13 Drug Release and Dissolution

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Define dissolution and describe relevant examples in the pharmaceutical sciences and practice of pharmacy.
2. Understand the differences among immediate-, modified-, delayed-, extended-, and controlled-release delivery systems.
3. Differentiate between zero-order and first-order release kinetics.
4. Define and understand intrinsic dissolution rate and define the driving force for dissolution.
5. Understand the effect of surface area on dissolution rate.
6. Differentiate the Hixson–Crowell, Noyes–Whitney, and Higuchi models of dissolution and release.
7. Understand the concept of sink conditions.
8. Define the Biopharmaceutics Classification System and discuss the role of permeability and solubility.
9. Understand how media properties can affect dissolution, for example, viscosity, pH, lipids, surfactants.
10. Describe and understand the mechanics of the most commonly used dissolution apparatuses.

Introduction*

Disintegration tests, official in the *United States Pharmacopeia*(USP) since 1950, are only indirectly related to drug bioavailability and product performance.1 In 1962, dissolved drug was known to be necessary for physiologic action and it was becoming increasingly recognized that capsule and tablet monographs in which the drug substance had a solubility of less than 1% in aqueous media should include a dissolution requirement. In 1968, the *USP/National Formulary* (NF) recommended the adoption of a basket-stirred-flask test apparatus (USP apparatus 1) to determine the dissolution of solid oral dosage forms.1 With the introduction of USP XIX/NF XIV in 1975, it was shown that a compendial in vivo bioavailability standard was not required, provided that a satisfactory in vitro–in vivo correlation (IVIVC) could be established. In 1978, the USP paddle apparatus was officially adopted and was found to be advantageous for disintegrating dosage forms. Today, the quality control of many drug products is based on the kinetics of drug release in vitro.2,3,4,5Drug release testing is also routinely used to predict how formulations or drug products are expected to perform in patients. These two distinct areas of dissolution and drug release testing have evolved over the past decade and will be described in this chapter.

The five types of dosage forms that can be characterized by release in vitro are: (*a*) solid oral dosage forms, (*b*) rectal dosage forms such as suppositories, (*c*) pulmonary (lung delivery) dosage forms, (*d*) modified-release dosage forms, and (*e*) semisolid products such as ointments, creams, and transdermal products. Over the last several years, the pharmaceutical industry, pharmaceutical scientists, and the Food and Drug Administration have worked together to improve the guidance available for classifying, studying, and documenting postapproval changes to manufacturing processes.5 The first round of this effort resulted in the publication of several SUPAC (Scale Up Post Approval Change) guidances, including the initial guidance, SUPAC-IR,3 for immediate-release drug products, followed by SUPAC-MR,5 for modified-release drug products, SUPAC-SS,4 for semisolids, and PAC-ATLS, for analytical lab changes. A number of additional SUPAC documents are in various stages of development. Parallel with these efforts, the explicit link between physicochemical properties such as drug dissolution and bioavailability was becoming formally recognized as reflected in the Biopharmaceutics Classification System (BCS), introduced in 1995.6 The BCS proposed a straightforward classification of drug products on the basis of their

solubility and permeability characteristics. Beginning in 1998, interest in studying the link between dissolution testing and bioavailability was revived and continues through today.[7,8,9,10,11] Standard pharmacopeial dissolution monographs were typically designed as quality control procedures to ensure that batch-to-batch drug product variability is kept within acceptable scientific and regulatory standards. However, with the widespread adoption of the BCS, the possibility of substituting dissolution tests for clinical studies has called the conditions of established compendial dissolution tests into question because there is now a need to better predict the in vivo performance of drug products. In this chapter, we cover the basic theoretical and analytical background for performing drug release and dissolution calculations, the release testing of oral drug products, the BCS and biorelevant dissolution conditions, and dissolution testing methods and apparatus, and provide numerous examples to help the student gain an understanding of dissolution and drug release.

Key Concept

Drug Release

Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism, and excretion, eventually becoming available for pharmacologic action. Drug release is described in several ways. Immediate release refers to the instantaneous availability of drug for absorption or pharmacologic action. *Immediate-release* drug products allow drugs to dissolve with no intention of delaying or prolonging dissolution or absorption of the drug. *Modified-release* dosage forms include both delayed- and extended-release drug products. *Delayed release* is defined as the release of a drug at a time other than immediately following administration. *Extended-release* products are formulated to make the drug available over an extended period after administration. Finally, *controlled release* includes extended-release and pulsatile-release products. *Pulsatile release* involves the release of finite amounts (or pulses) of drug at distinct time intervals that are programmed into the drug product.

Key Concept

Dissolution

Dissolution refers to the process by which a solid phase (e.g., a tablet or powder) goes into a solution phase such as water. In essence, when a drug “dissolves,” solid particles separate and mix molecule by molecule with the liquid and appear to become part of that liquid. Therefore, drug dissolution is the process by which drug molecules are liberated from a solid phase and enter into a solution phase. If particles remain in the solid phase once they are introduced into a solution, a pharmaceutical suspension results. Suspensions are covered in Chapters 17 and 18. In the vast majority of circumstances, only drugs in solution can be absorbed, distributed, metabolized, excreted, or even exert pharmacologic action. Thus, dissolution is an important process in the pharmaceutical sciences.

Terminology*

- **Drug Product:** A drug product is a finished dosage form (e.g., tablet and capsule) that contains a drug substance, generally, but not necessarily in association with one or more other ingredients (21 *Code of Federal Regulations* 314.3(b)). A solid oral dosage form includes but is not limited to tablets, chewable tablets, enteric-coated tablets, capsules, caplets, encapsulated beads, and gelcaps.
- **Drug Substance:** An active ingredient that is intended to furnish pharmacologic activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 *Code of Federal Regulations* 314.3(b)).

- **Enteric Coated:** Intended to delay the release of the drug (or drugs) until the dosage form has passed through the stomach. Enteric-coated products are delayed-release dosage forms.
- **Extended Release:** Extended-release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g., as a solution or an immediate-release dosage form).
- **Modified-Release Dosage Forms:** Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate-release dosage form. Modified-release solid oral dosage forms include both delayed- and extended-release drug products.
- **Immediate Release:** Allows the drug to dissolve in the gastrointestinal contents with no intention of delaying or prolonging the dissolution or absorption of the drug.
- **In Vitro–in Vivo Correlation:** A predictive mathematical model describing the relationship between an in vitro property of an oral dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed).

The Basics

Biopharmaceutics (Chapter 12) and the design of modern drug delivery systems (Chapter 23), as dealt with later, are based partly on principles of diffusion and dissolution theory. This chapter lays a foundation for the study of these topics by way of presenting concepts, illustrations, and worked examples. Drug release is introduced first because it is largely based on diffusion, which was introduced in Chapter 11. We then cover drug dissolution with examples from the literature and with applications of both subjects to pharmaceutical problems.

Drug dissolution and release patterns commonly fall into two groups: zero- and first-order release. Typically in the pharmaceutical sciences, zero-order release is achieved from nondisintegrating dosage forms such as topical or transdermal delivery systems, implantable depot systems, or oral controlled-release delivery systems. Because many of these delivery systems are covered inChapter 23 on drug delivery systems and Chapter 20 on pharmaceutical polymers, the mathematical basis will be introduced in this chapter. In

these cases, drug “dissolution” is commonly referred to as drug “release” because it is dependent on diffusion (Chapter 11). The advanced student can find a more in-depth treatment of the mathematical models of dissolution from the review by Costa and Sousa Lobo.13 The following sections review basic models with an emphasis on understanding the conceptual basis for drug release and dissolution. The student should view each equation as a short-hand way of describing the relationships among the parameters/factors that affect the process that is being described.

Key Concept

Zero-Order Release Kinetics

Zero-order release kinetics refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with low-soluble drugs, and other delivery systems. “Constant” release is defined in this context as the same amount of drug release per unit of time. In its simplest form, zero-order drug release can be represented as

$$Q = Q_0 + K_0 t \qquad (13\text{–}1)$$

where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 is the initial amount of drug in solution (it is usually zero), and K_0 is the zero-order release constant.

Dissolution

When a tablet or other solid drug form is introduced into a beaker of water or into the gastrointestinal tract, the drug begins to pass into solution from the intact solid. Unless the tablet is a contiguous polymeric device, the solid matrix also disintegrates into granules, and these granules deaggregate in turn into fine particles. Disintegration, deaggregation, and dissolution may occur simultaneously with the release of a drug from its delivery form. These steps are separated for clarification as depicted in Figure 13-1.

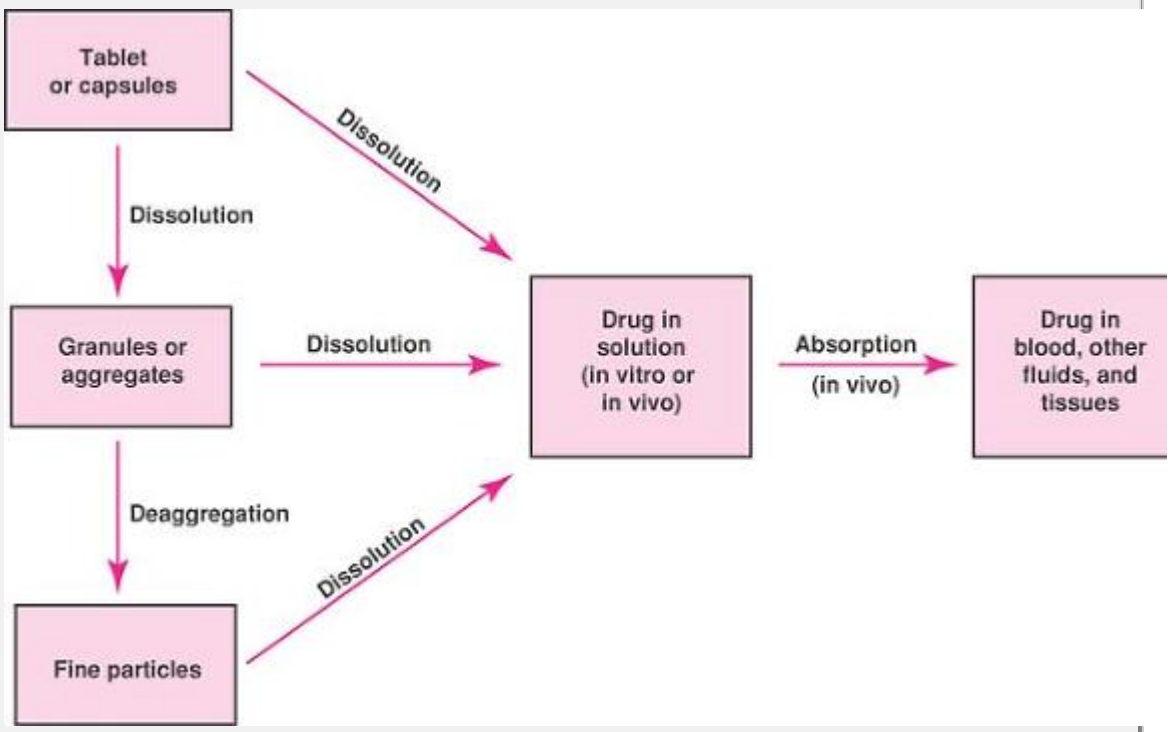

Fig. 13-1. Disintegration, deaggregation, and dissolution stages as a drug leaves a tablet or granular matrix. (From J. G. Wagner, *Biopharmaceutics and Relevant Pharmacokinetics*, Drug Intelligence Publications, Hamilton, IL, 1971, p. 99. With permission).

