8 MATHEMATICAL CONCEPTS OF CONTROLLED RELEASE

I. REACTION RATE AND RELEASE RATE

The kinetics used to describe the reaction rates can be used to describe the release rate of a drug from controlled-release dosage forms. The similarity between the two kinetics is shown in Figure 8.1. Let's consider a reaction in which drug *A* (closed circles) becomes product *P* (open circles), and a release in which drug molecules in Compartment 1 are released into Compartment 2.

A. ZERO-ORDER REACTION AND ZERO-ORDER RELEASE

From the reaction scheme in Figure 8.1, the following rate law is obtained.

$$R = \frac{-d[A]}{dt} = \frac{d[P]}{dt} \qquad R = \frac{-d[A_1]}{dt} = \frac{d[A_2]}{dt}$$

From the experiments, the following empirical rate law is found for zero-order reaction:

$$R = k[A]_0 = k \qquad R = k[A_1]_0 = k$$

Combining the rate law and empirical rata law leads to:

$$\frac{-d[A]}{dt} = k \left(\text{or } \frac{d[P]}{dt} = k \right) \qquad \frac{-d[A_1]}{dt} = k \left(\text{or } \frac{d[A_2]}{dt} = k \right)$$

Solving the above equation results in the zero-order equation:

$$[A] = [A]_0 - kt \qquad [A_1] = [A_1]_0 - kt$$

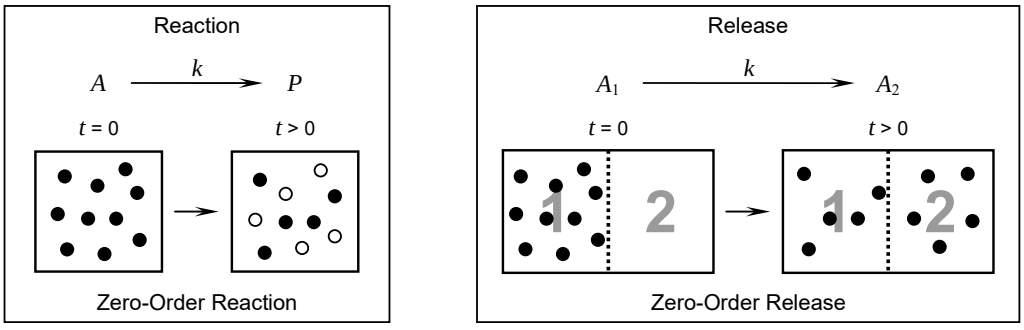

Figure 8.1 Comparison between a reaction and a drug release.

where $[A]_0$ and $[A_1]_0$ is the initial concentrations of $[A]$ and $[A_1]$, respectively.

The change in concentrations of $[A]$ and $[P]$ as well as the reaction rate as a function of time is shown in Figure 8.2 (left side). The right side of Figure 8.2 shows the change in concentrations of $[A_1]$ and $[A_2]$ as well as the release rate as a function of time.

As shown in Figure 8.2, the drug-release kinetics can be described by exactly the same equations used in the chemical kinetics. The following section shows another example of the first-order kinetics and the first-order release.

B. First-Order Reaction and First-Order Release

From the above reaction scheme, the following rate law is obtained:

$$R = \frac{-d[A]}{dt} = \frac{d[P]}{dt} \qquad R = \frac{-d[A_1]}{dt} = \frac{d[A_2]}{dt}$$

From the experiments, the following empirical rate law is found for first-order reaction:

$$R = k[A]^1 = k[A] \qquad R = k[A_1]^1 = k[A_1]$$

Combining the rate law and empirical rata law leads to:

$$\frac{-d[A]}{dt} = k[A]\left(\text{or } \frac{d[P]}{dt} = k[A]\right) \qquad \frac{-d[A_1]}{dt} = k[A_1]\left(\text{or } \frac{d[A_2]}{dt} = k[A_1]\right)$$

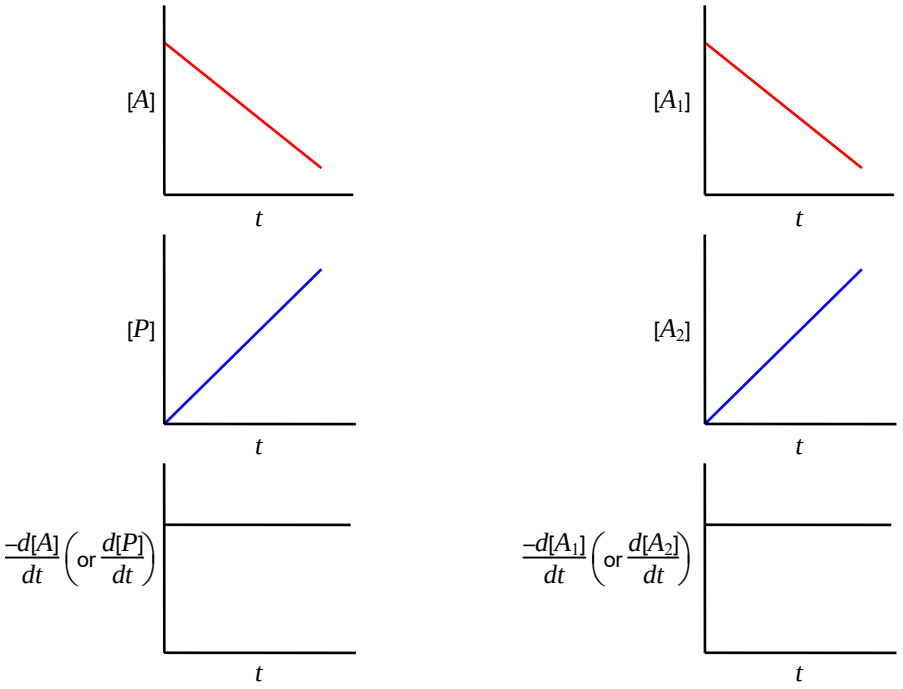

Figure 8.2 A comparison between the change in concentration of reactant and product in a zero-order reaction with the concentration of drug in Compartment 1 $[A_1]$ and Compartment 2 $[A_2]$ during zero-order drug release.

Solving the above equation results in the zero-order equation:

$$[A] = [A]_0 \exp(-kt) \qquad [A_1] = [A_1]_0 \exp(-kt)$$

or

$$\ln[A] = \ln[A]_0 - kt \qquad \ln[A_1] = \ln[A_1]_0 - kt$$

where $[A]_0$ and $[A_1]_0$ is the initial concentrations of $[A]$ and $[A_1]$, respectively.

The change in concentrations of $[A]$ and reaction rate as a function of time is shown in the left side of Figure 8.3. The right side of Figure 8.3 shows the change in concentrations of $[A_1]$ and the release rate as a function of time.

