APPENDIX A

GENERAL TERMINOLOGY

Following are the definitions of some major terms used in this book. Other terms are defined as required in each section.

A.1 BIOPHARMACEUTIC

"Biopharmaceutic" is originally used to mean the sciences related to the performance of a pharmaceutical product in a biological system (e.g., human body). Recently, the same word has been used to represent biological molecules (proteins, siRNA, etc.). In this book, "biopharmaceutic" is used as of its original meaning.

A.2 BIOAVAILABILITY (BA% OR *F*)

The bioavailability of a drug product is the fraction of an administered drug reaching the systemic circulation. Bioavailability is expressed as BA% or F in this book. In the case of oral absorption, F is usually defined based on the total amount of a drug that reached the systemic circulation after oral administration. This definition is used in this book unless otherwise noted. However, the bioavailability of a drug is essentially a time-dependent value. For example, the bioavailability is 10% until 1 h, 20% until 2 h, and so on.

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The oral bioavailability of a drug is expressed as $F = \mathrm{Fa} \times \mathrm{Fg} \times \mathrm{Fh}$, where Fa is the fraction of a dose absorbed, Fg is the fraction of a drug passing though the gut wall without metabolism, and Fh is the fraction of a drug passing though the liver without metabolism and biliary excretion.

A.3 DRUG DISPOSITION

Drug disposition is the fate of a drug after entering the systemic circulation. Drug disposition includes distribution to each body part, renal excretion, hepatic metabolism and elimination (except first-pass metabolism), etc.

A.4 FRACTION OF A DOSE ABSORBED (FA)

The fraction of a dose absorbed is the fraction of an administered drug that permeated the first biological barrier, for example, the apical membrane of the intestinal epithelial membrane (or the tight junction). Similar to bioavailability, in the case of oral administration, Fa is usually defined as the absorbed amount after oral administration. However, Fa is essentially a time-dependent value. For example, Fa is 15% until 1 h, 30% until 2 h, and so on.

A.5 MODELING/SIMULATION/*IN SILICO*

Modeling and simulation refers to a mathematical calculation of a more complex phenomenon from simpler phenomena, for example, from *in vitro* data to *in vivo* data. In this book, "*in silico*" means the prediction of a drug property solely from chemical structural information, for example, calculation of octanol–water partition coefficient (log P_{oct}) from chemical structure.

A.6 ACTIVE PHARMACEUTICAL INGREDIENT (API)

Active pharmaceutical ingredient is the raw material of a drug. It is usually in solid crystalline form, but could also be in amorphous or liquid states.

A.7 DRUG PRODUCT

Drug products are the formulated drugs such as tablets or capsules.

A.8 LIPOPHILICITY

As the scale of lipophilicity of a drug, octanol–water distribution coefficient (log D_{oct}) at a pH is employed in this book. The following classification is used in

this book:

- Low lipophilicity: log $D_{oct} < -0.5$
- Moderate lipophilicity: $-0.5 <$ log $D_{oct} < 0.5$
- High lipophilicity: $0.5 <$ log D_{oct}.

A.9 ACID AND BASE

When a drug is more than 50% dissociable at a neutral pH in aqueous media, it is called *dissociable* and *acid* or *base* unless otherwise noted. Acids have p$K_a < 6.0–7.4$ and bases have p$K_a > 6.0–7.4$.

A.10 SOLUBILITY

Solubility refers to *equilibrium solubility* in this book. The terminology related to solubility is discussed in Section 7.6.1. The following categorization is used in this book:

- Low solubility: <100 μg/ml (ca. 250 μM)
- Moderate solubility: >100 μg/ml, <1 mg/ml (ca. 0.25–2.5 mM)
- High solubility: >1 mg/ml (ca. 2.5 mM).

Unless otherwise noted, the solubility of a drug refers to that measured at a neutral pH of interest (e.g., pH 6.5 for oral absorption). However, the solubility of dissociable drugs largely depends on the pH of the media. For example, a base drug can have a high solubility at a low pH even though its solubility is low at a neutral pH.

A.11 MOLECULAR WEIGHT (MW)

The molecular weight of the free form of a drug, but not a salt or solvate, is used unless otherwise noted. The following categorization is used in this book:

- Small molecule: <250
- Moderate size molecule: >250, <450
- Large molecule: >450.

