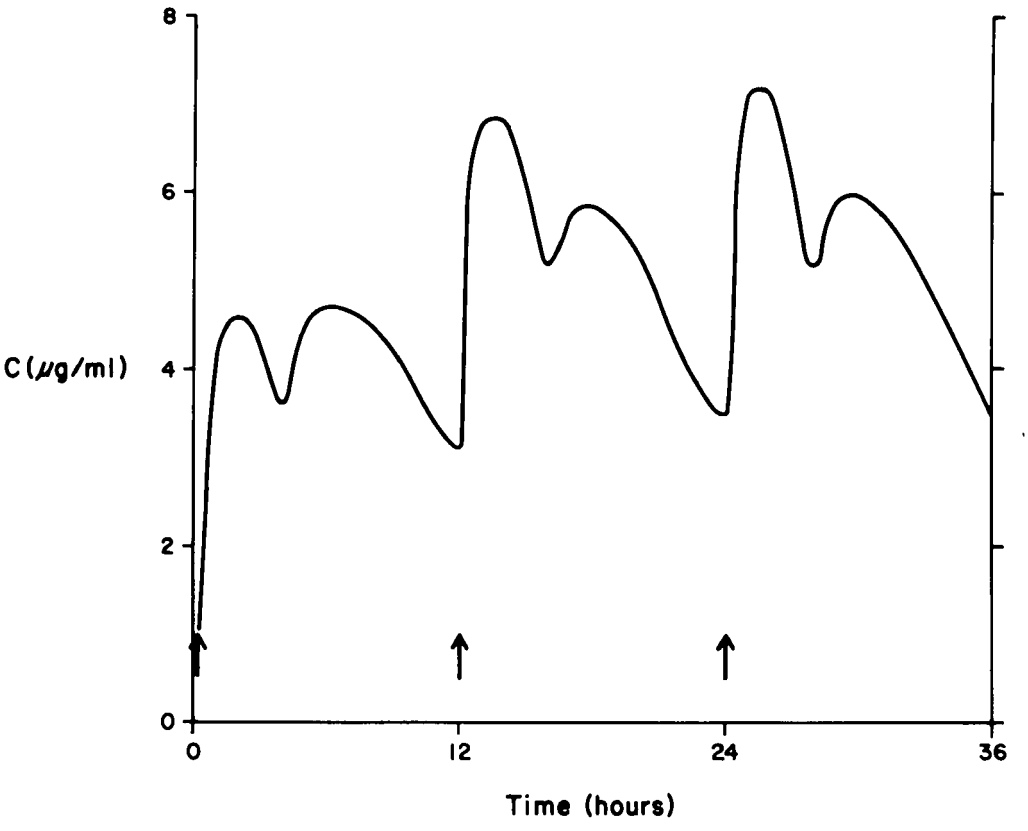


Figure 17

Predicted plasma theophylline concentration profile during repeated doses of the oral formulation in Figure 16. The dosing interval and total drug release time from each dose are 12 hours.

sibility of exceeding the therapeutic level shortly after each dose, and also undue accumulation with repeated dosing. If on the other hand, the amount of drug in the fast component is appropriately reduced (19), then a more acceptable profile is obtained as in Figure 18. In this case, by judicious dose adjustment, drug levels can be obtained that oscillate between a relatively narrow range with no accumulation. This is the ideal situation for this type of dosage form.

Of course it is impractical to have varying amounts of instantly released drug in different tablets, although one could perhaps instruct the patient to "take the blue tablet(s) furst and the pink tablet(s) afterwards." So one is