The half-life of ^{14}C is 5,730 y and is thus good for dating up to 70,000 y. The half-life of ^{238}U, which becomes ^{206}Pb, is 4.47 billion years. Stones contain uranium; thus, uranium can be used to date rock layers.

II. DOSE CALCULATION FOR CONTROLLED RELEASE

Calculation of the dose necessary to deliver a drug for a certain period of time using controlled-release dosage forms requires understanding of pharmacokinetic parameters. Pharmacokineticists produced one-compartment models (Widmark & Tanberg, 1924) and two-compartment models (Teorell, 1937). Parameters for absorption, distribution, metabolism, and elimination were formulated (Dominguez, 1950) and these advances led to the pharmacokinetic theory in 1953 (Döst & Von Hattingbert, 1972). Shortly thereafter, biopharmaceutics was born (Wagner, 1961).

The drug concentration in blood may not necessarily represent the efficacy of the drug. For example, as the blood level of digoxin decreases in time while its efficacy increases. This particular example shows that the important concentration of drug is the concentration of the drug in the target site (such as the tissue where the drug is acting) and not the concentra-

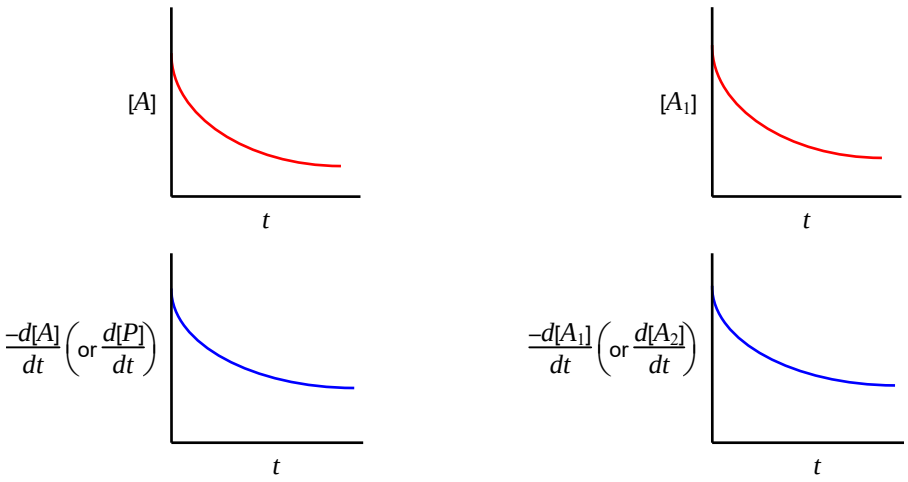

Figure 8.3 A comparison between the change in concentration of reactant in a first-order reaction with the concentration of drug in Compartment 1 $[A_1]$ during first-order drug release.

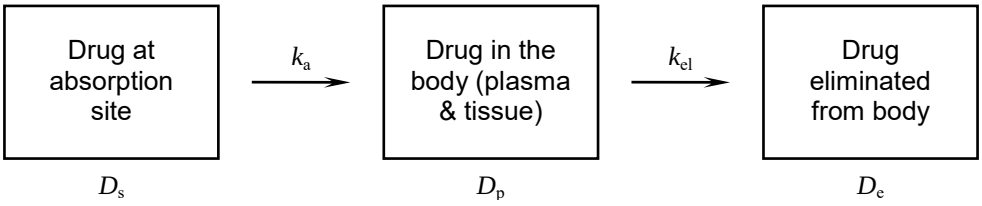

Figure 8.4 Sequence of a one-compartment open model.

tion of the drug in blood. In dose calculation for controlled-release formulations, one-compartment open model is often used.

A. One-Compartment Open Model

When a dosage form is administered orally, the drug absorption from the GI tract and drug elimination from the blood can be described by the one-compartment open model, which is based on the sequence in Figure 8.4.

There are two assumptions in this model. First, k_a and k_{el} are first-order rate constants. The absorption- and elimination-rate constants are usually first-order, and this is a good assumption. Second, we assume that there is a rapid equilibrium of drug concentration between plasma and tissues. In other words, we assume that the drug is distributed from the plasma to tissues and other body fluids so rapidly that the drug concentration in plasma is equal to that in tissues.

According to the model, the total amount of drug in the body at any time can be described by $[D_p] \times V_d$, where V_d is the total volume of distribution of the drug in the body. V_d is the imaginary value that is calculated from the following equation:

$$V_d = \frac{[\text{i.v. dose}]}{[D_p]_0}$$

Where $[D_p]_0$ is the drug concentration in the plasma immediately after injection. Since different drugs have different distribution between plasma and tissues, $[D_p]_0$ of drugs will be different. Naturally, V_d will be different for each drug.

B. Dose Calculation

Let's consider the oral administration of a drug and the drug absorption and elimination using the following simplified scheme.

$$\begin{array}{lccccc} & D_s & \xrightarrow{k_a} & D_p & \xrightarrow{k_{el}} & D_e \\ \text{Concentration} & [D_s] & & [D_p] & & [D_e] \end{array}$$

Change in drug conc. in plasma (R): $$R = \frac{d[D_p]}{dt} = k_a[D_s] - k_{el}[D_p]$$

or $$R = \frac{-d[D_p]}{dt} = -k_a[D_s] + k_{el}[D_p]$$

R here describes the rate of drug elimination in terms of the drug concentration in plasma. If the rate of drug elimination is described in terms of the total amount of drug, $[D_p]$ should be replaced with $[D_p]\cdot V_d$ as described below.

Total amount of drug: $[D_p]\cdot V_d$

Change in total amount (R): $R = \dfrac{-d([D_p]\cdot V_d)}{dt} = -k_a([D_s]\cdot V_d) + k_{el}([D_p]\cdot V_d)$

Figure 8.5 shows the pharmacokinetic profile of the drug after oral administration. After the initial dose in the absence of the sustaining dose, the drug concentration will reach the peak concentration $[D_p]_{max}$ at time t_{max} and then starts decreasing. By increasing the dose, $[D_p]_{max}$ will increase and this will result in longer duration of the drug in blood. The problem with this approach, however, is that the drug concentration in the blood may be far above the maximum safe concentration. For this reason, increasing the dose of the conventional dosage form is not a viable method of long-term drug delivery.

At $[D_p] = [D_p]_{max}$, the rate of drug elimination (R_{el}) in terms of the total drug amount is

$$R_{el} = k_{el}([D_p]_{max}\cdot V_d)$$

Since k_{el}, $[D_p]_{max}$, and V_d are constant values, R is also constant. If the rate of drug input to the body (in terms of the drug amount) from the controlled-release dosage forms is equal to the rate of drug elimination, then $[D_p]_{max}$ will be maintained (see Figure 8.6). Thus, the sustaining dose (M_s) can be calculated from the following equation.

$$M_s = k_{el}([D_p]_{max}\cdot V_d)t$$

Here M_s is the amount of a drug necessary to maintain the maximum concentration for desired time period.