A.12 PERMEABILITY OF A DRUG

The permeability of a drug has a dimension of length per time. This value changes depending on the morphology of the surface area. As there is no unified scale, the permeability range of a drug is defined based on the permeability of a drug

in the Caco-2 or MDCK assay (at pH 6.5). The following categorization is used in this book:

- Low permeability: $<1 \times 10^{-6}$ cm/s
- Moderate permeability: $>1 \times 10^{-6}$ cm/s, $<10 \times 10^{-6}$ cm/s
- High permeability: $>10 \times 10^{-6}$ cm/s

Unless otherwise noted, the permeability of a drug refers to that measured at a neutral pH of interest (e.g., pH 6.5 for oral absorption). Roughly speaking, each category of permeability corresponds to those of lipophilicity (i.e., a drug with low lipophilicity tends to have low permeability).

APPENDIX B

FLUID DYNAMICS

This section is a brief introduction to fluid dynamics. Historically, a simplified concept of the boundary layer, "the unstirred water layer," has been operationally used in the pharmaceutical sciences. However, to raise up biopharmaceutical modeling to the next level, it is necessary to understand the essential concepts of fluid dynamics. Unfortunately, fluid dynamics is usually not introduced in the textbooks of the pharmaceutical sciences. Therefore, a brief introduction to fluid dynamics is provided in this book.

B.1 NAVIER–STOKES EQUATION AND REYNOLDS NUMBER

The first principle of fluid dynamics is described by the Navier–Stokes (NS) equation (Fig. B.1). The NS equation is derived from Newton's second law (conservation of momentum) in mechanics. The NS equation is a nonlinear partial differential equation.

The Reynolds number characterizes the relative importance of each term in the NS equation. The Reynolds number (Re) is defined as

$$Re = \frac{U\rho_f L}{\mu} = \frac{UL}{\nu}$$

where U is the flow speed around an object, ρ_f is the density of the fluid, μ is the viscosity of the fluid, and ν is the kinematic viscosity of the fluid ($\nu = \mu/\rho_f$). The

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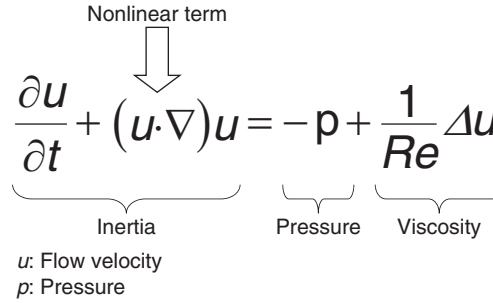


Figure B.1 Navier–Stokes equation (for noncompressive fluid).

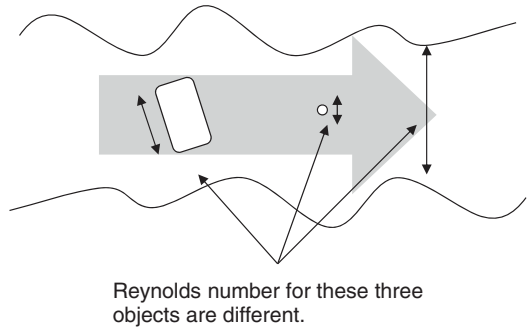


Figure B.2 Reynolds numbers of a particle, tablet, and intestinal tube.

Reynolds number can be interpreted as the balance between inertia and viscosity. The Reynolds number determines the flow regimen, "laminar" or "turbulence." When viscosity exceeds inertia ($Re < 1$), the flow pattern becomes laminar, whereas when inertia exceeds viscosity ($R \gg 1000$), the flow pattern becomes turbulent.

The representative length of an object is the length that mainly characterizes the flow pattern around the object. Therefore, even though two objects, for example, API particle (μm scale) and tablet (mm), are put in the same flow, the Reynolds numbers are different (Fig. B.2).

B.2 BOUNDARY LAYER APPROXIMATION

As shown in Figure B.3, on the fluid–object interface, there is a thin fluid layer where the fluid sticks to the object surface by its viscosity. As the distance from the object surface becomes larger, the effect of viscosity gradually becomes smaller and the flow begins to be governed by inertia, eventually becoming a potential flow. The layer within which the effect of viscosity cannot be neglected is called *the boundary layer*.

