CHAPTER 94

Sustained-Release Drug Delivery Systems

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The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration. That is, the drug-delivery system should deliver drug at a rate dictated by the needs of the body over the period of treatment. This idealized objective points to the two aspects most important to drug delivery, namely, *spatial placement* and *temporal delivery* of a drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained-release drug delivery system can be a major advance toward solving these two problems. It is for this reason that the science and technology responsible for development of sustained-release pharmaceuticals have been and continue to be the focus of a great deal of attention in both industrial and academic laboratories. There currently exist numerous products on the market formulated for both oral and parenteral routes of administration that claim sustained or controlled drug delivery. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the newer approaches under investigation may allow for spatial placement as well. This chapter will define and explain the nature of sustained-release drug therapy, briefly outline relevant physicochemical and biological properties of a drug that affect sustained-release performance and review the more common types of oral and parenteral sustained-release dosage forms. In addition, a brief discussion of some methods currently being used to develop targeted delivery systems will be presented.

Conventional Drug Therapy

To gain an appreciation for the value of sustained drug therapy it is useful to review some fundamental aspects of conventional drug delivery.[1] Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug, eg, a solution, suspension, capsule, tablet, etc, probably will produce a drug blood level versus time profile similar to that shown in Fig 1. The term "drug blood level" refers to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. It can be seen from this figure that administration of a drug by either intravenous injection or an extravascular route, eg, orally, intramuscularly or rectally, does not maintain drug blood levels within the therapeutic range for extended periods of time. The short duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by, for example, increasing the initial dose of an intravenous injection, as shown by the dotted line in the figure, toxic levels may be produced at early times. This approach obviously is undesirable and unsuitable. An alternate approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. This is shown in Fig 2 for the oral route. In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in multiple-dose therapy:

1. If the dosing interval is not appropriate for the biological half-life of the drug, large "peaks" and "valleys" in the drug blood level may result. For example, drugs with short half-lives require frequent dosings to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multiple-dosing can produce the desired drug blood level for extended periods of time. Frequently, however, these problems are significant enough to make drug therapy with conventional dosage forms less desirable than sustained-release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of sustained-release drug delivery systems. There are numerous potential advantages of sustained-release drug therapy that will be discussed in the next section.

Sustained-Release Drug Therapy

As already mentioned, conventional dosage forms include solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments and suppositories. For this discussion, these dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme:

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{k_r} \text{Absorption Pool} \xrightarrow[\text{absorption}]{k_a} \text{Target Area} \xrightarrow[\text{elimination}]{k_e}$$

The absorption pool represents a solution of the drug at the site of absorption, and the terms k_r, k_a and k_e are first-order rate constants for drug release, absorption and overall elimination, respectively. Immediate release from a conventional dosage form implies that $k_r >>> k_a$ or, alternatively, that absorption of drug across a biological membrane, such as the intestinal epithelium, is the rate-limiting step in delivery of the drug to its target area. For nonimmediate-release dosage forms, $k_r <<< k_a$, that is, release of drug from the dosage form is the rate-limiting step. This causes the above kinetic scheme to reduce to

$$\text{Dosage Form} \xrightarrow[\text{drug release}]{k_r} \text{Target Area} \xrightarrow[\text{elimination}]{k_e}$$

Essentially, the absorptive phase of the kinetic scheme becomes insignificant compared to the drug release phase. Thus, the effort to develop a nonimmediate-release delivery

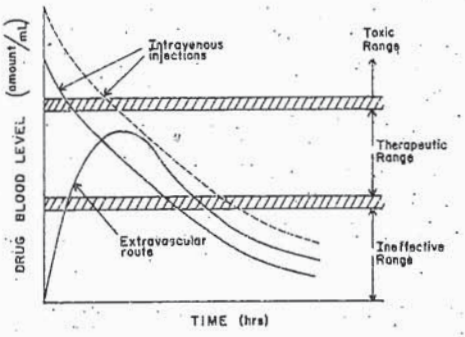


Fig 1. Typical drug blood level versus time profiles for intravenous injections and an extravascular route of administration.