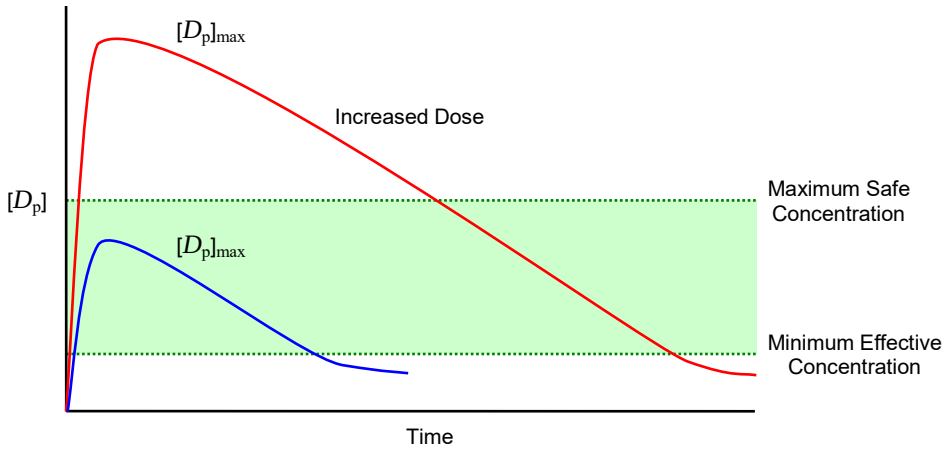

Figure 8.5 Pharmacokinetic profile of a drug after oral administration for a normal dose and an increased dose.

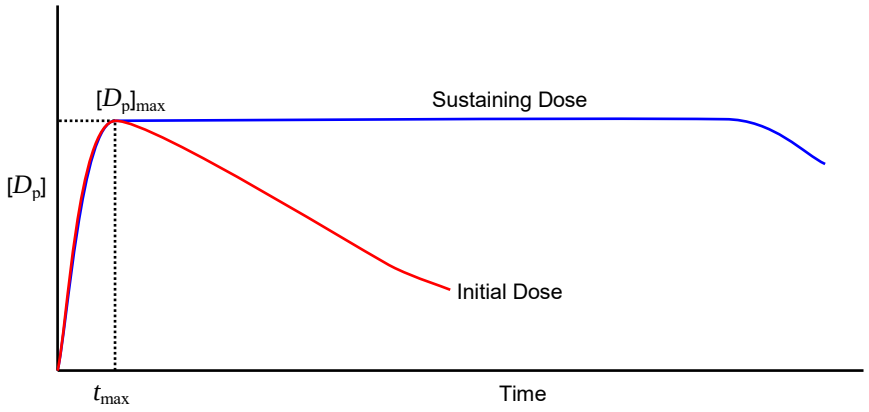

Figure 8.6 Comparison of a conventional dose and a controlled release dose.

The total amount of drug (M_t) necessary to make the controlled-release formulation is the sum of the initial dose (M_i) and the sustaining dose (M_s).

$$M_t = M_i + M_s$$

The initial dose (M_i) is also called the loading dose, since it enables the immediate attainment of the steady-state plasma level. It is the dose required to reach a desired drug concentration in blood.

Example 1

The following information was obtained for a new drug developed by your colleagues: $k_a = 0.05/\text{min} = 3/\text{h}$; $k_{el} = 0.003/\text{min} = 0.18/\text{h}$; $t_{max} = 60$ min = 1 h; $[D_p]_{max} = 0.042$ mg/mL; $M_i = 100$ mg; $V_d = 2000$ mL.

What is the total amount of the drug necessary to maintain the concentration of 0.042 mg/mL for 23 h more?

$$M_s = k_{el}([D_p]_{max} \cdot V_d)t$$

$$= (0.18/\text{h})(0.042 \text{ mg/mL})(2000 \text{ mL})(23 \text{ h}) = 348 \text{ mg}$$

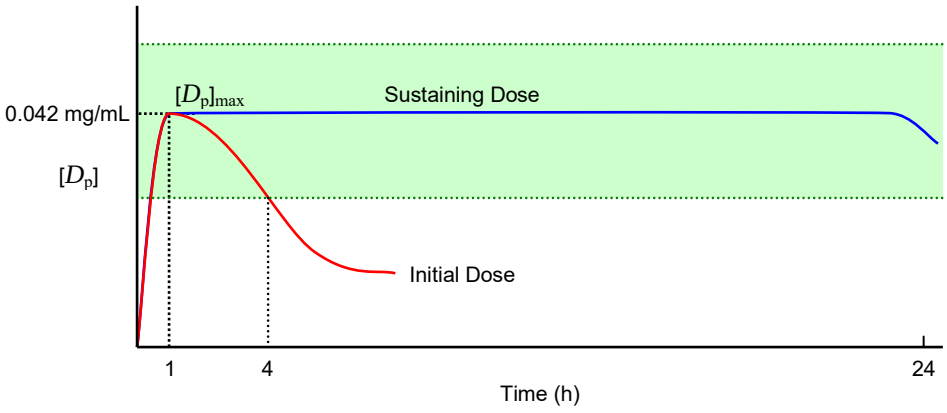

Figure 8.7 Drug concentration profile for Example 1.

Since $M_t = M_i + M_s$,

$$M_t = 100 \text{ mg} + 348 \text{ mg} = 448 \text{ mg}$$

If the drug has to be taken every 4 h by conventional means to maintain the therapeutic level, the total amount of the drug would be 600 mg. This is a larger amount than that required for delivery from a controlled-release dosage form.

C. Conventional vs Controlled-Release Formulation Bioequivalence

Once a controlled-release formulation is developed, it needs to be tested to see whether its *in vivo* performance is equivalent to multiple dosing of conventional dosage forms of the same drug. Usually, bioequivalence (*i.e.*, the extent and rate of absorption) of immediate-release drug products are determined using three classical pharmacokinetic parameters, such as area under the curve (AUC, the total area from time zero to infinity), C_{max} (peak plasma concentration), and t_{max} (time to reach C_{max}). These parameters, however, are not suitable for evaluation of the pharmacokinetic performance, particularly the rate of absorption, of controlled release formulations that yield flat plasma curves with multiple peaks. In a study assessing bioequivalence of a new diltiazem sustained-release formulation and Cardizem CD®, additional parameters were examined, such as MRT (mean arithmetic time), C_{max}/AUC, peak occupancy time (POT), t_{apical} (the arithmetic mean of the times associated with the concentrations within 25% of C_{max}), C_{apical} (the arithmetic mean of the concentration within 25% of C_{max}), and the percent fluctuation and flatness of the curve as assessed by the coefficient of variation of the C_{ss} (steady-state concentration) values obtained during a dosing interval at steady state (Bialer *et al.*, 1955). Although the new parameters examined are theoretically more attractive than the single-point parameters, C_{max} and t_{max}, for rate of absorption assessment, their utility in bioequivalence would require further examination with many other formulations.

