Learning objectives

Upon completion of this chapter, you should be able to answer the following questions:

- What is a solution?
- What is the difference between solubility and dissolution?
- What variables control a solute’s solubility?
- What variables control dissolution?
- What do solubility and dissolution have to do with each other?

Solubility, dissolution, and dissolution rate

Solubility and dissolution are different concepts, but are related. Solubility is the capacity of a solute to dissolve in a pure solvent. This means the maximum amount of solute that the pure solvent can hold in solution, at specified environmental conditions. Beyond this saturation concentration, a solute cannot further dissolve in the amount of solvent provided. It can exist tenuously in a supersaturated condition, but will eventually revert to the solvent’s true capacity. But what occurs between solutes and solvents that bestows the variability observed in solubilities in a given solvent? Solubility is a thermodynamic process: the system will tend to arrive at a point of lowest potential energy (PE) (Gibbs free energy), which is most thermodynamically stable. When we speak of solubility, it is understood to mean the ultimate outcome, without regard to how fast it occurs. Solubility provides us with important information, but it only tells us the endpoint, not how long it takes to get there.

Solute materials vary not only in the extent to which they will dissolve, but also how quickly they will reach their respective solubility limits. Solubility and dissolution rate are two distinct phenomena. Dissolution rate is a kinetic process. A solute may have poor solubility in a solvent, yet its dissolution rate may be rapid. Conversely, a solute can be very soluble, yet require a protracted amount of time to arrive at the final, saturation concentration. Some solutes dissolve very rapidly
in appropriate solvents, while others can take an inordinate amount of time to reach a desired concentration, or saturation. Why is this?

What affects total solubility, without regard for the time it takes to reach it? The answer is there are many parameters affecting solubility, which make it impossible to explain in a single statement or equation.

**Solubility**

Solubility can be expressed in precise or general terms. General terms include such categorizations as ‘slightly soluble,’ ‘soluble,’ ‘insoluble.’ Precise terms are expressed with units such as ‘g/L,’ ‘g/100 g,’ ‘g%,’ or ‘mg/mL.’ In either case, the object is to provide a measure of how much solute will ultimately dissolve in a given quantity of solvent – a capacity. It is the resting point for the equilibrium between undissolved solute and solubilized solute. As discussed in Chapters 1 and 2, the propensity for a solute to dissolve in a solvent is fundamentally dependent on intermolecular interactions, which lead to cohesive and adhesive forces between similar and dissimilar molecules. The extent to which cohesive and adhesive forces prevail correlates with the capacity a solvent has for a solute. This capacity will often also be dependent on specified conditions of temperature and atmospheric pressure, as solubility usually varies with changes in these two parameters. Once the capacity of a solvent to dissolve any further solute is reached, further addition of solute will simply result in settling of the solute to the bottom of the container (when considering aqueous-based solutions). Solutions can be made that are supersaturated by altering the temperature at which the solvent is added, and a concentration over the natural capacity at unaltered temperature of the solvent can be achieved. However, supersaturated solutions are unstable and easily precipitate out excess solute to reach the solubility capacity at the given temperature.

The dissolution rate can be expressed via the Noyes–Whitney equation:

\[
\frac{dm}{dt} = A \frac{D}{d} (C_s - C_b)
\]

where

\[
\frac{dm}{dt} = \text{solute dissolution rate (kg} \cdot \text{s}^{-1})
\]

\[
m = \text{mass of dissolved material (kg)}
\]

\[
t = \text{time (s)}
\]

\[
A = \text{surface area of the solute particle (m}^2\)
\]

\[
D = \text{diffusion coefficient (m} \cdot \text{s}^{-1}), \text{which is related, in part, to the viscosity of the solvent, and will be discussed further below.}
\]
\[ d = \text{thickness of the concentration gradient (m)} \]
\[ C_s = \text{particle surface (saturation) concentration (kg or moles/L)} \]
\[ C_b = \text{concentration in the bulk solvent/solution (kg or moles/L).} \]

**Key Point**

Solubility is an endpoint representing dissolution capacity. Dissolution rate can be expressed using the Noyes–Whitney equation.