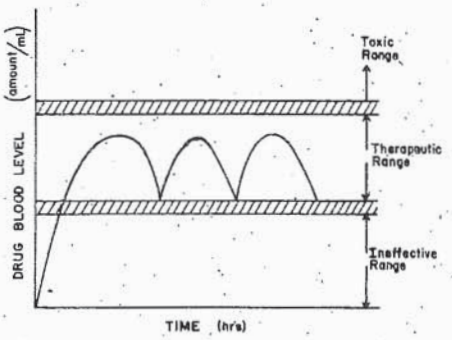


Fig 3. Typical drug blood level versus time profiles for delayed-release drug delivery by a repeat-action dosage form.

system must be directed primarily at altering the release rate by affecting the value of k_r. The many ways in which this has been attempted will be discussed later in this chapter.

Nonimmediate-release delivery systems may be divided conveniently into four categories:

1. Delayed release
2. Sustained release
   a. Controlled release
   b. Prolonged release
3. Site-specific release
4. Receptor release

Delayed-release systems are those that use repetitive, intermittent dosings of a drug from one or more immediate-release units incorporated into a single dosage form. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating. A delayed-release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range, as shown in Fig 3, but, nonetheless, is more effective for patient compliance than conventional dosage forms.

Sustained-release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a *controlled-release* system. If it is unsuccessful at this, but nevertheless prolongs therapeutic blood or tissue level of the drug for an extended period of time, it is considered a *prolonged-release* system. This is illustrated in Fig 4.

Site-specific and *receptor release* refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to, or in the diseased organ or tissue; for receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery.

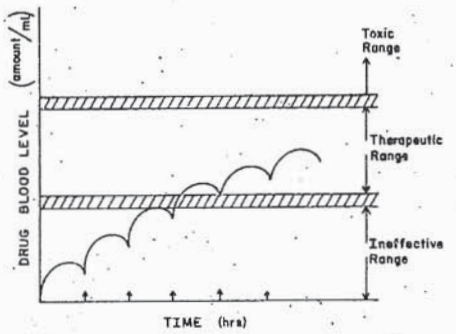
Release Rate and Dose Considerations[2]

Although it is not necessary or desirable to maintain a constant level of drug in the blood or target tissue for all therapeutic cases, this is the ideal goal of a sustained-release delivery system. In fact, in some cases optimum therapy is achieved by oscillating, rather than constant, drug levels. An example of this is antibiotic therapy, where the activity of the drug is required only during growth phases of the microorganism. A constant drug level will succeed at curing or controlling the condition, however, and this is true for most forms of therapy.

The objective in designing a sustained-release system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. That is, release from the dosage form should follow *zero-order* kinetics, as shown by

$$k_r^0 = \text{Rate In} = \text{Rate Out} = k_e \cdot C_d \cdot V_d \qquad (1)$$

where k_r^0 is the zero-order rate constant for drug release (amount/time), k_e is the first-order rate constant for overall drug elimination (time^{-1}), C_d is the desired drug level in the body (amount/volume) and V_d is the volume space in which the drug is distributed. The values of k_e, C_d and V_d needed to calculate k_r^0 are obtained from appropriately designed single-dose pharmacokinetic studies. Equation 1 provides the method to calculate the zero-order release rate constant necessary to maintain a constant drug blood or tissue level for the simplest case where drug is eliminated by first-order kinetics. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level. It is important to recognize that while zero-order release may be desirable theo-



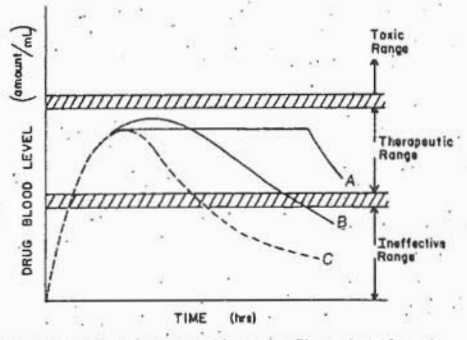


Fig 4. Drug blood level versus time profiles showing the relation-

retically, nonzero-order release may be equivalent clinically to constant release in many cases. Aside from the extent of intra- and intersubject variation is the observation that, for many drugs, modest changes in drug tissue levels do not result in an improvement in clinical performance. Thus, a nonconstant drug level may be indistinguishable clinically from a constant drug level.

