Remington: The Science and Practice of Pharmacy

Volume II

AUROBINDO EX1018, 1

19TH
EDITION

Remington: Practice of

ALFONSO R GENNARO
Chairman of the Editorial Board
and Editor

AUROBINDO EX1018, 2

The Science and Pharmacy

1995

MACK PUBLISHING COMPANY
Easton, Pennsylvania 18042

AUROBINDO EX1018, 3

Entered according to Act of Congress, in the year 1885 by Joseph P Remington,
in the Office of the Librarian of Congress, at Washington DC

Copyright 1889, 1894, 1905, 1907,1917, by Joseph P Remington

Copyright 1926, 1936, by the Joseph P Remington Estate

Copyright 1948, 1951, by The Philadelphia College of Pharmacy and Science

Copyright 1956, 1960, 1965, 1970, 1975, 1980, 1985, 1990, 1995, by The Philadelphia College of Pharmacy and Science

All Rights Reserved

Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

The use of structural formulas from USAN and the USP Dictionary of Drug Names is by permission of The USP Convention. The Convention is not responsible for any inaccuracy contained herein.

NOTICE—This text is not intended to represent, nor shall it be interpreted to be, the equivalent of or a substitute for the official United States Pharmacopeia (USP) and/or the National Formulary (NF). In the event of any difference or discrepancy between the current official USP or NF standards of strength, quality, purity, packaging and labeling for drugs and representations of them herein, the context and effect of the official compendia shall prevail.

Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

AUROBINDO EX1018, 4

CHAPTER 94

Sustained-Release Drug Delivery Systems

Charles S L Chiao, PhD
Anda SR Pharmaceuticals, Inc
Davie, FL 33314

Joseph R Robinson, PhD
Professor of Pharmacy
School of Pharmacy
University of Wisconsin
Madison, WI 53706

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:

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

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

AUROBINDO EX1018, 5

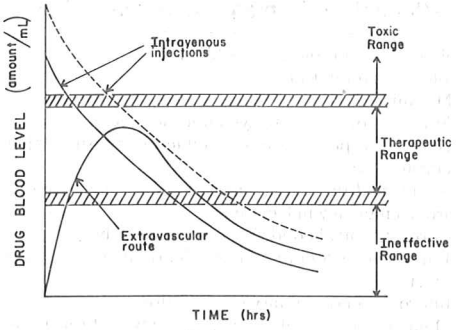

Fig 1. Typical drug blood level versus time profiles for intravenous injections and an extravascular route of administration.

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.

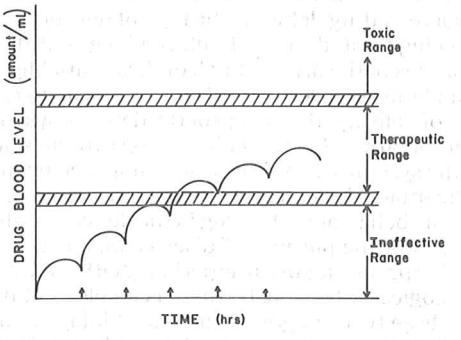

Fig 2. Typical drug blood level versus time profile following oral multiple-dose therapy.

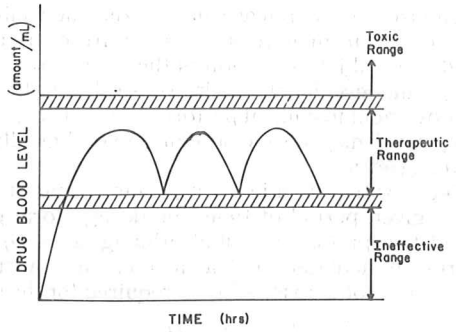

Fig 3. Typical drug blood level versus time profiles for delayed-release drug delivery by a repeat-action dosage form.

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-

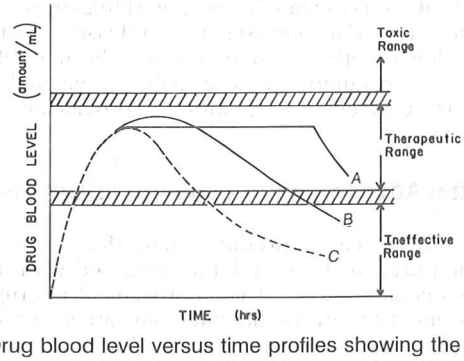

Fig 4. Drug blood level versus time profiles showing the relationship between controlled-release (*A*), prolonged-release (*B*) and conventional-release (*C*) drug delivery.

AUROBINDO EX1018, 6

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

$$W = D_i + D_m \tag{2}$$

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

$$W = D_i + k_r^0 T_d \tag{3}$$

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:

$$W = D_i + k_r^0 T_d - k_r^0 T_p \tag{4}$$

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

$$W = D_i + (k_e C_d / k_r) V_d \tag{5}$$

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

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

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 important component in the success of all self-administered 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.

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

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.

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. For purposes of this discussion, however, those attributes that

AUROBINDO EX1018, 7

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

$$dC/dt = k_D A C_s \tag{7}$$

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

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

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

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

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 ratio of the total solubility of the weak acid aspirin in the blood and gastric fluid:

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

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

$$K = C_0/C_w \tag{11}$$

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/water. Drugs with a partition coefficient that is higher or

AUROBINDO EX1018, 8

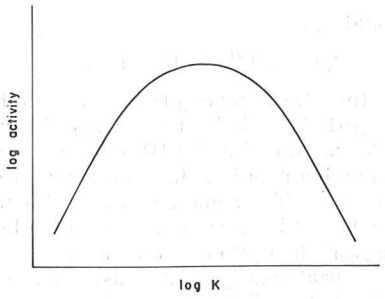

Fig 5. Typical relationship between drug activity and partition coefficient, *K*, generally known as the Hansch correlation.

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 bind ing 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 electrostatic effects. The presence of a hydrophobic moiety on the drug molecule also increases its binding potential. 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, $k_r <<< k_a$. 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 $k_r <<< k_a$ 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.

Distribution—For the design of sustained-release systems it is desirable to have as much information as possible

AUROBINDO EX1018, 9

regarding drug disposition, but in actual practice decisions usually are based on only a few pharmacokinetic parameters, one of which is the volume of distribution as given in Eq 1. The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. This, in turn, influences the formulation of that drug into a sustained-release system, primarily by restricting the magnitude of the release rate and the dose size which can be employed.[5] At present, the calculation of these quantities is based primarily on one-compartment pharmacokinetic models as described under terminology. A description of the estimation of these quantities based on multicompartment models is beyond the scope of this chapter. However, the main considerations that need to be dealt with if a two-compartment model is operative will be presented.

Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in tissue to that in plasma at the steady state, the so-called T/P ratio. The apparent volume of distribution is merely a proportionality constant which relates drug concentration in the blood or plasma to the total amount of drug in the body. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug dosing regimen and hence the need to employ sustained-release system. For drugs which obey a one-compartment model, the apparent volume of distribution is

$$V = \text{dose}/C_0 \tag{13}$$

where C_0 is the initial drug concentration immediately after an intravenous bolus injection, but before any drug has been eliminated. The application of this equation is based upon the assumption that the distribution of a drug between plasma and tissues takes place instantaneously. This is rarely a good assumption, and it usually is necessary to invoke multicompartment models to account for the finite time required for the drug to distribute fully throughout the available body space. In the case of a two-compartment model, it has been shown[7] that the best estimate of total volume of drug distribution is given by the apparent volume of distribution at steady state:

$$V_{ss} = (1 + k_{12}/k_{21})V_1 \tag{14}$$

where V_1 is the volume of the central compartment, k_{12} is the rate constant for distribution of drug from the central to the peripheral compartment and k_{21} is that from the peripheral to the central compartment. As its name implies, V_{ss} relates drug concentration in the blood or plasma at the steady state to the total amount of drug in the body during repetitive dosing or constant-rate infusion. The use of Eq 14 is limited to those instances where a steady-state drug concentration in both compartments has been reached; at any other time, it tends to overestimate or underestimate the total amount of drug in the body.

To avoid the ambiguity inherent in the apparent volume of distribution as an estimator of the amount of drug in the body, the T/P ratio also can be used. If the amount of drug in the central compartment, P, is known, the amount of drug in the peripheral compartment, T, and hence the total amount of drug in the body can be calculated[5] by

$$T/P = k_{12}(k_{21} - \beta) \tag{15}$$

Here, β is the slow disposition rate constant and k_{12} and k_{21} are as defined previously. The important point to note is that the T/P ratio estimates the relative distribution of drug between compartments, whereas V_{ss} estimates the extent of distribution in the body. Both parameters contribute to an estimation of the distribution characteristics of a drug, but their relative importance in this respect is open to debate.