In this model, \( C_s \) is the saturation concentration of the solute in question in the given solvent. The intrinsic dissolution rate \( (\text{kg} \cdot \text{m}^{-2} \cdot \text{s}) \) is the dissolution rate of a pure solute, normalized to the solute surface area, and actually decreases with time. The Noyes–Whitney equation is illustrated in Figure 3.1.

![Figure 3.1](image-url)

**Figure 3.1** Noyes–Whitney parameters for dissolution rate

Dissolution (with rate \( \frac{dm}{dt} \)) occurs from a solid with mass \( m \) and surface area \( A \), from the saturation concentration at the particle surface \( C_s \) to the concentration in the bulk solution \( C_b \). Concentration follows a gradient \( d \) with a coefficient \( D \).

The Noyes–Whitney equation provides much practical information relevant to the dissolution process. When we look at the equation parameters, we see the equation predicts the following:

- The diffusion coefficient, \( D \), which is in part related to solvent viscosity, will decrease with increasing solvent viscosity, and decreasing dissolution rate, \( \frac{dm}{dt} \). That is, \( D \) is inversely proportional to viscosity; \( D \) will be discussed shortly.
- Dissolution rate \( (\frac{dm}{dt}) \) will be faster with smaller particles because surface area \( (A) \) increases as particle size decreases. So, trituration or micronization of particles will usually speed up dissolution.
- Some type of stirring or agitation during dissolution will decrease the diffusion gradient \( (d) \) by removing solute molecules more quickly from the particle surface, increasing dissolution rate, \( \frac{dm}{dt} \).
If the solute is ionizable and/or a weak electrolyte, altering the solvent pH can affect the surface/saturation concentration, $C_s$. Depending on the characteristics of the solute and solvent, this change could either increase or decrease $C_s$, either decreasing or increasing the concentration gradient, respectively, and increase or decrease dissolution rate, respectively.

Solubility is a key point, representing capacity. Dissolution rate can be expressed using the Noyes–Whitney equation.

### Parameters that affect total solubility

I. The nature and strength of solute–solvent attractions (intermolecular interactions)
II. Polarities of the solute and solvent
III. The thermodynamics of the dissolution
IV. Temperature
V. Ionization of solute and solvent, and pH of the solvent

### I. The nature and strength of solute–solvent attractions (intermolecular interactions)

First, the perspective will be changed to that of the solvent. For the sake of discussion, it will be assumed the drug is present as a crystalline structure. Therefore, for this section, the opposite of dissolution is crystallization. The attraction of the solvent for solute molecules (adhesive forces) is in opposition to the attraction of solute molecules to themselves (cohesive forces), and these opposing actions can be represented using an equilibrium equation (Figure 3.2).

![Figure 3.2 Dissolution equilibrium](image)

If the solvent sufficiently interacts with solvent particles, the solute intermingles with the solvent. The crystalline structure of the solute is reduced and separated by the solvent into individual ions, atoms or molecules. This process can be visualized in Figure 3.3.

### Key Point

Dissolution is a thermodynamically favorable process. In order for a solute to dissolve in a solvent, the process must be thermodynamically favorable.
In the initial step, the solute is removed (attracted away from) its crystal. Following this, a space is created in a group of solvent molecules and the isolated solute molecule is inserted into this space. Since the solute molecules open to create a space for the solute molecule, the size or surface area of the solute molecule is important. Solute molecules must contact the solute, so large solute molecules will have a smaller surface area for solvent contact than will smaller molecules when considered as a whole. Therefore, solubility tends to decrease with increasing molecular surface area.

II. Polarities of the solute and solvent

The influences of polarity of the solute and solvent were discussed in Chapter 1 in terms of molecular dipoles – innate or induced. If the solvent contains polar molecules (e.g., water), polar solutes will be more attracted to the solvent than will nonpolar solutes. Nonpolar solutes will have some attraction to polar molecules, via dipole–induced dipole actions, but the magnitudes of these attractions will be much smaller. Therefore, polar solutes will generally be more soluble in polar solvents.