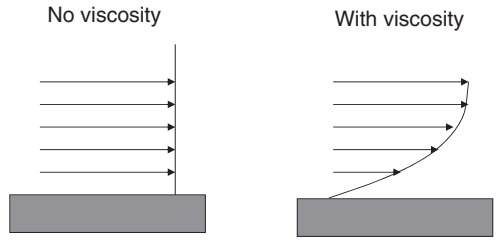


Figure B.3 Fluid flow with and without viscosity.

The concept of the boundary layer was introduced by Prandtl in 1904. The existence of a boundary layer on the object surface is concluded from the Navier–Stokes equation and no-slip condition at the object surface. In a fluid with viscosity, the boundary layer exists universally on the fluid–solid interface. By applying the concept of boundary layer, it becomes easier to obtain an approximate analytical solution for the flows and mass transfer in the boundary layer (the Navier–Stokes equation is converted to the boundary layer equations). This approximation is valid when *Re* is approximately in the range of 1–4 digits. When *Re* is smaller (called *creeping flow* or *Stokes flow*), the thickness of the boundary layer becomes comparable with the object size and the boundary layer approximation cannot be applicable. In this *Re* range, the Stokes' and Oseen's approximations can be used to derive analytical solutions from the Navier–Stokes equation. On the other hand, when *Re* is greater than 3–4 digits, the flow regimen becomes turbulent and the boundary layer approximation is not applicable.

B.3 THE BOUNDARY LAYER AND MASS TRANSFER

On the object surface ($\delta = 0$ in Fig. B.3), there is no convection by fluid flow and solute molecules have to self-diffuse. As the distance from the surface increases, the mass transfer by convection also increases. The diffusion resistance by the boundary layer is represented as a distance. In many textbooks of pharmaceutical science, it is described as if there is a distinct region where there is no flow (called *unstirred water layer*), and this region becomes the diffusion barrier for mass transfer (Fig. 3.4). However, this description is a conventional one.

B.4 THE THICKNESS OF THE BOUNDARY LAYER

Figure B.2 shows a plane in parallel to the flow from the left to the right. After the flow senses the head of the plane, the boundary layer starts to grow. Because of the fluid viscosity, the flow speed near the surface is slower than that of the main flow (U). At the surface of the plane, there is no flow (no-slip condition).

There are a few methods to define the thickness of the boundary layer (δ). δ is usually expressed in the form of

$$\delta \propto LRe^{-1/2}$$

By applying the boundary layer approximation, an approximate equation to calculate δ can be obtained. The boundary layer approximation is valid when $\delta < L$, $Re > 10-100$, and the flow regimen is laminar.

B.4.1 99% of Main Flow Speed

δ is defined as the distance from the plane at which the flow speed becomes 99% of the main stream flow speed (U_∞).

$$\delta_{99\%}(x) \approx 5.0\sqrt{\frac{\nu x}{U_\infty}} = 5.0xRe_x^{-1/2}$$

where Re_x is the Reynolds number defined based on the distance from the head of the plane, x as $\mathrm{Re}_x = xU_\infty/\nu$.

B.4.2 Displacement Thickness

Owing to the boundary layer where the flow speed becomes slower than the main stream, the flux becomes smaller compared to a flow without the boundary layer (Fig. B.3). This looks similar to the thickness of the plane being increased. This thickness is called *displacement thickness* and expressed as

$$\delta_{\mathrm{displacement}}(x) \approx 1.73\sqrt{\frac{\nu x}{U_\infty}} = 1.73x\mathrm{Re}_x^{-1/2}$$

B.4.3 Momentum Thickness

The thickness of the boundary layer can be defined based on the loss of momentum in the boundary layer.

$$\delta_{\mathrm{m}}(x) \approx 0.664\sqrt{\frac{\nu x}{U_\infty}} = 0.664xRe_x^{-1/2}$$