The effectiveness of a tablet in releasing its drug for systemic absorption depends somewhat on the rate of disintegration of the dosage forms and deaggregation of the granules. Ordinarily of more importance, however, is the dissolution rate of the solid drug. Frequently, dissolution is the limiting or rate-controlling step in the absorption of drugs with low solubility because it is often the slowest of the various stages involved in release of the drug from its dosage form and passage into systemic circulation. Classical dissolution has been reviewed by Wurster and Taylor,14 Wagner,15 and Leeson and Carstensen.16 Release rate processes in general are discussed by Higuchi.17 This has been an active area of research for many years, and reviews have appeared recently on numerous aspects of drug dissolution, including the influence of physicochemical properties of drugs on dissolution18 and on the modeling and comparison of dissolution profiles.13 Articles such as these will provide the student with a thorough yet broad overview of the current status of the field.

Several theories have been used to build mathematical models that describe drug dissolution from immediate- and modified-release dosage forms. In this chapter, the focus will be on drug dissolution

from solid dosage forms. Because dissolution is a kinetic process, the rate of dissolution reflects the amount of drug dissolved over a given time period. In certain cases, an equation can be exactly derived that describes the dissolution time dependence. This is called an analytical mathematical solution. However, in many cases, an analytical solution cannot be derived and an empirical relationship is used. Several common mathematical models will be covered in the following sections. The pharmacy student should keep in mind that the most important lesson to be learned at this stage is not how to derive these equations but rather how to use them as short-hand formulas to understand the different factors that affect dissolution rate and how dissolution patterns can vary and ultimately influence the efficacy of therapeutic regimens in patients.

The rate at which a solid dissolves in a solvent was proposed in quantitative terms by Noyes and Whitney19 in 1897 and elaborated subsequently by other workers. The equation can be written as

$$\frac{dM}{dt} = \frac{DS}{h}(C_s - C) \qquad (13\text{–}2)$$

or

$$\frac{dC}{dt} = \frac{DS}{Vh}(C_s - C) \qquad (13\text{–}3)$$

where M is the mass of solute dissolved in time t, dM/dt is the mass rate of dissolution (mass/time), D is the diffusion coefficient of the solute in solution, S is the surface area of the exposed solid, h is the thickness of the diffusion layer, C_s is the solubility of the solid (i.e., concentration of a saturated solution of the compound at the surface of the solid and at the temperature of the experiment), and C is the concentration of solute in the bulk solution and at time t. The quantity dC/dt is the dissolution rate, and V is the volume of solution.

In dissolution or mass transfer theory, it is assumed that an *aqueous diffusion layer* or *stagnant liquid film* of thickness h exists at the surface of a solid undergoing dissolution, as observed in Figure 13-2. This thickness, h, represents a stationary layer of solvent in which the solute molecules exist in concentrations from C_s to C. Beyond the static diffusion layer, at x greater than h, mixing occurs in the solution, and the drug is found at a uniform concentration, C, throughout the bulk phase.

Key Concept

First-Order Kinetics

The Noyes–Whitney19 equation is

$$dC/dt = K(C_s - C) \qquad (13\text{–}4)$$

where K is the "first-order" proportionality constant. The Hixson and Crowell20 equation further considers the surface area of the dissolving solid:

$$dM/dt = KS(C_s - C) \qquad (13\text{–}5)$$

where $K = D/h$

Key Concept

Driving Force for Dissolution and Sink Conditions

The saturation solubility of a drug is a key factor in the Noyes–Whitney19 equation. The driving force for dissolution is the concentration gradient across the boundary layer. Therefore, the driving force depends on the thickness of the boundary layer and the concentration of drug that is already dissolved. When the concentration of dissolved drug, C, is less than 20% of the saturation concentration, C_s, the system is said to operate under "sink conditions." The driving force for dissolution is greatest when the system is under sink conditions. Under sink conditions, equation (13-5) can be written in a simplified form:

$$Q_t = Q_0 e^{-Kt} \quad \text{or} \quad \ln(Q_t/Q_0) = Kt \qquad (13\text{–}6)$$

At the solid surface–diffusion layer interface, $x = 0$, the drug in the solid is in equilibrium with drug in the diffusion layer. The gradient, or change in concentration with distance across the diffusion layer, is constant, as shown by the straight downward-sloping line. This is the gradient represented in equations (13-2) and (13-3) by the term $(C_s - C)/h$. The similarity of the Noyes–Whitney19 equation to Fick's first law (Chapter 11) is evident in equation (13-2).

Therefore, when *C* is considerably less than the drug's solubility, C_s, the system is represented by *sink conditions*, and concentration *C*can be eliminated from equations (13-2) and (13-3). Equation (13-2)then becomes

$$dM/dt = DSC_s/h \qquad (13\text{–}7)$$

In the derivation of equations (13-2) and (13-3), it was assumed that*h* and *S* were constant, but this is not the case. The static diffusion layer thickness is altered by the force of agitation at the surface of the dissolving tablet and will be referred to later. The surface area, *S*, obviously does not remain constant as a powder, granule, or tablet dissolves, and it is difficult to obtain an accurate measure of *S* as the process continues. In experimental studies of dissolution, the surface may be controlled by placing a compressed pellet in a holder that exposes a surface of constant area. Although this ensures better adherence to the requirements of equations (13-2)through (13-7) and provides valuable information on the drug, it does not simulate the actual dissolution of the material in practice.

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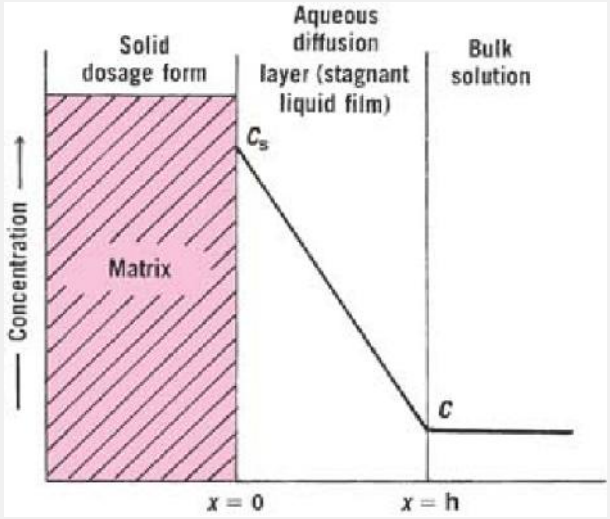

Fig. 13-2. Dissolution of a drug from a solid matrix, showing the stagnant diffusion layer between the dosage form surface and the bulk solution.

In calculating the diffusion coefficient and dissolution rate constant, the application of equations (13-2) through (13-7) is demonstrated by way of the following two examples.

Example 13-1

Calculate Dissolution Rate Constant

A preparation of drug granules weighing 0.55 g and having a total surface area of 0.28 m^2 (0.28×10^4 cm^2) is allowed to dissolve in 500 mL of water at 25°C. After the first minute, 0.76 g has passed into solution. The quantity *D*/*h* can be referred to as a dissolution rate constant, *k*.

If the solubility, C_s, of the drug is 15 mg/mL at 25 °C, what is *k*? From equation (12-7), *M* changes linearly with *t*initially, and

$$\frac{dM}{dt} = \frac{760 \text{ mg}}{60 \text{ sec}} = 12.67 \text{ mg/sec}$$

$$12.67 \text{ mg/sec} = k \times 0.28 \times 10^4 \text{ cm}^2 \times 15 \text{ mg/cm}^3$$

$$k = 3.02 \times 10^{-4} \text{ cm/sec}$$

In this example, 0.760 g dissolved in 500 mL after a time of 1 min, or 760 mg/500 mL = 1.5 mg/cm^3. This value is one tenth of the drug's solubility and can be omitted from equation (13-2) without introducing significant error, shown by employing the full equation(13-2):

$$k = \frac{12.67 \text{ mg/sec}}{(0.28 \times 10^4 \text{ cm}^2)(15 \text{ mg/cm}^3 - 1.5 \text{ mg/cm}^3)}$$

$$k = 3.35 \times 10^{-4} \text{ cm/sec}$$

When this result is compared with 3.02 × 10$^-$4 cm/sec, obtained using the less exact expression, it shows that “sink conditions” are in effect, and that the concentration term, *C*, can be omitted from the rate equation.

Example 13-2

Hixson–Crowell Cube-Root Law20

The diffusion layer thickness in Example 13-1 is estimated to be 5 × 10^{-3} cm. Calculate *D*, the diffusion coefficient, using the relation *k* = *D*/*h*.

We have

$$D = (3.35 \times 10^{-4} \text{ cm/sec}) \times (5 \times 10^{-3} \text{ cm})$$

$$= 1.68 \times 10^{-6} \text{ cm}^2\text{/sec}$$

If a dosage form's dimensions diminish proportionally in such a manner that the geometric shape of the dosage form stays constant as dissolution is occurring, then dissolution occurs in planes that are parallel to the dosage form surface and we use the Hixson–Crowell20 cube-root model to understand its behavior. It is thought that tablet dissolution occurs in this manner. For a drug powder consisting of uniformly sized particles, it is possible to derive an equation that expresses the rate of dissolution based on the cube root of the weight of the particles.

The radius of the particle is not assumed to be constant. The particle (sphere) shown in Figure 13-3 has a radius *r* and a surface area 4πr^2.

Through dissolution, the radius is reduced by *dr*, and the infinitesimal volume of this section lost is

$$dV = 4\pi r^2 \, dr \qquad \textbf{(13–8)}$$

For *N* such particles, the volume loss is

$$dV = 4N\pi r^2 \, dr \qquad \textbf{(13–9)}$$

The surface area of *N* particles is

$$S = 4N\pi r^2 \qquad \textbf{(13–10)}$$

Now, the infinitesimal mass change as represented by the Noyes–Whitney law,19 equation (**13–2**), is

$$-dM = kSC_s \, dt \qquad \textbf{(13–11)}$$

where *k* is used for *D*/*h* as in Example 13-1. The drug's density multiplied by the infinitesimal volume change, ρ *dV*, can be set equal to *dM*, or

$$-\rho \, dV = kSC_s \, dt \qquad \textbf{(13–12)}$$

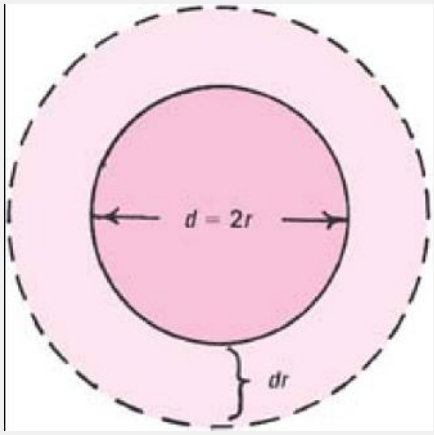

Fig. 13-3. Schematic of a particle, showing the change in surface area and volume as the particle dissolves. The volume, dV, dissolved in dt seconds is given by Thickness × Surface area = $dr \times 4\pi r^2$. (From J. T. Carstensen, *Pharmaceutics of Solids and Solid Dosage Forms*, Wiley, New York, 1977, p. 75. With permission.)