Metabolism—The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant(s) for the process(es) are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs, however, that present problems for their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect. Examples of drugs that are subject to intestinal metabolism upon oral dosing are hydralazine, salicylamide, nitroglycerin, isoproterenol, chlorpromazine and levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetin, propranolol and lidocaine.

Elimination and Biological Half-Life—The rate of elimination of a drug is described quantitatively by its biological half-life, $t_{1/2}$. The half-life of a drug is related to its apparent volume of distribution V and its systemic clearance:

$$t_{1/2} = 0.693\ V/Cl_s = 0.693\ V\,\text{AUC/dose} \tag{16}$$

The systemic clearance, Cl_s, is equal to the ratio of an intravenously administered dose to the total area under the drug blood level versus time curve, AUC. A drug with a short half-life requires frequent dosing and this makes it a desirable candidate for a sustained-release formulation. On the other hand, a drug with a long half-life is dosed at greater time intervals and thus there is less need for a sustained-release system. It is difficult to define precise upper and lower limits for the value of the half-life of a drug that best suits it for sustained-release formulation. In general, however, a drug with a half-life of less than 2 hours probably should not be used, since such systems will require unacceptably large release rates and large doses. At the other extreme, a drug with a half-life of greater than 8 hours also probably should not be used; in most instances, formulation of such a drug into a sustained-release system is unnecessary. Some examples of drugs with half-lives of less than 2 hours are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G and propylthiouracil. Examples of those with half-lives of greater than 8 hours are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin and warfarin.

Side Effects and Safety Considerations—There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration *range* is listed, with increasing toxic effects expected above this range and a falloff in desired therapeutic response observed below the range. For some drugs, the incidence of side effects, in addition to toxicity, is believed to be a function of plasma concentration.[8] As mentioned in the discussion on the potential advantages of sustained drug therapy, a sustained-release system can, at times, minimize side effects for a particular drug by controlling its plasma concentration and using less total drug over the time course of therapy.

The most widely used measure of the margin of safety of a drug is its therapeutic index, TI, discussed in Chapter 41 and defined in the following equation:

$$\text{TI} = \text{TD}_{50}/\text{ED}_{50} \tag{17}$$

where TD_{50} is the median toxic dose and ED_{50} is the median effective dose. The value of TI varies from as little as unity, where the effective dose is also producing toxic symptoms, to several thousand. For very "potent" drugs, whose therapeutic concentration range is narrow, the value of TI is small. In general, the larger the value of TI, the safer the drug. Drugs with very small values of TI usually are poor candidates for formulation into sustained-release products primarily due to technological limitations of precise control over release rates. A drug is considered to be relatively safe if its *TI* value exceeds 10. Examples of drugs with values of TI < 10 are aprobarbital, digitoxin, phenobarbital and digoxin.

Dose Size —Since a sustained-release system is designed to alleviate repetitive dosing, it naturally will contain a greater amount of drug than a corresponding conventional form. The typical administered dose of a drug in the conventional

AUROBINDO EX1018, 10

dosage form will give some indication of the total amount needed in the sustained-release preparation. For those drugs requiring large conventional doses, the volume of the sustained dose may be so large as to be impractical or unacceptable, depending on the route of administration. The same may be true of drugs which require a large release rate from the sustained-release system, eg, drugs with short half-lives. For the oral route the volume of the product is limited by patient acceptance. For the intramuscular, intravenous or subcutaneous routes, the limitation is tolerance of the drug at the injection site. It also should be mentioned that for drugs with a low therapeutic index, incorporation of amounts greater than the TD_{50} potentially may be dangerous if the system fails.

Oral Dosage Forms

For sustained-release systems, the oral route of administration has, by far, received the most attention. This is, in part, because there is more flexibility in dosage-form design for the oral route than there is for the parenteral route. Patient acceptance of the oral route is quite high. It is a relatively safe route of administration, compared to most parenteral routes, and the constraints of sterility and potential damage at the site of administration are minimal. In this section, the more common methods that are used to achieve sustained release of orally administered drugs are discussed.

Diffusion Systems

In these systems, the release rate of drug is determined by its diffusion through a water-insoluble polymer. There are basically two types of diffusion devices: *reservoir devices*, in which a core of drug is surrounded by a polymeric membrane, and *matrix devices*, in which dissolved or dispersed drug is distributed uniformly in an inert polymeric matrix. It should be mentioned that in actual practice many devices which use diffusion also rely upon some degree of dissolution to determine the release rate. Systems using dissolution will be discussed later in this section.

Reservoir Devices—The release of drug from a reservoir device is governed by Fick's first law of diffusion:

$$J = -D\, dC_m/dx \qquad (18)$$

where J is the flux of drug across a membrane in the direction of decreasing concentration (amount/area-time), D is the diffusion coefficient of the drug in the membrane (area/time) and dC_m/dx is the change in concentration of drug in the membrane over a distance x. If it is assumed that the drug on either side of the membrane is in equilibrium with the respective surface layer of the membrane, as shown in Fig 6[9], then the concentration just inside the membrane surface can be related to the concentration in the adjacent region by the expressions

$$K = C_{m(0)}/C_{(0)} \text{ at } x = 0 \qquad (19)$$

$$K = C_{m(l)}/C_{(l)} \text{ at } x = l \qquad (20)$$

where K is a partition coefficient. Assuming that D and K are constant, Eq 18 can be integrated to give

$$J = DK\Delta C/l \qquad (21)$$

where ΔC is the concentration difference across the membrane.

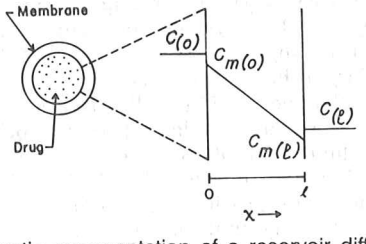

Fig 6. Schematic representation of a reservoir diffusion device. $C_{m(0)}$ and $C_{m(l)}$ represent concentrations of drug at the inside surfaces of the membrane and $C_{(0)}$ and $C_{(l)}$ represent concentrations in the adjacent regions. (Reproduced with permission.[9])

If the activity of the drug inside the reservoir is maintained constant and the value of K is less than unity, zero-order release can be achieved. This is the case when the drug is present as a solid, ie, its activity is unity. Depending on the shape of the device, the equation describing drug release will vary. Only the simplest geometry, that of a rectangular slab or "sandwich," will be presented here. For the slab geometry, the equation describing release is

$$dM_t/dt = ADK\Delta C/l \qquad (22)$$

where M_t is the mass of drug released after time t, dM_t/dt is the steady-state release rate at time t, A is the surface area of the device and D, K and l are as defined previously. Similar equations can be written for cylindrical or spherical geometric devices. In order to obtain a constant drug-release rate, it is necessary to maintain constant area, diffusion path length, concentration and diffusion coefficient. In other words, all of the terms on the right hand side of Eq 22 are held constant. This is often not the case in actual practice because one or more of the above terms will change in the product, thus nonzero-order release is frequently observed.

Common methods used to develop reservoir-type devices include microencapsulation of drug particles and press-coating of tablets containing drug cores. In most cases, particles coated by microencapsulation form a system where the drug is contained in the coating film as well as in the core of the microcapsule. Drug release usually involves a combination of dissolution and diffusion, with dissolution being the process that controls the release rate. If the encapsulating material is selected properly, diffusion will be the controlling process. Microencapsulation is discussed further with reference to systems using dissolution. Some materials used as the membrane barrier coat, alone or in combination, are hardened gelatin, methyl or ethylcelluloses, polyhydroxymethacrylate, hydroxypropylcellulose, polyvinylacetate and various waxes. Examples of some marketed products using an encapsulated reservoir of drug are shown in Table 2. Drug release from these products probably is based primarily on diffusion, but dissolution may be occurring as well.

Matrix Devices—The rate of release of a drug dispersed as a solid in an inert matrix has been described by Higuchi.[10,11] Figure 7 depicts the physical model for a planar slab. In this model, it is assumed that solid drug dissolves from the surface layer of the device first; when this layer becomes exhausted of drug, the next layer begins to be depleted by dissolution and diffusion through the matrix to the external solution. In this fashion, the interface between the region containing dissolved drug and that containing dispersed drug moves into the inte-

Table 2—Reservoir Diffusion Products

Product	Active ingredient(s)	Manufacturer
Plateau CAPS capsules		
Nico-400	Nicotinic acid	Jones
Nitro-Bid	Nitroglycerin	Marion
Cerespan capsules	Papaverine hydrochloride	Rhone-Poulenc Rorer
Histaspan capsules	Chlorpheniramine maleate, phenylephrine hydrochloride, methscopolamine nitrate	Rhone-Poulenc Rorer
Nitrospan capsules	Nitroglycerin	Rhone-Poulenc Rorer
Measurin tablets	Acetylsalicylic acid	Sanofi-Winthrop
Bronkodyl S-R capsules	Theophylline	Sanofi-Winthrop

AUROBINDO EX1018, 11

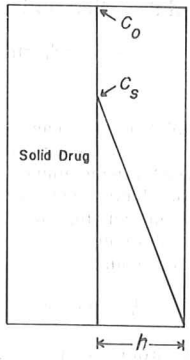

Fig 7. Schematic representation of the physical model used for a planar slab matrix diffusion device.

rior as a front. The assumptions made in deriving the mathematical model are as follows:

1. A pseudo-steady state is maintained during release.
2. The total amount of drug present per unit volume in the matrix, C_0, is substantially greater than the saturation solubility of the drug per unit volume in the matrix, C_s, ie, excess solute is present.
3. The release medium is a perfect sink at all times.
4. Drug particles are much smaller in diameter than the average distance of diffusion.
5. The diffusion coefficient remains constant.
6. No interaction occurs between the drug and the matrix.