Cardizem CD®, a once-daily diltiazem hydrochloride dosage form, was evaluated for safety, efficacy, and the relationship between peak and trough antihypertensive effects in a multicenter, placebo-controlled, parallel design trial (Meeves & Park, 1994). Cardizem CD® lowered supine diastolic and systolic blood pressure at trough significantly more than the placebo (–7.5 mm Hg vs –1.3 mm Hg, and –6.4 mm Hg vs 0.5 mm Hg, respectively). Cardizem CD® also showed no statistically significant differences in supine DBP between the peak effect hours, indicating a plateau of the peak antihypertensive effect 6–10 h postdose. The measurement of pharmacodynamics may be a better way of comparing bioequivalence than measuring pharmacokinetic parameters, since it is the pharmacodynamic results that matters.

Caution has to be exercised in using a certain dosage form (*e.g.*, a twice-daily dosage form) as a reference for assessing the extent of absorption for a once-daily dosage form. The pharmacokinetics of two sustained-release products of diltiazem, Dilapress® 120 mg tablets (designat-

ed for twice-daily dosing) and Dilapress® 240 mg tablets (designed for once-a-day treatment), were analyzed and characterized in comparison to other diltiazem sustained release formulations, such as Cardizem Retard®, Cardizem SR®, and Cardizem CD® (Bialer *et al*., 1994). The results showed Dilapress® 120 was bioequivalent to Cardizem SR® and to Cardizem Retard®. However, Dilapress® 240 had a slower absorption rate than Cardizem SR® and its extent of absorption was 56 ± 19% relative to that of Cardizem SR®. Interestingly, the bioavailability of Dilapress® 240 relative to Cardizem CD® was 118 ± 46%. This indicated that the bioavailability of Cardizem CD® (once-daily formulation) relative to that of Cardizem SR® (twice-daily formulation) was only 54 ± 29%. The reason for higher extent of absorption by the twice-daily formulation than the once-daily formulation was that the high dose of diltiazem from the twice-daily formulation may partially escape a saturable liver first-pass effect (Bialer *et al*., 1994). For drugs like diltiazem, once-daily treatment may not be necessarily better, since it may not reach the saturation stage in the liver first-pass effect process that diltiazem is susceptible to. This particular example indicates that a twice-daily diltiazem products may not be a good reference for assessing the extent of absorption for once-daily products.

Key points:

1. When a new drug entity is developed, it should be tested for its safety and bioefficacy through clinical studies. When a new formulation of an existing drug is developed, however, it can be approved without extensive clinical studies simply by showing the bioequivalence.
2. In comparing bioequivalence, the pharmacokinetic parameters can be used (*e.g*., AUV, t_m, D_m). If the dosage forms are different (*e.g*., comparison between conventional and controlled-release formulations) the pharmacodynamic parameters can be used for showing the bioequivalence.

III. DIFFUSION PROCESS IN POLYMER MEMBRANES

A. BROWNIAN MOTION

In 1827, Robert Brown, a Scottish botanist who studied pollen grains, observed under a microscope that some grains were haphazardly bouncing around when suspended in water. At that time, it was an unexplained observation, and he thought that the pollen grains were alive because they were moving. He thought that the dead things were not supposed to move. When he tracked the pathway of a single pollen grain as shown in the following figure, he noticed that the movement was continuous, totally irregular, unexpected, and quite chaotic. In scientific term, these properties can be described as "random." Such a random movement is known as "Brownian movement" or "Brownian motion" (see Figure 8.8)

Brownian motion greatly attracted the attention of theoreticians and experimentalists because it could be observed with colloid systems. Furthermore, it was a directly observable confirmation of gas-kinetic theory,

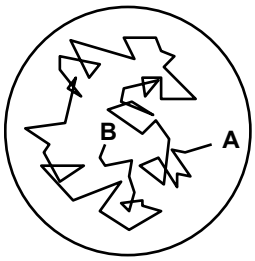

Figure 8.8 Example of a path of a particle undergoing Brownian motion. The distance between A and B can be calculated by the Einstein equation.

which was developed by Ludwig Boltzmann, an Australian scientist (1844–1906) in the 1860s. According to the theory, a suspended particle in a liquid (or a cloud system in a gas) must be in kinetic equilibrium with molecules of the medium. Thus, from the motion of the observable particles, insight can be obtained to predict the behavior of particles not directly observable, such as macromolecules in solution. The basic idea of the theory is that:

$$\tfrac{1}{2}mv^2 \text{ of a particle} = \tfrac{1}{2}\, mv^2 \text{ of molecules in the medium} = \tfrac{3}{2}kT$$

in which m is the mass of the particle or of a molecule of the medium and v^2 is the mean of the square of its velocity. The mean kinetic energy of each freely moving element is therefore completely determined by the temperature.

As shown in Figure 8.8, even a microscopically visible particle varies in direction many millions times per second, and it is impossible to measure directly the velocity of particles in the Brownian motion. Colloidal particles surrounded by water molecules experience continuous bombardment of water molecules on their surfaces. The colloidal particle that moves to a certain direction at one moment will change its direction at the next moment owing to the change in the direction of the net force exerted by the water molecules on the particle.

Although the exact path traversed per second is not measurable, it is possible to measure in the microscope the displacement that the particle experiences as a result of the long zigzag path that it traverses. For example, the distance between A and B in Figure 8.8 can be easily measured. In 1906, Einstein and von Smoluchowski simultaneously and independentaly deduced the following formula:

$$\Delta x^2 = 2Dt = 2\left(\frac{kT}{6\pi\eta r}\right)t$$

where Δx^2 is the mean of the square of the displacement during the time t projected on a chosen x direction, D is the diffusion coefficient of a particle, k is the Boltzman constant, η is the viscosity of the system and r is the radius of the spherical particle. For non-spherical particles the Stokes fac-

tor $6\pi\eta r$ is replaced by a more complicated factor. Diffusion coefficient of D_2O in water is 2.2×10^{-5} cm^2/s.

All molecules undergo Brownian motion, whether visible or not. Colloidal particles (which are smaller than 5 μm in diameter) also undergo Brownian motion. The intensity of the movement increases with increasing temperature. Thus, the distance that a particle migrated increases as temperature increases, as the above Einstein equation shows.

1. Drug Release by Brownian Movement

Drug molecules incorporated into the controlled release dosage forms are released into the environment as a result of Brownian motion. Consider drug molecules loaded in the device and separated from the environment by a polymer membrane. The drug molecules in the left chamber can move any direction. If we consider only one-dimensional movement, a particle undergoing random motion has 50% of possibility to move left and 50% of possibility to move right. Since drug molecules can move only through the polymer membrane, 50% of the drug molecules will move to the right chamber. If the released drug molecules are taken away (*e.g.*, by absorption by the body), 50% of the remaining drug molecules will be released again, and this is how drug molecules are released from the controlled release dosage forms.