Equations (13-9) and (13-10) are substituted into equation (13-12) to yield

$$-4\rho N\pi r^2 dr = 4N\pi r^2\, kC_s\, dt \qquad \textbf{(13–13)}$$

Equation (13-13) is divided through by $4N\pi r^2$ to give

$$-\rho\, dr = kC_s\, dt \qquad \textbf{(13–14)}$$

Integration with $r = r_0$ at $t = 0$ produces the expression

$$r = r_0 - \frac{kC_s t}{\rho} \qquad \textbf{(13–15)}$$

The radius of spherical particles can be replaced by the mass of Nparticles by using the relationship (see inside front cover for the volume of a sphere)

$$M = N\rho(\pi/6)d^3 \qquad \textbf{(13–16)}$$

where $d = 2r$, the diameter of the particle. Taking the cube root of equation (**13–16**) yields

$$M^{1/3} = [N\rho(\pi/6)]^{1/3} d \qquad \textbf{(13–17)}$$

The diameter, d, from equation (13-17) is substituted for $2r$ into equation (13-15), giving

$$M_0^{1/3} - M^{1/3} = \kappa t \qquad \textbf{(13–18)}$$

where

$$\kappa = [N\rho(\pi/6)]^{1/3}\frac{2kC_s}{\rho} = \frac{M_0^{1/3}}{d}\frac{2kC_s}{\rho} \qquad \textbf{(13–19)}$$

M_0 is the original mass of the drug particles. Equation (13-18) is known as the Hixson–Crowell cube-root law,20 and κ is the cube-root dissolution rate constant.

Example 13-3

Calculate Dissolution Rate Constant

A specially prepared tolbutamide powder of fairly uniformly sized particles with a diameter of 150 μm weighed 75 mg. Dissolution of the drug was determined in 1000 mL of water at 25°C as a function of time. Determine the value of κ, the cube-root dissolution rate constant, at each time interval and calculate the average value of κ. The data and results are set forward in the accompanying table.

DISSOLUTION OF TOLBUTAMIDE POWDER*

Time (min)	Concentration Dissolved (mg/mL)	Weight Undissolved, M(g)	$M_0^{1/3} - M^{1/3}$	κ ($g^{1/3}$/min)
0	0	0.0750(M_0)	0	—
10	0.01970	0.0553	0.0406	0.0041
20	0.0374	0.0376	0.0866	0.0043
30	0.0510	0.0240	0.1332	0.0044
40	0.0595	0.0155	0.1724	0.0043
50	0.0650	0.0100	0.2063	0.0041

$$\kappa_{av} = \frac{\sum \kappa}{5} = \frac{0.0212}{5} = 0.00424\ g^{1/3}/min$$

*Based on M. J. Miralles, M. S. Thesis, University of Texas, Austin, 1980.

In the situation in which the aqueous diffusion layer thickness of a spherical particle is comparable to or larger than the size of the sphere (e.g., micronized particles less than 50 μm in diameter), the change in particle radius with time becomes

$$r^2 = r_0^2 - \frac{2DC_s t}{\rho} \qquad (13\text{–}20)$$

and the estimated time for complete dissolution, τ (i.e., when $r^2 = 0$), is

$$\tau = \frac{\rho r_0^2}{2DC_s} \qquad (13\text{–}21)$$

Example 13-4
Dissolution Time

In clinical practice, diazepam injection (a sterile solution of diazepam in a propylene glycol–ethanol–water cosolvent system) is often diluted manyfold with normal saline injection. An incipient precipitation of diazepam occurs invariably upon addition of saline followed by complete dissolution within 1 min upon shaking. With C_s in water equal to 3 mg/mL, ρ about equal to 1.0 g/mL, and D equal to 5×10^{-6} cm^2/sec, calculate the time for complete dissolution when r_0 = 10 μm (10×10^{-4} cm).

We have

$$\tau = \frac{(1\ g/mL)(10 \times 10^{-4}\ cm)^2}{2(5 \times 10^{-6}\ cm^2/sec)(3 \times 10^{-3}\ g/mL)}$$
$$= 33\ sec$$
$$\text{If } r_0 = 25\ \mu m, \tau = 208\ sec$$

More Complex Models of Dissolution: Convective Diffusion

Convection, the transfer of heat (energy) and the presence of agitation accompanying the movement of a fluid, can be combined with diffusion to provide a *convective diffusion model* for the study of dissolution.21 The convective diffusion model, unlike the simpler Noyes–Whitney19 and Nernst–Brünner22 approaches, takes into consideration such factors as flow rate, mixing (agitation), and the dimensions of the dosage form. Nelson and Shah23 investigated the convective diffusion model for the dissolution of alkyl *p*-aminobenzoates as test compounds. De Smidt et al.24 also used a convective diffusion model in the study of the dissolution kinetics of griseofulvin in solutions of the solubilizing agent sodium dodecylsulfate.

Example 13-5
Drug Dissolution

De Smidt et al.24 introduced a drug dissolution rate approach to model the rates of dissolution of alkyl *p*-aminobenzoates in a specially designed diffusion cell. The model is based on convective diffusion, the equations of which can be used to calculate *R*, the rate of diffusion or permeation rate:

$$R = 0.808 D^{2/3} C_s \alpha^{1/3} b L^{2/3} \qquad (13\text{–}22)$$

for a rectangular tablet surface of width *b* and length *L* in the direction of flow, and

$$R = 2.157 D^{2/3} C_s \alpha^{1/3} r^{5/3} \qquad (13\text{–}23)$$

for a circular tablet surface of radius *r*. In these equations, *D*is the diffusivity or diffusion coefficient, C_s is the solubility, and α is the rate of shear as the solvent is pumped over the dissolving surface. The rate of shear is calculated from $\alpha = 6Q/H^2W$, where *Q* is the flow rate and *H* and *W* are the height and width, respectively, of a channel in the diffusion cell to allow the flow of solvent (water) over the dissolving tablet.

Experiments on dissolution rate, *R*, were carried out at 37°C with rectangular tablet surfaces containing the drug model ethyl *p*-aminobenzoate. The long axis of the rectangular surface was 25.4 mm and the short axis 3.175 mm.

(*a*, *b*) Compute the rate of dissolution, *R*, with the long axis,*L*, placed perpendicular to the direction of flow, and then with the long axis placed parallel to the direction of flow. The flow rate, *Q*, is 14.9 mL/min; the diffusivity and the solubility of the drug are $D = 9.86 \times 10^{-6}$ cm^2/sec and $C_s = 7.27 \times 10^{-6}$ mole/cm^3, respectively; and $H^2W = 0.3506$ cm^3.

(*c*) The experiment is repeated but using a disk with a circular surface of area equal to the surface area of the rectangle referred to in (*a*). Compute *R*, expressing the results in mole/min.

(*d*) What differences do you find between this model and the classic stagnant or unstirred diffusion layer model? You can refer to Nelson and Shah23 to check the answers given here.

(*a*) The rate of shear is

$$\alpha = 6Q/H^2W = 6 \times 14.9 \text{ cm}^3 \text{ min}^{-1}/0.3506 \text{ cm}^3 = 255.0 \text{ min}^{-1}$$

For the long axis perpendicular to flow, $b = 2.54$ cm and $L = 0.3175$ cm. Then,

$$\begin{aligned} R &= 0.808(9.86 \times 10^{-6} \text{ cm}^2/\text{sec} \times 60 \text{ sec/min})^{2/3} \\ &\quad \times (7.27 \times 10^{-6} \text{ mole/cm}^3) \times (255.0 \text{ min}^{-1})^{1/3} \\ &\quad \times (2.54 \text{ cm}) \times (0.3175 \text{ cm})^{2/3} \\ &= 3.10 \times 10^{-7} \text{ mole/min} \end{aligned}$$

(*b*) For the long axis parallel to the flow, $b = 0.3175$ cm and$L = 2.54$ cm. Then,

$$\begin{aligned} R &= 0.808(9.86 \times 10^{-6} \text{ cm}^2/\text{sec} \times 60 \text{ sec/min})^{2/3} \\ &\quad \times (7.27 \times 10^{-6} \text{ mole/cm}^3) \times (255.0 \text{ min}^{-1})^{1/3} \\ &\quad \times (0.3175 \text{ cm}) \times (2.54 \text{ cm})^{2/3} \\ &= 1.55 \times 10^{-7} \text{ mole/min} \end{aligned}$$

For the long axis perpendicular to the flow, *R* is twice the value when the long axis is parallel to the flow, as observed in (*a*) and (*b*):

$$R = 3.10 \times 10^{-7}/(1.55 \times 10^{-7}) = 2.0$$

(*c*) The surface area of the rectangular tablet is 2.54 cm × 0.3175 cm = 0.806 cm^2, which is also the surface area of the circular tablet or disk. Therefore, the radius, *r*, of the circular surface is $\pi r^2 = 0.806$, or $r = 0.507$ cm, and the rate, *R*, of diffusion or permeation for a tablet of circular surface [equation (13-23)] is

$$\begin{aligned} R &= 2.157(9.86 \times 10^{-6} \times 60 \text{ cm}^2/\text{min})^{2/3} \\ &\quad \times (7.27 \times 10^{-6} \text{ mole/cm})^3 \times (255 \text{ min}^{-1})^{1/3} \\ &\quad \times (0.507 \text{ cm})^{5/3} \\ &= 2.26 \times 10^{-7} \text{ mole/min} \end{aligned}$$

(*d*) The convective diffusion (CD) model, which takes into account fluid flow as well as diffusion, has several parameters in common with the classic diffusion model. These include the solubility, C_s, diffusion coefficient or diffusivity, *D*, and the dimensions of a rectangular or

circular surface, *b*, *L*, and *r*. In the classic model, *R* is proportional to *D*, where in the CD model, *R* is proportional to $D^{2/3}$. In the classic model, *R* is proportional to the surface area, *S*, of a rectangle or disk; in the CD model, *R* is proportional to a reduced function of surface area, that is, $bL^{2/3}$ or $r^{5/3}$. A new parameter, α, the rate of shear over the dissolving surface, is introduced in the CD model; it is calculated from the flow rate and the dimensions of the diffusion cell.

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Drug Release

Release from dosage forms and subsequent absorption are controlled by the physical chemical properties of drug and delivery system and the physiologic and physical chemical properties of the biologic system. Drug concentration, aqueous solubility, molecular size, crystal form, protein binding, and pK_a are among the physical chemical factors that must be understood to design a delivery system that exhibits controlled- or sustained-release characteristics.25

The Higuchi (Equation) Model26,27

Higuchi developed a theoretical model for studying the release of water-soluble and poorly soluble drugs from a variety of matrices, including semisolid and solids. We will cover the factors that control drug release from solid dosage forms later in this chapter. A powdered drug is homogeneously dispersed throughout the matrix of an erodible tablet. The drug is assumed to dissolve in the polymer matrix and to diffuse out from the surface of the device. As the drug is released, the distance for diffusion becomes increasingly greater. The boundary that forms between drug and empty matrix therefore recedes into the tablet as drug is eluted. A schematic illustration of such a device is shown in Figure 13-4a. Figure 13-4b shows a granular matrix with interconnecting pores or capillaries. The drug is leached out of this device by entrance of the surrounding medium.Figure 13-4c depicts the concentration profile and shows the receding depletion zone that moves to the center of the tablet as the drug is released.

