CHAPTER 1

INTRODUCTION

> "The eternal mystery of the world is its comprehensibility. The fact that it is comprehensible is a miracle."
>
> —Albert Einstein

The aim of this chapter is to discuss the whole picture of oral absorption of a drug in a comprehensive and descriptive manner without using any mathematical equation.

1.1 AN ILLUSTRATIVE DESCRIPTION OF ORAL DRUG ABSORPTION: THE WHOLE STORY

The oral absorption of a drug is a sequential process of dissolution and intestinal membrane permeation of a drug in the gastrointestinal (GI) tract (Fig. 1.1).

After dosing a drug product (e.g., tablet and capsule), the formulation disintegrates to release solid particles of active pharmaceutical ingredient (API) ① in Fig. 1.1). The released API particles then dissolve into the GI fluid as molecularly dispersed drug molecules ②. The maximum amount of a drug dissolved in the GI fluids is limited by the solubility of the drug in the fluids. In some cases, after an initial API form (such as a salt form) being dissolved, a transient supersaturated state is produced, and then, another solid form (i.e., a free base or an acid) can precipitate out in the intestinal fluid via nucleation ③. The dissolved

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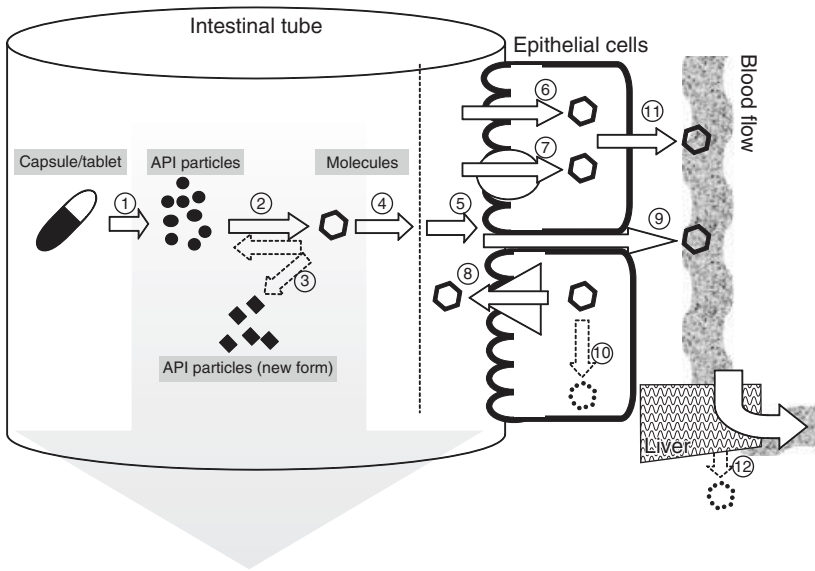

Figure 1.1 Schematic presentation of oral drug absorption processes: disintegration, dissolution, permeation, and transit.

drug molecules are conveyed close to the intestinal wall by the macromixing of the intestinal fluid (④) and further diffuse through the unstirred water layer (UWL), which is adjacent to the epithelial cellular membrane (⑤). The drug molecules then permeate the apical membrane of the epithelial cells mainly by passive diffusion (⑥) but in some cases, via a carrier protein (a transporter) such as PEP-T1 (⑦). If the drug is a substrate for an efflux transporter such as P-gp, a portion of the drug molecules is carried back to the apical side (⑧). Some drugs pass through the intercellular junction (the paracellular route) (⑨). In the epithelial cells, the drug could be metabolized by enzymes such as CYP3A4 (⑩). After passing through the basolateral membrane (⑪), the drug molecules reach the portal vein. The drug molecules in the portal vein then pass through the liver and reach the systemic circulation (⑫).

1.2 THREE REGIMES OF ORAL DRUG ABSORPTION

The central dogma of oral drug absorption is the interplay between solubility, the dissolution rate and permeability of a drug. On the basis of the central dogma, the three rate-limiting steps of oral absorption can be defined. Crystal clear understanding of these regimes is the first step toward understanding biopharmaceutical modeling [1]. Figure 1.2 shows the schematic presentation of the rate-limiting steps in the oral absorption of a drug [2].

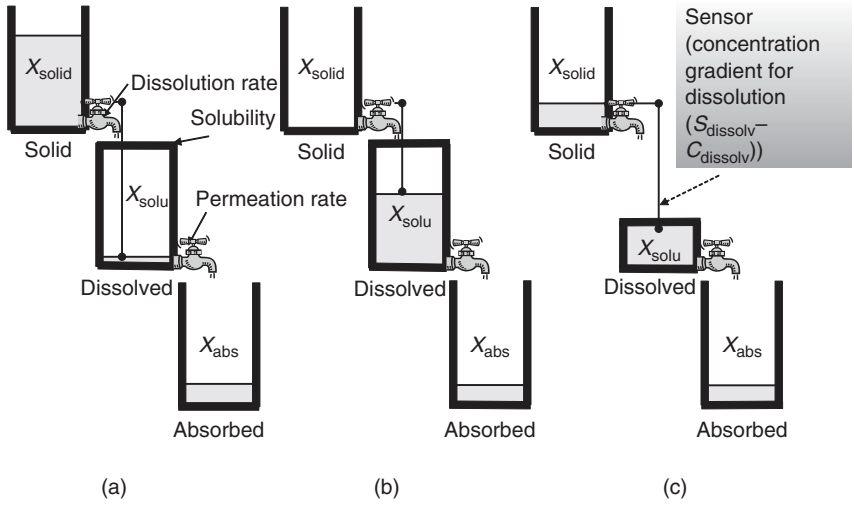

Figure 1.2 Rate-limiting steps in oral absorption of a drug represented by the bucket model [2]. (a) Dissolution rate limited; (b) permeability limited; and (c) solubility–permeability limited.

- Dissolution rate-limited absorption (DRL) (Fig. 1.2a)
  - — In this case, the dissolution rate of API is much slower than the permeation rate. Once the API is dissolved, the drug molecules instantly permeate the intestinal membrane and get absorbed into the body. The dissolved drug molecules does not accumulate in the intestinal fluid as it is rapidly removed by the intestinal membrane permeation. Therefore, the dissolved drug concentration ($C_{dissolv}$) in the intestinal fluid is maintained well below the saturated solubility of a drug ($S_{dissolv}$). In this case, the rate of drug absorption is determined by the dissolution rate. The fraction of a dose absorbed (Fa%) is not dependent on the dose strengths of a drug (Figs. 1.2a, 1.3), whereas particle size reduction will be effective in increasing Fa% (Fig. 1.4).
- Permeability-limited absorption (PL) (Fig. 1.2b)
  - — In this case, the API dissolves immediately and completely in the intestinal fluid; however, the permeation of the drug is slow. Owing to the slow permeation clearance, the dissolved drug molecules accumulate in the intestinal fluid. The dissolved drug concentration does not reach its saturated solubility when the administered drug amount (Dose) is smaller than the solubilization capacity of the intestinal fluid (Dose $< S_{dissolv} \times V_{GI}$ (intestinal fluid volume)) (Fig. 1.2b). In this case, the rate of drug absorption is determined by the permeation rate. Fa% is not dependent on the dose strength and particle size of a drug (Fig. 1.4).

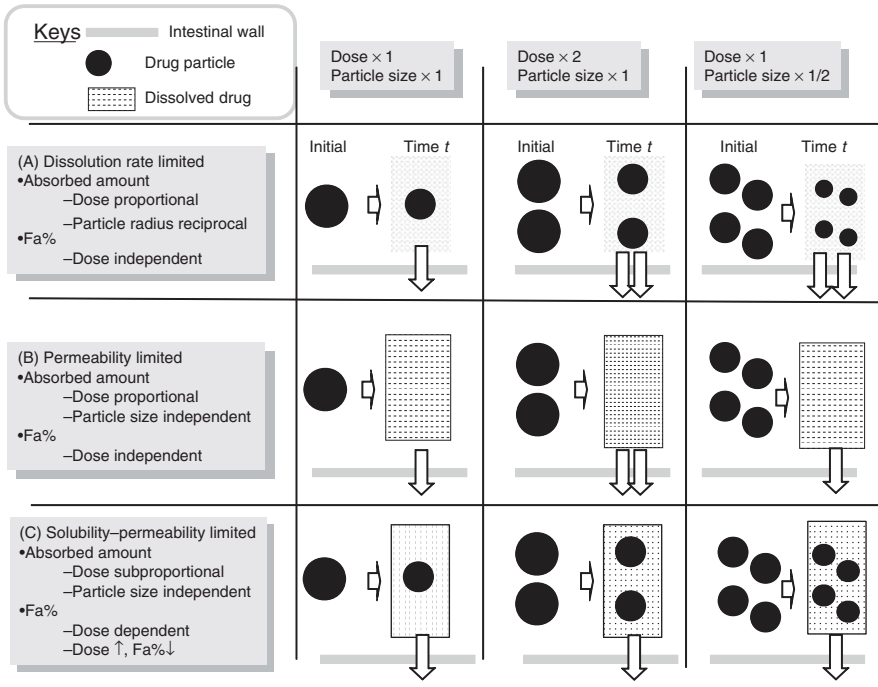

Figure 1.3 The effect of dose and particle size in each rate-limiting step cases.