To achieve a therapeutic level promptly and sustain the level for a given period of time, the dosage form generally consists of two parts: an initial priming dose, D_i, that releases drug immediately and a maintenance or sustaining dose, D_m. The total dose, W, thus required for the system is

$$W = D_i + D_m \quad (2)$$

For a system where the maintenance dose releases drug by a zero-order process for a specified period of time, the total dose[2] is

$$W = D_i + k_r^0 T_d \quad (3)$$

where k_r^0 is the zero-order rate constant for drug release and T_d is the total time desired for sustained release from one dose. If the maintenance dose begins the release of drug at the time of dosing ($t = 0$), it will add to that which is provided by the initial dose, thus increasing the initial drug level. In this case a correction factor is needed to account for the added drug from the maintenance dose:

$$W = D_i + k_r^0 T_d - k_r^0 T_p \quad (4)$$

The correction factor, $k_r^0 T_p$, is the amount of drug provided during the period from $t = 0$ to the time of the peak drug level, T_p. No correction factor is needed if the dosage form is constructed in such a fashion that the maintenance dose does not begin to release drug until time T_p.

It already has been mentioned that a perfectly invariant drug blood or tissue level versus time profile is the ideal goal of a sustained-release system. The way to achieve this, in the simplest case, is by use of a maintenance dose that releases its drug by zero-order kinetics. However, satisfactory approximations of a constant drug level can be obtained by suitable combinations of the initial dose and a maintenance dose that releases its drug by a first-order process. The total dose for such a system is

$$W = D_i + (k_e C_d / k_r) V_d \quad (5)$$

where k_r is the first-order rate constant for drug release (time^{-1}), and k_e, C_d and V_d are as defined previously. If the maintenance dose begins releasing drug at $t = 0$, a correction factor is required just as it was in the zero-order case. The correct expression in this case is

$$W = D_i + (k_e C_d / k_r) V_d - D_m k_e T_p \quad (6)$$

In order to maintain drug blood levels within the therapeutic range over the entire time course of therapy, most sustained-release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses. For an ideal sustained-release system that releases drug by zero-order kinetics, the multiple dosing regimen is analogous to that used for a constant intravenous infusion, as discussed in Chapter 42. For those sustained-release systems having release kinetics other than zero-order, the multiple dosing regimen is more complex and its analysis is beyond the scope of this chapter; Welling and Dobrinska[3] provide more detailed discussion.

Potential Advantages of Sustained Drug Therapy

All sustained-release products share the common goal of improving drug therapy over that achieved with their non-sustained counterparts. This improvement in drug therapy is represented by several potential advantages of the use of sustained-release systems, as shown in Table 1.

Patient compliance has been recognized as a necessary and drug therapy. Minimizing or eliminating patient compliance problems is an obvious advantage of sustained-release therapy. Because of the nature of its release kinetics, a sustained-release system should be able to use less total drug over the time course of therapy than a conventional preparation. The advantages of this are a decrease or elimination of both local and systemic side effects, less potentiation or reduction in drug activity with chronic use and minimization of drug accumulation in body tissues with chronic dosing.

Unquestionably the most important reason for sustained-drug therapy is improved efficiency in treatment, ie, optimized therapy. The result of obtaining constant drug blood levels from a sustained-release system is to achieve promptly the desired effect and maintain it for an extended period of time. Reduction or elimination of fluctuations in the drug blood level allows better disease state management. In addition, the method by which sustained release is achieved can improve the bioavailability of some drugs. For example, drugs susceptible to enzymatic inactivation or bacterial decomposition can be protected by encapsulation in polymer systems suitable for sustained release. For drugs that have a "specific window" for absorption, increased bioavailability can be attained by localizing the sustained-release delivery system in certain regions of the gastrointestinal tract. Improved efficiency in treatment also can take the form of a special therapeutic effect not possible with a conventional dosage form (see Table 1).

The last potential advantage listed in Table 1, that of economy, can be examined from two points of view. Although the initial unit cost of most sustained-drug delivery systems usually is greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be less. Economy also may result from a decrease in nursing time/hospitalization, less lost work time, etc.