Based on Fig 7, the change in amount of drug released per unit area, dM, with a change in the depleted zone thickness, dh, is

$$dM = C_0 dh - (C_s/2)dh \tag{23}$$

where C_0 and C_s are as defined above. However, based on Fick's first law

$$dM = (D_m C_s/h)dt \tag{24}$$

where D_m is the diffusion coefficient in the matrix. If Eqs 23 and 24 are equated, solved for h and that value of h substituted back into the integrated form of Eq 24, an equation for M is obtained:

$$M = [C_s D_m(2C_0 - C_s)t]^{1/2} \tag{25}$$

Similarly, a drug released from a porous or granular matrix is described by

$$M = [D_s C_a(\epsilon/T)(2C_0 - \epsilon C_a)t]^{1/2} \tag{26}$$

where ϵ is porosity of the matrix, T is *tortuosity*, C_a is the solubility of the drug in the release medium and D_s is the diffusion coefficient of drug in the release medium. In this system, drug is leached from the matrix through channels or pores.

For purposes of data treatment, Eqs 25 and 26 are conveniently reduced to

$$M = kt^{1/2} \tag{27}$$

where k is a constant, so that a plot of amount of drug released versus the square root of time should be linear if the release of the drug from the matrix is diffusion-controlled. The release rate of drug from such a device is not zero-order, since it decreases with time but, as previously mentioned, this may be clinically equivalent to constant release for many drugs.

The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers and fatty compounds. Plastic matrices which have been investigated include methyl acrylate–methyl methacrylate, polyvinyl chloride and polyethylene. The Gradumet tablet (*Abbott*) is an example of a dosage form using a plastic matrix. Hydrophilic polymers include methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and carbopol 934. Fatty compounds include various waxes such as carnauba wax and glyceryl tristearate. An example of a dosage form using a wax matrix is the Lontab tablet (*Ciba*).

The most common method of preparation is to mix the drug with the matrix material and then compress the mixture into tablets. In the case of wax matrices, the drug generally is dispersed in molten wax, which is then congealed, granulated and compressed into cores. In any sustained-release system it is necessary for a portion of the drug to be available immediately as a priming dose, and the remainder to be released in a sustained fashion. This is accomplished in a matrix tablet by placing the priming dose in a coat of the tablet. The coat can be applied by press coating or by conventional pan or air suspension coating. Some marketed matrix diffusion products are listed in Table 3.

Dissolution Systems

As mentioned earlier in the chapter, a drug with a slow dissolution rate will yield an inherently sustained blood level. In principle, then, it would seem possible to prepare sustained-release products by decreasing the dissolution rate of drugs which are highly water-soluble. This can be done by preparing an appropriate salt or derivative, by coating the drug with a slowly soluble material or by incorporating it into a tablet with a slowly soluble carrier. Ideally, the surface area available for dissolution must remain constant in order to achieve a constant release rate. This is, however, difficult to achieve in practice.

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. In this case the dissolution process at steady state is described by the Noyes-Whitney equation:

$$dC/dt = k_D A(C_s - C) = (D/h)A(C_s - C) \tag{28}$$

where dC/dt is the dissolution rate, k_D is the dissolution rate constant, A is the total surface area, C_s is the saturation solubility of the solid and C is the concentration of solute in the bulk solution. The dissolution-rate constant, k_D, is equal to the diffusion coefficient, D, divided by the thickness of the diffusion layer, h. The above equation predicts a constant dissolution rate if the surface area, diffusion coefficient, diffusion layer thickness and concentration difference are kept constant. However, as dissolution proceeds, all of these parameters may change, especially surface area. For spherical particles, the change in area can be related to the weight of the particle and, under the assumption of sink conditions, Eq 28 becomes the cube-root dissolution equation

$$w_0^{1/3} - w^{1/3} = k_D' t \tag{29}$$

where k_D' is the cube-root dissolution-rate constant, and w_0 and w are initial weight and weight of the amount remaining at time t, respectively.

Two common formulations relying on dissolution to determine release rate of drug are shown in Fig 8. Most of the products fall into two categories: encapsulated dissolution systems and matrix dissolution systems.

Table 3—Matrix Diffusion Products

Product	Active ingredient(s)	Manufacturer
Gradumet tablets		Abbott
Desoxyn	Methamphetamine HCl	
Fero-Gradumet	Ferrous sulfate	
Fero-Grad-500	Ferrous sulfate, sodium ascorbate	
Tral	Hexocyclium methylsulfate	
Lontab tablets		Ciba
PBZ-SR	Tripelennamine HCl	
Procan SR tablets	Procainamide HCl	Parke-Davis
Choledyl SA tablets	Oxtriphylline	Parke-Davis

AUROBINDO EX1018, 12

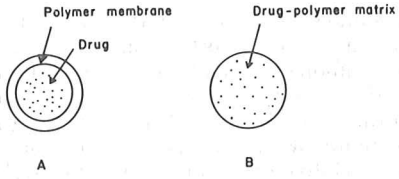

Fig 8. Schematic representation of systems using dissolution. A, encapsulated formulation where drug release is determined by thickness and dissolution rate of the polymer membrane; B, matrix formulation where drug release is determined by dissolution rate of the polymer.

Encapsulated dissolution systems can be prepared either by coating particles or granules of drug with varying thicknesses of slowly soluble polymers or by microencapsulation. Microencapsulation can be accomplished by using phase separation, interfacial polymerization, heat-fusion or the solvent-evaporation method. The coating materials may be selected from a wide variety of natural and synthetic polymers, depending on the drug to be coated and the release characteristics desired. The most commonly used coating materials include gelatin, carnauba wax, shellacs, ethylcellulose, cellulose acetate phthalate or cellulose acetate butyrate. Drug release from microcapsules, is a mass-transport phenomenon; and can be controlled by adjusting the size of microcapsules, thickness of coating materials and the diffusivity of core materials. The coating thickness of microcapsules is normally very thin, and for a given coating-core ratio, it decreases rapidly as the microcapsule size decreases. The thickness can be varied from less than 1 μm to 200 μm by changing the amount of coating material from 3 to 30% of the total weight. If only a few different thicknesses are used, usually three or four, drugs will be released at different, predetermined times to give a delayed release effect, ie, repeat-action. If a spectrum of different thicknesses is employed, a more uniform blood level of the drug can be obtained. Microcapsules commonly are filled into capsules and rarely are tableted as their coatings tend to disrupt during compression. A partial listing of some marketed sustained-release products relying primarily on encapsulated dissolution are shown in Table 4.

Matrix dissolution devices are prepared by compressing the drug with a slowly soluble polymer carrier into a tablet form. There are two general methods of preparing drug–wax particles: congealing and aqueous dispersion methods. In the congealing method, drug is mixed with a wax material and either spray-congealed or congealed and screened. In the aqueous dispersion method, the drug–wax mixture simply is sprayed or placed in water and the resulting particles are collected. Matrix tablets also are made by direct compression of a mixture of drug, polymer and excipients. Examples of marketed products relying primarily on matrix dissolution are listed in Table 5.