III. The thermodynamics of the dissolution

Recall the Gibbs free energy equation, \( \Delta G = \Delta H - T\Delta S \), where \( \Delta G \) is the change in Gibbs free energy (energy to do work), \( \Delta H \) is the change in enthalpy, and \( \Delta S \) is the change in entropy.
the change in entropy. Increases in enthalpy are thermodynamically unfavorable when taken alone, whereas increases in entropy are favorable when taken alone. Overall, to be thermodynamically favorable, a negative $\Delta G$ is required. This equation can be used to represent the three steps of dissolution described above, keeping the system isothermal.

Using Figure 3.3, step one of the dissolution scheme, breaking of the solute lattice to free a solute particle, can be represented with $\Delta H_1$ and $\Delta S_1$. This action increases enthalpy but decreases entropy ($\Delta H \uparrow$, $\Delta S \downarrow$).

Step two, the opening of the solvent, can be represented with $\Delta H_2$ and $\Delta S_2$. This action increases enthalpy ($\Delta H$), while the change in entropy depends on whether or not the solvent molecules need to be ordered to allow the solute molecule in ($\Delta H \uparrow$, $\Delta S \downarrow\uparrow$).

Step three, the insertion of solute into the solvent, can be represented with $\Delta H_3$ and $\Delta S_3$. This action increases enthalpy but decreases entropy ($\Delta H \uparrow$, $\Delta S \downarrow$).

Overall, the process involves enthalpy ($H$) changes of $\Delta H_1$, $\Delta H_2$ and $\Delta H_3$. It also involves entropy ($S$) changes of $\Delta S_1$, $\Delta S_2$ and $\Delta S_3$. Thermodynamically, we are interested in the total, final change only. For the three-step process, the free energy of solution is: $\Delta G_{\text{soln}} = (\Delta H_1 + \Delta H_2 + \Delta H_3) - T(\Delta S_1 + \Delta S_2 + \Delta S_3)$. As stated above, in order for a solute to dissolve, the overall $\Delta G$ must be negative. This obviously is the case when $\Sigma \Delta H$ is less than $\Sigma \Delta S$ ($\Sigma \Delta H < \Sigma \Delta S$), regardless of the individual values.

Another way of looking at this three-step process is simply considering the sum of work done to accomplish each of the steps. If solvent molecules are labeled as ‘1’, and solute molecules as ‘2’, the simple ‘work equations’ are: 1) step one gains PE and the work done $= w_{22}$ (work of two solute molecules); the work in step two $= w_{11}$; the increase in PE, or work, is $-w_{12}$ for closing the hole, and an additional $-w_{12}$ for net work in the final step. Therefore, the overall work $= w_{22} + w_{11} - 2w_{12}$. Using either approach, the three-step dissolution process must be thermodynamically favorable in order for it to occur. That said, even a thermodynamically favorable change only can occur – there is no certainty it will occur.

**IV. Temperature**

Temperature affects solubility and is also thermodynamically related. The effect of temperature on solubility depends whether the particular dissolution process is endothermic or exothermic in nature and the ambient environmental conditions. Endothermic processes are reactions in which heat is absorbed ($\Delta H > 0$). Exothermic processes are those in which heat is released ($\Delta H < 0$). If the ambient temperature is relatively high, exothermic dissolution processes will be inhibited, while endothermic dissolution processes will be improved. So, high ambient temperatures will increase the solubility of solutes with endothermic dissolution processes, but decrease the solubility of those with exothermic processes.
V. Ionization of solute and solvent, and pH of the solvent

It is assumed the reader is familiar with the Henderson–Hasselbalch equation, 
\[ \text{pH} = pK_a + \log \left( \frac{[A^-]}{[HA]} \right), \]
where \([A^-]\) = molar concentration of a conjugate base (ionized form), and \([HA]\) = molar concentration of an undissociated (unionized) weak acid. The pH of the solvent can greatly impact the solubility of ionizable solutes. Acidic drugs are less soluble in acid solutions because more of the drug tends to be in the unionized form, which is less able to interact with the solvent (water) than the ionized form. The dependence of the solubility of an acidic drug on ionization of the drug, in acidic conditions, is represented by equation A:

\[ \text{pH} - pK_a = \log \left( \frac{S - S_0}{S_0} \right) \]

where \(S\) is the solubility of the of the ionized drug and \(S_0\) is the solubility of the unionized drug.