Higuchi26 developed an equation for the release of a drug from an ointment base and later27 applied it to diffusion of solid drugs dispersed in homogeneous and granular matrix dosage systems (Fig. 13-4). Recall that Fick's first law (Chapter 11),

$$\frac{dM}{S\,dt} = \frac{dQ}{dt} = \frac{DC_s}{h} \qquad \textbf{(13–24)}$$

can be applied to the case of a drug embedded in a polymer matrix, where *dQ*/*dt* is the rate of drug released per unit area of exposed surface of the matrix. Because the boundary between the drug matrix and the drug-depleted matrix recedes with time, the thickness of the empty matrix, *dh*, through which the drug diffuses also increases with time.

Whereas C_s is the solubility or saturation concentration of drug in the matrix, *A* is the total concentration (amount per unit volume), dissolved and undissolved, of drug in the matrix.

As drug passes out of a homogeneous matrix (Fig. 13-4a), the boundary of drug (represented by the dashed vertical line in Fig. 13-4c) moves to the left by an infinitesimal distance, *dh*. The infinitesimal amount, *dQ*, of drug released because of this shift of the front is given by the approximate linear expression

$$dQ = A\,dh - \frac{1}{2}C_s\,dh \qquad \textbf{(13–25)}$$

Now, *dQ* of equation **(**13-35**)** is substituted into equation **(**13-34**)**, integration is carried out, and the resulting equation

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is solved for *h*. The steps of the derivation as given by Higuchi26 are

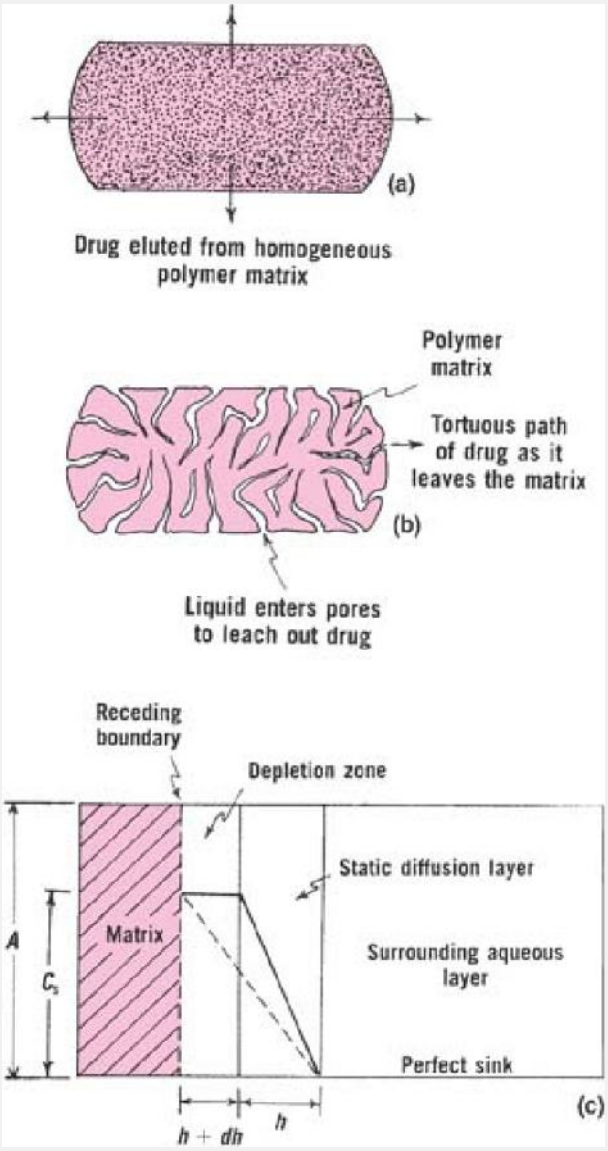

Fig. 13-4. Release of drug from homogeneous and granular matrix dosage forms. (*a*) Drug eluted from a homogeneous polymer matrix. (*b*) Drug leached from a heterogeneous or granular matrix. (*c*) Schematic of the solid matrix and its receding boundary as drug diffuses from the dosage form. (From T. Higuchi, J. Pharm. Sci.**50,** 874, 1961. With permission.)

$$\left(A - \frac{1}{2}C_s\right) dh = \frac{DC_s}{h} dt \qquad \textbf{(13–26)}$$

$$\frac{2A - C_s}{2DC_s} \int h\, dh = \int dt \qquad \textbf{(13–27)}$$

$$t = \frac{(2A - C_s)}{4DC_s} h^2 + C \qquad \textbf{(13–28)}$$

The integration constant, C, can be evaluated at $t = 0$, at which $h = 0$, giving

$$t = \frac{(2A - C_s)h^2}{4DC_s} \qquad \textbf{(13–29)}$$

$$h = \left(\frac{4DC_s t}{2A - C_s}\right)^{1/2} \qquad \textbf{(13–30)}$$

The amount of drug depleted per unit area of matrix, Q, at time t is obtained by integrating equation (13-25) to yield

$$Q = hA - \frac{1}{2}hC_s \qquad \textbf{(13–31)}$$

Substituting equation (**13–30**) into (**13–31**) produces the result

$$Q = \left(\frac{DC_s t}{2A - C_s}\right)^{1/2} (2A - C_s) \qquad \textbf{(13–32)}$$

which is known as the Higuchi equation:

$$Q = [D(2A - C_s)C_s t]^{1/2} \qquad \textbf{(13–33)}$$

The instantaneous rate of release of a drug at time t is obtained by differentiating equation (13-33) to yield

$$\frac{dQ}{dt} = \frac{1}{2}\left[\frac{D(2A - C_s)C_s}{t}\right]^{1/2} \qquad \textbf{(13–34)}$$

Ordinarily, A is much greater than C_s, and equation (13-33) reduces to

$$Q = (2ADC_s t)^{1/2} \qquad \textbf{(13–35)}$$

and equation (13-34) becomes

$$\frac{dQ}{dt} = \left(\frac{ADC_s}{2t}\right)^{1/2} \qquad \textbf{(13–36)}$$

for the release of a drug from a homogeneous polymer matrix–type delivery system. Equation (13-35) indicates that the amount of drug released is proportional to the square root of A, the total amount of drug in unit volume of matrix; D, the diffusion coefficient of the drug in the matrix; C_s, the solubility of drug in polymeric matrix; and t, the time.

The rate of release, dQ/dt, can be altered by increasing or decreasing the drug's solubility, C_s, in the polymer by complexation. The total concentration, A, of drug that the physician prescribes is also seen to affect the rate of drug release.

Example 13-6
Drug Release

(*a*) What is the amount of drug per unit area, Q, released from a tablet matrix at time t = 120 min? The total concentration of drug in the homogeneous matrix, A, is 0.02 g/cm^3. The drug's solubility, C_s, is 1.0 × 10^{-3} g/cm^3 in the polymer. The diffusion coefficient, D, of the drug in the polymer matrix at 25°C is 6.0 × 10^{-6} cm^2/sec or 360 × 10^{-6}cm^2/min.

We use equation (13-35):

$$\begin{aligned} Q &= [2(0.02\ \text{g/cm}^3)(360 \times 10^{-6}\ \text{cm}^2/\text{min}) \\ &\quad \times (1.0 \times 10^{-3}\ \text{g/cm}^3)(120\ \text{min})]^{1/2} \\ &= 1.3 \times 10^{-3}\ \text{g/cm}^2 \end{aligned}$$

(*b*) What is the instantaneous rate of drug release occurring at 120 min?

We have

$$\begin{aligned} dQ/dt &= \left[\frac{(0.02)(360 \times 10^{-6})(1.0 \times 10^{-3})}{2 \times 120}\right]^{1/2} \\ &= 5.5 \times 10^{-6}\ \text{g cm}^{-2}\text{min}^{-1} \end{aligned}$$

Release from Granular Matrices: Porosity and Tortuosity

The release of a solid drug from a granular matrix (Fig. 13-4b) involves the simultaneous penetration of the surrounding liquid, dissolution of the drug, and leaching out of the drug through interstitial channels or pores. A granule is, in fact, defined as a porous rather than a homogeneous matrix. The volume and

length of the opening in the matrix must be accounted for in the diffusional equation, leading to a second form of the Higuchi equation:

$$Q = \left[\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t\right]^{1/2} \qquad \textbf{(13–37)}$$

where ε is the porosity of the matrix and *τ* is the tortuosity of the capillary system, both parameters being dimensionless quantities.

Porosity, ε, is the fraction of matrix that exists as pores or channels into which the surrounding liquid can penetrate. The porosity term, ε, in equation **(**13-37**)** is the total porosity of the matrix after the drug has been extracted. This is equal to the initial porosity, ε_0, due to pores and channels in the matrix before the leaching process begins and the porosity created by extracting the drug. If *A* g/cm^3 of drug is extracted from the matrix and the drug's specific volume or reciprocal density is 1/ρ cm^3/g, then the drug's concentration, *A*, is converted to volume fraction of drug that will create an additional void space or porosity in the matrix once it is extracted. The total porosity of the matrix, ε, becomes

$$\varepsilon = \varepsilon_0 + A(1/\rho) \qquad \textbf{(13–38)}$$

The initial porosity, ε_0, of a compressed tablet can be considered to be small (a few percent) relative to the porosity, *A*/ρ, created by the dissolution and removal of the drug from the device. Therefore, the porosity frequently is calculated conveniently by disregarding ε_0 and writing

$$\varepsilon \cong A/\rho \qquad \textbf{(13–39)}$$

Tablet porosity and its measurement and applications in pharmacy are discussed in more detail in sections Capsule-Type Devices and Dissolution and Release from Oral Drug Products.

Equation **(**13-37**)** differs from equation **(**13-33**)** only in the addition of ε and *τ*. Equation **(**13-33**)** is applicable to release from a homogeneous tablet that gradually erodes and releases the drug into the bathing medium. Equation **(**13-37**)** applies instead to a drug-release mechanism based on entrance of the surrounding medium into a polymer matrix, where it dissolves and leaches out the soluble drug, leaving a shell of polymer and empty pores. In equation **(**13-37**)**, diffusivity is multiplied by porosity, a fractional quantity, to account for the decrease in *D* brought about by empty pores in the matrix. The apparent solubility of the drug, C_s, is also reduced by the volume fraction term, which represents porosity.

Tortuosity, *τ*, is introduced into equation **(**13-37**)** to account for an increase in the path length of diffusion due to branching and bending of the pores, as compared to the shortest “straight-through” pores. Tortuosity tends to reduce the amount of drug release in a given interval of time, and so it appears in the denominator under the square root sign. A straight channel has a tortuosity of unity, and a channel through spherical beads of uniform size has a tortuosity of 2 or 3. At times, an unreasonable value of, say, 1000 is obtained for *τ*, as Desai et al28a noted. When this occurs, the pathway for diffusion evidently is not adequately described by the concept of tortuosity, and the system must be studied in more detail to determine the factors controlling matrix permeability. Methods for obtaining diffusivity, porosity, tortuosity, and other quantities required in an analysis of drug diffusion are given by Desai et al.28b

Equation **(**13-37**)** has been adapted to describe the kinetics of lyophilization,29 commonly called *freeze-drying*, of a frozen aqueous solution containing drug and an inert matrix-building substance (e.g., mannitol or lactose). The process involves the simultaneous change in the receding boundary with time, phase transition at the ice–vapor interface governed by the Clausius–Clapeyron pressure–temperature relationship, and water vapor diffusion across the pore path length of the dry matrix under low-temperature and vacuum conditions.