B. Fick's Law

Let's consider the release of drug molecules through the polymer membrane that is h cm thick. The concentrations of drug in the donor side and the receptor side are C_d and C_r, respectively, and C_d is greater than C_r. The difference between C_d and C_r is ΔC (see Figure 8.10).

Let's now define M, M/S, and $M/S{\cdot}t$ as follows: M is the total amount of solute (in grams or moles) crossing a surface S (in cm^2) in time t (in seconds); M/S (in g/cm^2 or mol/cm^2) is the amount of solute crossing 1 cm^2 of surface in time t; and $M/S{\cdot}t$ (in g/cm$^2{\cdot}$s) is the amount of solute crossing 1 cm^2 of surface in 1 s where $M/S{\cdot}t$ is known as flux (or flow) and "J" is usually used to represent flux. Thus,

$$J = M/S{\cdot}t \quad \text{or} \quad M = J{\cdot}S{\cdot}t$$

According to Fick's law, flux (J) is also described by $D{\cdot}\Delta C/h$, where D

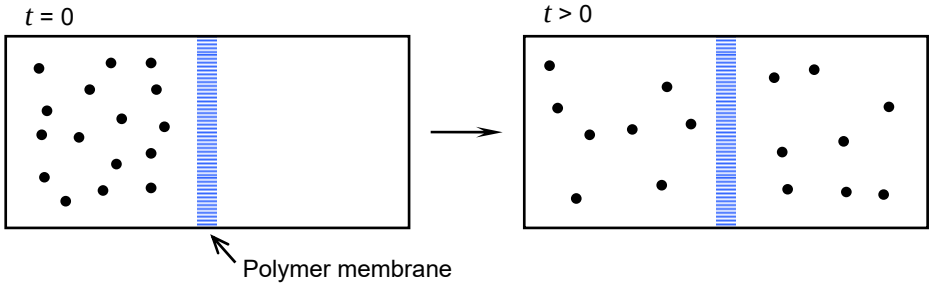

Figure 8.9 Illustration of drug release by Brownian movement.

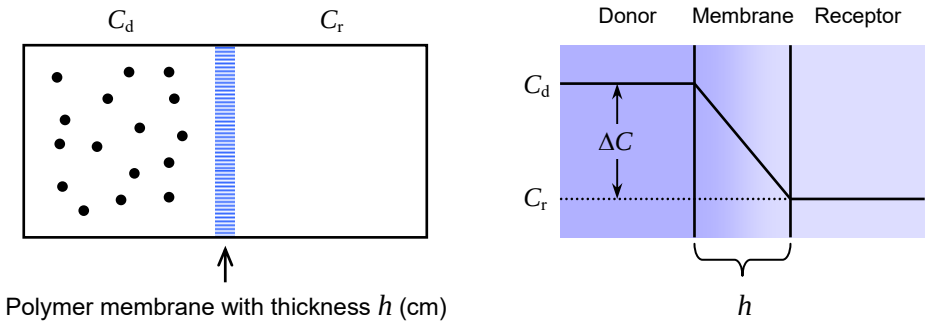

Figure 8.10 Illustration of drug release through a porous membrane with drug concentration C_d on the donor side and C_r on the receptor side (left). Diagram of the concentration differential between the donor and receptor sides and the concentration gradient through the porous membrane (right).

is the diffusion coefficient of the drug molecule in the unit of cm^2/sec. Thus, we have

$$M = J \cdot S \cdot t = (D \cdot \Delta C/h) \cdot S \cdot t$$

Using this equation, one can calculate the total amount of drug released in a given time t. Since this equation is the most fundamental equation in the study of drug delivery from the controlled-release dosage forms, it is necessary to remember this equation.

C. Partition Coefficient (or Distribution Coefficient)

When a fresh polymer membrane is placed into the drug solution, drug molecules will diffuse into the polymer membrane until equilibrium is reached. Let's define C and C_1 as equilibrium concentrations of drug in solution and polymer membrane, respectively. Partition coefficient, K, is defined as C_1/C.

The partition coefficient can be used to calculate the drug concentration inside polymer membrane. As in Section B above, if a fresh polymer membrane is used to control drug release, the concentration gradient inside the polymer membrane depends on the partition coefficient.

The following example (see Figure 8.12) shows the concentration gradients at different K values. In the following examples, $K = C_1/C_d = C_2/C_r$. Note that there is no drug molecules inside the polymer membrane; if $K = 0$, the both C_1 and C_2 are zero. One question you may think about is how

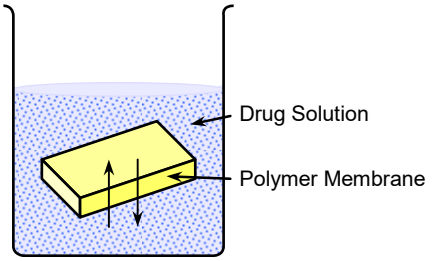

Figure 8.11 Partitioning of a drug from a solution into a polymer membrane.

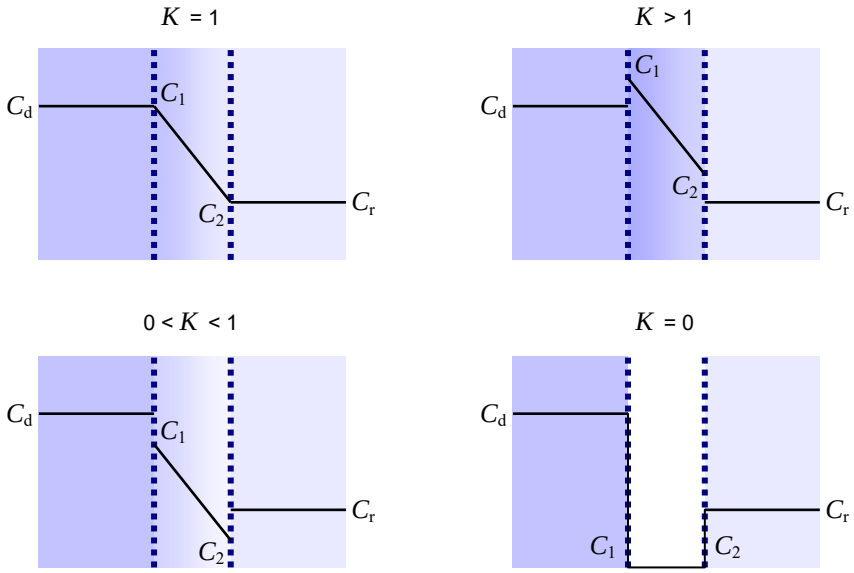

Figure 8.12 Illustration of concentration gradients with different partition coefficients.

the concentration gradient looks like when the sink condition is maintained in the receptor side.