- Solubility-permeability-limited absorption (SL) (Fig. 1.2c)
  - — When the dissolution rate of a drug is much faster than the permeation rate and the solubilization capacity of the intestinal fluid is smaller than the dose strength (Dose $> S_{\text{dissolv}} \times V_{\text{GI}}$), the dissolved drug molecules accumulate in the intestinal fluid and the dissolved drug concentration reaches the saturated solubility of the drug. In this case, the total absorption flux is determined as the maximum amount of dissolved drug ($= S_{\text{dissolv}} \times V_{\text{GI}}$) multiplied by the permeation rate of the drug (Fig. 1.2c). This case is further categorized by the rate-limiting step in the permeation process, that is, solubility–epithelial membrane permeability limited (SL-E) and solubility-UWL permeability limited (SL-U) cases [3]. Fa% decreases as the dose strength increases (Fig. 1.4).[1] Particle size reduction will not be effective in increasing Fa% for SL-E cases but could be effective for SL-U cases (Section 4.7.2).

The balance of the dissolution rate coefficient (k_{diss}), the permeation rate coefficient (k_{perm}) and the ratio of dose strength to the solubilization capacity of the

[1] In some cases, this dose subproportionality in oral absorption can be cancelled out by supraproportionality in systemic elimination clearance (Section 5.5.3).

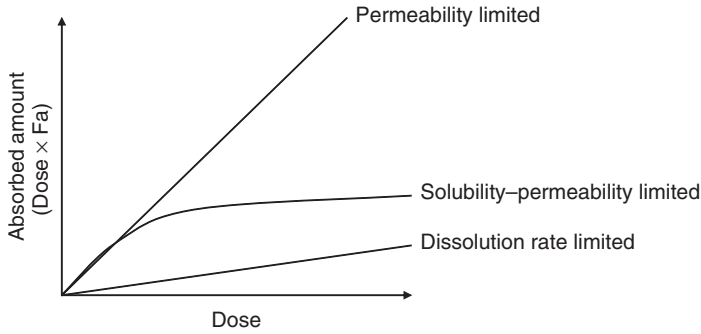

Figure 1.4 Typical dose–absorbed amount relationship.

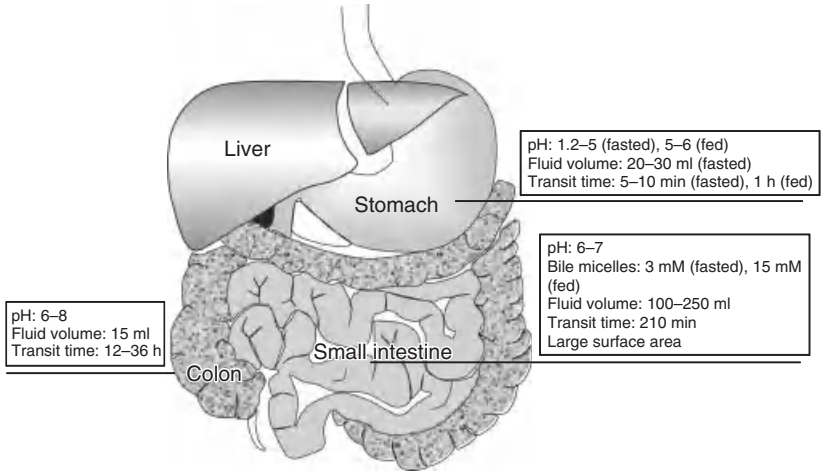

Figure 1.5 Gastrointestinal tract and key characteristics.

GI fluid (Dose/$S_{\text{dissolv}} \times V_{\text{GI}}$) determines the regime of oral drug absorption. The last parameter is called the dose number (Do). The dose number is one of the most important parameters in biopharmaceutical modeling.

1.3 PHYSIOLOGY OF THE STOMACH, SMALL INTESTINE, AND COLON

The GI tract can be roughly divided into the stomach, the small intestine, and the colon (Fig. 1.5). In humans, the pH of the stomach fluid is 1.2–2.5 in the fasted state but 5–6 in the fed state. The fluid volume in the stomach is ca. 30 ml. The pH of the intestinal fluid is 6.0–7.0 and is maintained relatively constant. The fluid volume in the small intestine is ca. 100–250 ml. Bile acid concentration in the small intestine is ca. 3 mM in the fasted state and 10–15 mM in the fed

state. The pH of the colonic fluid is 6.0–8.0. The fluid volume in the colon is ca. 15 ml.

Drug absorption mainly occurs in the small intestine as it has the largest absorptive surface area and the largest fluid volume in the GI tract. Bile micelles can enhance the solubility and dissolution rate of a lipophilic drug. The stomach pH can affect the solubility and dissolution of a free base and its salt. It can also affect the precipitation of free acid from its salt. For low permeability and/or low solubility drugs, colonic absorption is usually negligible because of the small absorptive surface area, small fluid volume, solidification of the fluid, lack of bile micelles, etc.

1.4 DRUG AND API FORM

The patterns of oral drug absorption can be also categorized from the viewpoint of the properties of the drug molecule and API solid form.

A drug can be categorized as undissociable or dissociable ones. The dissociable drug is then further categorized as acid, base, or zwitterions. The API solid form of an acid, base, and zwitterion can be categorized as a free form or a salt form (e.g., HCl salt of a base). For PL cases, the difference of a solid form does not affect the oral absorption of a drug. On the other hand, for DRL and SL cases, the solid form of a drug has a significant impact on the oral absorption of a drug.

1.4.1 Undissociable and Free Acid Drugs

In the case of undissociable drugs and free acid drugs, the effect of the stomach pH on the solubility and dissolution rate of the drug is negligible. This is the simplest cases for biopharmaceutical modeling. A practically reasonable predictability is anticipated (Chapter 8) [4].

1.4.2 Free Base Drugs

Free base drugs dissolve better in the low pH environment of the stomach than in the small intestine. However, as the stomach contents move into the small intestine, the pH is neutralized and the solubility of the drug is decreased. The drug particles, which once reduced its size by dissolution in the stomach, regrows in the small intestine (the dissolved drug molecule moves back to the solid surface of the free base particles) [5]. The biopharmaceutical modeling for this case is simpler compared to the salt cases. A practically reasonable predictability is anticipated (Chapter 8) [6].

1.4.3 Salt Form Cases

In the case of salts, the oral absorption process is much more complex. A salt form drug usually dissolves rapidly in the GI fluid. However, once the dissolved

drug concentration hits the critical supersaturation concentration, the free form drug precipitates out as a solid. To represent this phenomena in biopharmaceutical modeling, a nucleation theory has to be taken into account [7]. However, little is known about the nucleation of drug molecules in the GI environment. Therefore, the extent and duration of supersaturation in the GI tract is currently not quantitatively predictable from *in vitro* data. A similar scenario can be applied for cocrystalline, amorphous solid form, and supersaturable formulations. To improve the biopharmaceutical modeling in the future, this area requires significant investigations.

1.5 THE CONCEPT OF MECHANISTIC MODELING

The mechanistic modeling approach is pursued in this book. To enable computational simulation, the processes that consist of drug absorption must be reduced down to the molecular level mechanisms. The network of theoretical equations connects the overall processes of drug absorption from the molecular level mechanism to the plasma concentration (C_p) time profile of a drug in humans (can be further connected to pharmacological effects via pharmacokinetic–pharmacodynamic (PKPD) modeling). The whole network of theoretical equations of oral drug absorption is called the gastrointestinal unified theoretical (GUT) framework in this book. As described above, oral drug absorption consists of four main processes, dissolution, permeation, nucleation, and GI transit. These processes are further reduced down to the molecular level mechanisms. Ideally, all processes of oral drug absorption should be described by mechanistic mathematical equations that have physical meanings at the molecular level. Therefore, the GUT framework shares the same philosophy of the "analysis"–"synthesis" approach employed by systems biology and physiologically based pharmacokinetic (PBPK) modeling.

Empirical multivariant statistical models (e.g., artificial neural network) are one of the other modeling approaches. Multiple drug parameters are used as input parameters and connected to outcome values using linear or nonlinear empirical equations. There are many investigations applying this approach for the prediction of oral drug absorption [8–11]. However, in the GUT framework, this approach is not pursued unless otherwise inevitable.

The "analysis" (reductionist) approach is rather a traditional approach in the history of science since Galileo's era, and this approach has been incredibly successful. This approach revealed many mysteries of astronomy, physics, chemistry, and finally, biology. However, an analytical understanding of each part does not mean the understanding of relationship between each part and their role on the total performance. For example, understanding of enzyme-level activity is not sufficient (but necessary) to understand how our brain works. With the aid of computational power, the "synthesis" approach has become available. We can now understand the relationship between primary processes and simulate the total performance. In computational systems biology, the networks of enzyme reactions and their effect on the phenotype is described by mechanistic mathematical

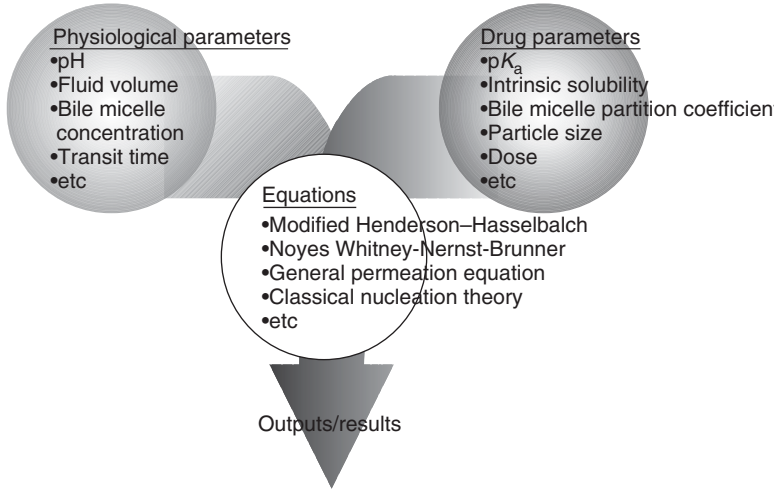

Figure 1.6 Physiological and drug parameters and theoretical equations.

models. By pursuing this approach, we will be able to model the disease state and find a clue to cure the patient. In this book, we pursue the same approach with systems biology. However, in addition to biological processes, the drug substance and formulation perspectives must be taken into account in biopharmaceutical modeling. By using the mechanistic modeling approach, we will be able to control the total bioperformance of a drug by designing the molecular structure, API form, and formulation of the drug.

