Formulation of controlled-release products

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A substantial number of prolonged-release theophylline products are commercially available, each claiming some benefit over a competing product. This paper provides a brief overview of the controlled drug delivery area, starting with the theoretical base of such products, typical biologic constraints related to the oral route of administration, and finally an overview of the type and characteristics of the various sustained- or controlled-release products presently available. It is important to recognize that the preparation of most sustained-release products is on an empirical basis and that it is common to test such products in healthy volunteers under a protocol that bears very little relationship to expected performance in the clinic. Controlled drug delivery, a field that is at least 40 years old in terms of successful commercial products, is just beginning to emerge as a discipline with a strong theory and clinical base. (J ALLERGY CLIN IMMUNOL 1986;78:676-81.)

The modern era of commercial sustained- or controlled-release dosage forms is now approximately 35 years old. During the first 20 to 25 years of this period, these products provided prolongation of drug levels in the bloodstream but did not provide the invariant control over these levels to warrant the term controlled release. Indeed, very few modern products perform well enough to be called controlled release, although many companies use this term rather loosely. It is unfortunate that nomenclature in this field has not yet been standardized, and as a result the attractive terms to characterize these products, for example, sustained, controlled, or novel, all of which are suggestive of some performance characteristics, have led to considerable confusion in the marketplace.

Moreover, the recent introduction of an orally administered once-daily product, with the prospect of many more to come in the future, raises substantial issues as to how these products should be tested for approval purposes and how they should be comparatively assessed clinically. In an attempt to put the area of extended-release products in perspective, this presentation will begin with definitions and the theoretical base of extended-release products, provide a description of the usual approaches to formulate such products, and conclude with a listing of issues presently surrounding the field.

DEFINITIONS

Two elements are typically associated with controlled drug release: spatial placement or targeting and rate of drug delivery. The ability to deliver a drug to an organ, a subset of cells within that organ, or a specific receptor site is an attractive goal for all drugs. However, targeting is not really germane to the purpose of this conference. The second feature requires precise control over release of drug from the dosage form; the yardstick for such control must be some in vivo index, and commonly it is the drug level in the bloodstream as a function of time. Given that there is commonly no correlation between in vitro assessment and in vivo performance, actual in vivo testing must be the primary index.

Because this is a subjective measure at the moment, it becomes difficult to assign the term controlled release to a specific product. To this end, we will use the term extended release to encompass both sustained- and controlled-release drug delivery systems.

THEORETICAL BASIS[1]

A buzz phrase associated with extended-release products is that "they must show zero-order release" to be called controlled release. Indeed, companies now often engage in the frequently meaningless exercise of comparing release rates by stating, "My release rate is closer to zero order than yours" or, "My release rate remains zero order for a longer time than yours." It is helpful to review briefly where this zero-order concept arose and the assumptions inherent in its application.

Many drugs are eliminated from the body in first-order fashion with an associated first-order rate con-

stant having units of reciprocal time. First-order processes are characterized by a dependency on concentration. Thus, the rate at which drug is eliminated from the body is given by

$$-\frac{dC}{dt} = k_1[C_D] \tag{1}$$

where the negative rate indicates a decline in drug concentration with time, k_1 is the first-order rate constant, and C_D is the desired blood drug concentration, such as the midpoint of the therapeutic range.

If we wished to maintain a particular drug concentration in the blood, drug would need to be replaced at the same rate it is being eliminated. Thus,

$$\begin{aligned} \text{Rate of drug in} &= \text{Rate of drug out} \\ &= k_1[C_D] \end{aligned} \tag{2}$$

Examination of equation 2 reveals that the "rate of drug in" is in units of concentration per time, which is a zero-order input. Conversion from a concentration—to an amount basis—occurs by multiplying equation 2 by a drug's volume of distribution. Thus,

$$k_0 = k_1 \times C_D \times V_D \tag{3}$$

where k_0 is equal to the zero-order rate constant describing release of the drug from the dosage form. It is this analysis that gives the usual comment that the necessary drug release rate from a controlled-delivery dosage form, to produce a drug plasma profile for which a substantial portion is invariant with time, is zero order. Conceptually, this is akin to intravenous drip therapy in which a steady-state drug level is maintained by infusing drug at a constant rate equal to the rate of drug elimination from the body.