Soluble Drugs in Topical Vehicles and Matrices

The original Higuchi model26,27 does not provide a fit to experimental data when the drug has a significant solubility in the tablet or ointment base. The model can be extended to drug release from homogeneous solid or semisolid vehicles, however, using a quadratic expression introduced by Bottari et al.30:

$$Q^2 + 2DRA^*Q - 2DA^*C_s t = 0 \qquad \textbf{(13–40)}$$

Here,

$$A^* = A - \frac{1}{2}(C_s + C_v) \qquad (13\text{–}41)$$

Q is the amount of drug released per unit area of the dosage form, *D*is an effective diffusivity of the drug in the vehicle, *A* is the total concentration of drug, C_s is the solubility of drug in the vehicle, C_v is the concentration of drug at the vehicle–barrier interface, and *R* is the diffusional resistance afforded by the barrier between the donor vehicle and the receptor phase. *A* is an effective area as defined in equation (13-41) and is used when *A* is only about three or four times greater than C_s.

When

$$Q^2 \gg 2DRA^*Q \qquad (13\text{–}42)$$

equation (13-40) reduces to one form of the Higuchi equation [equation (13-35)]:

$$Q = (2A^*DC_st)^{1/2} \qquad (13\text{–}42a)$$

Under these conditions, resistance to diffusion, *R*, is no longer significant at the interface between vehicle and receptor phase. When C_s is not negligible in relation to *A*, the vehicle-controlled model of Higuchi becomes

$$Q = [D(2A - C_s)C_st]^{1/2} \qquad (13\text{–}42b)$$

as derived earlier equation (13-33).

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The quadratic expression of Bottari, equation (13-40), should allow one to determine diffusion of drugs in ointment vehicles or homogeneous polymer matrices when C_s becomes significant in relation to *A*. The approach of Bottari et al.30 follows.

Because it is a second-degree power series in *Q*, equation (13-40)can be solved using the well-known quadratic approach. One writes

$$aQ^2 + bQ + c = 0 \qquad (13\text{–}43)$$

where, with reference to equation (13-40), *a* is unity, *b* = 2*DRA*, and *c*= -2*DAC*s*t*. Equation (13-43) has the well-known solution

$$Q = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \qquad (13\text{–}44)$$

or

$$Q = \frac{-2DRA^* + \sqrt{(2DRA^*)^2 + (2DA^*C_st)}}{2} \qquad (13\text{–}45)$$

where the positive root is taken for physical significance. If a lag time occurs, *t* in equation (13-45) is replaced by (t - t_L) for the steady-state period. Bottari et al.30 obtained satisfactory values for *b* and *c* by use of a least-square fit of equation (13-40) involving the release of benzocaine from suspension-type aqueous gels. *R*, the diffusional resistance, is determined from steady-state permeation, and C_v is then obtained from the expression

$$C_v = R(dQ/dt) \qquad (13\text{–}46)$$

The application of equation (13-40) is demonstrated in the following example.

Example 13-7

Calculate *Q*

Calculate *Q*, the amount in milligrams, of micronized benzocaine released per cm^2 of surface area from an aqueous gel after 9000 sec (2.5 hr) in a diffusion cell. Assume that the total concentration, *A*, is 10.9 mg/mL; the solubility, C_s, is 1.31 mg/mL; C_v = 1.05 mg/mL; the diffusional resistance, *R*, of a silicone rubber barrier separating the gel from the donor compartment is 8.10×10^3 sec/cm; and the diffusivity, *D*, of the drug in the gel is 9.14×10^{-6} cm^2/sec. From equation (13-41),

$$A^* = 10.9 \text{ mg/mL} - \frac{1}{2}(1.31 + 1.05) \text{ mg/mL} = 9.72 \text{ mg/mL}$$

Then,

$$DRA^* = (9.14 \times 10^{-6}\ \text{cm}^2/\text{sec}) \times (8.10 \times 10^3\ \text{sec/cm}) \times (9.72\ \text{mg/mL}) = 0.7196\ \text{mg/cm}^2$$

$$DA^*C_s t = (9.14 \times 10^{-6})(9.72)(1.31)(9000) = 1.047\ \text{mg}^2/\text{cm}^4$$

$$Q = -0.7196 + [(0.7196)^2 + 2(1.047)]^{1/2}\ \text{mg/cm}^2$$

$$= -0.7196 + [1.616] = 0.90\ \text{mg/cm}^2$$

The $Q_{(calc)}$ of 0.90 mg/cm^2 compares well with $Q_{(obs)}$ = 0.88 mg/cm^2.
A slight increase in accuracy can be obtained by replacing t= 9000 sec with t = (9000 - 405) sec, in which the lag time t= 405 sec is obtained from a plot of experimental Q values versus $t^{1/2}$. This correction yields a $Q_{(calc)}$ = 0.87 mg/cm^2.
(*b*) Calculate Q using equation (13–42*b*) and compare the result with that obtained in (*a*).
We have

$$Q = \{(9.14 \times 10^{-6})[(2 \times 10.9) - 1.31](1.31)(9000)\}^{1/2}$$

$$= 1.49\ \text{mg/cm}^2$$

Paul and coworkers31 studied cases in which A, the matrix loading of drug per unit volume in a polymeric dosage form, may be greater than, equal to, or less than the equilibrium solubility, C_s, of the drug in a matrix. The model is a refinement of the original Higuchi approach,26,27 providing an accurate set of equations that describe release rates of drugs, fertilizers, pesticides, antioxidants, and preservatives in commercial and industrial applications over the entire range of ratios of A to C_s.

Capsule-Type Device

A silastic capsule, as depicted in Figure 13-5a, has become a popular sustained and controlled delivery form in pharmacy and medicine.32,33,34 The release of a drug from a silastic capsule is shown schematically in Figure 13-5b. The molecules of the crystalline drug lying against the inside wall of the capsule leave their crystals, pass into the polymer wall by a dissolution process, diffuse through the wall, and pass into the liquid diffusion layer and the medium surrounding the capsule. The concentration differences across the polymer wall of thickness, h_m, and the stagnant diffusion layer of thickness, h_a, are represented by the lines C_p - C_m and C_s -C_b, respectively, where C_p is the solubility of the drug in the polymer and C_m is the concentration at the polymer–solution interface, that is, the concentration of drug in the polymer in contact with the solution. On the other hand, C_s is the concentration of the drug in the solution at the polymer–solution interface,

and it is seen in Figure 13-5b to be somewhat below the solubility of drug in polymer at the interface. There is a real difference between the solubility of the drug in the polymer and that in the solution, although both exist at the interface. Finally, C_b is the concentration of the drug in the bulk solution surrounding the capsule.

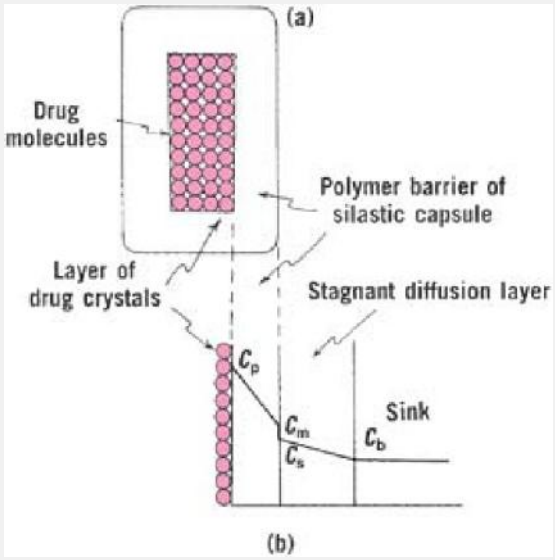

Fig. 13-5. Diffusion of drug from an elastic capsule. (*a*) Drug in the capsule surrounded by a polymer barrier; (*b*) diffusion of drug through the polymer wall and stagnant aqueous diffusion layer and into the receptor compartment at sink conditions. (From Y. W. Chien, in J. R. Robinson (Ed.), *Sustained and Controlled Release Drug Delivery Systems*, Marcel Dekker, New York, 1978, p. 229; Y. W. Chien, Chem. Pharm. Bull.**24,** 147, 1976.)

To express the rate of drug release under sink conditions, Chien32used the following expression:

$$Q = \frac{K_r D_a D_m}{K_r D_a h_m + D_m h_a} C_p t \qquad \textbf{(13–47)}$$

In equation **(**13-47**)**, Q is the amount of drug released per unit surface area of the capsule and K_r is the partition coefficient, defined as:

$$K_r = C_s / C_p \qquad \textbf{(13–48)}$$

When diffusion through the capsule membrane or film is the limiting factor in drug release, that is, when $K_r D_a h_m$ is much greater than$D_m h_a$, equation **(**13-47**)** reduces to:

$$Q = \frac{D_m}{h_m} C_p t \qquad \textbf{(13–49)}$$

and when the limiting factor is passage through the diffusion layer$D_m h_a \gg K_r D_a h_m$),

$$Q = \frac{D_a}{h_a} C_s t = \frac{K_r D_a}{h_a} C_p t \qquad \textbf{(13–50)}$$

The right-hand expression can be written because $C_s = K_r C_p$ as defined earlier, in equation **(**13-48**)**. The rate of drug release, Q/t, for a polymer-controlled process can be calculated from the slope of a linear Q-versus-t plot, and from equation **(**13-49**)** is seen to equal $C_p D_m / h_m$. Likewise, Q/t, for the diffusion-layer–controlled process, resulting from plotting Q versus t, is found to be $C_s D_a / h_a$. Furthermore, a plot of the release rate, Q/t, versus C_s, the solubility of the drug in the surrounding medium, should be linear with a slope of D_a/h_a.

Example 13-8

Progesterone Release Rate

The partition coefficient, $K_r = C_s/C_p$, of progesterone is 0.022; the solution diffusivity, D_a, is 4.994×10^{-2} cm^2/day; the silastic membrane diffusivity, D_m, is 14.26×10^{-2}cm^2/day; the solubility of progesterone in the silastic membrane, C_p, is 513 μg/cm^3; the thickness of the capsule membrane, h_m, is 0.080 cm; and that of the diffusion layer,h_a, as estimated by Chien,30 is 0.008 cm.