Table 1—Potential Advantages of Sustained Drug Therapy

1. Avoid patient compliance problems
2. Employ less total drug
   a. Minimize or eliminate local side effects
   b. Minimize or eliminate systemic side effects
   c. Obtain less potentiation or reduction in drug activity with chronic use
   d. Minimize drug accumulation with chronic dosing
3. Improve efficiency in treatment
   a. Cure or control condition more promptly
   b. Improve control of condition, ie, reduce fluctuation in drug level
   c. Improve bioavailability of some drugs
   d. Make use of special effects, eg, sustained-release aspirin for morning relief of arthritis by dosing before bedtime
4. Economy

Drug Properties Relevant to Sustained-Release Formulation

The design of sustained-release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constraints upon choices for the route of delivery, the design of the delivery system and the length of therapy. Of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug. It is these properties that have the greatest effect on the behavior of the drug in the delivery system and in the body. For the purpose of discussion, it is convenient to describe the properties of a drug as being either physicochemical or biological. Obviously, there is no clearcut distinction between these two categories since the biological properties of a drug are a function of its physicochemical properties.

can be determined from *in vitro* experiments will be considered as physicochemical properties. Included as biological properties will be those that result from typical pharmacokinetic studies on the absorption, distribution, metabolism and excretion (ADME) characteristics of a drug and those resulting from pharmacological studies.

Physicochemical Properties

Aqueous Solubility and pK_a—It is well known that in order for a drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. Two of the most important physicochemical properties of a drug that influence its absorptive behavior are its aqueous solubility and, if it is a weak acid or base (as are most drugs), its pK_a. These properties play an influential role in performance of nonsustained-release products; their role is even greater in sustained-release systems.

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membranes. Dissolution rate is related to aqueous solubility as shown by the Noyes-Whitney equation which, under sink conditions, is

$$dC/dt = k_D A C_s \qquad (7)$$

where dC/dt is the dissolution rate, k_D is the dissolution rate constant, A is the total surface area of the drug particles and C_s is the aqueous saturation solubility of the drug. The dissolution rate is constant only if surface area, A, remains constant, but the important point to note is that the initial rate is proportional directly to aqueous solubility C_s. Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems.

It will be recalled from Chapter 16 that the aqueous solubility of weak acids and bases is governed by the pK_a of the compound and the pH of the medium. For a weak acid

$$S_t = S_0(1 + K_a/[H^+]) = S_0(1 + 10^{pH-pK_a}) \qquad (8)$$

where S_t is the total solubility (both the ionized and unionized forms) of the weak acid, S_0 is the solubility of the unionized form, K_a is the acid dissociation constant and $[H^+]$ is the hydrogen ion concentration of the medium. Equation 8 predicts that the total solubility, S_t, of a weak acid with a given pK_a can be affected by the pH of the medium. Similarly, for a weak base

$$S_t = S_0(1 + [H^+]/K_a) = S_0(1 + 10^{pK_a-pH}) \qquad (9)$$

where S_t is the total solubility (both the conjugate acid and free-base forms) of the weak base, S_0 is the solubility of the free-base form and K_a is the acid dissociation constant of the conjugate acid. Analogous to Eq 8, Eq 9 predicts that the total solubility, S_t, of a weak base whose conjugate acid has a given pK_a can be affected by the pH of the medium. Considering the pH-partition hypothesis, the importance of Eqs 8 and 9 relative to drug absorption is evident. The pH-partition hypothesis simply states that the un-ionized form of a drug will be absorbed preferentially, in a passive manner, through membranes. Since weakly acidic drugs will exist in the stomach (pH = 1 to 2) primarily in the un-ionized form, their absorption will be favored from this acidic environment. On the other hand, weakly basic drugs will exist primarily in the ionized form (conjugate acid) at the same site, and their absorption will be poor. In the upper portion of the small intestine, the pH is more alkaline (pH = 5 to 7) and the reverse will be expected for weak acids and bases. The ratio of Eq 8 or 9 written for either the pH of the gastric or intestinal fluid and the pH of blood is indicative of the driving force for absorption based on pH gradient. For example, consider the and gastric fluid:

$$R = (1 + 10^{pH_b-pK_a})/(1 + 10^{pH_g-pK_a}) \qquad (10)$$

where pH_b is the pH of blood (pH 7.2), pH_g is the pH of the gastric fluid (pH 2) and the pK_a of aspirin is about 3.4. Substituting these values into Eq 10 gives a value for R of $10^{3.8}$ which indicates that aspirin is in a form to be well-absorbed from the stomach. The same calculation for intestinal pH (about 7) yields a ratio close to 1, implying a less-favorable driving force for absorption at that location. Ideally, the release of an ionizable drug from a sustained-release system should be "programmed" in accordance with the variation in pH of the different segments of the gastrointestinal (GI) tract so that the amount of preferentially absorbed species, and thus the plasma level of drug, will be approximately constant throughout the time course of drug action.

In general, extremes in the aqueous solubility of a drug are undesirable for formulation into a sustained-release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. In most instances, formulation of such a drug into a sustained-release system is redundant. Even if a poorly soluble drug was considered as a candidate for formulation into a sustained-release system, a restraint would be placed upon the type of delivery system which could be used. For example, any system relying upon diffusion of drug through a polymer as the rate-limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is the concentration of drug in the polymer or solution and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it often is quite difficult to decrease its dissolution rate and slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is, however, one possible method for preparing sustained-release dosage forms. This will be elaborated upon elsewhere in this chapter.

Partition Coefficient—Between the time that a drug is administered and the time it is eliminated from the body, it must diffuse through a variety of biological membranes which act primarily as lipid-like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil/water partition coefficient, defined as

$$K = C_0/C_w \qquad (11)$$

where C_0 is the equilibrium concentration of all forms of the drug, eg, ionized and un-ionized, in an organic phase at equilibrium, and C_w is the equilibrium concentration of all forms in an aqueous phase. A frequently used solvent for the organic phase is 1-octanol. Although not always valid, an approximation to the value of K may be obtained by the ratio of the solubility of the drug in 1-octanol to that in water. In general, drugs with extremely large values of K are very oil-soluble and will partition into membranes quite readily. The relationship between tissue permeation and partition coefficient for the drug generally is known as the *Hansch correlation*, discussed in Chapter 28. In general, it describes a parabolic relationship between the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient for a series of drugs as shown in Fig 5. The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor; as a first approximation, the more effectively a drug crosses membranes, the greater its activity. There is also an optimum partition coefficient for a drug at which it most effectively permeates membranes and thus shows greatest activity. Values of the partition coefficient below this optimum result in decreased lipid solubility, and the drug will remain localized in the first aqueous phase it contacts. Values larger than the optimum result in poorer aqueous solubility, but enhanced lipid solubility and the drug will not partition out of the lipid membrane once it gets in. The value of K at which optimum activity is observed is approximately 1000/1 in 1-octanol/

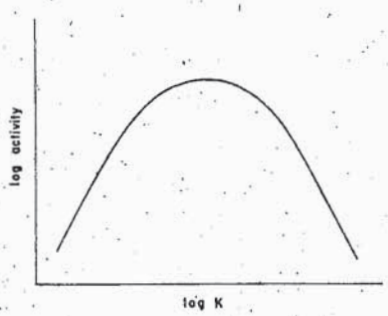


Fig 5. Typical relationship between drug activity and partition coefficient, K, generally known as the Hansch correlation.

lower than the optimum are, in general, poorer candidates for formulation into sustained-release dosage forms.

Drug Stability—Of importance for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug in the solid state undergoes degradation at a much slower rate than a drug in suspension or solution, it would seem possible to improve significantly the relative bioavailability of a drug, which is unstable in the GI tract, by placing it in a slowly available sustained-release form. For those drugs that are unstable in the stomach, the most appropriate sustaining unit would be one that releases its contents only in the intestine. The reverse is the case for those drugs that are unstable in the environment of the intestine; the most appropriate sustaining unit in this case would be one that releases its contents only in the stomach. However, most sustained-release systems currently in use release their contents over the entire length of the GI tract. Thus, drugs with significant stability problems in any particular area of the GI tract are less suitable for formulation into sustained-release systems that deliver their contents uniformly over the length of the GI tract. Delivery systems that remain localized in a certain area of the GI tract eg, bioadhesive drug delivery system, and act as reservoirs for drug release are much more advantageous for drugs that not only suffer from stability problems but have other bioavailability problems as well. Development of this type of system is still in its infancy.