Table 4—Encapsulated Dissolution Products

Product	Active ingredient(s)	Manufacturer
Spansule capsules		SmithKline Beecham
Dexedrine	Dextroamphetamine sulfate	
Hispril	Diphenylpyraline HCl	
Ornade	Phenylpropanolamine HCl, chlorpheniramine maleate	
Thorazine	Chlorpromazine HCl	
Contac capsules	Phenylpropanolamine HCl, chlorpheniramine maleate	SmithKline Beecham
Sequel capsules		Lederle
Artane	Trihexyphenidyl HCl	
Diamox	Acetazolamide	
Ferro-sequels	Ferrous fumarate, docusate sodium	

Table 5—Matrix Dissolution Products

Product	Active ingredient(s)	Manufacturer
Extentab tablets		Robins
Dimetane	Brompheniramine maleate	
Dimetapp	Brompheniramine maleate, phenylpropanolamine HCl	
Donnatal	Phenobarbital, hyoscamine sulfate, atropine sulfate, scopolamine hydrobromide	
Quinidex	Quinidine sulfate	
Timespan tablets		Roche
Mestinon	Pyridostigmine bromide	
Dospan tablets		Lakeside
Tenuate	Diethylpropion HCl	
Chronotab tablets		Schering
Disophrol	Dexbrompheniramine maleate, pseudoephedrine sulfate	
Tempule capsules		Rhone-Poulenc Rorer
Nicobid	Nicotinic acid	
Pentritol	Pentaerythritol tetranitrate	
Repetab tablets		Schering
Chlor-trimeton	Chlorpheniramine maleate	
Demazin	Chlorpheniramine maleate, phenylephrine HCl	
Polaramine	Dexchlorpheniramine maleate	
Trilafon	Perphenazine	

Osmotic Systems

Osmotic pressure can be employed as the driving force to generate a constant release of drug provided a constant osmotic pressure is maintained and a few other features of the physical system are constrained. Consider a tablet consisting of a core of an osmotically active drug, or a core of an osmotically inactive drug, in combination with an osmotically active salt surrounded by a semipermeable membrane containing a small orifice, as shown in Fig 9. The membrane will allow free diffusion of water, but not drug. When the tablet is exposed to water or any fluid in the body, water will flow into the tablet due to osmotic pressure difference and the volume flow rate, dV/dt, of water into the tablet is

$$dV/dt = (kA/h)(\Delta\pi - \Delta P) \qquad (30)$$

where k, A and h are the membrane permeability, area and thickness, respectively, $\Delta\pi$ is the osmotic pressure difference and ΔP is the hydrostatic pressure difference. If the orifice is sufficiently large, the hydrostatic pressure difference will be small compared to the osmotic pressure difference, and Eq 30 becomes

$$dV/dt = (kA/h)\Delta\pi \qquad (31)$$

Thus, the volume flow rate of water into the tablet is determined by permeability, area and thickness of the membrane. The drug will be pumped out of the tablet through the orifice at a controlled rate, dM/dt, equal to the volume flow rate of water into the tablet multiplied by the drug concentration, C_s:

$$dM/dt = (dV/dt)C_s \qquad (32)$$

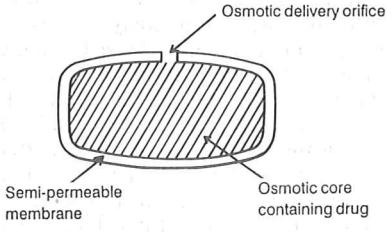

Fig 9. Schematic diagram of an osmotic tablet. (Reproduced with permission.[12])

AUROBINDO EX1018, 13

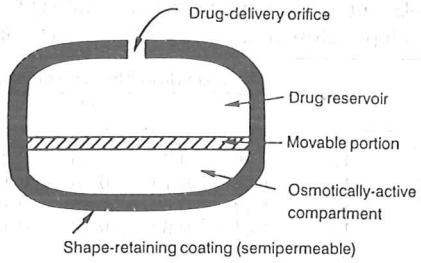

Fig 10. Osmotic pressure-controlled drug-delivery system with two compartments separated by a movable partition.[13]

The release rate will be constant until the concentration of drug inside the tablet falls below saturation.

Several modifications of the osmotic pressure-controlled drug delivery system have been developed. A layer of bioerodible polymer can be applied to the external surface of the semipermeable membrane. A system consists of two compartments separated by a movable partition, as shown in Fig. 10. For a system that does not have an orifice, hydraulic pressure is built up inside as the GI fluid is imbibed until the wall ruptures and the contents are released to the environment.

The advantage of the osmotic system is that it requires only osmotic pressure to be effective and is essentially independent of the environment. The drug release rate can be predetermined precisely regardless of pH change through the GI tract. Some materials used as the semipermeable membrane include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose and polyvinyl chloride. Drugs that have demonstrated successful release rates from an osmotic system *in vivo* after oral dosing are potassium chloride and acetazolamide.

Ion-Exchange Resins

Ion-exchange resins are water-insoluble crosslinked polymers containing salt forming groups in repeating positions on the polymer chain. Drug is bound to the resin by repeated exposure of the resin to the drug in a chromatographic column, or by prolonged contact of the resin with the drug solution. The drug-resin then is washed to remove contaminating ions and dried to form particles or beads. Drug release from the drug–resin complex depends on the ionic environment, ie, pH and electrolyte concentration, within the GI tract as well as properties of the resin.

Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GI tract, as shown in Fig 11, followed by diffusion of the free drug molecule out of the resin. The rate of diffusion is controlled by the area of diffusion, diffusional pathlength and extent of crosslinking in the resin. A modification of the release rate can be made by coating the drug–resin complex. Further improvement of this ion-exchange type drug delivery system is called the Penn Kinetic system. In this system, the drug-containing resin granules first are treated with an impregnating polymer such as PEG 4000 to retard the rate of swelling in water and further coated with a water-insoluble polymer, such as ethylcellulose, to serve as a rate-limiting barrier to control the drug release.

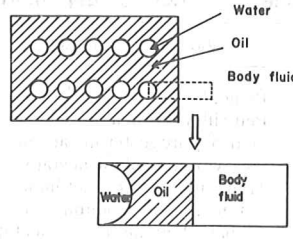

Fig 11. Schematic of drug release from ion-exchange resin.

Most ion-exchange resins currently employed in sustained-release products contain sulfonic acid groups that exchange cationic drugs such as those with an amine functionality. Examples of some of these drugs are amphetamine, phenyl *t*-butylamine (phentermine), phenyltoloxamine and hydrocodone, as shown in Table 6.

Prodrugs

A prodrug is a compound formed by chemical modification of a biologically active compound which will liberate the active compound *in vivo* by enzymatic or hydrolytic cleavage. The primary purpose of employing a prodrug for oral administration is to increase intestinal absorption or to reduce local side effects, such as GI irritation by aspirin. On this basis, one generally does not classify a prodrug as a sustained-release dosage form. However, the ability to bio-reversibly modify the physicochemical properties of a drug allows better intestinal transport properties and hence influences the drug blood level versus time profile. Thus, prodrugs can be used to increase the strategies for sustained release and, in a limited sense, can be sustaining in their own right.

As an example of the use of a prodrug as a sustaining mechanism, consider a water-soluble drug which is modified to a water-insoluble prodrug. The prodrug will have a slower dissolution rate in an aqueous medium than the parent drug and, thus, the appearance of the parent drug in plasma will be slowed. This is observed with theophylline and its prodrug, 7,7′-succinylditheophylline. Alternatively, a water-soluble prodrug of a water-insoluble parent drug can be made to be a substrate for enzymes in the brush border region of the microvilli. The water-soluble prodrug complexes with the enzyme just prior to reaching the membrane surface, is metabolized and its membrane/water partition coefficient increases. The result is an increase in the blood level of the drug. See Chapter 28.

Parenteral Dosage Forms

The most common types of dosage forms used for parenteral sustained-release drug therapy are intramuscular (IM) injections, implants for subcutaneous tissues and various body cavities and transdermal devices. Due to physiological and anatomical constraints, many of the other parenteral routes of administration, eg, intravenous, intra-arterial, intrathecal and intraperitoneal, are not as useful in this regard. The application of the former three types of dosage forms to sustained-release drug delivery will be discussed in this section. The final section is devoted to other parenteral dosage forms being developed for targeted drug delivery.

Intramuscular Injections

Aqueous Solutions—It is conceivable and likely that increased viscosity of the medium not only decreases molecular diffusion but also localizes the injected volume. Thus, the absorptive area is reduced and the rate of drug release is controlled. Examples of thickening agents are methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone.

Complex Formation—The formation of a dissociable complex of a drug with a macromolecule is the same physicochemi-

Table 6—Ion-Exchange Products

Product	Active ingredient(s)	Manufacturer
Biphetamine capsules	Amphetamine, dextroamphetamine	Pennwalt
Tussionex capsules, tablets, suspension	Hydrocodone, chlorpheniramine	Pennwalt
Ionamin capsules	Phentermine	Pennwalt

AUROBINDO EX1018, 14

cal phenomenon which occurs when a drug binds to a plasma protein. In this sense, the drug–macromolecule complex can serve as a reservoir at the site of injection for sustained drug release to the surrounding tissues. The macromolecules used are either biological polymers, such as antibodies and proteins, or synthetic polymers, such as methylcellulose, sodium carboxymethyl-cellulose or polyvinylpyrrolidone. Drug release from the polymer is governed by the degree of association, as given by

$$D + P \overset{K_a}{\rightleftharpoons} DP \tag{33}$$

where D, P and DP represent drug, polymer and complex, respectively, and K_a is the apparent association constant. Only that fraction of the drug which is free, f, can be absorbed:

$$f = \frac{(D)}{(DP) + (D)} = \frac{1}{1 + K_a(P)} \tag{34}$$

where (D), (P) and (DP) are equilibrium concentrations of drug, polymer and complex, respectively. If $K_a(P)$ is much greater than 1, Eq 34 reduces to

$$f = 1/[K_a(P)] \tag{35}$$

The rate of absorption of the drug, $d(C)/dt$, therefore is described by

$$d(C)/dt = k_a f(D_t) = [k_a(D_t)]/[K_a(P)] \tag{36}$$

where (D_t) is the total drug concentration at the absorption site, ie, $(DP) + (D)$, and k_a is the absorption-rate constant. It can be seen from Eq 36 that the rate of absorption can be controlled effectively by the type and concentration of polymer used, assuming that dissociation is instantaneous compared to absorption.