The mechanistic biopharmaceutical modeling consists of theoretical model equations, physiological parameters, and drug parameters (Fig. 1.6). All of these factors significantly affect the performance of biopharmaceutical modeling. The physiological and drug parameters are often thought to have less error than the mechanistic model equations. However, this notion is incorrect. The physiological data in the literature have large variation and some physiological parameters have not been obtained yet. In addition, a drug parameter can have a large error (variation) when an experiment is not properly performed. Even in the case of solubility measurement, it often has more than twofold variation for low solubility drugs. Therefore, in addition to the theoretical models, the physiological and drug parameters are also discussed in Chapters 6 and 7.

The first step to construct the GUT framework is the unification of the concept of dissolved drug concentration (C_{dissolv}) [7]. We will start the next chapter with defining the dissolved drug concentration.

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CHAPTER 2

THEORETICAL FRAMEWORK I: SOLUBILITY

"Everything should be made as simple as possible, but not simpler."

—Albert Einstein

Figure 2.1 shows the network of equations, which consist of the gastrointestinal unified theoretical framework (GUT framework) [1]. The GUT framework is discussed in the following four sections. This framework is constructed based on the unified definition of "dissolved drug concentration (C_{dissolv})" and "fraction (f)" of each molecular species.

2.1 DEFINITION OF CONCENTRATION

Even though the definitions of concentration look trivial and often being omitted in the literature, clear understanding of this point is important for biopharmaceutical modeling.[1]

[1]The readers of this book may think that this kind of basic definition should not be cited in a book for advanced scientists. However, a lot of misunderstandings about oral absorption actually come from the confusion of the concepts of concentration. Another often observed confusion is among "fraction (f)," "concentration (C)," and "solubility (S)." The concept of these terms is critically important for biopharmaceutical modeling and should be clearly understood.

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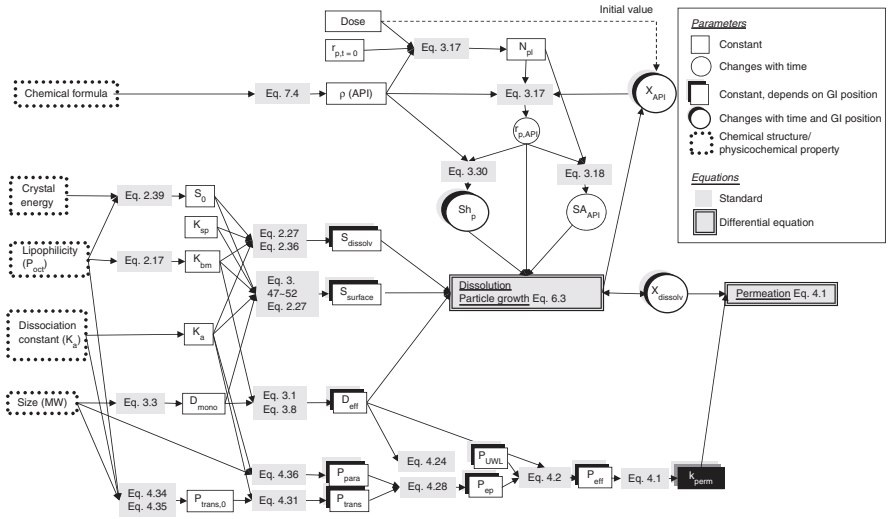


Figure 2.1 Network of equations consisting of the GUT framework.

2.1.1 Total Concentration

Total concentration of a drug (C_{tot}) is the amount of a drug substance in a fluid, regardless of the substance being undissolved solid or dissolved molecules. For example, when 100 mg of a solid drug is diluted to 1 ml with a fluid, the concentration is 100 mg/ml, regardless of whether the drug is completely dissolved or not in the fluid. This point is often miscommunicated by a formulation scientist and a biologist. Biologists often tacitly assume complete dissolution in the assay media, whereas a formulation scientist uses this expression for a suspension formulation.

2.1.2 Dissolved Drug Concentration

"Dissolved drug concentration ($C_{dissolv}$)" is used in this book to express the concentration of dissolved drug molecules in the fluid. Drug molecules can exist in various states in a fluid (Fig. 2.2). After adding a solid compound to a blank medium, if it looks transparent to the eye, we often say it is "dissolved" and the medium is typically called a *solution*. However, the molecule can exist in this transparent solution as (i) a monomer (a single molecule surrounded by solvent molecules), (ii) a dimer or higher self-aggregate, (iii) complexes with large molecules (such as cyclodextrin), (iv) the micelle included state, or even (v) nanoscale particles. In the literature, with the exception of the last case, these are referred to as *solubilized* (the last example is often referred to as *nanosuspension*). We use this definition of "solution" in this chapter unless otherwise noted. In this book, undissociated monomer molecules, dissociated monomer molecules, and bile-micelle-bound molecules are considered in the theoretical

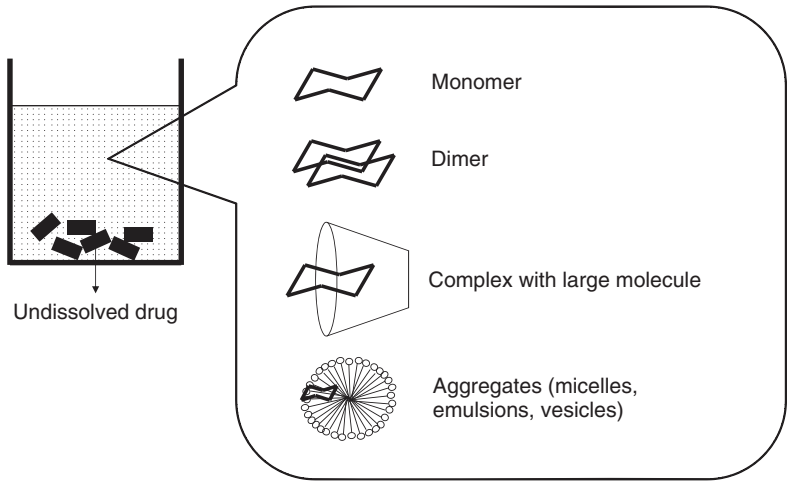


Figure 2.2 Dissolved drug molecules in the gastrointestinal fluid.

framework unless otherwise noted. The dissolved drug concentration (C_{dissolv}) in the gastrointestinal (GI) fluid is expressed as the sum of each species as

$$X_{\text{dissolv}} = \sum_z X_{u,z} + X_{\text{bm}} \tag{2.1}$$

$$C_{\text{dissolv}} = \frac{X_{\text{dissolv}}}{V_{\text{GI}}} = \sum_z C_{u,z} + C_{\text{bm}} \tag{2.2}$$

where X is the amount of drug (weight or mole) and C is the concentration (X/V_{GI}). The subscripts u, z (expressed as $+, -, ++, --, \ldots$ in the following sections), and bm indicate unbound monomer molecules, charge of molecules, and bile-micelle-bound monomer molecules, respectively. V_{GI} is the fluid volume in a GI position.

2.1.3 Effective Concentration

The effective concentration for a reaction, such as dissolution and permeation, depends on the "availability" of the molecular state for the reaction. For example, the dissolution of drug particles can be carried out as both the unbound monomer and the bile-micelle-included state. On the other hand, passive transcellular permeation across the intestinal epithelial membrane occurs mainly for unionized unbound monomer molecules (pH partition and free fraction theories) (Fig. 2.3).