Calculate the rate of release of progesterone from the capsule and express it in μg/cm^2 per day. Compare the calculated result with the observed value, Q/t = 64.50 μg/cm^2 per day.
Using equation (13-47), we find

$$Q/t = \frac{C_p K_r D_a D_m}{K_r D_a h_m + D_m h_a}$$

$$Q/t = \frac{(513\ \mu g/cm^3)(0.022)(4.994 \times 10^{-2}\ cm^2/day) \times (14.26 \times 10^{-2}\ cm^2/day)}{(0.022)(4.994 \times 10^{-2}\ cm^2/day)(0.080\ cm) + (14.26 \times 10^{-2}\ cm^2/day)(0.008\ cm)}$$

$$Q/t = \frac{0.08037}{0.00123} = 65.34\ \mu g/cm^2\ \text{per day}$$

In the example just given, (*a*) is $K_r D_a h_m \gg D_m h_a$ or (*b*) is $D_m h_a \gg K D_a h_m$? (*c*). What conclusion can be drawn regarding matrix or diffusion-layer control?
We have

$$K_r D_a h_m = 8.79 \times 10^{-5};\ D_m h_a = 1.14 \times 10^{-3}$$

$$D_m h_a/(K_r D_a h_m + D_m h_a) = (1.14 \times 10^{-3})/[(8.79 \times 10^{-5}) + (1.14 \times 10^{-3})] = 0.93$$

Therefore, $D_m h_a \gg K_r D_a h_m$, and the system is 93% under aqueous diffusion-layer control. It should thus be possible to use the simplified equation (13-50):

$$Q/t = \frac{K_r D_a C_p}{h_a} = \frac{(0.022)(4.994 \times 10^{-2})(513)}{0.008}$$

$$= 70.45\ \mu g/cm^2\ \text{per day}$$

Although $D_m h_a$ is larger than $K_r D_a h_m$ by about one order of magnitude (i.e., $D_m h_a / K D_a h_m$ = 13), it is evident that a considerably better result is obtained by using the full expression, equation (13-47).

Example 13-9
Calculate Membrane Thickness
Two new contraceptive steroid esters, A and B, were synthesized, and the parameters determined for release from polymeric capsules are as follows32:

	K_r	D_a(cm^2/day)	D_m(cm^2/day)	C_p(μg/cm^3)	h_a (cm)	$Q/t_{(obs)}$(μg/cm^2 per day)
A	0.15	25×10^{-2}	2.6×10^{-2}	100	0.008	24.50
B	0.04	4.0×10^{-2}	3.0×10^{-2}	85	0.008	10.32

Using equation (13-47) and the quantities in the table, calculate values of h_m in centimeter for these capsule membranes.
We have

$$Q/t = \frac{C_p K_r D_a D_m}{K_r D_a h_m + D_m h_a}$$

$$(Q/t)(K_r D_a h_m + D_m h_a) = C_p K_r D_a D_m$$

$$(Q/t)(K_r D_a h_m) = C_p K_r D_a D_m - D_m h_a (Q/t)$$

$$h_m = \frac{C_p K_r D_a D_m - D_m h_a (Q/t)}{(Q/t) K_r D_a}$$

For capsule A,

$$h_m = \frac{(100)(0.15)(25 \times 10^{-2})(2.6 \times 10^{-2}) - (2.6 \times 10^{-2})(0.008)(24.50)}{(24.50)(0.15)(25 \times 10^{-2})}$$

$$h_m = \frac{0.0924}{0.9188}\text{cm} = 0.101\ \text{cm}$$

Note that all units cancel except centimeter in the equation for h_m. The reader should carry out the calculations for compound B. (*Answer:* 0.097 cm)

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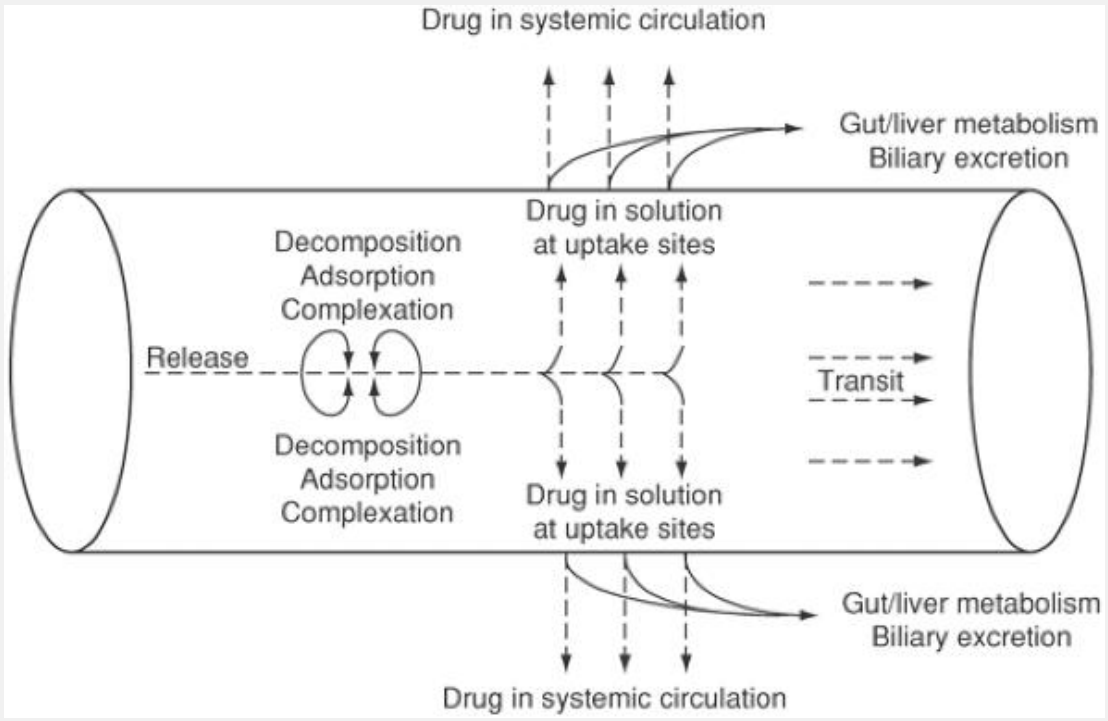

Fig. 13-6. A schematic representation of the factors that determine the fraction of drug that is absorbed from a drug product across the intestinal mucosa. Decomposition, adsorption to intestinal components, or complexation can reduce the amount of drug available for absorption. Drug uptake is controlled by the drug's permeability through the intestinal mucosa and the length of time that it stays at the absorption site (i.e., residence time). The longer it stays within the "absorption window" and the higher the permeability, the more is the drug absorbed across the intestinal mucosa. (From J. B. Dressman, G. L. Amidon, C. Reppas, and V. P. Shah,

Pharm. Res. **15,** 11, 1998. With permission.)

Dissolution and Release from Oral Drug Products

After a solid dosage form such as a tablet is administered by mouth to a patient, it must first disintegrate into larger clusters of particles known as aggregates. Deaggregation then occurs and individual particles are liberated. Finally, particles dissolve, releasing the active drug into solution. Dissolution is a time-dependent (or kinetic) process that represents the final step of drug release, which is ultimately required before a drug can be absorbed or exert a pharmacologic effect. For immediate-release dosage forms, the rate of drug release and dissolution relative to the rate of transit through the intestine and the permeability profile of the small intestine to the drug determines the rate and the extent of drug absorption (Fig. 13-6). If drug dissolution is slow compared with drug absorption, less drug may be absorbed, especially if the drug is absorbed preferentially in certain locations ("absorption windows") of the gastrointestinal tract. Slower absorption due to slower dissolution can also result in lower peak drug blood levels. On the other hand, semisolid dosage forms such as topical drug products are applied to the skin and remain in the area of application. As described in the SUPAC-SS Guidance,[4b] semisolid dosage forms are complex formulations having complex structural elements. Often they are composed of two phases (oil and water), one of which is a continuous (external) phase, the other of which is a dispersed (internal) phase. The active ingredient is often dissolved in one phase even though occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend on various factors: the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology. These factors combine to determine the release characteristics of the drug as well as other characteristics, such as viscosity.

Table 13-1 The Biopharmaceutics Classification System (BCS)*,†

Class I	Class II	Class III	Class IV
High solubility, high permeability	Low solubility, high permeability	High solubility, low permeability	Low solubility, low permeability

*From G. L. Amidon, H. Lennernas, V. P. Shah, and J. R. Crison, Pharm. Res. **12,** 413, 1995.

†The goal of the system is to provide guidance as to when in vitro studies may be used in lieu of clinical studies to establish the bioequivalence of two products.

The BCS6 categorizes drugs into four types (Table 13-1), depending on their solubility and permeability characteristics. Solubility is covered in Chapter 9 and permeability in Chapter 11. For the purposes of this chapter, it would be helpful to give some perspective on the role of solubility, permeability, and drug release on the availability of drug in the human body after oral administration. In most situations, only drug that dissolves and is released from the drug product will be available for absorption through the intestinal tissues and into the blood stream of patients. Therefore, the rate at which the drug dissolves (in other words, dissolution rate) and its solubility become important factors, and these have already been discussed in some detail. Permeability is a measure of how rapidly a drug can penetrate a biologic

tissue such as the intestinal mucosa and appears on the other side (e.g., the blood side). Therefore, a drug must be soluble and permeable
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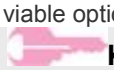
for absorption to occur. To classify drugs according to these two important factors, the BCS was proposed. According to the BCS, class I drugs are well absorbed (more than 90% absorbed) because they are highly permeable and go rapidly into solution. Poor absorption of class I drugs is only expected if they are unstable or if they undergo reactions (such as binding or complexation) in the intestine that inactivate them. Bioavailability could also be low if they are metabolized in the intestine or liver or are subject to secretory processes such as intestinal or enterohepatic cycling. Class II drugs are those with solubilities too low to be consistent with complete absorption even though they are highly membrane permeable. Class III drugs have good solubility but low permeability. In other words, they are unable to permeate the gut wall quickly enough for absorption to be complete. Class IV drugs have neither sufficient solubility nor permeability for absorption to be complete. Class IV drugs tend to be the most problematic, although there are numerous examples of class IV drugs that are successfully used in the clinic. The student should keep in mind that even though class IV drugs do not possess optimal properties, some drugs in this category may still be absorbed well enough so that oral administration is a viable option.



Key Concept

The Role of Dissolution Testing

In a 1998 review article, Dressman and colleagues7summarized the situation well: Dissolution tests are used for many purposes in the pharmaceutical industry: in the development of new products, for quality control, and to assist with the determination of bioequivalence. Recent regulatory developments such as the Biopharmaceutics Classification Scheme have highlighted the importance of dissolution in the regulation of postapproval changes and introduced the possibility of substituting dissolution tests for clinical studies in some cases. Therefore, there is a need to develop dissolution tests that better predict the in vivo performance of drug products. This could be achieved if the conditions of the gastrointestinal tract were successfully reconstructed in vivo.

Numerous factors need to be considered if dissolution tests are to be considered biorelevant. They are the composition, hydrodynamics (fluid flow patterns), and volume of the contents in the gastrointestinal tract. Biorelevant media considerations are covered in this section and the apparatus used to measure dissolution are covered in the next. Other aspects are also covered throughout the book. The student who wants to study this in more detail is referred to the original review article.

Typically, the BCS is used to build an IVIVC. According to the Food and Drug Administration Guidance document, an IVIVC is “a predictive mathematical model describing the relationship between an in vitro property of an oral dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed).”5 Because the focus of this chapter is drug dissolution and release, we will focus on aspects of IVIVCs related only to these phenomena. Correlation of in vivo results with dissolution tests is likely to be best for class II drugs because dissolution rate is the principal limiting characteristic to absorption. Another case where good IVIVCs are often obtained is when a class I drug is formulated as an extended-release product. This is because the release profile controls the rate of absorption and absorption profile. In the first case, drug dissolution (and solubility) are the rate-limiting step for absorption, whereas in the second case, the drug has adequate solubility and permeability, so its ability to be absorbed is controlled by its availability in the lumen of the gastrointestinal tract. Therefore, release from the dosage form is the key process. These examples highlight the practical differences between the processes of drug dissolution and release. Controlled-release products work using a combination of mechanisms and are covered in Chapter 21.