B.5 SHERWOOD NUMBER

As discussed above, the boundary layer is the resistance for mass transfer. In the boundary layer, as the position of the fluid approaches the object surface, the mass transfer by convection becomes smaller and the molecular diffusion begins

to be dominant. At the object surface, there is no flow and the mass transfer is only by molecular diffusion. On the other hand, in the outside of the boundary layer, the mass transfer is dominated by convection. The concentration boundary layer ($\delta_c(x)$), where a concentration gradient exists is usually much smaller than that of the flow momentum boundary layer ($\delta_m(x)$) in aqueous media. The ratio of the $\delta_c(x)/\delta_m(x)$ is related to the Schmidt number (Sc).

$$\frac{\delta_c(x)}{\delta_m(x)} = Sc^{-1/3} = \left(\frac{\nu}{D_{eff}}\right)^{-1/3}$$

where D_{eff} is the diffusion coefficient of a solute. By rearranging this equation,

$$\delta_c(x) = \delta_m(x)Sc^{-1/3} = 0.664xRe_x^{-1/2}Sc^{-1/3} = xSh_x^{-1}, \quad Sh_x = \frac{1}{0.664}Re_x^{1/2}Sc^{1/3}$$

The local Sherwood number and local δ_c at a point (x) on the object surface varies point-by-point (Fig. B.4). Therefore, to calculate the mass transfer from/to the object, the average Sherwood number for the object is often used. In this book, the Sherwood number means the average Sherwood number of an object unless otherwise indicated.

For a plate with a length (L), the Sh becomes

$$Sh_{plane} = 0.66Re_{plane}^{1/2}Sc^{1/3}, \quad \delta_c(x) = \frac{L_{plane}}{Sh_{plane}}$$

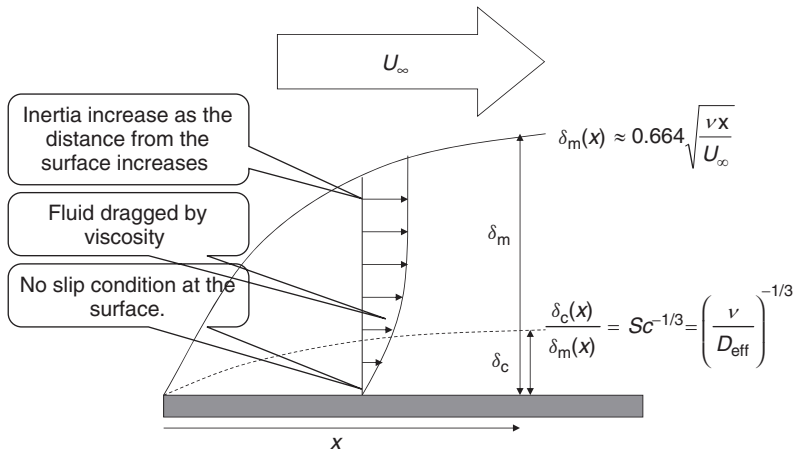


Figure B.4 Boundary layer on a plate placed in parallel to flow.

where Re_{plane} is the Reynolds number defined based on the length of the plane (L_{plane}). The mass transfer from/into the plane is then expressed as

$$\frac{dX}{dt} = SA_{\text{plane}} \frac{D_{\text{eff}}}{\delta_C(x)} \Delta C$$

In general, when the boundary layer concept is applied, the Sherwood number becomes

$$Sh \propto Re^{1/2} Sc^{1/3}$$

These equations are valid in a laminar flow. However, even in turbulent flow, the boundary layer exists (which is called *viscous sublayer*).

B.6 TURBULENCE

As *Re* increases from a single digit to 3–6 digit order, the flow regimen gradually changes from laminar to turbulent. The turbulent flow is characterized as the assemblage of fluid dynamical eddies (vortex) of variable scales. Large-scale eddies are introduced when the fluid flow contacts with the object. The large eddies cascade down to smaller-scale eddies until their energy is dissipated by viscosity. For understanding the essence of turbulence, Lewis Fry Richardson expressed the essence of turbulence as (a parody of On Poetry, A Rhapsody (Swift,1733)),

> Big whirls have little whirls
>
> That feed on their velocity,
>
> And little whirls have lesser whirls
>
> And so on to viscosity
>
> (in the molecular sense.)[1]

Even though the large-scale eddy is not isotropic, the small size eddies produced by the crumbling of large eddies have isotropic energy distribution. Regardless of the way a large eddy is produced, the structure of the small eddy becomes the same. This is called *hypothesis of local isotropy* introduced by Kolmogorov. The minimum scale of Kolmogorov (η) is

$$\eta = \left(\frac{\nu^3}{\varepsilon} \right)^{1/4}$$

where ε is the energy per fluid weight introduced by the large eddy. When the minimum scale of eddy is close to the drug particle size, the mass transfer by this eddy becomes significant (Fig. 3.10).