The effective concentration of a reaction is expressed as the fraction of the dissolved drug concentration. For example, concentration of the undissociated

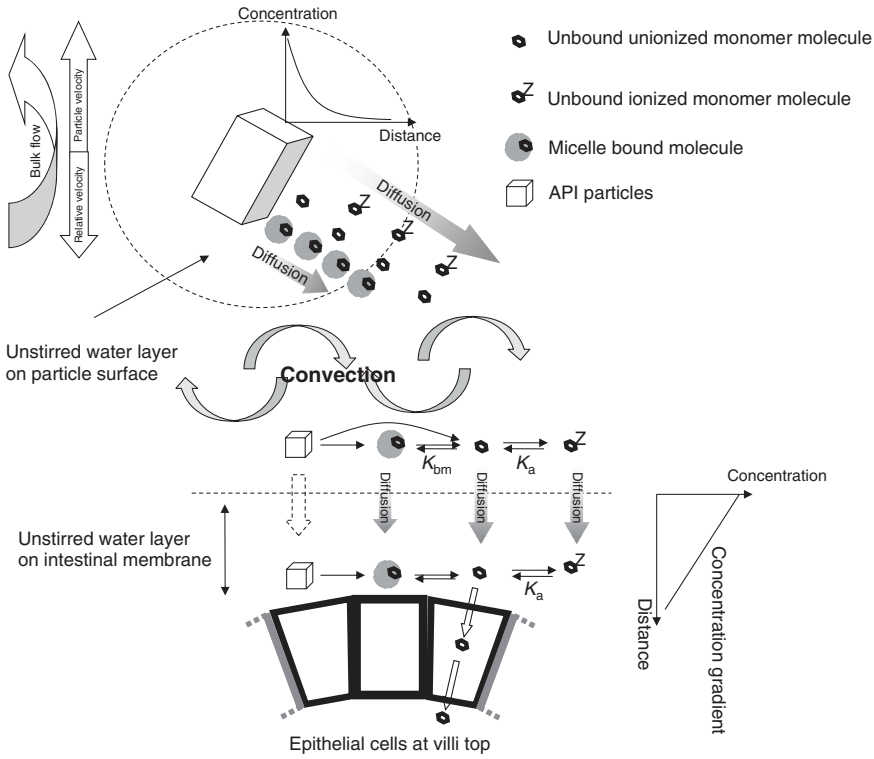


Figure 2.3 Schematic representation of dissolution and permeation.

unbound monomer molecule is expressed as

$$C_{u,0} = f_u f_0 C_{dissolv} \tag{2.3}$$

where f_u is the fraction of unbound monomer molecules and f_0 is the fraction of undissociated molecules. This expression is the same as that for plasma concentration and unbound fraction used in pharmacokinetics (PK).

2.2 ACID–BASE AND BILE-MICELLE-BINDING EQUILIBRIUMS

The fraction of undissociated monomer molecule (f_0) is determined by the dissociation constant (pK_a) of a drug and pH of the fluid. The famous Henderson–Hasselbalch (HH) equation is derived from the acid–base chemical equilibrium equation.[2] The derivation of the HH equation is often omitted in

[2]The acid–base and bile-micelle-binding equilibrium is achieved immediately compared to the timescales of other processes of oral absorption. In general, the reaction rates of these dynamic equilibriums are more than one order faster than the other processes such as dissolution and permeation. Therefore, pseudoequilibrium approximation is appropriate.

TABLE 2.1 Fraction of Undissociated Species

Fraction of undissociated species	(f_0)
Monoprotic acid	$\dfrac{1}{1+\frac{K_a}{[H^+]}}$
Monoprotic base	$\dfrac{1}{1+\dfrac{[H^+]}{K_a}}$
Diprotic acid	$\dfrac{1}{1+\dfrac{K_{a1}}{[H^+]}+\dfrac{K_{a1}K_{a2}}{[H^+]^2}}$
Diprotic base	$\dfrac{1}{1+\dfrac{[H^+]}{K_{a1}}+\dfrac{[H^+]^2}{K_{a1}K_{a2}}}$

a standard textbook of pharmacy; however, it is very important for the clear understanding of biopharmaceutical modeling (Table 2.1).

2.2.1 Monoprotic Acid and Base

In the case of an acid, the chemical equilibrium can be written as Equation 2.4 (cf. the parenthesis "[]" indicates the "dissolved drug concentration" of the molecular species (Section 2.1)).

$$[AH] \overset{k_a}{\rightleftharpoons} [A^-] + [H^+] \tag{2.4}$$

$$K_a = \frac{[A^-][H^+]}{[AH]} \quad \text{cf.} K_a = 10^{-pK_a}, [H^+] = 10^{-pH} \tag{2.5}$$

where $[H^+]$, $[AH]$, and $[A^-]$ are the concentrations of proton, the undissociated, and the ionized (anion) drug molecules, respectively. This equation is based on the law of mass action. In addition, this equation describes the definition of K_a. K_a is the pH at which the concentrations of undissociated and dissociated species become equal (i.e., $[A^-]/[AH] = 1$). The fraction of the undissociated (unionized) molecular species (f_0) in the total monomer concentration ($C_{u,0} + C_{u,-}$) is then written as

$$f_0 = \frac{\text{Undissociated monomer}}{\text{Total monomer}} = \frac{[AH]}{[AH]+[A^-]} = \frac{1}{1+\dfrac{[A^-]}{[AH]}} = \frac{1}{1+\dfrac{K_a}{[H^+]}} \tag{2.6}$$

Figure 2.4 shows the relationship between pH, pK_a, and f_0 for an acid with $pK_a = 4.5$. When the pH is lower (so the fluid is acidic, the proton concentration

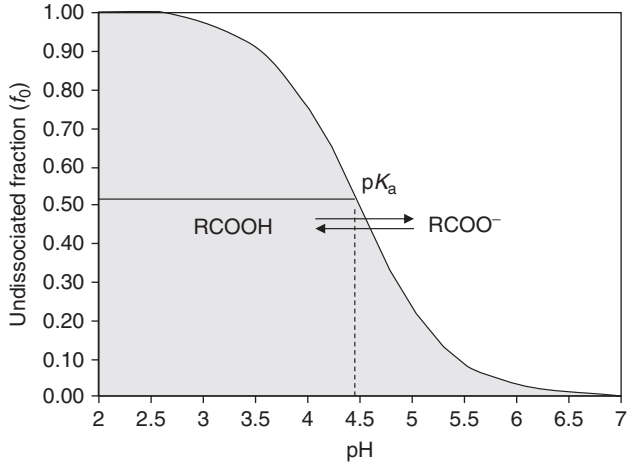


Figure 2.4 The relationship between pH, pK_a, and f_0 for an acid with p$K_a = 4.5$.

is higher), the equilibrium is pushed to the left-hand side of Equation 2.4 and the fraction of undissociated molecules increases, whereas when the pH is higher (the fluid is alkaline, the proton concentration is lower), the equilibrium is pushed to the right-hand side of Equation 2.4 and the fraction of anion molecule increases.

In the case of a base,

$$[BH^+] \overset{K_a}{\rightleftharpoons} [B] + [H^+] \tag{2.7}$$

$$K_a = \frac{[B][H^+]}{[BH^+]} \tag{2.8}$$

Therefore,

$$f_0 = \frac{1}{1 + \dfrac{[H+]}{K_a}} \tag{2.9}$$

Note that the position of the undissociated and the charged drug[3] concentrations in the equation is swapped as for an acid case. When the pH is higher (the fluid is alkaline, the proton concentration is lower), the fraction of undissociated molecules increases ($[H^+]/K_a$ becomes smaller in Equation 2.9).

[3]This is "proton-associated (proton bound)" species. Conceptually, this proton binding can be treated in the same manner as bile-micelle binding. This community of concept helps us to understand the theoretical scheme.

Example The undissociated fractions of an acid with pK_a of 4 at pH 2, 4, and 6 are calculated as follows:

$$K_a = 10^{-pK_a} = 10^{-4} = 0.0001$$

At pH 2,

$$[H^+] = 10^{-pH} = 10^{-2} = 0.01$$

$$f_0 = \frac{1}{1 + \dfrac{0.0001}{0.01}} = \frac{1}{1 + 0.01} = 0.99$$

Similarly, at pH 4,

$$f_0 = \frac{1}{1 + \dfrac{0.0001}{0.0001}} = \frac{1}{1 + 1} = 0.5$$

And at pH 6,

$$f_0 = \frac{1}{1 + \dfrac{0.0001}{0.000001}} = \frac{1}{1 + 100} = 0.01$$

2.2.2 Multivalent Cases

For a divalent acid,

$$[AH_2] \overset{K_{a1}}{\rightleftharpoons} [AH^-] + [H^+], [AH^-] \overset{K_{a2}}{\rightleftharpoons} [A^{2-}] + [H^+] \tag{2.10}$$

$$K_{a1} = \frac{[AH^-][H^+]}{[AH_2]}, K_{a2} = \frac{[A^{2-}][H^+]}{[AH^-]} \tag{2.11}$$

The fraction of the undissociated molecular species is then given as

$$\begin{aligned} f_0 &= \frac{[AH_2]}{[AH_2] + [AH^-] + [A^{2-}]} = \frac{1}{1 + \frac{[AH^-]}{[AH_2]} + \frac{[A^{2-}]}{[AH_2]}} \\ &= \frac{1}{1 + \dfrac{[AH^-]}{[AH_2]} + \dfrac{[AH^-]}{[AH_2]}\dfrac{[A^{2-}]}{[AH^-]}} = \frac{1}{1 + \dfrac{K_{a1}}{[H^+]} + \dfrac{K_{a1}K_{a2}}{[H^+]^2}} \end{aligned} \tag{2.12}$$

An equation for a divalent base can be derived similarly.