The solubility of basic drugs in relation to pH is represented by equation B:

\[ \text{pH} - pK_a = \log \left( \frac{S_0}{S - S_0} \right) \]

where \(S\) is the solubility of the of the unionized drug and \(S_0\) is the solubility of the ionized drug.

The zwitterion form has the lowest solubility, \(S_0\). At pH values below the iso-electric point (\(pK_a\)), equation B is used. For pH values above the isolectric point, equation A is used.

The previous discussion tells us why there are specific solubility limits, but not why there are different dissolution rates.

Dissolution

What is dissolution, exactly? In simple terms it is the process of a solute dispersing/dissociating in a solvent, forming a molecular-level, chemically and physically homogenous dispersion, called a solution. In contrast to solubility, when we speak of dissolution, it is understood that rate is a major consideration. Solubility is an endpoint. Dissolution is a process. There are different types of solutions of course. Examples of solutions, with all phase combinations, are shown in Table 3.1.

For this text, discussion is focused on liquid-in-liquid and solid-in-liquid solutions – and so the solubility and dissolution for such solutions. Within ‘solid-in-liquid solutions,’ there are two major types of dissolution. In the first type, the solution’s phase contains the same solute chemical entity as is found in the original solid phase. Upon removal of solvent, the solute can be recovered unaltered by the dissolution process. An example is the dissolution of sucrose in water (Figure 3.4).
In the situation described, dissolution occurs without the requirement of ionization. Thus, the intermolecular interactions discussed in Chapter 1 play prominent roles in the first type of dissolution.

For the second type of dissolution, the original solute is either not recoverable, or not completely recoverable. The resulting solution contains a compound that is different from that of the original solid phase. This change is generally due to some chemical reaction between the solute and solvent. When the solvent is removed, some or all of the solute is different from what was originally added to the solvent.

An example is that of (modern) ‘aspirin’ (acetylsalicylic acid) in plain water (Figure 3.5). While in solution, some of the aspirin hydrolyzes, forming acetic acid and salicylic acid. When water is removed, some of the original acetylsalicylic acid may be recovered, but also acetic and salicylic acids. Here, in order for dissolution to occur, the solute was required to ionize, and then the solvent was required to exert enough influence on the ions to overcome their cohesive forces.

**Dissolution is a process**

For either mode of dissolution, and in order for dissolution to occur – with or without an accompanying chemical reaction – the solute particle size is first

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**Table 3.1 Examples of different types of solutions**

<table>
<thead>
<tr>
<th>Solute</th>
<th>Solvent</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas</td>
<td>Gas</td>
<td>Air</td>
</tr>
<tr>
<td>Liquid</td>
<td>Gas</td>
<td>Water vapor in air</td>
</tr>
<tr>
<td>Solid</td>
<td>Gas</td>
<td>Iodine vapor in air</td>
</tr>
<tr>
<td>Gas</td>
<td>Liquid</td>
<td>Carbonated water</td>
</tr>
<tr>
<td>Liquid</td>
<td>Liquid</td>
<td>Alcohol in water</td>
</tr>
<tr>
<td>Solid</td>
<td>Liquid</td>
<td>Sucrose in water</td>
</tr>
<tr>
<td>Gas</td>
<td>Solid</td>
<td>Hydrogen in palladium</td>
</tr>
<tr>
<td>Liquid</td>
<td>Solid</td>
<td>Mineral oil in paraffin</td>
</tr>
<tr>
<td>Solid</td>
<td>Solid</td>
<td>Solder (tin in lead)</td>
</tr>
</tbody>
</table>

---

**Figure 3.4** Dissolution when solute remains the same chemical entity

When sucrose dissolves in water it remains unchanged. When the solvent (water) is removed, sucrose is recovered.
reduced. This initiates the process of dissolution. This process is measured as rate. The Noyes–Whitney equation describes dissolution in a single equation. But what occurs on a smaller scale? Solubility is now assumed, but we are now interested in how quickly the endpoint arrives. This can be a simple one-step consideration, with one associated rate, or dissolution can involve multiple steps, each with its own rate. The collection of individual rates results in an overall dissolution rate that we can observe.