There are several physicochemical and physiologic factors that control the dissolution of drug products in humans and need to be considered when designing dissolution tests. They are the composition, mixing patterns (i.e., hydrodynamics), and volume of the contents in the gastrointestinal tract. These are reviewed in detail by Dressman et al.7 The student must keep in mind that the gastrointestinal tract is an organ with a multitude of functions and drug products; foods and nutrients can remain in the gastrointestinal tract for up to 24 to 30 hr if they are not completely absorbed. The conditions of the gastrointestinal tract vary with the location of the segment of interest. To link the three key factors that control the dissolution of drugs in the gastrointestinal tract with the mathematical understanding developed earlier in the chapter, let us reexamine the Noyes–Whitney equation19 with some commonly used modifications7 as introduced by Levich21 and Nernst–Brunner22

$$\frac{dX_d}{dt} = \frac{AD}{\delta}\left(C_s \frac{Xd}{V}\right) \qquad \textbf{(13–51)}$$

where A is the effective surface area of the drug, D is the diffusion coefficient of the drug, δ is the diffusion boundary layer thickness adjacent to the dissolving surface, C_s is the saturation solubility of the drug under intestinal conditions, X_d is the amount of drug already in solution, and V is the volume of the dissolution media. To manipulate the effective surface area of a drug, a formulator may attempt to reduce the particle size to increase wettability. In the intestine, however, there are natural surface tension–reducing agents that promote drug dissolution. Most of these natural surfactants are found in the secretions that come from the stomach and bile. If one were to design a biorelevant dissolution test

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for drugs with poor dissolution characteristics, it would be important to account for the natural surfactants located in the stomach and the intestine. The maximum solubility of the drug in the intestine is influenced by many factors (solubility is covered in Chapter 9) such as the buffer capacity, pH, the presence of food, and natural surfactants such as bile salts and lecithin. Dressman et al.35showed that the presence of a meal in humans immediately raised the pH of the stomach from its normally acidic state (pH 1.5–3.0) to pH 5.5 to 7.0. This could dramatically affect the solubility of drugs, which, in turn, can affect the oral bioavailability. The diffusivity of the drug, or its natural ability to diffuse through the intestinal contents, will be a function of the viscosity of the intestinal contents. Viscosity will depend on the level of natural secretions, which may vary in the fed and fasted states, and the presence of food. The boundary layer thickness around the dissolving particle will depend on how vigorous local mixing is. In other words, if motility or mixing is higher, then the stagnant layer surrounding the particle will be smaller. If mixing is reduced, then the stagnant layer becomes larger and may alter dissolution. For dissolution to proceed, there must be a driving force. As shown in equation **(**13-51**)**, the “driving force” is represented by the term $C_s - X_d/V$. If the difference between C_s andX_d/V is great, then the rate of drug dissolution, X_d/dt, will be greater. As the concentration of dissolved drug (X_d/V) becomes larger, the driving force is reduced. So, the relevant question is, “How can drug dissolution in the gastrointestinal tract ever be complete?” To maximize drug dissolution, the concentration of dissolved drug must be minimized. Of course, this happens when the drug is absorbed through the intestinal wall and into the blood. The rate of absorption is related to the permeability of the drug (Chapter 15) and intestinal drug concentration, X_d/V. For passively absorbed drugs, the greater the intestinal drug concentration, the faster is the rate of absorption. Therefore, dissolved drug concentrations in the intestine can be kept low, which enhances dissolution. When X_d/V is no greater than 20% of C_s, this condition is met and is known as “sink conditions.” Maintaining sink conditions in a dissolution test is another matter altogether, but is a very important concern.

Biorelevant Media

Based on all of the previous considerations, biorelevant media have been proposed. The rationale for proposing the various components was provided in the previous comments. Because of the significant difference between the stomach and the intestine, media representative of the gastric and intestinal environments is commonly used. The major differences between gastric and intestinal media are the pH and presence of bile. Another important consideration is the absence or presence of food in the

stomach. When food is absent, conditions between patients do not vary too much. Because the stomach is acidic (<pH 3) in most patients in the fasted state, the main variables are the type and volume of liquid administered with the dosage form. If water is the administered fluid, the buffer capacity is low, and this would not be a factor in dissolution testing. Although it is known that the surface tension of gastric contents is reduced, the exact physiologic agents that are responsible are not known. Therefore, sodium lauryl sulfate is commonly used in dissolution testing to achieve this effect. The composition of simulated fasted-state gastric fluid (pH 1.2) is rather simple and is listed in Table 13-2. In the fed state, the conditions of the stomach are highly dependent on the type and quantity of meal ingested. Simulated intestinal fluid (SIF) is described in the 26th edition of the *United States Pharmacopeia* as a 0.05 M buffer solution containing potassium dihydrogen phosphate (Table 13-2). The pH of this buffer is 6.8 and falls within the range of normal intestinal pH. Pancreatin may also be added if a more biorelevant form of the medium is required. Pancreatin is a mixture of the fat-dissolving enzyme lipase, the protein-degrading enzymes called proteases, and those that break down carbohydrates, like amylase. If SIF does not contain pancreatin, it is indicated using the notation SIFsp, where the "sp" means "sans pancreatin" or "without pancreatin." Some of the parameters that can profoundly influence the dissolution rate of drug products such as the buffer capacity, pH, and surfactant concentrations and how they can be introduced into a biorelevant dissolution test have been discussed. Other considerations are the volume of the contents in the stomach or intestinal segment and the duration of the test as it related to residence time in the stomach or intestinal segment.

Table 13-2 Composition of Dissolution Media for in Vitro Dissolution Testing

Medium	Composition	Amount
Simulated gastric fluid	NaCl	2.0 g
pH 1.2 (SGFsp), USP 26	Concentrated HCl	7.0 mL
	Deionized water to	1.0 L*
Simulated intestinal fluid	KH_2PO_4	68.05 g
pH 6.8 (SIFsp), USP 26	NaOH	8.96 g
	Deionized water to	10.0 L†
*Add 3.2 g of pepsin for SGF.		
†Add X g of pancreatin for SIF.		

Methods and Apparatus

The objective of most pharmacopeial dissolution monographs is to establish procedures for evaluating batch-to-batch consistency in the dissolution of drug products. Similar dissolution characteristics for different batches of the same drug product imply similar performance of the product in humans. Although there are many customized and original dissolution testing devices reported in the literature,

the purpose of this section is to introduce the basic apparatus used in compendial testing of immediate- and modified-release oral dosage forms.
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USP Methods I and II for Dissolution[36,37,38]

The most commonly used methods for evaluating dissolution first appeared in the 13th edition of the *United States Pharmacopeia* in early 1970. These methods are known as the USP basket (method I) and paddle (method II) methods and are referred to as "closed-system" methods because a fixed volume of dissolution medium is used. In practice, a rotating basket or paddle provides a steady stirring motion in a large vessel with 500 to 1000 mL of fluid that is immersed in a temperature-controlled water bath (Fig. 13-7a)[36,39]Variants of these two standard apparatuses have been reported and are depicted in Figure 13-7b (see Shiu[36] for a complete discussion). The devices are very simple, robust, and easily standardized. Descriptions for apparatus specifications are detailed in the current version of the USP. The USP basket and paddle methods are the methods of choice for dissolution testing of immediate-release oral solid dosage forms. The use of alternative dissolution methods should be considered only after USP methods I and II are found to be unsatisfactory. Biorelevant dissolution media were discussed in the previous section. Other commonly used media include (*a*) water,
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(*b*) 0.1 N HCl, (*c*) buffer solutions, (*d*) water or buffers with surfactants, and (*e*) low-content alcoholic aqueous solutions. The temperature of the medium is usually maintained at body temperature (37°C) for dissolution testing. Although water is one of the most commonly listed dissolution media found in USP monographs, it may not be physiologically relevant due to the lack of buffering capacity. In the following examples, a variety of conditions are used that result in significantly different dissolution profiles, suggesting that the appropriate selection of dissolution conditions must be made.

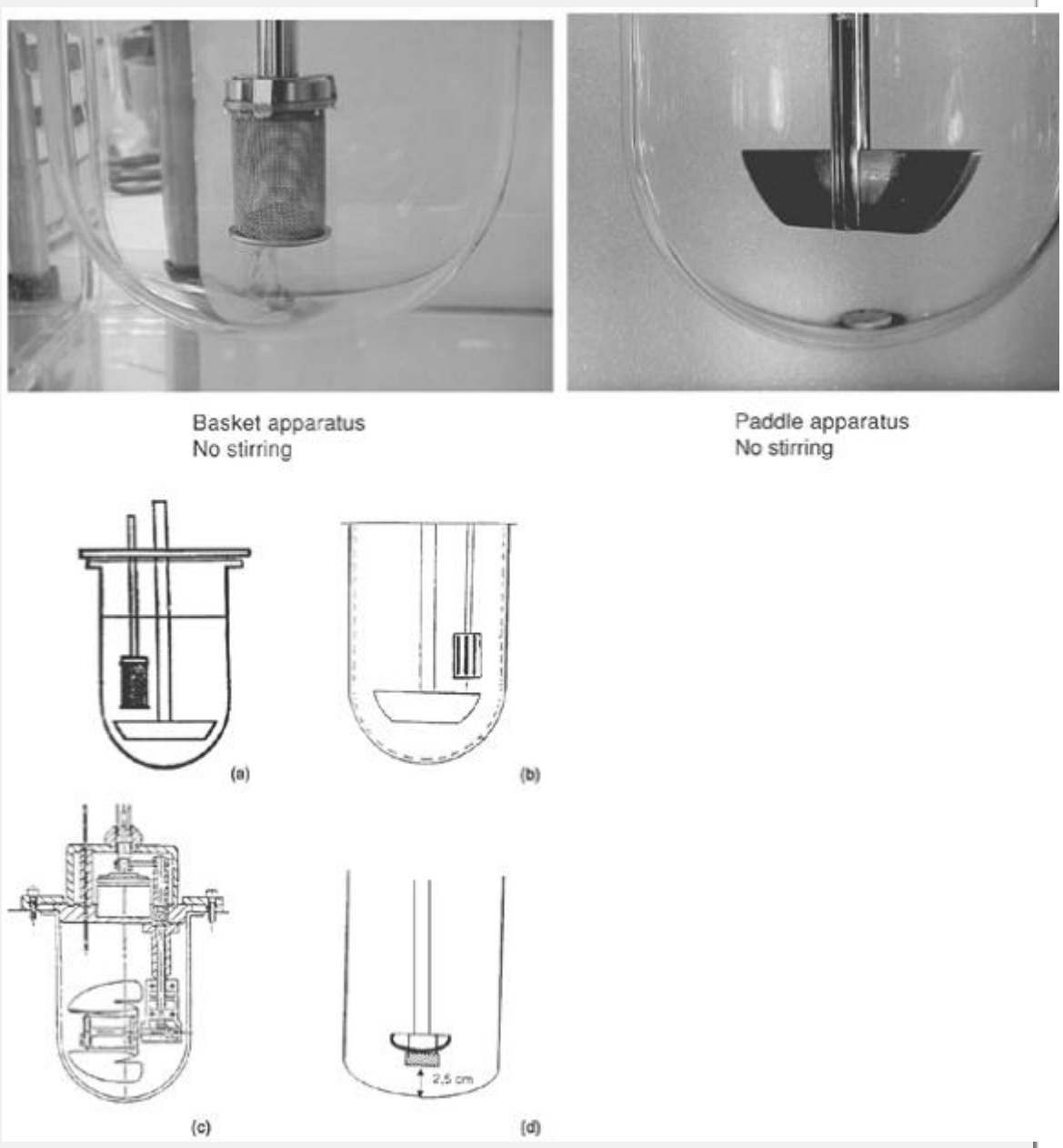

Fig. 13-7. (Top) Pictures of USP basket and paddle apparatus. Note the dye coming from the tablet in the basket in the left panel. Types of dissolution apparatus include (*a*) a stationary basket-rotating paddle for immediate-release oral solid dosage forms, (*b*) a modified stationary basket rotating paddle for suppositories, (*c*) a rotating dialysis cell, and (*d*) a rotating paddle–rotating basket. (From G. K. Shiu, Drug Inf. J. **30,** 1045, 1996. With permission.)