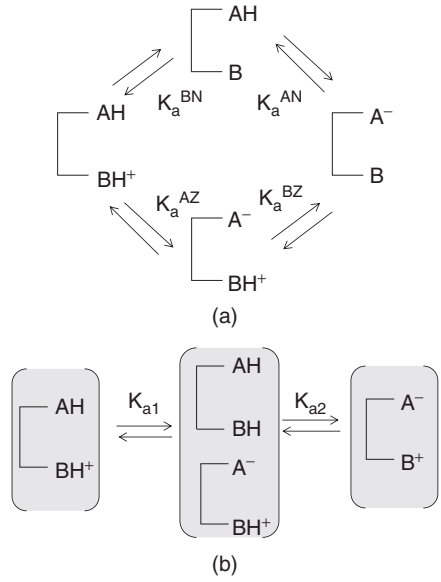


Figure 2.5 (a) Micro pK_a and (b) macro pK_a.

Zwitter ionic cases are much more complex, as both of undissociated and zwitter ionic species are of charge neutral (Fig. 2.5) [2]. To calculate the fractions of undissociated and zwitter ionic species (f_0 and f_{+-}, respectively), the microscopic pK_a value have to be obtained. However, there is no simple experimental method to determine the microscopic pK_a (Section 7.2).

2.2.3 Bile-Micelle Partitioning

The bile-micelle partitioning is another important equilibrium of drug molecules in the intestinal fluid. Drug molecules bound to bile micelles behave differently from unbound ones during dissolution and permeation of the drug. Therefore, the bile-micelle-unbound fraction (f_u) has to be explicitly taken into account for biopharmaceutical modeling. The bile-micelle binding can be treated in a similar way to acid–base equilibrium.[4] Since it is difficult to define the concentration of micelles, the bile-micelle partition coefficient (K_{bm}) is usually defined based on the bile acid concentration ([M]) [3].

$$K_{bm} = \frac{[D - M]/[M]}{[D]/[Water]} \tag{2.13}$$

[4]"Bile binding" is a like "proton binding of a base."

$$f_u = \frac{C_u}{C_{dissolv}} = \frac{[\text{Drug in water}]}{[\text{Drug in water}] + [\text{Drug in micelles}]}$$

$$= \frac{1}{1 + \dfrac{[D-M]}{[D]}} = \frac{1}{1 + \dfrac{K_{bm}[M]}{[\text{Water}]}} \tag{2.14}$$

The bile-micelle partition coefficient changes depending on the molecular charge, that is, $K_{bm,0}$ for the undissociated molecule, $K_{bm,-}$ the for monoprotic anion, and $K_{bm,+}$ for monoprotic cation are different. The K_{bm} values can be back-calculated from the solubility values in a bile-micelle media (such as FaSSIF, Section 7.6.2) and its blank media.

2.2.4 Modified Henderson–Hasselbalch Equation

Finally, when all the equilibriums are taken into account [4–6], the fraction of the unbound undissociated monomer molecule ($C_{u,0}/C_{dissolv}$) for acid is

$$\frac{C_{u,0}}{C_{dissolv}} = f_0 \times f_u = \frac{[AH]}{[AH]+[A^-]} \times \frac{[AH]+[A^-]}{[AH]+[A^-]+[A-M]+[A^- - M]}$$

$$= \frac{[AH]}{[AH]+[A^-]+[A-M]+[A^- - M]}$$

$$= \frac{1}{1 + \dfrac{[A^-]}{[AH]} + \dfrac{[AH-M]}{[AH]} + \dfrac{[A^-]}{[AH]}\dfrac{[A^- - M]}{[A^-]}}$$

$$= \frac{1}{1 + \dfrac{K_a}{[H^+]} + \dfrac{K_{bm,0}[M]}{[\text{Water}]} + \dfrac{K_a}{[H^+]}\dfrac{K_{bm,-}[M]}{[\text{Water}]}} \tag{2.15}$$

Similarly, for a monoprotic base,

$$\frac{C_{u,0}}{C_{dissolv}} = f_0 \times f_u = \frac{1}{1 + \dfrac{[H^+]}{K_a} + \dfrac{K_{bm,0}[M]}{[\text{Water}]} + \dfrac{[H^+]}{K_a}\dfrac{K_{bm,+}[M]}{[\text{Water}]}} \tag{2.16}$$

These equations are called *modified HH equation* in this book. The pH solubility profile of dipyridamole in a biorelevant media containing bile micelles is shown in Figure 2.6 [1, 3].

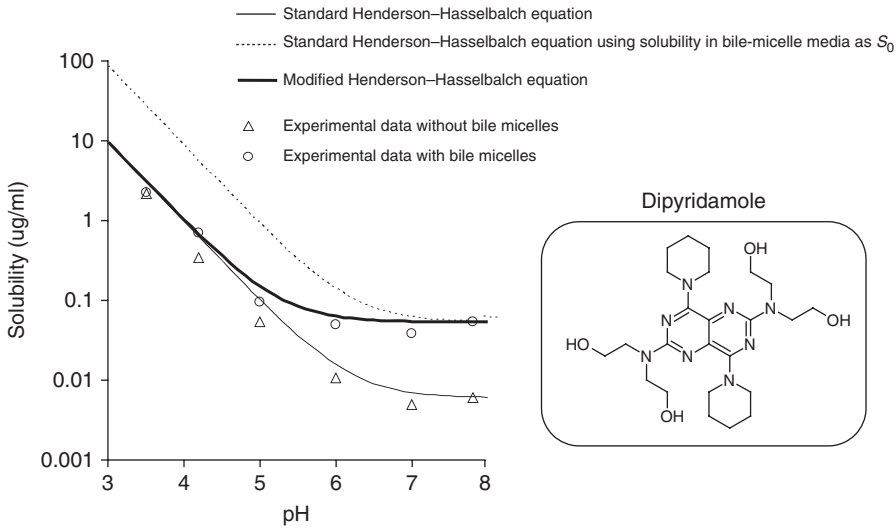


Figure 2.6 pH solubility profile of dipyridamol in biorelevant media containing bile micelles [3].

2.2.5 K_{bm} from Log P_{oct}

K_{bm} can be roughly calculated from the octanol water partition coefficient (P_{oct}) as [3]

$$\log K_{bm,0} = 0.74 \log P_{oct} + 2.29 \tag{2.17}$$

The bile-micelle partition coefficients of monocation and anion ($K_{bm,+}$ and $K_{bm,-}$, respectively) can be estimated as [7, 8]

$$\log K_{bm,+} \approx \log K_{bm,0} - 1 \tag{2.18}$$

$$\log K_{bm,-} \approx \log K_{bm,0} - 2 \tag{2.19}$$

2.3 EQUILIBRIUM SOLUBILITY

2.3.1 Definition of Equilibrium Solubility

The solubility of a drug is defined based on the equilibrium state between the dissolved drug molecules and the undissolved solid drug molecules (Figs. 2.7 and 2.2).[5] At equilibrium, the chemical potential at the solid surface (free

[5]Please also refer to Section 7.6.1 for detailed definitions of solubility.

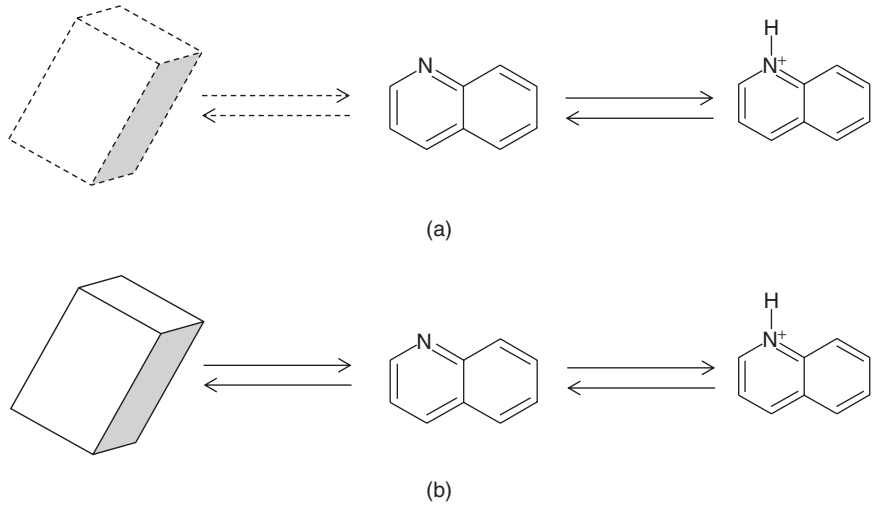


Figure 2.7 (a) Complete and (b) incomplete dissolution of a drug in a fluid.

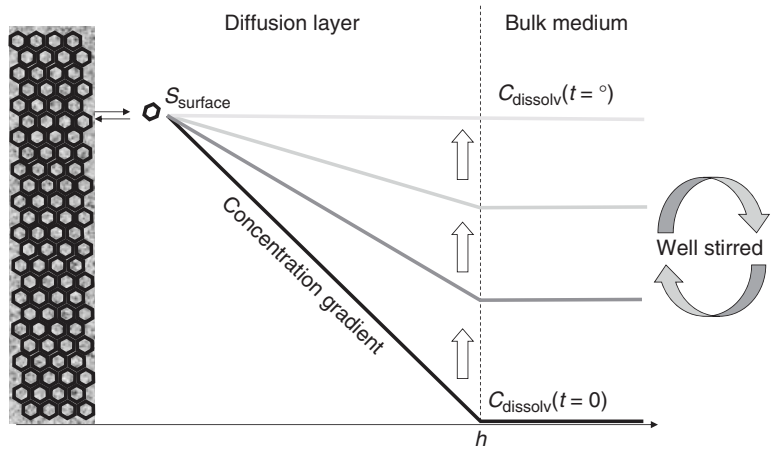


Figure 2.8 Detachment of a molecule from the solid surface and concentration gradient in the diffusion layer.

energy/mole) is equal to that in the fluid. When we look at the solid surface at a molecular level, there is a dynamic equilibrium determined by the balance of detaching and attaching rates (Fig. 2.8). The term *thermodynamic solubility* is also used in the literature but not used in this book.