Complexes also can be formed between drugs and small molecules, such as caffeine, rather than macromolecules. The motive behind formation of a drug–small molecule complex is to alter the physicochemical properties of the drug and thus affect changes in its biological disposition. Unlike macromolecular complexes, drug–small molecule complexes are capable of being absorbed. They usually have very small association constants, however, which means that most of the drug is free. This nullifies any advantage gained from alteration of properties upon complexation. If the drug molecule is large, relative to the complexing agent, the association constant will be greater and the complex more stable. This is the approach that has been taken commercially with polypeptide hormones, such as adrenocorticotropic hormone (ACTH) and insulin, and with vitamins such as cyanocobalamin (vitamin B_{12}). The ACTH product, Acthar Gel HP (*Arcum*) consists of an ACTH–zinc tannate complex suspended in a gelatin solution. Tannic acid acts as the complexing agent and gelatin inhibits protein binding of ACTH. With this product, the sustained effect is due to, among other things, a reduction in solubility of the parent drug upon complexation, and not dissociation. In this respect they are much like aqueous suspensions.

Aqueous Suspensions—The rate-limiting step in drug release from an aqueous suspension is dissolution, as given by the Noyes-Whitney equation (Eq 28). The parameters influencing dissolution rate were shown to be surface area (ie, particle size), diffusion coefficient and saturation solubility of the drug. Variation in these parameters for an intramuscular injection is limited by the constraints of stability, occlusion of needles, pain upon injection, minimum effective concentration and other factors. For example, one common approach to decrease dissolution rate is to decrease total surface area by increasing particle size. This generally extends the duration of action of the drug, as illustrated by the data in Table 7.[14] However, increasing the particle size causes an increase in sedimentation rate, as indicated by Stoke's law, resulting in an unstable suspension. In addition, for some drugs there is an upper limit on particle size beyond which therapeutic levels are not attained even though sustained release is achieved.

Table 7—Effect of Particle Size of Penicillin G Procaine in Aqueous Suspension on the Drug Blood Levels in Rabbits[a]

Particle size[b] (μm)	Average drug blood level (hr)					
	1	4	24	28	48	72
150–250	1.37	1.29	0.82	0.86	0.31	0.12
105–150	1.24	1.50	0.76	0.28	0.16	0.01
58–105	1.54	1.44	0.47	0.25	0.12	—
35–38	1.64	1.51	0.62	0.33	0.15	—
<35	2.40	2.36	0.33	0.16	0.07	—
1–2	2.14	2.22	0.06	0.02	—	—

[a] Compiled from data by Buckwalter and Dickison.[14]
[b] Each aqueous suspension contains 300,000 units/mL of penicillin G procaine with the specified particle-size range.

Another approach to decrease dissolution rate is to decrease the diffusion coefficient by increasing the viscosity of the suspension. For example, injectable nalbuphine HCl suspension containing methylcellulose was found to have prolonged action in dogs compared to a true solution.[15] Recall that the diffusion coefficient is related inversely to viscosity by the Stokes-Einstein relation. An increase in viscosity causes a decrease in sedimentation rate (again by Stoke's law), thus countering the effect of increased particle size. By appropriately varying viscosity and particle size, a stable suspension, that offers sustained release resulting in therapeutic drug blood levels, can be produced.

Probably the most common approach to decrease dissolution rate is to decrease the saturation-solubility of the drug. This is accomplished through the formation of less-soluble salts or prodrug derivatives or by employing polymorphic crystal forms. A typical example of decreasing dissolution rate through salt formation is provided by penicillin G procaine, a sparingly soluble form of penicillin G. Other examples of marketed aqueous suspensions based upon use of less-soluble salts or derivatives of the parent drug are contained in Table 8.

Solubility varies with polymorphic form because different arrangements of molecules in the solid state give rise to different lattice energies. An example of extending duration of action by use of a crystalline polymorph is insulin zinc suspension. Although insulin normally is administered subcutaneously, it is included here merely to illustrate the principle. Insulin precipitates as an insoluble complex in the presence of zinc chloride and, depending on the pH, either an amorphous or crystalline form results. The crystalline form is less soluble than the amorphous form and will result in a longer duration of action than the amorphous form. The two forms can be mixed in various proportions to generate products offering a wide spectrum of duration of action. A list of these products and their reported durations of action is shown in Table 9.[16]

Oil Solutions and Oil Suspensions—In the case of oil solutions the release rate of a drug is determined by partitioning of the drug out of the oil into the surrounding aqueous medium. The partitioning phenomenon is an equilibrium process described by the apparent oil/water partition coefficient given in Eq 11. Only that fractional concentration of

Table 8—Aqueous Suspensions

Product	Active ingredient(s)	Manufacturer
Crysticillin A.S.	Penicillin G procaine	Apothecon
Wycillin	Penicillin G procaine	Wyeth–Ayerst
Depo-Provera	Medroxyprogesterone acetate	Upjohn
Depo-Medrol	Methylprednisolone acetate	Upjohn
Aristospan	Triamcinolone hexacetonide	Lederle
Celeston Soluspan	Betamethasone sodium phosphate, betamethasone acetate	Schering

AUROBINDO EX1018, 15

Table 9—Commercial Insulin Zinc Suspensions and their Reported Durations of Action[a]

Product	Manufacturer	Duration of action (hr)
Semilente Iletin I	Lilly	12–16
Lente Iletin I	Lilly	24
Ultralente Iletin I	Lilly	>36

[a] Compiled from *Physicians' Desk Reference.*[16]

drug in the aqueous phase, f, is available for absorption:

$$f = (1 + \alpha)/(1 + K\alpha) \quad (37)$$

where K is the apparent oil/water partition coefficient and α is the ratio V_0/V_w, the volume of the oil phase to that of the aqueous phase. This equation indicates that the fraction of drug that is available for absorption is controlled by the partition coefficient and the ratio of the volumes of the two phases (α), and that it remains constant so long as α is constant. Since V_w is a physiological parameter, it usually is constant, and therefore the value of α is determined solely by the volume of solution injected, V_0. The rate of drug absorption is described by an equation analogous to Eq 36:

$$d(C)/dt = k_a f(D_t) \quad (38)$$

where (D_t) is the total drug concentration in both phases. The success of an oil solution in achieving sustained release depends on the magnitude of K, which is a function of the drug involved and the oil selected. Only those drugs which are appreciably oil-soluble and have the desired partition characteristics are suitable. Some oils which may be used for intramuscular injection are sesame, olive, arachnis, maize, almond, cottonseed and castor oil. Table 10 contains a partial listing of marketed oil-solution products.

Drug release from oil suspensions combines the principles involved in aqueous suspensions and oil solutions. With the suspended particles acting as a drug reservoir, the drug particles first must dissolve in the oil phase and then partition into the aqueous medium. The concentration of drug in the oil phase remains close to its equilibrium solubility since excess solid is present, unlike an oil solution, but this has no bearing on the fractional concentration in the aqueous phase, as shown in Eq 37. As expected, the duration of action obtained from oil suspensions is longer than that from oil solutions. A list of some marketed oil-suspension products is shown in Table 11.

Emulsions—In the case where dissolved drug makes up the entire oil phase in an O/W emulsion, Higuchi[17] showed that the release rate at steady state can be described by

$$\text{rate} = 4\pi(a_0^2 + 2D\Delta Ct/d)^{1/2}D\Delta C \quad (39)$$

where a_0 is the initial radius of the droplet, D is the diffusion coefficient, ΔC is the concentration difference between the surface of the droplet and the bulk phase, d is the density of the solute and t is time. In the case where the solute makes

Table 10—Oil Solutions

Product	Active ingredient(s)	Manufacturer
Prolixin Enanthate	Fluphenazine enanthate in sesame oil	Apothecon
Prolixin Decanoate	Fuphenazine decanoate in sesame oil	Apothecon
Deca-Durabolin	Nandrolone decanoate in sesame oil	Organon
Depo-Testosterone	Testosterone cypionate in cottonseed oil	Upjohn
Ditate-DS	Testosterone enanthate, estradiol valerate in sesame oil	Savage
Delatestryl	Testosterone enanthate in sesame oil	Gynex

Table 11—Oil Suspensions

Product	Active ingredient(s)	Manufacturer
Solganal	Aurothioglucose in sesame oil	Schering

up only part of the oil phase, appropriate corrections for the distribution coefficient of solute between oil and water phases and partial molal volume of the solute in the droplet must be made.