For zero-order input to be meaningful to therapy, some important assumptions or verifications need to be made: (1) drug elimination is first order; (2) pharmacodynamics parallels pharmacokinetics; (3) the therapeutic range can be defined—the narrower the therapeutic range, the more meaningful is the constant blood drug level; and (4) the coefficient of variation about the drug concentration–time line is small enough to establish whether a zero-, first-, or mixed-order input would make a difference.

BIOLOGIC CONSTRAINTS

A number of biologic constraints make preparation of extended-release products difficult or impossible. These need to be put in perspective before discussion of specific approaches to preparation of these products.

Variable metabolism. A number of drugs such as theophylline and dextromethorphan show consider-

TABLE I. Salient characteristics of the gastrointestinal tract

Length		
Small intestine = 3.0 M		
Large intestine = 1.5 M		
Surface area = 2,000,000 cm²		
Resting volume of stomach = 50 ml		
General flow pattern = Laminar		
pH		
Stomach		
Distal 1-3, with food 3-5		
Proximal -3, with food -5		
Small bowel		
Duodenum = 6		
Jejunum = 8		
Large bowel		
Colon = 5-7		
Osmolarity		
Stomach = Variable		
Small bowel = Iso-osmotic with blood, 330 mOsm/L		
Large bowel = Variable		
Transit times in adults		
	Solution	*Digestible solid*
Stomach	50 min	Up to 8 hr
Small bowel		4-9 hr
	2-6 hr	
Large bowel		3 hr-3 days

Modified from Park K, Wood RW, Robinson JR. Oral controlled release systems. In: Langer RS, Wise DL, eds. Medical applications of controlled release; vol 1. Boca Raton, Florida: CRC Press. 1984.

able variation in rate of metabolism in the population. Because extended-release products are not made for individual patients but rather for the population at large, it is worthwhile recalling that a slower or faster elimination rate constant can give a higher or lower steady-state drug level. Provided that the therapeutic range is broad enough, as in the case of dextromethorphan, this need not be a serious problem. However, for some drugs, alteration in the dosing frequency with the extended-release product may be necessary, and perhaps for some patients these products cannot be used at all.

The oral route. The dominant route of drug delivery continues to be the oral route, an area in which considerable research has been done to understand (and ideally someday control) the microenvironment and normal physiologic processes such as gastrointestinal transit. It is somewhat embarrassing to know so little about the gastrointestinal tract that we can only offer conjecture as to movement of dosage forms through this conduit, the influence of specific foods on movement and release of drug, degradation, and absorption.

TABLE II. Biologic parameters influencing the design of oral extended-release products

Parameter	Drugs requiring special considerations or deemed poor candidates
Absorption	Drugs absorbed by specialized transport processes
	Drugs absorbed at special sites of the gastrointestinal tract
	Drugs that are slowly absorbed
Metabolism	Drugs extensively metabolized by gut microbial flora
	Drugs extensively metabolized during transit across the gastrointestinal wall or during the first pass through the liver
Half-life	Drugs with either extremly short or long half-lives
Margin of safety	Drugs with narrow therapeutic indices

However, what we do know needs to be put in perspective relative to extended-release products. Pertinent features of the gastrointestinal tract are shown in Table I.[2]

Gastrointestinal transit has always been a limiting factor in the preparation of once-daily administered drug products. Thus, assuming a generous 5 to 10 seconds for a dosage form to pass the esophagus, about 2 or 3 hours to leave the fasted stomach, and about 3 hours for small bowel transit, it appears that about 6 to 8 hours after ingestion the drug delivery system is in the large bowel, where, with a decreased surface area, less absorption occurs. In the presence of food, this can be extended to perhaps 12 to 14 hours. Under these conditions, and assuming that the drug itself does not have a long biologic half-life, once-daily dosing is difficult to achieve unless (1) gastrointestinal transit time can be prolonged or (2) the drug is well enough absorbed in the large bowel to replace drug that is being eliminated from the blood.