To measure the solubility of a drug, the amount of the drug (Dose) added to the fluid must exceed the solubilization capacity of the fluid, that is,

solubility × fluid volume.[6] The dose number (Do) is defined as (in a broad sense)[7]

$$\text{Do} = \frac{\text{Dose}}{\text{Solubility} \times \text{Fluid volume}} \tag{2.20}$$

For the Do > 1 cases, when a solid drug is added to the fluid, a portion of the added drug remains undissolved in the fluid. For example, when 10 mg of a drug with an equilibrium solubility of 1 mg/ml is added to 2 ml of the fluid, Do is 5(= 10 mg/(1 mg/ml × 2 ml). In this case, 2 mg gets dissolved and 8 mg remains undissolved. When Do < 1, the drug completely dissolves in the fluid (Fig. 2.7). For example, when the above drug is added to 20 ml of the fluid, Do is 0.5 (= 10 mg/(1 mg/ml × 20 ml).

The concept of the dose number can be expanded and generally defined when a solid material is added to a fluid. The dose number determines whether a portion of the solid drug remains undissolved in the fluid and participates in the equilibrium network of drug molecules in the fluid (Fig. 2.7). In the absence of the undissolved drug in the fluid (i.e., Do < 1, the drug is completely dissolved in the fluid), the equilibriums in the solution are sufficient to describe the concentration of each molecular species in the fluid, for example, pH equilibrium and bile-micelle-binding equilibrium. However, in the presence of undissolved drug material (i.e., Do > 1), the equilibrium between the solid drug (remaining undissolved) and the dissolved drug have to be additionally taken into account.

2.3.2 pH–Solubility Profile (pH-Controlled Region)

The typical pH–equilibrium solubility profile of a monobasic compound is shown in Figure 2.9. The pH–solubility profile can be divided into "pH" and "common ionic effect" controlled regions. The pH–solubility profile of a drug in a simple buffer (without solubilizers such as micelles) is controlled by the pK_a, intrinsic solubility (S_0), and solubility product (K_{sp}) of a drug, as well as the pH and the common ion concentration in the fluid. The smaller value of the pH-controlled or common-ion-controlled solubility determines the actual solubility of a drug experimentally observed.

The pH–solubility curve in the pH-controlled region is derived as follows. In the case of an acid, when an excess amount of a solid drug coexists in a fluid at a pH where no dissociation occurs (i.e., pH $\ll$ pK_a of the drug), the equilibrium between the solid and the dissolved drug is written as

$$\langle \text{AH} \rangle \rightleftharpoons [\text{AH}] \tag{2.21}$$

[6]Whether an excess undissolved solid drug exists in the fluid or not is very important in biopharmaceutics. The dose number is the central parameter that governs the biopharmaceutical characteristics of a drug.

[7]In the regulatory context, the minimum solubility in the GI physiological pH range and the fluid volume of 250 ml is used to calculate the dose number. However, the dose number has wider and deeper implication in biopharmaceutical modeling, hence, used as a generalized concept in this book.

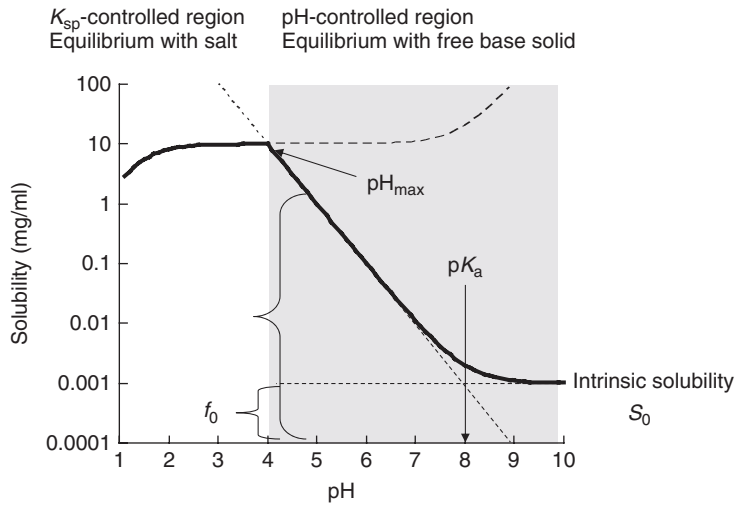


Figure 2.9 Typical pH–solubility profile of a base.

where ⟨AH⟩ represents the solid form of the undissociated drug (cf. [] indicates the "dissolved drug concentration" (Section 2.1). When the system is at equilibrium in this pH region, [AH] equals the intrinsic solubility of the undissociated drug (S_0).

As the pH goes up, the acid molecules start to dissociate. Therefore, we add a pH–pK_a equilibrium:

$$\langle \mathrm{AH} \rangle \rightleftharpoons [\mathrm{AH}] \tag{2.22}$$

$$[\mathrm{AH}] \overset{K_a}{\rightleftharpoons} [\mathrm{A}^-] + [\mathrm{H}^+] \tag{2.23}$$

As far as the solid form of the undissociated acid coexists in equilibrium with [AH] (i.e., Do > 1), the concentration of the dissolved free acid ([AH]) remains constant and equals to S_0. As described in Section 2.2.1, [A^-] can be determined by pK_a, pH, and [AH].

$$[\mathrm{A}^-] = \frac{K_a}{[\mathrm{H}^+]}[\mathrm{AH}] \quad \left(\text{cf. } K_a = \frac{[\mathrm{A}^-][\mathrm{H}^+]}{[\mathrm{AH}]}\right) \tag{2.24}$$

Therefore, the total dissolved drug concentration in a buffer ($S_{buffer} = [AH] + [A^-]$) when [AH] is in equilibrium with the solid undissociated acid can be described as

$$S_{buffer} = [\mathrm{AH}] + [\mathrm{A}^-] = S_0 + \frac{K_a}{[\mathrm{H}^+]}S_0 = S_0\left(1 + \frac{K_a}{[\mathrm{H}^+]}\right) = \frac{S_0}{f_0} \tag{2.25}$$

When we rewrite this,

$$S_0 = f_0 S_{\text{buffer}} \quad \text{or} \quad f_0 = \frac{S_0}{S_{\text{buffer}}} \tag{2.26}$$

Example The solubility of an acidic drug ($pK_a = 4, S_0 = 0.001$ mg/ml) at pH 6.0 can be calculated as

$$S_{\text{buffer}} = \frac{S_0}{f_0} = \frac{0.001}{0.01} = 0.1$$

In Figure 2.10, the concept of concentration, fraction, and solubility are illustrated.

- Complete Dissolution Case (Do < 1)
  - When the added solid drug is completely dissolved in the fluid at all pH (Do < 1), the dissolved drug concentration does not depend on pH ($[AH] + [A^-]$ = added drug amount/fluid volume), however, the fractions (ratios) and the concentrations of undissociated and dissociated species changes (Figs. 2.10a and 2.4).
- Incomplete Dissolution Case (Do > 1)
  - When an excess amount of solid drug is added (D > 1), [AH] is in equilibrium with the solid of undissolved free acid (AH). Therefore, [AH] remains constant (as S_0, which is independent of pH), but the ratio of $[A^-]$ and [AH] increases as pH increases. Therefore, as pH increases, dissolved drug concentration ($= [AH] + [A^-]$) becomes higher (Fig. 2.10b).[8]

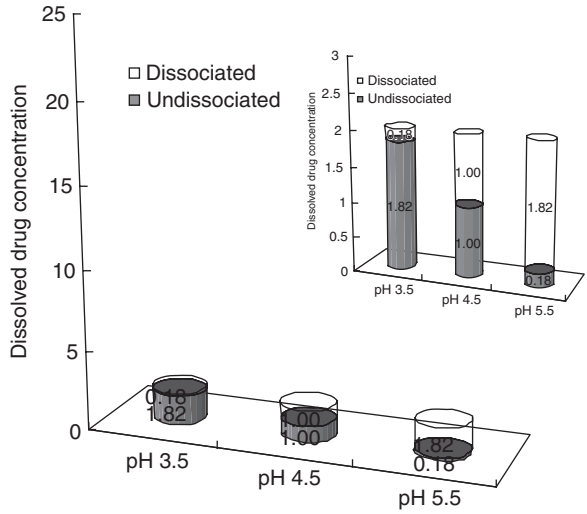
2.3.3 Solubility in a Biorelevant Media with Bile Micelles (pH-Controlled Region)

As discussed in Section 2.2.4, the bile-micelle-binding equilibrium can be treated in a similar way to acid–base equilibrium. The solubility of undissociable acid and base drugs in a biorelevant media with bile micelles (S_{dissolv}) can be written as

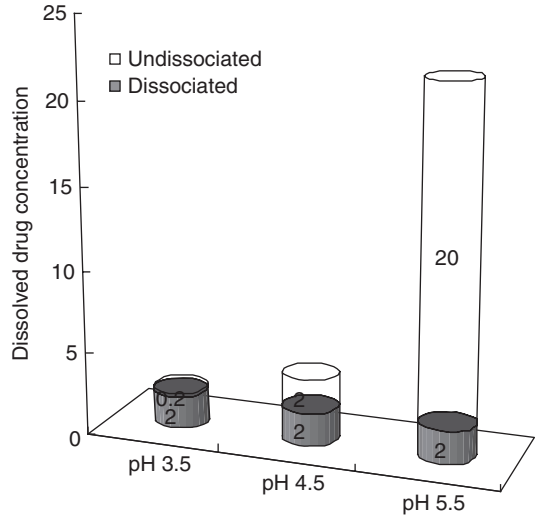
$$S_{\text{dissolv}} = \frac{S_0}{f_u} = S_0 \left(1 + \frac{K_{\text{bm}}[\text{Bile acid}]}{[\text{Water}]}\right) \qquad \text{Undissociable} \tag{2.27}$$

$$S_{\text{dissolv}} = \frac{S_0}{f_u f_0} = S_0 \left(1 + \frac{K_a}{[H^+]} + \frac{K_{\text{bm},0}[\text{Bile acid}]}{[\text{Water}]} + \frac{K_a}{[H^+]} \frac{K_{\text{bm},-}[\text{Bile acid}]}{[\text{Water}]}\right) \qquad \text{Monoprotic acid} \tag{2.28}$$

[8]The ratio of undissociated and dissociated species (of dissolved drug) is the same, regardless of Do.