Example 2

Since the release of drug molecules through the polymer membrane requires partition of drug molecules into the polymer membrane, the partition coefficient should be added to the equation $M = (D \cdot \Delta C/h) \cdot S \cdot t$. In this equation, ΔC is the difference between C_d and C_r. The driving force for the diffusion of drug molecules through the polymer membrane, however, is the difference in concentrations (*i.e.*, thermodynamic activities) inside the polymer membrane. Thus, the concentration gradient should be $K \cdot \Delta C/h$ instead of $\Delta C/h$. Therefore:

$$M = (D \cdot K \cdot \Delta C/h) \cdot S \cdot t$$

In many cases when the thickness (h) of the polymer membrane is not known, $D \cdot K/h$ is treated as one variable, and such variable is known as the permeability (P). The units of the permeability are cm/s.

D. Solution-Diffusion Membranes

One method to control the drug release from a controlled-release dosage form is to use polymeric membranes. Drug molecules in the drug reservoir are released into the environment by diffusing through the polymeric membranes or polymeric matrix. Figure 8.13 illustrates the drug-release process through a polymer membrane.

When drug molecules are released through nonporous and homogeneous polymer membranes, such as silicone rubber, polyethylene, nylon film, or the like, drug molecules undergo three distinct steps. First, drug molecules have to partition into the polymer membrane from the drug res-

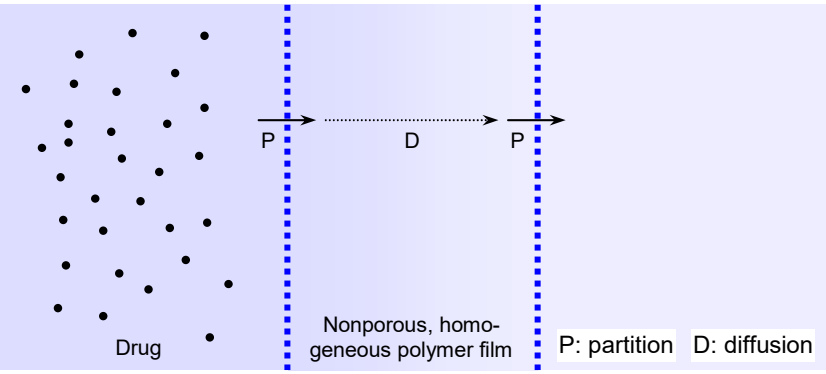

Figure 8.13 Illustration of the drug-release process through a polymer membrane.

ervoir. Second, drug molecules entering the polymer membrane must migrate through the polymer matrix by a diffusion process that occurs because of the concentration difference. And third, the drug molecules reaching the other end of the polymer membrane must partition into the aqueous medium surrounding the polymer membrane.

Polymer membranes, through which drug molecules are release by such a partition–diffusion–partition process, are known as solution-diffusion membranes. Solution-diffusion membranes are useful for the release of drug molecules that have molecular weight of 400 Da or smaller. Delivery of higher molecular weight drugs, including peptides and proteins, requires other types of polymer membranes.

QUESTIONS

(a) Which one of the following polymers may not used as a solution-diffusion membrane?
(b) Polyethylene at pH 2, nylon at pH 7, cellulose acetate at pH 2, cellulose acetate phthalate at pH 7.

E. Lag-Time and Burst Effects

The two important phenomena in controlled drug delivery are the lag-time effect and the burst effect. To understand these effects we will consider diffusion of drug molecules through polymer membranes first.

1. Diffusion through a Polymer Membrane

Let's consider the diffusion cell in Figure 8.14. The left side of the diffusion cell is filled with a saturated drug solution. The concentration on the donor side (C_d) is maintained constant by having a suspension of the drug.

The conditions for this experiment are:

1. C_d is maintained constant by having a suspension.
2. The initial concentration in the receptor side is zero ($C_r = 0$ at $t = 0$, $C_r \neq 0$ at $t > 0$).

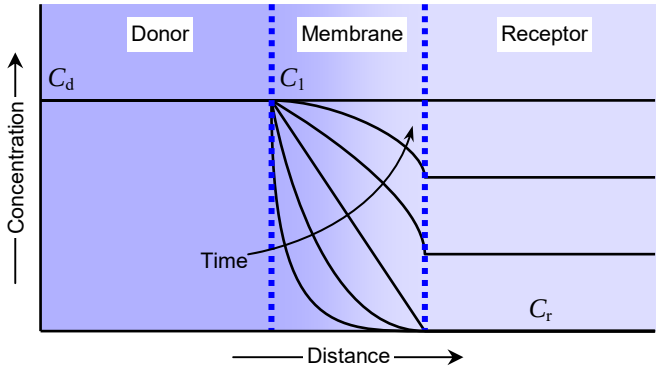

Figure 8.14 Illustration of diffusion through a polymer membrane and the change in concentration within the membrane as a function of time.

3. A fresh new polymer membrane is used ($C_1 = 0$ at $t = 0$, and $K = 1$)

Then the change in the concentration profile inside the polymer membrane as a function of time can be described as shown below.

In this experimental condition, drug molecules continue to release to the receptor side until its concentration (C_r) reaches to the same level as that of the donor side (C_d).

2. Diffusion through a Polymer Membrane under Sink Conditions

Consider if the above experimental conditions are changed in such a way that any drug released through the polymer membrane is removed immediately. Thus, the concentration at the receptor side (C_r) is always maintained at zero. This condition is known as sink conditions (see Figure 8.15). This condition resembles the real situation in drug delivery to the body, since drug molecules are absorbed into the body after released from the dosage form.

The conditions in this experiment are:

1. C_d is maintained constant by having drug suspension.

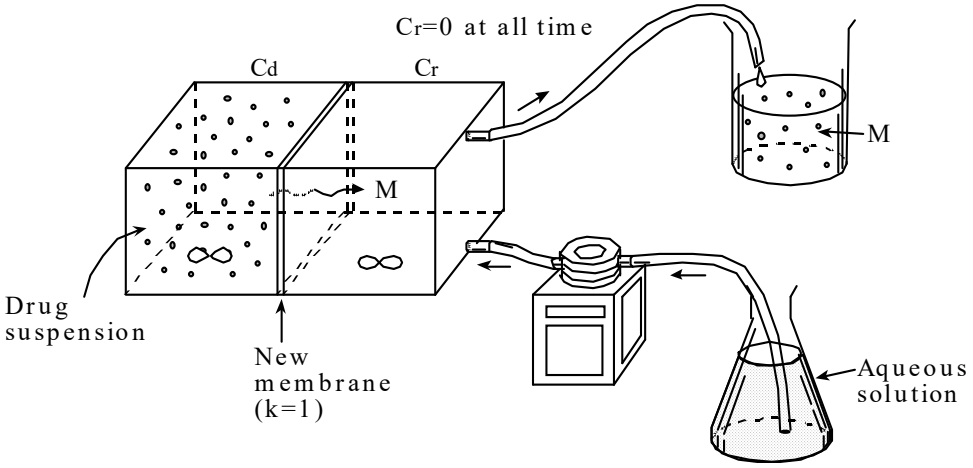

Figure 8.15 Experimental apparatus for achieving sink conditions.