The presence of metabolizing enzymes at the site of absorption is not necessarily a negative factor in sustained-release formulation. Indeed, the prodrug approach to drug delivery takes advantage of the presence of these enzymes to regenerate the parent molecule of an inactive drug derivative. This will be amplified upon below and in Chapter 28.

Protein Binding

Chapters 14 and 43 described the occurrence of drug binding to plasma proteins (eg, albumin) and the resulting retention of drug in the vascular space. Distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug–protein complex can serve therefore as a reservoir in the vascular space for sustained drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus, the protein binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug, and such drugs generally do not require a sustained-release dosage form. However, drugs that exhibit a high degree of binding to plasma proteins also might bind to biopolymers in the GI tract, which could have an influence on sustained-drug delivery.

The main forces of attraction responsible for binding are van der Waals forces, hydrogen bonding and electrostatic forces. In general, charged compounds have a greater tendency to bind a protein than uncharged compounds, due to Some drugs that exhibit greater than 95% binding at therapeutic levels are amitriptyline, bishydroxycoumarin, diazepam, diazoxide, dicumarol and novobiocin.

Molecular Size and Diffusivity—As previously discussed, a drug must diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes, drugs in many sustained-release systems must diffuse through a rate-controlling membrane or matrix. The ability of a drug to diffuse through membranes, its so called diffusivity (diffusion coefficient), is a function of its molecular size (or molecular weight). An important influence upon the value of the diffusivity, D, in polymers is the molecular size (or molecular weight) of the diffusing species. In most polymers, it is possible to relate $\log D$ empirically to some function of molecular size, as shown in Eq 12:[4]

$$\log D = -s_v \log v + k_v = -s_M \log M + k_m \qquad (12)$$

where v is molecular volume, M is molecular weight and s_v, s_M, k_v and k_m are constants. The value of D thus is related to the size and shape of the cavities as well as size and shape of drugs. Generally, values of the diffusion coefficient for intermediate-molecular-weight drugs, ie, 150 to 400, through flexible polymers range from 10^{-6} to 10^{-9} cm^2/sec, with values on the order of 10^{-8} being most common.[5] A value of approximately 10^{-6} is typical for these drugs through water as the medium. It is of interest to note that the value of D for one gas in another is on the order of 10^{-1} cm^2/sec, and for one liquid through another, 10^{-5} cm^2/sec. For drugs with a molecular weight greater than 500, the diffusion coefficients in many polymers frequently are so small that they are difficult to quantify, ie, less than 10^{-12} cm^2/sec. Thus, high-molecular-weight drugs and/or polymeric drugs should be expected to display very slow-release kinetics in sustained-release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.

Biological Properties

Absorption—The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into a sustained-release system. Since the rate-limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of the drug relative to its release is essential if the system is to be successful. As stated previously in discussing terminology, $k_r \ll k_a$. This becomes most critical in the case of oral administration. Assuming that the transit time of a drug through the absorptive area of the GI tract is between 9 and 12 hours, the maximum absorption half-life should be 3 to 4 hours.[6] This corresponds to a minimum absorption rate constant k_a of 0.17 hr^{-1} to 0.23 hr^{-1} necessary for about 80 to 95% absorption over a 9- to 12-hour transit time. For a drug with a very rapid rate of absorption (ie, $k_a \gg 0.23$ hr^{-1}), the above discussion implies that a first-order release-rate constant k_r less than 0.17 hr^{-1} is likely to result in unacceptably poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into sustained-release systems where the criterion that $k_r \ll k_a$ must be met.

The extent and uniformity of the absorption of a drug, as reflected by its bioavailability and the fraction of the total dose absorbed, may be quite low for a variety of reasons. This usually is not a prohibitive factor in its formulation into a sustained-release system. Some possible reasons for a low extent of absorption are poor water solubility, small partition coefficient, acid hydrolysis and metabolism, or site-specific absorption. The latter reason also is responsible for nonuniformity of absorption. Many of these problems can be overcome by an appropriately designed sustained-release system, as exemplified by the discussion under the potential advantages of sustained drug therapy.

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