The release rate from W/O emulsions has been treated by Windheuser *et al.*[18] The W/O emulsion is viewed as a uniform dispersion of water droplets containing the drug throughout an external oil phase. Figure 11 depicts a simplified model of the system. Drug release is assumed to proceed via diffusion through the external phase rather than by breaking of the emulsion, and the body fluid acts as a perfect sink. The rate of disappearance of drug from the aqueous phase, $d(C)/dt$, is described by

$$d(C)/dt = -k(C_0)e^{-kt} \quad (40)$$

where (C_0) is the initial concentration in the aqueous phase and k is the rate constant of disappearance of drug from the aqueous phase. The constant k is given by

$$k = ADK/Vl \quad (41)$$

where A is surface area of the droplet, D is the diffusion coefficient of the drug, K is the partition coefficient of the drug between oil and water, V is the volume of the aqueous phase and l is the effective thickness of the oil phase. For a given drug, a fast rate of release is favored by a large K, small droplets (ie, large A for a fixed V) and a phase-volume ratio favoring the oil phase.

If the body fluid is not a perfect sink, an estimate of the fraction of drug in the body fluid can be made using arguments analogous to those for the oil-solution case. Making several simplifying assumptions, an equation identical to Eq 37 is obtained. Based on this argument alone, no apparent advantage is gained by administering a W/O emulsion rather than an oil solution as far as sustained release is concerned. Similar results can be obtained for drug release from O/W emulsions. The development of multiple emulsions for sustained release has gained more attention,[18] although they are more complex than their two-phase counterparts from the standpoint of formulation, stability and drug release. Magnetic emulsions also have been tried as a drug carrier for chemotherapeutic agents.[19]

Implants

Application of biocompatible polymers to the construction of implantable therapeutic systems for achieving a better control of the duration of drug activity and precision of dosing actually started with the discovery of the silicone elastomer. The rate of drug release was found to be controlled by the thickness and surface area of the membrane as well as the polarity of the penetrant. Toward the end of the 1960s, a concentrated effort was made to expand the silicone elastomer-based implantable therapeutic system technology to other biocompatible polymers, in an attempt to control the release of water-soluble molecules. Some of these systems include a microporous membrane made from an ethylene/vinyl acetate copolymer for the ocular delivery of pilocarpine, a biodegradable (lactic/glycolic) copolymer for subcutaneous and intramuscular controlled administration of narcotic antagonists, a bioerodible polysaccharide polymer for the delivery of anti-inflammatory steroids, hydrogel for the subcutaneous controlled administration of estrus synchronizing agents or implantable therapeutic systems activated by osmotic pressure, vapor pressure, magnetism, etc.

The most recent implant systems approved by FDA is the Norplant system (*Wyeth-Ayerst*). The Norplant system kit

AUROBINDO EX1018, 16

contains levonorgestrel implants, made of silastic (dimethylsiloxane/methylvinyl siloxane copolymer). The capsules are sealed with silastic adhesive and sterilized. The Norplant system is inserted in a superficial plane beneath the skin of the upper arm. The Norplant system is indicated for the prevention of pregnancy for as long as 5 years and is a reversible contraceptive system. The capsules may be removed at the end of the 5th year. New capsules may be inserted at that time if continuing contraceptive protection is desired.

Controlled Drug Release by Diffusion—In membrane permeation-type controlled drug delivery, the drug is encapsulated within a compartment that is enclosed by a rate-limiting polymeric membrane. The drug reservoir may contain either drug particles or a dispersion (or a solution) of solid drug in a liquid or a solid type dispersing medium. The polymeric membrane may be fabricated from a homogeneous or a heterogeneous nonporous polymeric material or a microporous or semipermeable membrane. The encapsulation of the drug reservoir inside the polymeric membrane may be accomplished by molding, encapsulation, microencapsulation or other techniques.

The drug release (dQ/dt) from this type of implantable therapeutic systems should be constant and defined by

$$\frac{dQ}{dt} = \frac{C_R}{\frac{1}{P_m} + \frac{1}{P_d}} \tag{42}$$

where C_R is the drug concentration in the reservoir compartment and P_m and P_d are the permeability coefficients of the rate-controlling membrane and of the hydrodynamic diffusion layer existing on the surface of the membrane, respectively. P_m and P_d are defined as

$$P_m = \frac{K_{m/r} D_m}{\delta_m} \tag{43}$$

$$P_d = \frac{K_{a/m} D_a}{\delta_d} \tag{44}$$

where $K_{m/r}$ and $K_{a/m}$ are the partition coefficients for the interfacial partitioning of drug molecules from the reservoir to the membrane and from the membrane to the aqueous diffusion layer, respectively. D_m and D_a are the diffusion coefficients in the membrane and in the aqueous diffusion layer, respectively, and δ_m and δ_a are the thickness of the membrane and of the aqueous diffusion layer, respectively.

Substituting Eq 43 and Eq 44 for P_m and P_d in Eq 42 and then integrating gives

$$\frac{Q}{t} = \frac{K_{m/r} K_{a/m} D_a D_m}{K_{m/r} D_m \delta_d + K_{a/m} D_a \delta_m} \cdot C_R \tag{45}$$

which defines the rate of drug release at the steady-state from a membrane permeation-type controlled drug-delivery device. Examples of this type implantable therapeutic system are Progestasert IUD and Ocusert system.[20]

In matrix diffusion-type controlled drug delivery, the drug reservoir is formed by the homogeneous dispersion of drug particles throughout a lipophilic or hydrophilic polymer matrix. The dispersion of the drug particles in the polymer matrix may be accomplished by blending the drug with a viscous liquid polymer or a semisolid polymer at room temperature, followed by crosslinking of the polymer, or by mixing the drug particles with a melted polymer at an elevated temperature. It also can be fabricated by dissolving the drug particles and/or the polymer in an organic solvent followed by mixing and evaporation of the solvent in a mold at an elevated temperature or under vacuum.

The rate of drug release from this type of delivery device is not constant and is defined by

$$\frac{dQ}{dt} = \left(\frac{AC_p D_p}{2t}\right)^{1/2} \tag{46}$$

where A is the initial drug loading dose dispersed in the polymer matrix and C_p and D_p are the solubility and diffusivity of the drug molecules in the polymer, respectively. Integration of Eq 46 gives

$$\frac{Q}{t^{1/2}} = (2AC_p D_p)^{1/2} \tag{47}$$

which defines the flux of drug release at the steady state from a matrix diffusion type drug delivery device. Examples of this type of implantable therapeutic system are the contraceptive vaginal ring[21] and Compudose implant.[22]

In microreservoir dissolution-controlled drug delivery, the drug reservoir, which is a suspension of drug particles in an aqueous solution of a water-miscible polymer, forms a homogeneous dispersion of a multitude of discrete, unleachable, microscopic drug reservoirs in a polymer matrix. The microdispersion may be generated by using a high-energy-dispersing technique. Release of the drug from this type of drug-delivery device follows either an interfacial partition or a matrix diffusion-controlled process. An example of this type drug delivery device is the Syncro-Mate-C Implant.[20]

Controlled Drug Release by Activation—In osmotic pressure activated drug delivery, the drug reservoir, which is a liquid formulation, is contained within a semipermeable housing. The drug is released in solution form at a controlled, constant rate under an osmotic pressure gradient. An example of this type of drug delivery device is the Alzet osmotic pump.

Infusaid is an example of an implantable infusion pump using vapor pressure activation theory, in which the vapor chamber contains a vaporizable fluid which vaporizes at body temperature and creates a vapor pressure. Under the vapor pressure created, a bellows moves upward and forces the drug to be released. Implantable drug-delivery devices also can be activated by magnetism, ultrasound or hydrolysis.

Implants are typically placed subcutaneously to sustain drug release via various mechanisms. Both nonbiodegradable polymers, such as silicone elastomer (polydimethylsiloxane), and biodegradable polymers, such as poly(caprolactone), poly(lactic acid) or poly(glycolic acid), can be used. An ideal implantable therapeutic system should be biostable, biocompatible, with minimal tissue-implant interactions, nontoxic, noncarcinogenic, removable if required and should release drug at a constant, programmed rate for a predetermined duration of medication.