[1]Lewis Fry Richardson, Weather prediction by numerical process, Cambridge, 1922.

B.7 FORMATION OF EDDIES

The flow pattern behind a cylinder is the best example to understand the mechanism of a vortex formation. When a cylinder is put in flow (such as a pier column in a river), a street of vortex is observed (Figs. B.5 and B.6). This is called *Karman vortex street*. Near the cylinder wall, owing to the viscosity of the fluid, the fluid tend to stick to the wall (viscosity wins here), whereas at the distance from the cylinder, the flow becomes uniform and the flow speed becomes close to that of the main flow (inertia wins here). The change of the flow speed in the boundary layer causes a shear force and introduces an eddy (Figure B.6).

B.8 COMPUTATIONAL FLUID DYNAMICS

The Navier–Stokes equation is a nonlinear partial differential equation. As discussed above, for simple (but important) situations, the NS equation can

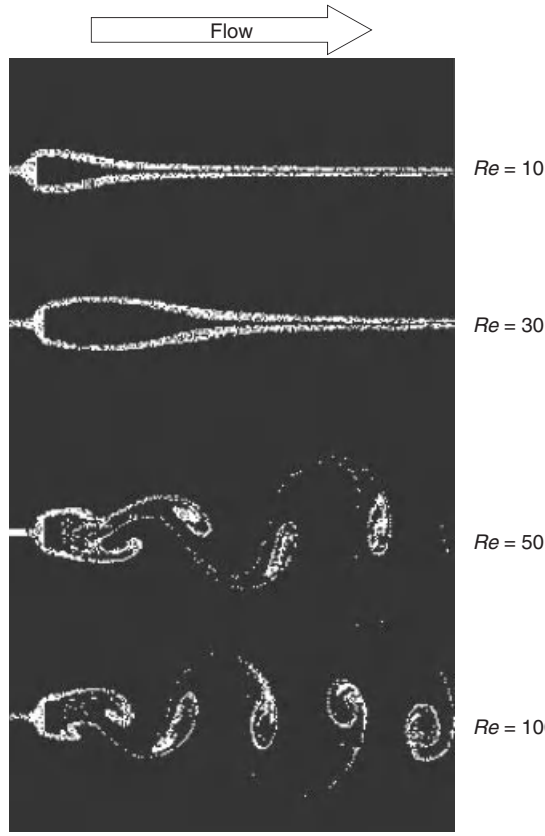
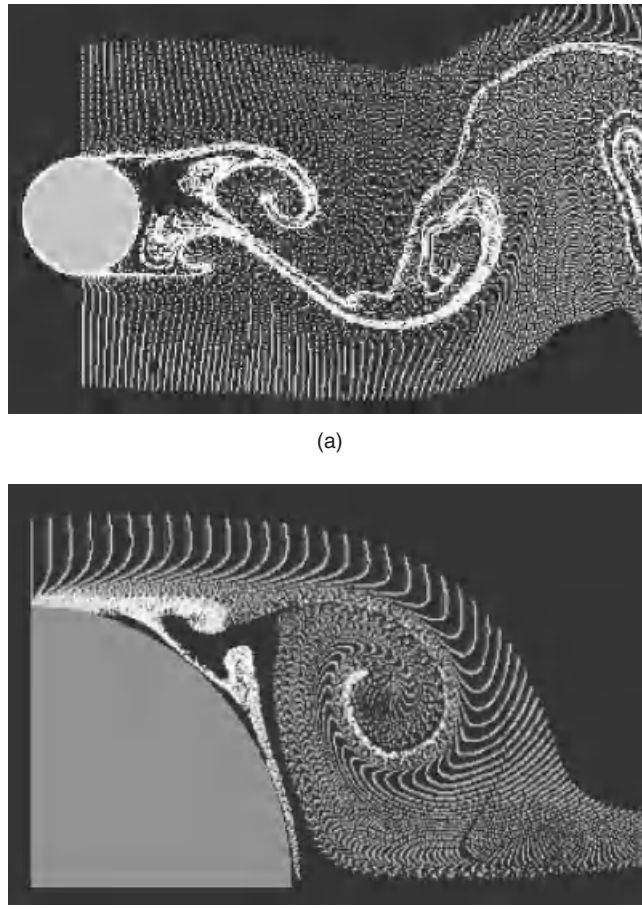