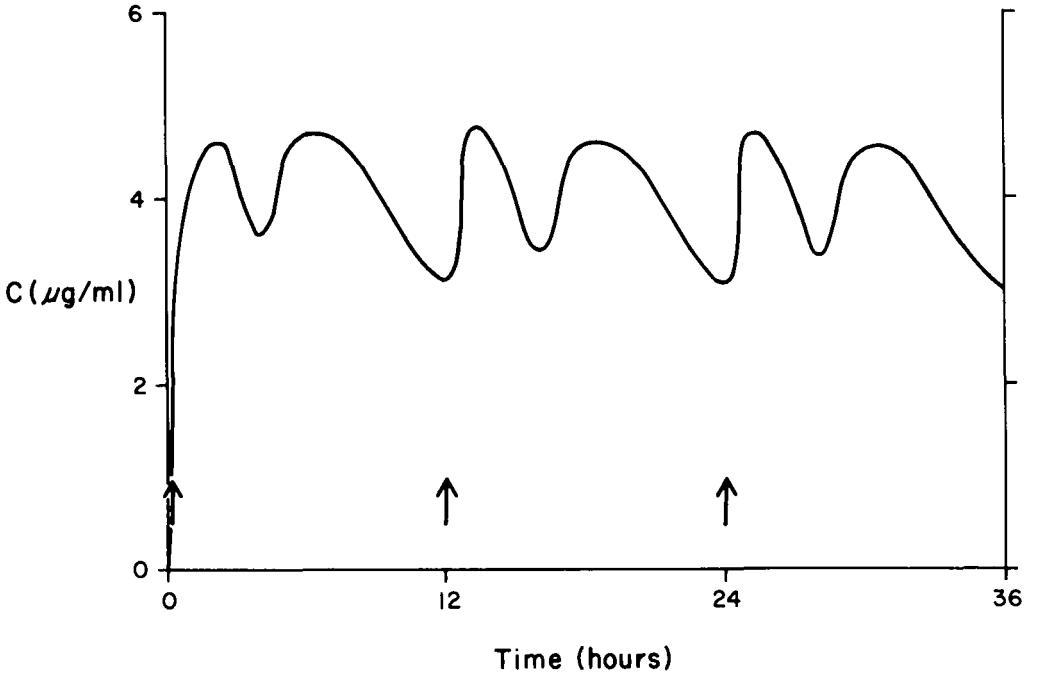


Figure 18

Predicted plasma theophylline concentration profile during repeated doses of the oral formulation in Figure 16. In this instance D_i has been reduced to 100 mg for the second and third doses. The dosing interval and total drug release time from each dose are 12 hours.

presented with a compromise of either achieving required levels quickly and then accepting the wide range of drug levels with subsequent doses, or achieving the ideal continuous drug profile at steady-state and accepting the slight delay in achieving that level. It is not possible to rapidly achieve required drug levels and then maintain them with minimum oscillation from the same formulation with this model system.

CONCLUSIONS

It is clear from the above arguments that controlled release formulations can be prepared using basic principles depending on the desired release pattern and blood-level profile. It is clear also that quite different criteria

may apply to drug release patterns when one is considering single and repeated doses.

The above methods contain several simplifying assumptions, but nonetheless provide a rational basis for controlled release dosage form design. The methods thus represent a compromise between ideality and that which is feasible in practice. The methods are of general application, but may not always apply to individual cases. For example some drugs may exhibit a marked absorption window, or may be susceptible to bacterial degradation in distal regions of the GI tract, thus reducing effective absorption time. The opposite effect occurs with formuations designed to remain in the stomach or small intestine for prolonged periods. First-pass clearance may also be important for drugs that undergo extensive hepatic metabolism or that are excreted to a large extent in bile.

Thus before initiating a program to develop a controlled release formulation for a particular drug, it is mandatory to understand the pharmacokinetic characteristics, the pharmacokinetic: pharmacodynamic relationships, the efficacy of absorption in various regions of the GI tract, and the susceptibility of the compound to degradation by GI enzymes and bacteria. Failure to consider these at the outset may result in waste of both time and money.

Despite the great number of sustained release products currently available (Table I) in the United States and elsewhere, there have been few attempts to interpret in vivo drug level data in terms of in vitro or theoretical release patterns, or to address the unique problems that accompany single and repeated doses of these dosage forms.

There are some notable exceptions, particularly in the more recent literature, and some of these are described elsewhere in this Symposium. Attempts to develop a truly zero-order release dosage form have found expression in the osmotic-pump, recently introduced for controlled-release indomethacin (27,28), and also in a matrix system for controlled release theophylline (Theo-Dur®) (5,31). While these dosage forms offer no advantage over other controlled release forms following single doses, they may provide ideal sustained plateau levels at steady-state.

A variety of controlled release dosage forms have recently been introduced for beta-adrenergic blocking agents such as oxprenolol (30), propranolol (31), and metoprolol (12,36) compounds that otherwise have to be administered with multiple daily doses. Studies with metoprolol demonstrated comparable effects on heart rate and blood pressure from twice-daily doses of 100 mg as conventional tablets and once-daily doses of 200 mg as a polymer coated granule formulation (32). Following both single (12) and repeated (32) doses plasma levels of metoprolol exhibited double peaks similar to those predicted for Model III in this discussion.

Controlled release dosage forms are thus entering a new era, not only of development but also of more rigid testing and characterization in terms of in vitro-in vivo relationships, predicted and actual release patterns, and pharmacokinetic:pharmacodynamic relationships. The next decade is likely to witness a proliferation of sophisticated controlled releast products, particularly in cardiovascular, respiration, and CNS therapy, and perhaps in the area of antimicrobial chemotherapy. Cognizance of simple kinetic principles, similar to those described here, will improve the focus, economy, and success of this work.

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