(a)



(b)

Figure 2.10 Fraction, concentration, and solubility. (a) Do <1 at all pH and (b) Do >1 at all pH. (a) 2 mg of a drug (acid, $pK_a = 4.5$, $S_0 = 2$ mg/mL) added to 1 mL. (b) An excess amount added.

$$S_{\text{dissolv}} = \frac{S_0}{f_u f_0} = S_0 \left(1 + \frac{[H^+]}{K_a} + \frac{K_{bm,0}[\text{Bile acid}]}{[\text{Water}]} + \frac{[H^+]}{K_a}\frac{K_{bm,+}[\text{Bile acid}]}{[\text{Water}]}\right) \quad \text{Monoprotic base} \quad (2.29)$$

2.3.4 Estimation of Unbound Fraction from the Solubilities with and without Bile Micelles

From Equation 2.29, the unbound fraction (f_u) can be back-estimated from the solubilities in the media with and without bile micelles ($S_{dissolv}$ and S_{buffer}, respectively).

$$f_u = \frac{S_{buffer}}{S_{dissolv}} = \frac{S_0/f_0}{S_{dissolv}} \tag{2.30}$$

This method is practically useful as S_{blank} and $S_{dissolv}$ is usually available during drug discovery.

It should be emphasized that, as in the same manner with acid–base equilibrium, when the fluid is in equilibrium with excess amount of a solid drug (i.e., Do > 1), even when bile-micelle concentration is increased, the concentration of unbound drugs remains constant (and equals S_{blank}), whereas $C_{dissolv}(=S_{dissolv})$ is increased and the fractions of unbound drugs is decreased. On the other hand, when the drug is completely dissolved in the fluid (i.e., Do < 1), both the concentration and the fraction of unbound drugs are decreased as bile-micelle concentration is increased. This point is important especially when considering the food effects on oral absorption of a drug, as the food intake increases the bile-micelle concentration in the GI tract (Sections 12.2.2.1 and 12.2.3.1).

2.3.5 Common Ionic Effect

The solubility of a salt is described by the solubility product (K_{sp}). In the case of a salt of base drug,

$$< BH^+X^- > \overset{K_{sp}}{\rightleftharpoons} [BH^+]_{sat} + [X^-] \tag{2.31}$$

$$K_{sp} = \frac{[BH^+]_{sat}[X^-]}{\langle BH^+X^- \rangle} \tag{2.32}$$

where the subscript "sat" indicates the saturated species (species of equilibrium maker), and $\langle BH^+X^- \rangle$ is the activity of the solid part of the salt and is defined as 1. Therefore,

$$K_{sp} = [BH^+]_{sat}[X^-] \tag{2.33}$$

When we consider the case that the fluid pH is adjusted by an acid, HX (e.g., HCl) and ionic strength is adjusted by a salt, MX (e.g., NaCl), because of the charge neutrality in the fluid, the sum of the anions ($= [X^-] + [OH^-]$) equals the sum of the cations ($= [H^+] + [BH^+] + [M^+]$).

$$[X^-] + [OH^-] = [BH^+]_{sat} + [H^+] + [M^+] \tag{2.34}$$

By inserting this charge neutrality equation into the solubility product equation,

$$K_{sp} = [BH^+]_{sat}\left([BH^+]_{sat} + [H^+] + [M^+] - \frac{K_w}{[H^+]}\right) \tag{2.35}$$

where K_w is the ionic product of water ($K_w = [H^+][OH^-] = 1 \times 10^{-14}$ M^2). This equation is a quadratic equation of $[BH^+]_{sat}$ and can be solved as

$$[BH^+]_{sat} = \frac{-\left([H^+] + [M^+] - \frac{K_w}{[H^+]}\right) + \sqrt{\left([H^+] + [M^+] - \frac{K_w}{[H^+]}\right)^2 + 4K_{sp}}}{2} \tag{2.36}$$

The dissolved drug solubility is the sum of B and BH^+. Therefore, using the HH equation for mono bases,

$$\begin{aligned} S_{dissolv} &= [BH^+]_{sat} + [B] = [BH^+]_{sat}\left(1 + \frac{[B]}{[BH^+]_{sat}}\right) \\ &= [BH^+]_{sat}\left(1 + \frac{K_a}{[H^+]}\right) \quad pH < pH_{max} \end{aligned} \tag{2.37}$$

where pH_{max} is the pH of the maximum solubility, the system changes from the pH-controlled region to the common-ion-effect-controlled region. Similar equation can be derived for acid drugs.

In the pH-controlled region (acid: $pH < pH_{max}$, base: $pH > pH_{max}$), the slope of the logarithmic pH–solubility plot is 1. Therefore, one unit shift of pH or pK_a results in 10-fold change in solubility. The maximum solubility of the pH–equilibrium solubility profile is limited by the solubility product. In the common-ion-effect-controlled region, the equilibrium solubility of a drug depends largely on the concentration of the counterions (common ion effect) but less on the pH (concentration of H_3O^+). Therefore, the species of the counterion is an important factor when we measure the pH–equilibrium solubility profile (K_{sp} is different among the counterion species such as Cl^-, $CH_3SO_3^-$).

Na^+ and Cl^- are most often used, as they are the major ionic species in the physiological condition.

In this book, the intrinsic solubility of a salt (S_{salt}) is defined as

$$S_{salt} \equiv \sqrt{K_{sp}} \tag{2.38}$$

2.3.6 Important Conclusion from the pH–Equilibrium Solubility Profile Theory

From the theories of the pH–equilibrium solubility profile, it is concluded that, regardless of the initial solid form (free or salt) used for a solubility measurement, the pH–equilibrium solubility profile becomes identical in the pH-controlled region.[9] Figure 2.11 shows some experimental data [10]. For example, even when we start with an HCl salt of a base, as the pH is titrated above the pH_{max}, the free base precipitates out and $S_{dissolv}$ is determined based on the equilibrium with the solid of the free base (not HCl salt). In other words, the pH–equilibrium solubility profiles measured from a free base and its salt become identical when the pH is well maintained by the buffer. This situation is very different from the equilibrium solubility in an unbuffered media (i.e., pure water), as the initial pH can be shifted by the added drug. In this case, the final pH and the equilibrium solubility become different depending on the starting solid material. In drug discovery, a strong buffer (e.g., 50 mM phosphate buffer) is often used for the solubility measurement. Therefore, an identical (or very similar) solubility value is usually reported for a free drug and its salt.

Even though the equilibrium solubility measured from a free form and a salt form becomes the same in a buffer, the bioavailabilities of a free base and its salt are usually significantly different. This suggests that the equilibrium solubility in a buffer at a pH cannot be simply used for biopharmaceutical modeling of a salt (as it is identical to a free base).[10] The reasons that salt formation increases the oral absorption of a poor solubility drug are (i) salt formation increases the dissolution rate (by increasing the solid surface solubility), and/or (ii) a supersaturated concentration can be produced in the gastrointestinal fluid after the dissolution of a salt (Sections 3.3 and 11.1) (the dissolved drug molecules at the transient supersaturated concentration are absorbed before the dissolved drug concentration settle down to the equilibrium solubility (which is identical to that of the free base form)). The difference in the dissolution and precipitation mechanisms between a free form and a salt should be taken into account in biopharmaceutic modeling.[11,12]

2.3.7 Yalkowsky's General Solubility Equation

The intrinsic solubility of a drug (free form) in water is determined by the hydration energy of a drug molecule and the sublime energy (Fig. 2.12). Yalkowsky's

[9]We are assuming that the precipitated free form has the same solid form with the other free form. When the pH titration method is used without enough equilibrium time, the pH–*apparent* solubility curve can deviate from the theoretical HH curve. When the drug forms aggregate, equilibrium to the aggregate state must additionally be taken into account [9].

[10]This is one of the most often observed mistakes in biopharmaceutical modeling.

[11]In some literature, this important aspect was unremarked.

[12]For appropriate modeling for a salt, a nucleation theory is required.