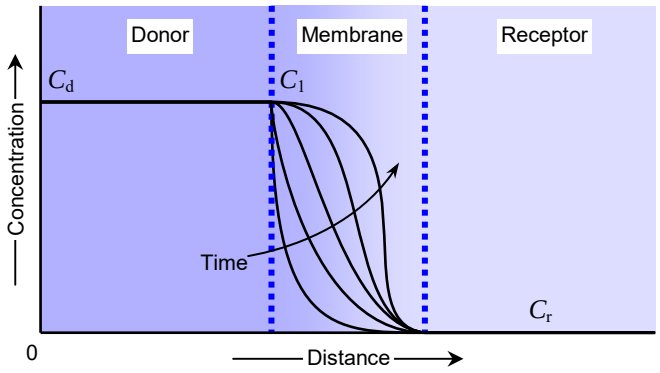

Figure 8.16 Illustration of diffusion through a polymer membrane and the change in concentration within the membrane as a function of time under sink conditions.

2. The concentration in the receptor side is maintained zero all the time ($C_r = 0$ at $t \geq 0$).
3. A fresh new polymer membrane is used ($C_1 = 0$ at $t = 0$, and $K = 1$)

Once the drug molecules reach the other side of the membrane and are released into the receptor side in the sink condition (see Figure 8.16), the concentration gradient at the steady state is established. At the steady state, the concentration gradient inside the polymer membrane remains constant at all points of the membrane.

3. Lag Time

As shown in the previous section, it takes time for drug molecules in the donor side to appear in the receptor side if fresh polymer membrane is used. Under sink conditions, drug molecules will be released at a constant rate into the receptor side and steady state is reached. The time to reach steady state is known as the "lag time."

As shown in the following figure, the lag time can be calculated from the drug-release profile by extrapolating to the *x*-axis the cumulative amount of the released drug.

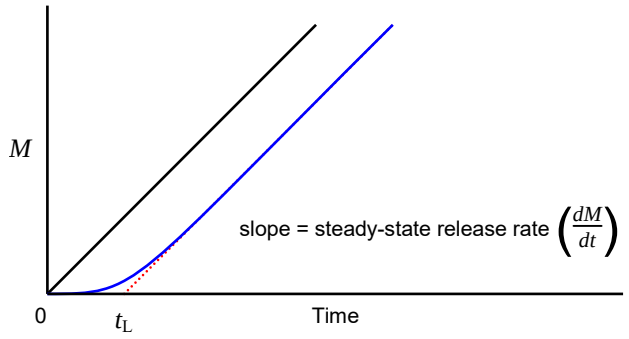

Figure 8.17 Determination of the lag time by extrapolation.

The cumulative amount of drug released through the membrane can be described by the following equation:

$$M = S{\cdot}D{\cdot}K{\cdot}(\Delta C/h){\cdot}(t - t_L)$$

Mathematically, is equivalent to $h^2/6D$. Thus, the above equation can be rewritten as:

$$M = S{\cdot}D{\cdot}K{\cdot}(\Delta C/h){\cdot}(t - h^2/6D)$$

The equation suggests that the lag time can be calculated if the thickness of the membrane (h) and the diffusion coefficient of a drug in the membrane (D) are known. Alternatively, the lag time can be measured from experiments, and from the measured values, other information such as h or D can be obtained.

4. Burst Effect

If we maintain the same experimental condition as described above for diffusion through polymer membrane under the sink condition, but the only difference in the present case is that instead of a fresh polymer membrane, we use a membrane saturated with the drug before measuring the drug release. In this case, the drug concentration profile inside the polymer membrane will change as shown in Figure 8.18. The concentration inside the membrane will decrease until a steady state is reached.

The drug release profile is shown in Figure 8.19. The cumulative amount of drug released through the presaturated membrane can be described by:

$$M = S{\cdot}D{\cdot}K{\cdot}(\Delta C/h){\cdot}(t + t_B)$$

Mathematically, is equivalent to $h^2/3D$. Thus, the above equation can be rewritten as:

$$M = S{\cdot}D{\cdot}K{\cdot}(\Delta C/h){\cdot}(t + h^2/3D)$$

As shown in Figure 8.19, the burst effect is an initial release of drug at a higher rate than the steady-state release rate.

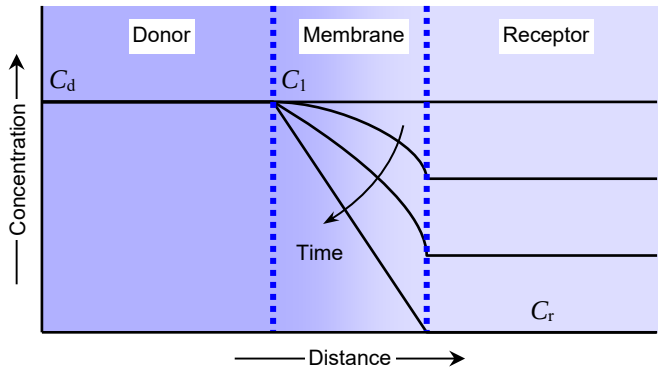

Figure 8.18 Illustration of diffusion through a polymer membrane and the change in concentration within the membrane as a function of time when the membrane is first saturated with drug.

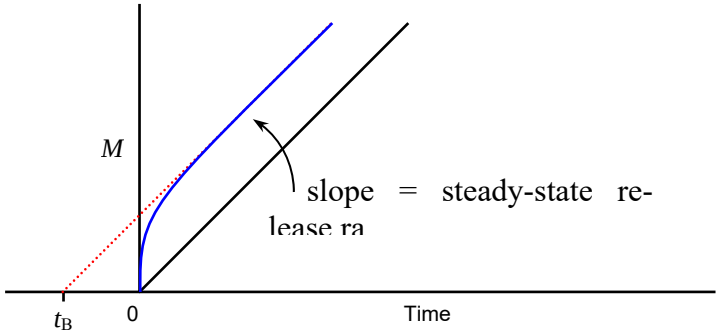

Figure 8.19 Determination of the burst effect by extrapolation.

Examples

a. Effect of the diffusion coefficient on the lag time.

If the thickness of a polymer membrane is 100 μm and D of a drug is 1×10^{-7} cm^2/s, then what will be the lag time?

$$t_L = \frac{h^2}{6D} = \frac{(0.01 \text{ cm})^2}{6(1 \times 10^{-7} \text{ cm}^2/\text{s})} = 167 \text{ s}$$

Note that we have to convert 100 μm to 0.01 cm to have the same unit as the diffusion coefficient.