An additional constraint is the recognition that gastrointestinal transit time will vary with factors such as age, disease, or trauma. Perhaps the most significant of these variables for the population at large is age. It is firmly established that stomach emptying is considerably slower in the elderly and faster in the very young. Complete gastrointestinal transit time is correspondingly reflective of this. For specific drugs and drug delivery systems, such an effect can be sub-

stantial in terms of how much drug is absorbed from the dosage form and the pharmacokinetics of this absorption.

The influence of the presence of food on performance of certain non-extended-release products has been well established in the literature. For extended-release products, a body of literature also exists; when specific approaches to sustaining drug delivery are discussed, such an influence is often intuitively obvious. In some cases, however, with newer polymers being used for extended drug delivery systems, the interactions that occur with specific foods are less obvious. Table II lists some of the additional biologic parameters influencing the design and performance of extended-release products.

METHODS TO PREPARE EXTENDED-RELEASE PRODUCTS

The usual approaches to prepare extended-release products are listed in Table III. For purposes of discussion at this conference, we can ignore transdermal products and pumps and group the remaining products into three categories: (1) dissolution controlled, (2) diffusion controlled, and (3) osmotic pressure controlled. It should be recognized that overlap is likely to exist with all three mechanisms for a specific product. Thus, it is likely that for a dissolving pellet or tablet, additional release of drug occurs as a result of both diffusion and osmotic pressure. Nevertheless, it is convenient to discuss products by using this grouping.

Before we elaborate on these three mechanisms, a brief discussion of a fourth approach to prepare extended-release products is warranted. The ion-exchange principle has been used for a variety of drugs, including theophylline, although to our knowledge no commercial theophylline products using this technology are yet available in the United States. A Food and Drug Administration submission for one such product has been made, however. In this approach, an ion-exchange resin with anionic or cationic groups is allowed to form a chemical compound with the drug and is then coated with a barrier of some sort. When it is ingested, suitable counterions replace the drug and the released drug diffuses through the barrier coat for eventual absorption. Obviously, this technique can be used only for charged drugs and indeed only charged drugs that are sufficiently acidic or basic that a substantial amount of drug can be loaded on the resin polymer. In the case of theophylline, binding to the polymer is relatively low and thus only a modest amount of drug can be put on the polymer. No clinical data are yet available, so that no assessment of performance can be made.

DISSOLUTION CONTROL

Recall that it is desirable to have a constant or zero-order release of drug from the dosage form. This is commonly difficult to achieve with a dissolving system because in most cases the surface area is continually decreasing.

The usual mathematical expression to describe dissolution of a solid is

$$-\frac{dM}{dt} = k\ A\ C \qquad (4)$$

where $-dM/dt$ is the rate of dissolution, k is the rate constant describing the process, A is the surface area, and C is the concentration of drug. For a zero-order system, all of the terms on the right-hand side of the equation must be constant. For a dissolving solid, with a constantly shrinking size, this is not possible unless special precautions are taken, for example, only one face of a solid dissolves. This is not usually the case so that we do not ordinarily see a blood level versus time profile in which a significant portion of the curve is flat with a slope of zero, indicative of a zero-order release system, but rather we see a more or less bell-shaped profile.

Two usual approaches have been taken to formulate dissolution-controlled extended-release products: (1) encapsulated products and (2) matrix products.

In the encapsulated products, drug is coated with variable-thickness dissolving materials. As the coat dissolves, drug is released, and because there is a distribution of coating thickness, a continuous or discrete supply of drug ensues. This is the basis of the SKF Spansule (Smith Kline & French, Philadelphia, Pa.) and many other products on the market. These coated beads or pellets can be put in a capsule or compressed into a tablet. When they are compressed into a tablet, some cracking or fusion of the coat occurs so that the release rate may be faster than predicted by surface area of the noncompressed particle. Substances traditionally used as coatings include various waxes and erodible polymers. Some of these substances, namely, the waxes and pharmaceutical glaze (shellac), undergo an aging phenomenon wherein changes in the material cause a difference in release rate of drug over time. Typically, about a 10% difference in release rate will be seen 1 to 2 years after manufacture.