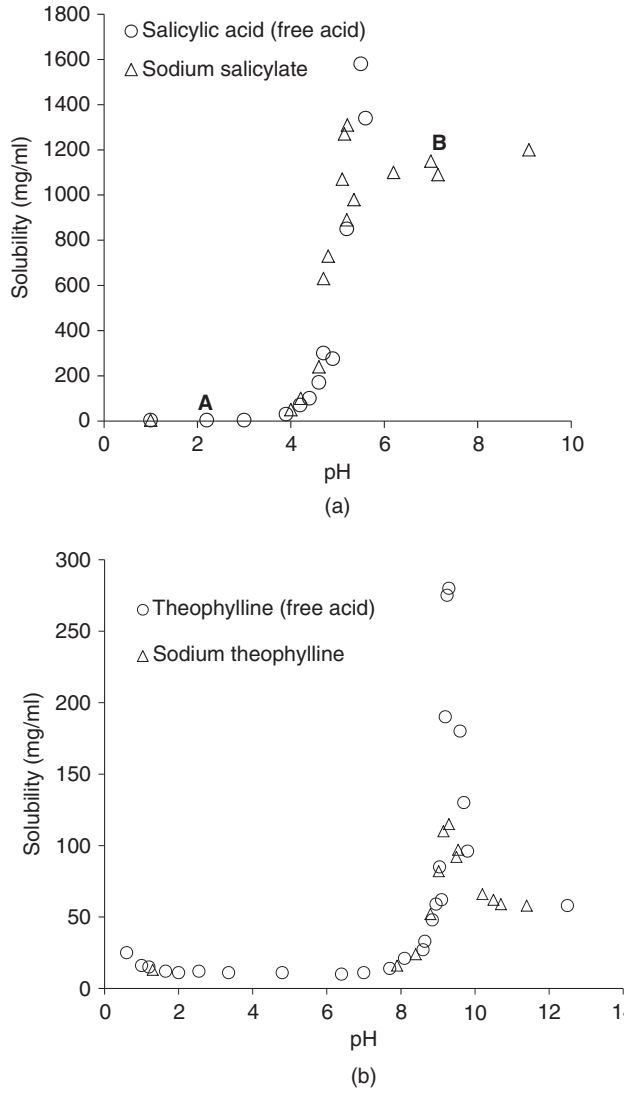


Figure 2.11 pH solubility profile of (a) salicylic acid and (b) theophylline measured from the free acids and the sodium salts. (a) The pH–solubility profiles of salicylic acid (free acid, circle) and sodium salicylate (triangle). Points A (pH 2.3) and B (pH 6.9) represent the pH values and concentrations of saturated solutions of salicylic acid and its sodium salt in pure water. (b) The pH solubility profiles of theophylline (free acid, circle) and sodium theophylline (triangle). *Source:* Adapted from Reference 10 with permission.

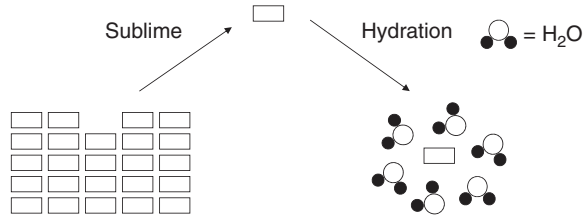


Figure 2.12 Sublime and hydration.

general solubility equation is a simple but very useful equation [11, 12].

$$\log S_0(\mathrm{M}) = -\log P_{\mathrm{oct}} - 1.1\frac{\Delta S_{\mathrm{f}}(\mathrm{m.p.} - 25)}{1364} + 0.54 \tag{2.39}$$

$$\Delta S_{\mathrm{f}} = 13.5 + 2.5(n - 5) \tag{2.40}$$

where ΔS_{f} is the entropy of fusion, n is the number of nonhydrogen atoms ($n > 5$) in a flexible chain, and m.p. is the melting point of a drug. This equation can be further simplified to

$$\log S_0(\mathrm{M}) = -\log P_{\mathrm{oct}} - 0.01(\mathrm{m.p.} - 25) + 0.50 \tag{2.41}$$

In this equation, the log P_{oct} reflects the hydration energy, and the melting point reflects the crystal lattice energy. Roughly speaking, a change in m.p. of 100°C will change the solubility 10-fold. This equation cannot be applied for enantiotropic polymorph cases (Section 7.5.2.4). The average error of this equation is 0.42 log units [13].

Equations 2.40 and 2.41 can be used to diagnose the main reasons for poor solubility. When high lipophilicity is the main reason, micelle solubilization would be effective to increase the solubility of a drug [14–16]. When high melting point is the reason, structural modification to reduce the lattice energy would be effective, for example, introducing a steric barrier for molecular stacking or removing an intermolecular hydrogen bond in the crystalline.

As the solubility measurement is not straightforward and the experimental data is sometimes accompanied with an artifact error, cross validation of the experimental solubility value with the predicted value by this equation is important[13] (Section 7.6).

2.3.8 Solubility Increase by Converting to an Amorphous Form

An amorphous solid form is often used to enhance the bioavailability of a poor solubility drug (Section 11.1.2.3). We can define the solubility of an amorphous form of a drug in the same manner as that for a crystalline form. As the

[13] A decomposition temperature is often misleadingly reported as the melting point of a drug.

chemical potential of an amorphous form is higher than that of a crystalline form, the dissolved drug concentration, which is in equilibrium (transiently) with the undissolved amorphous solid (= solubility of amorphous form), is also higher than that of the crystalline form.[14] The intrinsic solubility of an amorphous form ($S_{0,A}$) can be estimated from that of the crystalline form ($S_{0,C}$) as [17]

$$\frac{S_{0,A}}{S_{0,C}} = \exp\left(\frac{\Delta S_m}{R}\ln\left(\frac{T_m}{T}\right)\right) \tag{2.42}$$

where R is the gas constant, T is the absolute temperature, and ΔS_m is the entropy of melting. ΔS_m can be calculated using $\Delta S_m = \Delta H_m/T_m$, where ΔH_m is the enthalpy of melting and T_m is the melting temperature. ΔH_m and T_m can be measured by differential scanning calorimeter (DSC) (Section 7.5.3.3).

2.3.9 Solubility Increase by Particle Size Reduction (Nanoparticles)

The solid surface energy increases as the surface area increases. Therefore, theoretically, particle size reduction increases the solubility of a drug. According to the Ostwald–Freundlich equation (Kelvin equation), the increase in solubility by particle size reduction can be estimated as

$$\frac{S_{0,r_p}}{S_{0,\infty}} = \exp\left(\frac{2\gamma v_m}{r_p RT}\right) \tag{2.43}$$

where S_{0,r_p} and $S_{0,\infty}$ are the solubility of particles with radius r_p and that of an infinitely large particle (larger than several micrometers), respectively, γ is the interfacial tension between the solid surface and the fluid and v_m is the molar volume of a drug. A simple calculation scheme for γ from $S_{0,\infty}$ has been reported [18].

$$\gamma = \frac{k_B T}{(v_m/N_A)^{2/3}} \times 0.33 \times \left(-\ln\left(\frac{S_{0,\infty}}{55.6}\right) - 5\right) \tag{2.44}$$

where N_A is the Avogadro constant (6.022×10^{23} mol^{-1}) and k_B is the Boltzmann constant (1.38×10^{-23} J/K). v_m can be estimated as [19]

$$v_m(\text{cm}^3/\text{mol}) = 3.85 \sum_{\text{atom}} m_{\text{atom}} \cdot v_{\text{atom}} \tag{2.45}$$

where m_{atom} is the number of atoms in the molecule and v_{atom} is the relative volume of the atom, which is 1 for H, 2 for the first short period in the periodic table (LiF), 4 for NaCl, 5 for KBr, and 7.5 for RbI.

[14] An amorphous form converts to a crystalline. However, the induction time before crystallization to occur can be long enough to achieve a transient equilibrium with the amorphous solid.

It is theoretically suggested that the increase in solubility by particle size reduction is less than 15% even at approximately 150 nm range [20]. This theoretical suggestion was recently confirmed by careful experiments [20]. The filtration and centrifuge methods are often used in solubility measurements to separate the fluid from the undissolved drug. However, these methods lead to overestimation of the solubility of nanoparticles because of the incomplete separation of nanoparticles from the fluid. A few alternative methods have been introduced to measure the solubility of nanoparticles (Section 7.6.3.4).

2.3.10 Cocrystal

The solubility of a cocrystal can be defined in the same manner as that for a salt [21].

$$\langle \mathrm{DC} \rangle \overset{K_{sp}}{\longleftrightarrow} [\mathrm{Drug}]_{sat} + [\mathrm{Coformer}] \tag{2.46}$$

$$K_{sp} = \frac{[\mathrm{Drug}]_{sat}[\mathrm{Coformer}]}{\langle \mathrm{DC} \rangle} \tag{2.47}$$

where the subscript "sat" indicates the saturated species and <DC> is the activity of the solid cocrystal and is defined as 1. Therefore,

$$K_{sp} = [\mathrm{Drug}]_{sat}[\mathrm{Coformer}] \tag{2.48}$$

The intrinsic solubility of a cocrystal ($S_{cocrystal}$) is then defined as

$$S_{cocrystal} \equiv \sqrt{K_{sp}} \tag{2.49}$$

Cocrystal solubility always refers to intrinsic solubility in pure solvent as defined by this equation.

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