Transdermal Systems

Among other things, the skin serves as a barrier against penetration of microorganisms, viruses and toxic chemicals, and as a restraint against loss of physiologically vital fluids. A discussion of the fundamentals of percutaneous drug absorption, sometimes referred to as transdermal absorption, can be found in Chapter 90. Investigation of mechanisms of transdermal drug absorption has led to new approaches in using this route for systemic drug delivery. The intensity of interest in the potential biomedical applications of transdermal controlled-drug administration is demonstrated in the increasing research activity in the development of various types of transdermal therapeutic systems for long-term continuous infusion of therapeutic agents, including antihypertensive, antianginal, analgesic, steroidal and contraceptive drugs. Several technologies have been developed to provide rate control over the release and the transdermal permeation of drugs.

Membrane-Moderated Systems—In this system, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable backing and a rate-controlling polymeric membrane as shown in Fig 12. The drug molecules may be released only through the rate-controlling polymeric membrane. The rate-limiting membrane can be a microporous or a nonporous polymeric membrane. On the external surface of the membrane, a thin layer of drug-

AUROBINDO EX1018, 17

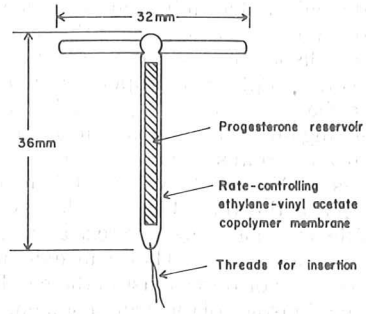

Fig 12. Model of a water-in-oil emulsion. (Reproduced with permission.[1])

compatible, hypoallergenic adhesive polymer, eg, silicone or polyacrylate adhesive, may be applied to achieve an intimate contact of the transdermal system with the skin. The rate of drug release from this type of drug-delivery system can be tailored by varying the polymer composition, permeability coefficient or thickness of the rate-limiting membrane and adhesive. Examples of this type of transdermal therapeutic system are the nitroglycerin-releasing transdermal therapeutic system such as Transderm-Nitro (*Ciba*), scopolamine-releasing transdermal therapeutic system such as Transderm-Scop system (*Ciba*) and clonidine-releasing transdermal therapeutic system such as Catapres transdermal therapeutic system (*Boehringer Ingelheim*). A typical *in vitro* release rate versus time profile from such a system is shown in Fig. 13.

Adhesive Diffusion-Controlled Systems—In this system the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer and then spreading the medicated adhesive, by solvent casting, onto a flat sheet of drug-impermeable backing membrane to form a thin drug-reservoir layer. On the top of the drug-reservoir layer, layers of non-medicated, rate-controlling adhesive polymer of constant thickness are applied to produce an adhesive diffusion-controlled drug-delivery system. Examples of this type of transdermal drug delivery system are the nitroglycerin-releasing transdermal therapeutic system such as the Deponit system (*Pharma-Schwartz*) and isosorbide dinitrate-releasing transdermal therapeutic system such as Frandol tape (*Toaeiyo*).

Matrix Dispersion-Type Systems—In this system, the drug reservoir is formed by homogeneously dispersing the drugs in a hydrophilic or lipophilic polymer matrix, and the medicated polymer then is molded into a medicated disc with a defined surface area and controlled thickness. The disc then is glued onto an occlusive baseplate in a compartment fabricated from a drug-impermeable backing. The adhesive polymer is spread along the circumference to form a strip of adhesive rim around the medicated disc. Example of this type of transdermal drug-delivery system is the nitroglycerin-releasing transdermal therapeutic system such as the Nitro-Dur system (*Key*).

Microreservoir Systems—In this system, the drug reservoir is formed by first suspending the drug particles in an aqueous solution of water-soluble polymer and then dispersing homogeneously in a lipophilic polymer, by high-shear mechanical force, to form a large number of unleachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately crosslinking the polymer *in situ*, which produces a medicated

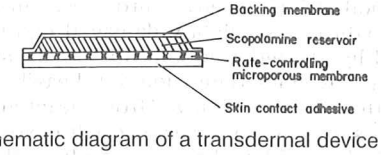

Fig 13. Schematic diagram of a transdermal device for delivery of scopolamine.

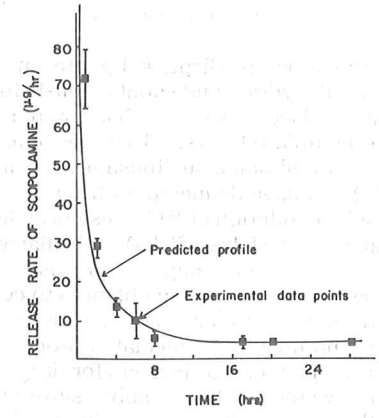

Fig 14. *In-vitro* release rate versus time profile for scopolamine from a transdermal device. (Reproduced with permission.[12])

polymer disk with a constant surface area and a fixed thickness. A transdermal therapeutic system is produced, in which the medicated disc is positioned at the center and surrounded by an adhesive rim. Example of this type of transdermal therapeutic system is the nitroglycerin-releasing system such as the Nitrodisc system (*Searle*).

Targeted Delivery Systems

Nanoparticles

Nanoparticles are one of several types of systems known collectively as colloidal drug delivery systems. Also included in this group are microcapsules, nanocapsules, macromolecular complexes, polymeric beads, microspheres and liposomes. A nanoparticle is a particle containing dispersed drug with a diameter of 200 to 500 nm. The size of a nanoparticle allows it to be administered intravenously via injection, unlike many other colloidal systems which occlude both needles and capillaries. Materials used in the preparation of nanoparticles are sterilizable, nontoxic and biodegradable; examples are albumin, ethylcellulose, casein and gelatin. They usually are prepared by a process similar to the coacervation method of microencapsulation.

There have been two main applications of nanoparticles: as carriers of medical diagnostic agents such as radioisotopic technetium-99m and fluorescein isothiocyanate, and for the delivery of liver flukicides in veterinary medicine. Radioisotopes are used to study the morphology, physiology and blood flow of various organs in the body. The liver commonly is visualized with a technetium-99m/sulfur colloid. Preparation of technetium-99m gelatin nanoparticles, and subsequent intravenous injection into mice, revealed that they are taken up rapidly by the reticuloendothelial system and localized mainly in the liver.[23] The reticuloendothelial system consists of phagocytic cells designed to cleanse the bloodstream of bacteria, viruses, cell debris and other unwanted foreign particles. The behavior of nanoparticles *in vivo* is the same as that exhibited by other colloidal systems of similar size, and points to the possibility of using nanoparticles to target drugs to the liver and phagocytic cells. The use of fluorescein isothiocyanate (FITC) was aimed at determining the availability of surface amino groups on gelatin or albumin nanoparticles. Since FITC is known to bind to amino groups, any such binding on the surface of a nanoparticle would reveal the presence of amino groups and thus their possible use as binding sites for drug molecules as well. Results indicated that free amino groups are, indeed, present on the surface of the nanoparticle.[23] In addition, preliminary work showed that FITC gelatin nanoparticles incubated with tumor cells *in vitro* are taken up by the tumor cells. This observation suggests the possible use of nanoparticles for the targeted delivery of anticancer agents to tumorous tissue.

AUROBINDO EX1018, 18

Liposomes

When phospholipids are dispersed gently in an aqueous medium, they swell, hydrate and spontaneously form multilamellar concentric bilayer vesicles with layers of aqueous media separating the lipid bilayers. These systems commonly are referred to as multilamellar liposomes or multilamellar vesicles (MLVs) and have diameters of from 25 nm to 4 μm. Sonication or solvent dilution of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 300 to 500 Å, containing an aqueous solution in the core. Liposomes bear many resemblances to cellular membranes and have been used for over a decade to study membrane behavior and membrane-mediated processes. It also is possible to use liposomes as carriers for drugs and macromolecules since water- or lipid-soluble substances can be entrapped in the aqueous spaces or within the bilayer itself, respectively. More recent studies have been aimed at investigating the potential of these drug-bearing liposomes for site-specific or receptor release of their active agent.

Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. Physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. They show low permeability to ionic and polar substances, including many drugs, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars or drugs. In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins such as cytochrome-C bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly; most liposome formulations used for drug delivery contain cholesterol to help form a more closely packed bilayer system during preparation. Serum high-density lipoproteins cause significant leakage in the membrane, probably due to removal of phospholipid.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient in terms of trapping water-soluble drug but seem to be somewhat less stable than other types of vesicles. In addition to liposome characteristics, an important determinant in drug entrapment is the physicochemical properties of the drug itself. As mentioned previously, polar drugs are trapped in the aqueous spaces and nonpolar drugs bind to the lipid bilayer of the vesicle. Polar drugs are released when the bilayer is broken, or by permeation but, nonpolar drugs remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes can interact with cells by four different mechanisms:[24]

1. Endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils.
2. Adsorption to the cell surface either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components.
3. Fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm.
4. Transfer of liposomal lipids to cellular or subcellular membranes, or *vice versa*, without any association of the liposome contents.