In the matrix product, drug is uniformly dispersed in a solid water-soluble carrier, and small particles or spheres of the resultant material are put in a capsule or compressed into a tablet. As the carrier dissolves, the drug becomes available for dissolution and absorption. Indeed, it is the dissolution rate of the carrier that controls the rate of drug release. Carrier ma-

TABLE III. Common approaches to prepare controlled-release products

A. Continuous-release systems
1. Barrier-coated beads or granules
2. Coated ion-exchange resins
3. Low-density hydrocolloids
4. Wax matrices
5. Plastic matrices
6. Osmotic systems
7. Transdermal devices
8. Pumps
9. Formation of less-soluble complexes, for example, tannates
B. Intermittent-release systems
1. Repeat action

terials include the usual waxes, polymers, and sugars.

DIFFUSION CONTROL

Diffusion-controlled systems can, in theory, produce a zero-order release of drug, although in practice they usually do not. Such systems utilize water-soluble polymers as either diffusion membranes or carriers, as will be discussed later. The general expression governing release of drug is shown as equation 5:

$$\frac{dM}{dt} = \frac{A\ D\ K}{l}\ \Delta C \qquad (5)$$

where dM/dt is the rate of appearance of drug, A is the surface area through which the drug will diffuse, D is the diffusion coefficient for drug in the polymer, K is the partition coefficient for drug to the membrane, l is the thickness of the membrane, and ΔC is the difference in concentration of drug inside and outside of the membrane. As with dissolution control, if we can maintain all of the terms on the right-hand side of the equation constant, a constant rate of drug release can be obtained. With polymers that do not dissolve or change their physical dimensions, it is possible to maintain essentially constant conditions.

As with dissolution-controlled systems, there are essentially two groups of diffusion-controlled products: (1) reservoir systems and (2) matrix systems.

The reservoir product consists of a central core of drug surrounded by a water-insoluble polymeric membrane. Drug partitions into the membrane, diffuses across the barrier, and becomes available on the other side for eventual absorption. In these products, it is essential that the barrier film remain intact and that the thickness of the coat be controlled as closely as possible, if reproducible results are to be obtained. These coated particles, as with their dissolving coun-

terparts, can be incorporated into a capsule directly or compressed into a tablet. The concerns expressed earlier regarding compression of particles and changes in release rate apply equally well here.

Matrix particles consist of drug dispersed or dissolved in a water-insoluble polymeric material. When placed in the gastrointestinal tract, drug dissolves and diffuses out of the polymer or, if soluble in the polymer to begin with, simply diffuses out of the polymer. The insoluble polymer is then passed into the feces. These types of products commonly do not give a zero-order release but give a close approximation to zero order, the so-called square root of time relationship. An important element of these products is that they require close standards on manufacturing because relatively small changes in the characteristics of such products can have a profound effect on in vivo performance.

OSMOTIC CONTROL

Osmotic pressure can be used to cause release of drug from a dosage form, and a constant rate of drug release will occur provided a constant osmotic pressure is maintained. The essentials of the system are a membrane-bound core consisting of drug and electrolyte. The rigid, semipermeable membrane will allow free diffusion of water but not of drug or electrolyte, and the membrane has a small hole to permit exit of the drug. When the system is exposed to water, water will flow into the tablet because of the osmotic pressure difference; the rate of water flow into the tablet is given by

$$dV/dt = Ak/h \, (\Delta\pi - \Delta P) \qquad (6)$$

where A is the area of the membrane, h is its thickness, k is the permeability of the membrane to water, $\Delta\pi$ is the osmotic pressure difference, and ΔP is the hydrostatic pressure difference.

If the orifice in the membrane is sufficiently large, or if a flexible bag is used inside the tablet, the hydrostatic pressure becomes negligible and equation 6 reduces to

$$dV/dt = Ak/h \, (\Delta\pi) \qquad (7)$$

From this expression, it is clear that the rate of water flow can be controlled by area, thickness, and permeability of the membrane.

The drug will be pumped out of the tablet through the orifice at a controlled rate equal to the volume uptake through the semipermeable membrane. Thus,

$$\frac{dM}{dt} = dV/dt \, (C_s) \qquad (8)$$

where C_s is the drug concentration in the tablet.

As long as excess electrolyte and drug remain in the tablet and the dimensions of the polymer coat do not change, a constant rate of drug delivery is expected. Depletion of electrolyte will cause the dosage form to be no longer osmotically driven, and it becomes simple diffusion controlled.