What will be the lag time, if $D = 1 \times 10^{-10}$ cm^2/s?

b. Effect of the membrane thickness on the lag time.

What will be the lag times if D of a drug is 1×10^{-9} cm^2/s and the membrane thickness is 10 μm, 100 μm, 1,000 μm, or 10,000 μm?

Membrane thickness	t_L
10 μm	166 s = 2.8 min
100 μm	16,666 s = 278 min = 4.6 h
1,000 μm	1.7×10^6 s = 463 h = 19 d
10,000 μm	1,930 d = 5.3 y

These examples show that for polymer membranes with thicknesses used in controlled release dosage forms the lag time is in the order of days to weeks, since it is not likely that the polymer membrane with 10,000 μm will be used in the controlled release dosage forms. This has a practical implication. When controlled-release dosage forms are manufactured, they will be ship to the patients, but the time between manufacturing and clinical use may vary from months to years. Thus, it is easy to expect that during that time period, the polymer membranes will be saturated with drug. So, when patients use the controlled-release dosage forms employing polymer membranes, they will most likely experience the burst effect. This means that the initial release rate of the drug is higher than the desired release rate established at the steady state.

The following figure shows the cumulative amounts of drug released and the drug release rates through the membrane with the burst effect, the

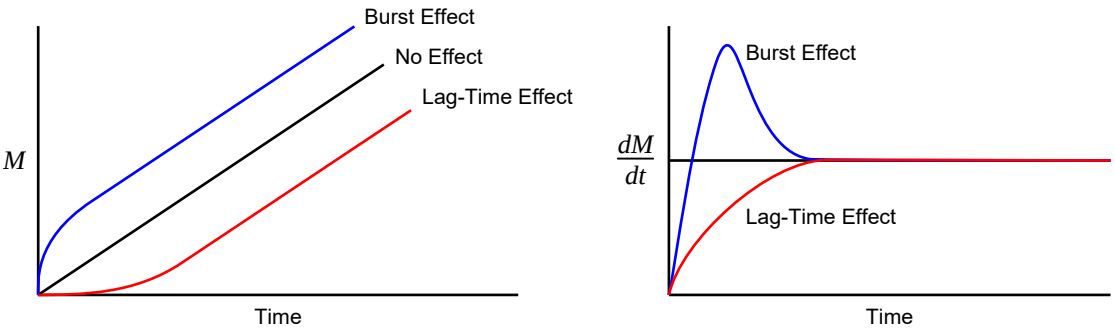

Figure 8.20 Comparison of change in drug concentration (left) and drug-release rate (right) for systems with a burst effect, with a time-lag effect, or with no effect.

time-lag effect, and without any effect. Note that the slopes of the three situations are the same; this means that the drug-release rate (dM/dt) is the same once steady state is reached. The linear increase in M is known as the zero-order release. Once the steady state is reached, the zero-order release is observed regardless of the thickness of the polymer membrane.

5. Boundary Layer Effect

In the above experiments, we assumed that both sides of the diffusion cell are well mixed so that the released drug molecules are homogeneously distributed throughout the available space. In real situations, that may not be the case. For example, if the bulk solution is not well mixed, the water layer immediately adjacent to the polymer membrane is stagnant. For water-insoluble drugs (*i.e.*, hydrophobic drugs such as steroids), the concentration in the stagnant water layer can increase and reach the drug solubility in aqueous solution. Such a stagnant water layer is known as the "boundary layer." For water-insoluble drugs (such as steroids), the concentration in the boundary layer can reach the drug solubility. In this case, the drug diffusion through the boundary layer is the rate limiting step.

Since drug molecules have to diffuse through the boundary layer to be mixed into the bulk solution, the presence of a boundary layer is just the

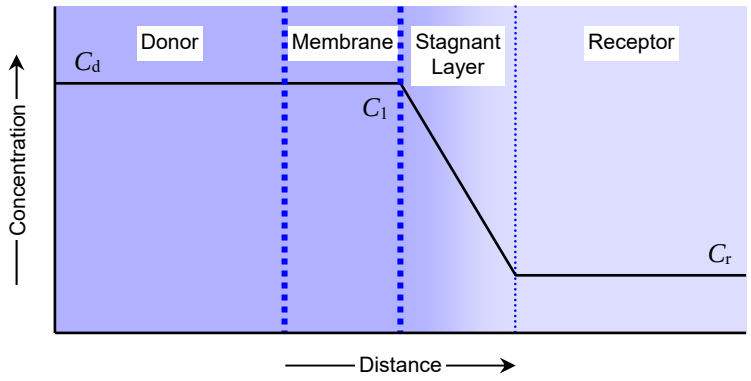

Figure 8.21 Illustration of drug diffusion through a membrane and an adjacent boundary layer (stagnant layer).

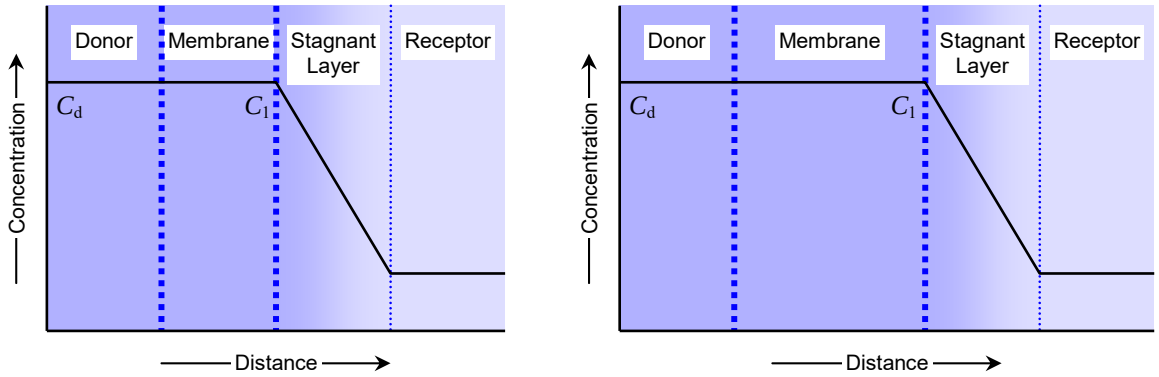

Figure 8.22 The presences of boundary layers causes drug diffusion through a polymer membrane to produce the same concentration of drug in the receptor side regardless of the membrane thickness.

same as having another polymer layer that retards the release of the drug.

The presence of boundary layer is highly likely in the body where the stirring of the solution is very poor. If the boundary layer is significant, the drug release rate will be independent of the type and thickness of the polymer membrane. In such cases, the drug release rate can be increased only by increasing the surface area.

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