It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity and surface charge. They may persist in tissues for hours or days, depending on their composition, and half-lives in the blood range from minutes to several hours. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but the physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow and lymphoid organs.

Attempts to overcome the limitation on targeting of liposomes have centered around two approaches. One is the use of antibodies, bound to the liposome surface, to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. A second approach is to use carbohydrate determinants as recognition sites. Carbohydrate determinants are glycoprotein or glycolipid cell-surface components that play a role in cell–cell recognition, interaction and adhesion. Although the precise mechanism of their action is still unknown, they show potential in directing liposomes to particular cell types by their inclusion in the liposomal membrane. A discussion of the factors influencing targeting of liposomes has been given by Gregoriadis *et al.*[25] Potential therapeutic applications of liposomes include their use in the treatment of malignant tumors, lysosomal storage diseases, intracellular parasites, metal toxicity and diabetes. The liposome acts as the carrier of the active agent used in treatment of these conditions. Most of the applications involve intravenous injection of the liposomal preparation, but other routes of administration are conceivable. For example, liposome-entrapped insulin may offer some degree of protection of drug from gastric degradation and the possibility of GI absorption by endocytosis. Further details of current applications of liposome-entrapped drugs can be found in the literature.[24,25]

Resealed Erythrocytes

When erythrocytes are suspended in a hypotonic medium, they swell to about one and a half times their normal size, and the membrane ruptures resulting in the formation of pores with diameters of 200 to 500 Å. The pores allow equilibration of the intracellular and extracellular solutions. If the ionic strength of the medium then is adjusted to isotonicity and the cells are incubated at 37°, the pores will close and cause the erythrocyte to "reseal." Using this technique with a drug present in the extracellular solution, it is possible to entrap up to 40% of the drug inside the resealed erythrocyte and to use this system for targeted delivery via intravenous injection. The advantages of using resealed erythrocytes as drug carriers are that they are biodegradable, fully biocompatible and nonimmunogenic, exhibit flexibility in circulation time depending on their physicochemical properties, the entrapped drug is shielded from immunologic detection and chemical modification of drug is not required.

The assessment of resealed erythrocytes for use in targeted delivery has been facilitated by studies on the behavior of normal and modified reinfused erythrocytes. In general, normal aging erythrocytes, slightly damaged erythrocytes and those coated lightly with antibodies are sequestered in the spleen after intravenous reinfusion, but heavily damaged or modified erythrocytes are removed from the circulation by the liver.[26] This suggests that resealed erythrocytes can be targeted selectively to either the liver or spleen, depending on

AUROBINDO EX1018, 19

their membrane characteristics. In addition to coating with antibodies, removal of portions of cell-surface carbohydrates reduces the circulating half-life. The ability of resealed erythrocytes to deliver drug to the liver or spleen can be viewed as a disadvantage in that other organs and tissues are inaccessible. Thus, the application of this system to targeted delivery has been limited mainly to treatment of lysosomal storage diseases and metal toxicity, where the site of drug action is in the reticuloendothelial system. A more detailed discussion of the application of resealed erythrocytes has been presented by Ihler.[27]

Immunologically Based Systems

As discussed in the section pertaining to intramuscular injections, the formation of dissociable complex of a drug with a macromolecule is a viable method of achieving a sustained-release effect. If the macromolecule used is an antibody, an antigen-specific targeted effect also can be achieved. In addition to complex formation by noncovalent forces, drugs also may be linked covalently to antibodies, provided the activity of both drug and antibody is retained or the activity of drug is recoverable after release.

Most studies of antibody–drug systems have employed covalent conjugation of the drug to the antibody. Chemical crosslinking agents are used commonly to attach a drug to an antibody by reacting with appropriate groups available on both species. Among the crosslinking agents used are carbodiimide, glutaraldehyde, bisazobenzidine, cyanuric chloride, diethylmalonimidate or various mixed anhydrides. The reaction should allow effective control of the antibody–drug conjugate size, and the crosslink must readily be broken by available lysosomal hydrolases within the receptor cell, if drug release is critical to activity.

Certain specificities expressed on tumor cells, referred to as membrane-bound tumor-associated antigens (TAAs), may be exploited for the purpose of targeting antibody–drug conjugates directly at the malignant tumor by various parenteral routes of administration. Since anticancer drugs are indiscriminate to cell type in their action, a targeted delivery system for these drugs would offer a significant improvement in cancer chemotherapy. A wide variety of antineoplastic drugs have been conjugated to tumor-specific antibodies. Three that have received the most attention are chlorambucil, adriamycin and methotrexate. The effectiveness of these systems depends on the nature of the crosslinking agent and the method of reaction. The interested reader is directed to two reviews that discuss the use of antibody–drug conjugates for treatment of tumors.[28,29]

References

1. Lee VHK, Robinson JR, Lee VHL: In Robinson JR, Lee VHL, eds: *Controlled Drug Delivery*, 2nd ed, Marcel Dekker, New York, 3, 1987.
2. Robinson JR, Eriksen SP: *J Pharm Sci 55:* 1254, 1966.
3. Welling PG, Dobrinska MR, in Robinson JR, Lee VHL, eds: *Controlled Drug Delivery*, 2nd ed, Marcel Dekker, New York, 253, 1987.
4. Flynn GL, Yalkowsky SH, Roseman T: *J Pharm Sci 63:* 479, 1974.
5. Burnette RR, in Robinson JR, Lee VHL, eds: *Controlled Drug Delivery*, 2nd ed, Marcel Dekker, New York, 95, 1987.
6. Gibaldi M, Perrier D: *Pharmacokinetics*, 2nd ed, Marcel Dekker, New York, 189, 1982.
7. Riegelman S, Loo JCK, Rowland M: *J Pharm Sci 57:* 128, 1968.
8. Wagner JG: *Am J Pharm 141:* 5, 1969.
9. Park K, Wood RW, Robinson JR, in Langer R, Wise D, eds: *Medical Applications of Controlled Release Technology*, CRC Press, Boca Raton, FL, 171, 1985.
10. Higuchi T: *J Pharm Sci 50:* 874, 1961.
11. Higuchi T: *Ibid 52:* 1145, 1963.
12. Chandrasekaran SK, Benson H, Urquhart J, in Robinson JR, ed: *Sustained and Controlled Release Drug Delivery Systems*, Marcel Dekker, New York, 557, 1978.
13. Hui HW, Robinson JR, Lee VHL: In Robinson JR, Lee VHL, eds: *Controlled Drug Delivery*, 2nd ed, Marcel Dekker, New York, 373, 1987.
14. Buckwalter R, Dickinson J: *J APhA 47:* 661, 1958.
15. Hussain MA *et al: Drug Dev Ind Pharm 17:* 67, 1991.
16. *Physician's Desk Reference*, 48th ed, Medical Economics, Oradell, NJ 1994.
17. Higuchi WI: *J Pharm Sci 53:* 405, 1964.
18. Windheuser JL, Best ML, Perrin JH: *Bull Parenter Drug Assoc 24:* 286, 1970.
19. Brodin AF, Kavaliunas DR, Frank SG: *Acta Pharm Suec 15:* 1, 1978.
20. Chien YW: In Chien YW, ed: *Novel Drug Delivery Systems*, 2nd ed, Marcel Dekker, New York, 1, 1992.
21. *Ibid:* 43, 1992.
22. Hsieh DST, Smith N, Chien YW: In Meyers WE, Dunn RL, eds: *Proceeding of 11th International Symposium on Controlled Release of Bioactive Materials*, The Controlled Release Society, Chicago, 134, 1984.
23. Oppenheim RC: *J Steroid Biochem 6:* 182, 1975.
24. Juliano RL, Layton D: *Ibid:* 200, 1980.
25. Gregoriadis G *et al:* In Gregoriadis C, Senior J, Trout A, eds: *Targeting of Drugs*, Plenum, New York, 155, 1982.
26. Cooper RA: In William WJ *et al*, eds: *Hematology*, 2nd ed, McGraw-Hill, New York, 216, 1977.
27. Ihler G: In Gregoriadis C, ed: *Drug Carriers in Biology and Medicine*, Academic, London, 129, 1979.
28. Arnon R: In Spreafics F, Arnon R, eds: *Tumor-Associated Antigens and Their Specific Immune Response*, Academic, New York, 287, 1979.
29. O'Neill GJ: In Gregoriadis G, ed: *Drug Carriers in Biology and Medicine*, Academic, London, 23, 1979.

AUROBINDO EX1018, 20