As an introduction, a diagram of the dissolution of a tablet or capsule is illustrated below (Figure 3.6). For tablets and capsules there are three steps to dissolution. These three steps are disintegration, deaggregation, and dissolution. From any point (Figure 3.6), direct dissolution can occur, and in fact, all steps may be occurring simultaneously.

**Key Point**

Dissolution of a solid in a liquid often actually involves three steps:

- Disintegration
- Deaggregation
- Dissolution

Figure 3.7 illustrates the observations made for dissolution of a tablet if it followed the longest series of steps as outlined above.

If we were to look closely, even dissolution from a powder form can be a multi-step process. Depending on the solute particle size (degree of particle size reduction), the dissolution process of powders in solvent can be visualized as shown in Figure 3.8.
Figure 3.6  The dissolution process

The dissolution of a solid solute can be visualized as a general movement from the largest form, to granules or aggregates, then to fine particles, before becoming molecularly dispersed (dissolved). However, removal of molecules (dissolution) from the various steps of decreasing particle size can occur any time during the overall process.

Figure 3.7  Disintegration, deaggregation, and the solution process

An illustration of the steps for tablet dissolution also shows how dissolution of various forms of solutes can occur. Though dissolution can occur from all forms of a solute (dosage form, granules/aggregates or fine particles), the major path is through all three forms.
Each of the steps of dissolution has its own rate. These rates can be expressed as $\frac{dS}{dt}$ (solid to granules/aggregates), $\frac{dG}{dt}$ (granules/aggregates to fine particles), $\frac{dP}{dt}$ (particles to solution), and all the equations for individual steps to solution. Of course, each step can lead directly to dissolution, as previously stated. Visualizing this would lead to a rather complicated picture of these steps, as shown in Figure 3.9.

The sum of the equations would be quite unwieldy. Each step in Figure 3.9 is shown moving one direction, when each is truly an equilibrium equation. Most

![Diagram of dissolution process]

**Figure 3.8** Process of dissolution restricted to smaller particles

If solute particles have been mechanically reduced (e.g., by trituration), the process of dissolution can be viewed as involving the lower portion of the scheme depicted in Figure 3.6.

To consider all of the dissociation components, we would need to combine and summate $-\frac{dT_a}{dt}$, $-\frac{dG_p}{dt}$, $-\frac{dG_s}{dt}$, $-\frac{dT}{dt}$, and $-\frac{dP}{dt}$. This obviously would be very cumbersome.

**Figure 3.9** A mathematical scheme for dissolution

of the processes occur as illustrated in Figure 3.8. The Noyes–Whitney equation helps us avoid complication by focusing on the most important step of dissolution: movement of fine particles into solution.

Therefore, this discussion will center on what occurs after the drug delivery system provides granules or aggregates (‘chunks’). Of particular interest is what transpires with fine particles. Intermolecular interactions between the solvent and large ‘chunks’ of solute cause the solute to be reduced to fine particles. All the while, when solute particles have detached from the larger pieces, dissolution has been occurring. However, once the solute is reduced to fine particles, its increase in total available surface area lends to optimum interaction with the solvent. As the system/total particle size is reduced, the total solute surface area greatly increases. From the point that the solute has been reduced to fine particles, wetting – especially immersional wetting (discussed below) – is occurring. Wetting involves displacing air from the particle surface, along with creating effective interfacial contact between the solute and solvent.

**Fine particles and wetting**

If we now focus on only actions at the fine particle level, the process of fine particle dissolution can be thought of as following three steps. The first, as just mentioned, is wetting of the solute by the solvent. This is followed by immersion of the solute in the solvent, which involves not only favorable interfacial energetics, but also the thermodynamics discussed above. Finally, diffusion of molecules of solute into the bulk solution must occur (Figure 3.10).