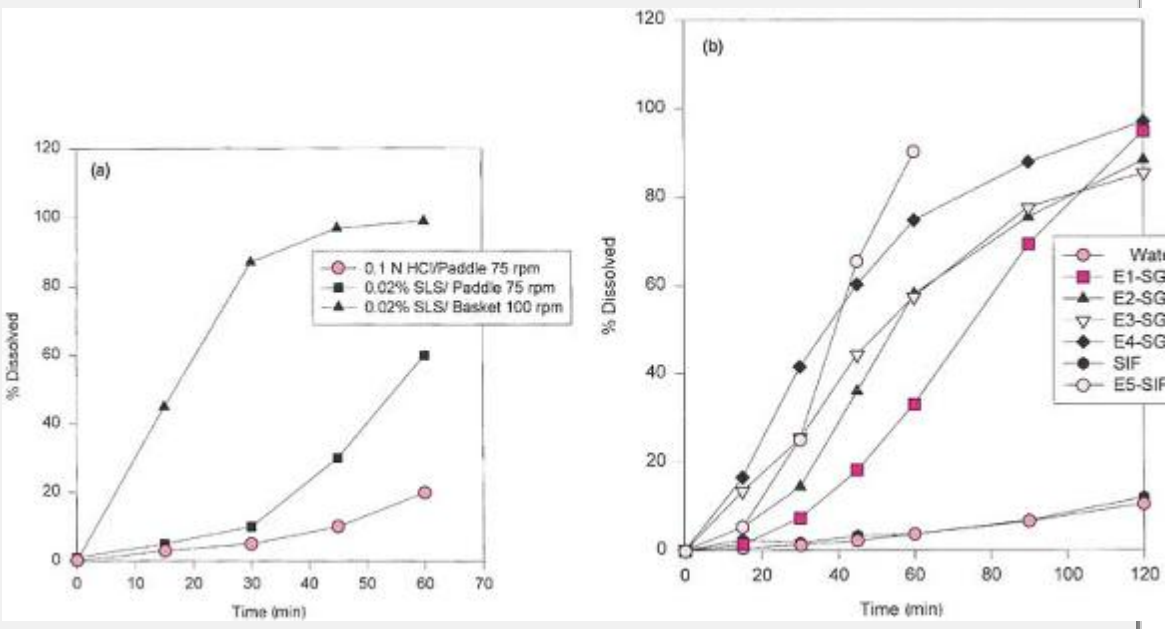

Fig. 13-8. (*a*) Dissolution profiles of norethindrone acetate of a norethindrone acetate: ethinyl estradiol combination tablet by various dissolution media and methods. (*b*) Dissolution profiles of theophylline from an aged theophylline soft gelatin product under various dissolution media by USP basket method at 100 rpm rotating speed. E1, E2, E3, and E4 are pepsin with increasing enzyme activity. E5 is a commercially available intestinal enzyme, pancreatin. (From G. K. Shiu, Drug Inf. J. **30,** 1045, 1996. With permission.)

Example 13-10

Dissolution Profiles of Norethindrone Acetate(Fig. 13-8a)

Before 1990, water was used as the dissolution medium for testing combination of oral contraceptive drug products. Water was used for norethindrone (NE): ethyl estradiol (EE) tablets and 3% isopropanol was used for NE: mestranol (ME) tablets. The dissolution data for norethindrone are shown in Figure 13-8a. An example of an acceptable dissolution profile is seen when the dissolution medium is 0.1 N HCl with 0.02% sodium lauryl sulfate in the USP basket method at 100 rpm. (Example taken from Shiu36; original data in Nguyen et al.40)

Example 13-11

Dissolution Profiles of Theophylline from Soft Gelatin Capsules36 (Fig. 13-8b)

This example shows the role of biorelevant dissolution media. Inclusion of the appropriate enzymes in the dissolution medium has been considered appropriate because they are found naturally in the gastrointestinal tract. We often assume that the dosage form assists in improving bioavailability. This example shows that this is not always the case; this example is consistent with the report of a workshop published in 1996,41 where it was recognized that discrepancies between dissolution and bioavailability occur because the gel that comprises soft and hard gelatin capsules becomes cross-linked. In this example, the dissolution of theophylline from aged soft gelatin capsules was studied in a variety of media: water, increasing amounts of pepsin in simulated gastric fluid (SGF) (E1 through E4), SIF, and SIF with pancreatin (Fig. 13-8b). The highest dissolution rates were observed in the media with enzymes present, and for pepsin, an increase in dissolution was observed with increasing pepsin activity, showing the role of the soft gelatin capsule dosage form in hindering the release of theophylline.

*Special Considerations for Modified-Release Dosage Forms: USP Apparatuses 3 and 4**

Modified-release delivery systems are similar in size and shape to conventional immediate-release dosage forms. For example, shown in Figure 13-9 are nifedipine (Procardia® XL) "tablets," which are actually nondisintegrating osmotic pumps (Chapter 21). The mechanisms for controlling the release of the drugs are becoming very sophisticated, and special consideration must be given to how drug release is

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evaluated. Regulatory guidances recommend four dissolution apparatuses for modified-release dosage forms. Although the existing apparatuses are adequate for the intended purpose, equipment may require either modifications or completely new designs to accommodate these new release mechanisms. For example, nondisintegrating dosage forms (e.g., Procardia XL) requiring a delivery orifice for drug release may dictate a special design or modification of the dissolution apparatus so that the orifice is not blocked. In contrast, disintegrating or eroding delivery systems pose the challenge of transferring the dosage form to different media without losing any of the pieces. In general, methods of agitation, changing the medium, and holding the dosage form in the medium without obstructing the release mechanism are relevant to drug testing. A challenging component of a dissolution test for a modified-release delivery system is changing the media to obtain a pH gradient or to simulate fed and fasted conditions. The ability to easily change the medium is the focus of commercially available dissolution equipment targeted for modified-release delivery systems, and several equipment designs are available. The USP Apparatus 3, a reciprocating cylinder, dips a transparent cylinder containing the dosage form at a rate determined by the operator.[43,44] The tubes have a mesh base to allow the medium to drain into a sampling reservoir as the tube moves up and down, thus creating convective forces for dissolution. The cylinders can also be transferred to different media at specified times, automatically. A second design is the rotating bottle apparatus, which also allows for changing of medium to simulate a pH gradient or fed and fasted conditions. The USP Apparatus 4 is a flowthrough cell containing the dosage form that is fed with dissolution medium from a reservoir. Directing the fluid through a porous glass plate or a bed of beads produces a dispersed flow of medium. Turbulent or laminar flow can be achieved by changing the bottom barrier. As with Apparatus 3, the medium can be changed to provide a pH gradient, surfactants, and other medium components.

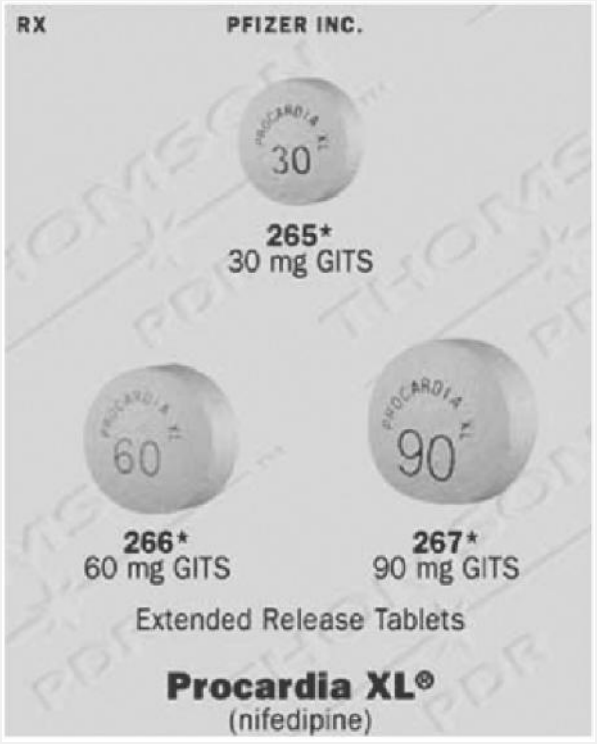

Fig. 13-9. Procardia® XL tablets. These tablets are orally delivered osmotic pumps that release drug through a laser-drilled orifice. Although the tablets look like conventional tablets, they behave differently. For example, they do not disintegrate and are excreted in the stool intact. (From*Physicians' Desk Reference*, 58th Ed., Thomson PDR, Montvale, N. J., 2004. With permission.)

Chapter Summary

Dissolution and drug release are fundamental concepts that affect the practice of pharmacy on a daily basis. Examples include patients who now have to take only one tablet daily instead of one tablet three times daily because they are taking the osmotic pump form of the medication. Not only does drug delivery improve convenience for patients but it also improves compliance as they adhere to treatment regimens that may have been too complex. At this point the student should understand these concepts and understand the differences among immediate-, modified-, delayed-, extended-, and controlled-release delivery systems. You should also be able to differentiate between zero-order and first-order release kinetics as well as understand intrinsic dissolution rate and the driving force for dissolution. Understanding the effect of surface area and sink conditions on dissolution rate is critical and helps explain why drugs are so well absorbed after oral administration. The BCS was discussed and the important role of permeability and solubility was demonstrated. Finally, the student should have an appreciation for the different roles that dissolution testing plays in the pharmaceutical sciences (a quality control versus predictive role) and understand how media properties such as viscosity, pH, lipids, and surfactants can affect dissolution.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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*Much of this opening section was adapted from Cohen et al.1

*This section was adapted with some modification from reference 12.

*Modified from Crison.42

Chapter Legacy

Fifth Edition: published as Chapter 13 (Drug Release and Dissolution). Updated by Patrick Sinko.

Sixth Edition: published as Chapter 13 (Drug Release and Dissolution). Updated by Patrick Sinko.