Osmotic tablets, in theory, are essentially independent of the environment insofar as release rate of drug is concerned. They depend only on water for drug release, and irrespective of pH and other environmental solutes, their release rate will be constant.

These products are not without problems in formulation, especially for either very water-soluble or water-insoluble drugs. Moreover, should these products become lodged in a fold of the gastrointestinal tract they can create a high concentration gradient at the tissue surface, which can be a problem for drugs with irritation potential.

PRODUCT EVALUATION

The usual approach to assess extended release products is to use an in vitro procedure of some type. Ordinarily, the official USP procedure of a rotating basket or the paddle method is used, and data for the drug in solution are obtained as a function of time. Such data cannot usually be used alone unless a corresponding in vitro–in vivo correlation has first been established. This is usually not available, and, indeed, the Bioavailability Unit at FDA uses the term association rather than correlation when dealing with extended-release systems.

Because in vitro systems cannot be used and full-blown clinical experience generally is lacking and may take years to completely assess, we are left with bioavailability studies to determine some expected performance aspects of an extended-release product. The nature of these studies in terms of protocol will determine the clinical predictiveness of such products.

Typically, the protocol for bioavailability studies of extended-release products has been derived from their non-sustained-release counterparts with suitable modification. It is not the intent of this presentation to analyze this area, but it is worthwhile recognizing that: (1) Extended-release products are considerably different from non-sustained-release products, and the protocols to assess these products must be cognizant of these differences. (2) Although some elements of the protocol are generic to all extended-release products, sufficient differences in the design and construction of each product exist to influence its clinical performance. Special recognition of these differences is essential. (3) Manufacturers of extended-release products usually do not know the precise mechanism(s) of release in vivo, and thus the protocol must be

broad enough to encompass a variety of potential mechanisms.

Reflecting our personal biases, we give below a small, but not exhaustive, list of factors that must be considered in a bioavailability protocol: (1) different patient populations (for drugs with a differential in metabolism); (2) various age groups; (3) foods in general and specific foods in particular; (4) healthy subjects and patients; (5) traumatized patients (to assess the influence of cessation of gastrointestinal tract motility); and (6) product-related intrasubject and intersubject variability.

All of these points merit serious consideration in their own right, but one point in particular, namely, intrasubject and intersubject variability, requires additional comment. For extended-release products, it is anticipated that the dosage form can introduce more or less intrasubject and intersubject variability with respect to the plasma levels obtained. Current assessment focuses on the steady-state peak-to-trough ratio as a useful index of product performance. However, the extent of intrasubject and intersubject variability may be appreciable. Because we recognize that intrasubject variation is not usually assessed, it remains for the intersubject variability to be examined and compared between products.

From our perspective, we recognize that our understanding of gastrointestinal tract physiology and constituents of the gastrointestinal tract as they influence extended-release products is at an early stage. Although we have had approximately 35 years of experience with orally administered controlled-release products, only recently have we been able to achieve a relatively constant plasma drug level over a specified period of time, and this only for a few drug products. The combined vagaries of the gastrointestinal tract and patient population and the limits on our technical capabilities lead us to view our present situation as relatively primitive. However, given the level of interest in extended-release products, we are optimistic that we will witness significant strides over the next 5 to 10 years.

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Estimation of theophylline absorption rate by means of the Wagner-Nelson equation

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The elimination rate constant of theophylline to be used in calculating the cumulative amount absorbed per milliliter of the volume of distribution is estimated from terminal theophylline concentrations of the same data set as that analyzed for absorption kinetics. Erroneous results are obtained if the elimination rate constant is obtained from a different treatment such as an oral solution or elixir or from intravenous data, and/or if the wrong asymptotic value is used. So-called "trickle absorption" is shown to be an artifact. Published data indicate appreciable intrasubject variation in the elimination rate constant of theophylline. (J ALLERGY CLIN IMMUNOL 1986;78:681-8.)

Equation 1 is the Wagner-Nelson[1] equation:

$$\frac{A_T}{V} = C_T + k_e(AUC\ 0\text{-}T) \qquad (1)$$

where A_T is the cumulative amount of drug absorbed to time T; V is the volume of distribution of the drug;