Figure B.5 Kerman vortex street. *Source:* Computational simulation by a program provided in Reference 1.



(a)

(b)

Figure B.6 Formation of eddy at the cylinder surface. *Source:* Computational simulation by a program provided in Reference 1.

be analytically solved by applying an approximation. However, for most situations, it is impossible to derive an analytical solution from the NS equation. The Computational Fluid Dynamics (CFD), which numerically solves the Navier–Stokes equation using a high speed computer, can be used for such cases.

The finite element method is widely used to solve the NS equation. The space is separated by meshes and the flow at each grid is calculated. Figure B.7 shows the mesh system used for the CFD calculation of the USP II paddle method [2]. The mesh size determines the minimum size of flow patterns captured by the CFD simulation. For example, the mesh system of Figure B.7 can capture the flow pattern around the paddle ($d = 10$ cm), but not the API particles (<0.1 cm). In

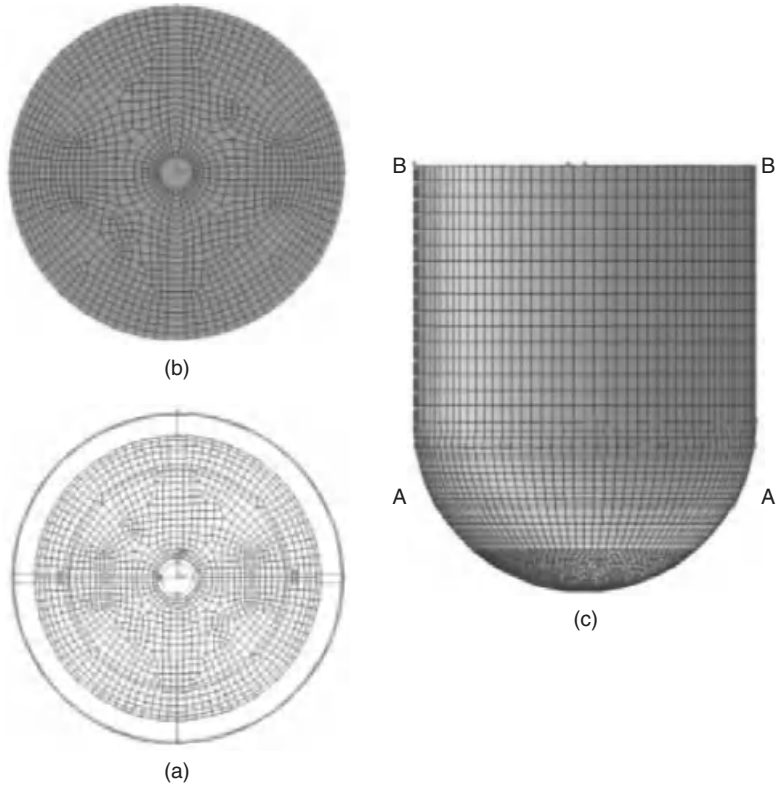


Figure B.7 Mesh used in the CFD simulation for the USP paddle apparatus: (a) iso-surface at A–A; (b) iso-surface at B–B; and (c) axial, side view. *Source*: Adapted from Reference 2 with permission.

Figure B.7, 80262 meshes are used. CFD requires massive computational power so that it cannot be directly used for biopharmaceutical modeling at present.

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2. Bai, G., Armenante, P.M., Plank, R.V., Gentzler, M., Ford, K., Harmon, P. (2007). Hydrodynamic investigation of USP dissolution test apparatus II. *J. Pharm. Sci*., 96, 2327–2349.

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