**Key Point**

Fine particle dissolution follows these steps:

- Wetting
- Immersion
- Diffusion

_Wetting:_ When preparing a solution using a solute powder and liquid solvent, slow wetting of the solute by the solvent can be a hindrance to what might otherwise be a quick and easy dissolution process. Physically, air pockets can be trapped inside the powder, slowing the initial ability of the powder to contact the solvent well. In addition, interfacial interactions are very important for dissolution – again intermolecular interactions are emphasized, this time with regard to solute, solvent and environmental interactions. The ability for a solvent to wet a solute is dependent on
surface tension. Young’s equation is a method of accounting for, and using, surface tension values to predict how easily a solute will be wetted, and ultimately dissolved. First, the solvent needs to spread over the surface of the solute. Then, the solvent needs to immerse the solute. Both of these steps, along with illustration of the parameters of Young’s equation, are shown in Figure 3.11. Young’s equation is:

\[ \gamma_{SA} = \gamma_{SL} + \gamma_{LA} \cos \theta \]

Since the value of \( \theta \) will be between 0° and 90°, \( \theta \) varies from 1 to 0, and \( \gamma_{LA} \cos \theta \) will be zero, or a positive value. \( \gamma_{SA} \) = surface tension of the solid at the solid–air boundary, \( \gamma_{SL} \) = solid–liquid interfacial tension, \( \gamma_{LA} \) = surface tension of the liquid–air boundary, and \( \theta \) is the contact angle between the solid and liquid. If \( \theta \) is less than zero, the substance is considered hydrophilic. If \( \theta \) is greater than 90°, the substance is considered hydrophobic. When water is the solvent, a hydrophilic solute is desirable.

**Key Point**

Young’s equation is used to calculate solute and solvent surface tension values, and explain and predict the wettability of the solute, and so is a predictor of ease of dissolution.
For the initial step – spreading of the solvent over the solute – the spreading coefficient ($S$) is important:

$$S = \gamma_{LA} (\cos \theta - 1)$$

Positive values for $S$ indicate the solvent will completely spread over the surface of the solute, whereas negative values for $S$ are indicative of difficulty in wetting the solute surface. If $(\cos \theta - 1)$ is positive, the value of $S$ is positive and spreading of the solvent is favored. If $(\cos \theta - 1)$ is negative, the value of $S$ is negative and the solvent spreading is unfavorable/unlikely. Spontaneous wetting occurs if the contact angle is $0^\circ$ (Figure 3.12).

**Figure 3.11** Illustration of the components of Young’s equation

This figure illustrates the forces acting on (A) a liquid droplet on a solid surface and (B) the liquid on a partially immersed solid. (A) Initial spreading of the solvent over the solute: the components of Young’s equation in relation to the particle surface ($x$-axis) and the wetting process are shown. (B) Spreading of the solvent over partially immersed solute: Young’s equation extended to the immersion process is shown. $\gamma_{SA}$, the surface tension between the solid and air; $\gamma_{LA}$, between the liquid (solvent) and air; and $\gamma_{SL}$, the inferred extension between solid and liquid (solvent).
Immersional wetting, the subsequent step to spreading (Figure 3.12), is also dictated by the angle the solute surface makes with the air–liquid interface.

Another way to approach the concept of wetting is shown in Figure 3.13. For solid–liquid systems, there are forces of adhesion and cohesion. As has been outlined above, the solid (solute) must be wetted by liquid before the solid can dissolve in it. In Figure 3.13(A), the solid is in contact with the liquid, so the energy existing between the solid and liquid can be defined using the interfacial free energy, or surface tension, \( \gamma_{S/L} \), and adhesive work is proportional to the solid and liquid surface tensions, minus the solid–liquid interfacial tension. If the liquid and solid are conceptually separated, there are two surface tensions created: one between the solid and air (\( \gamma_{S/A} \)), the other between the liquid and the air (\( \gamma_{L/A} \)). The work of adhesion is proportional to the energy required to separate the liquid from the solid:

\[
W_A = \gamma_{S/A} + \gamma_{S/L} - \gamma_{S/L}
\]

In Figure 3.13(B), the liquid is in contact with the liquid (itself), so the energy existing between the liquid and liquid is the work of cohesion, because by separating the liquid from itself, two liquid–air interfaces are created, each with a surface tension (\( \gamma_{L/A} \)). There is no interfacial tension between the two liquid ‘pieces’ before separation because the liquid is a single phase. The work of cohesion then is:

\[
W_C = \gamma_L + \gamma_L = 2\gamma_L
\]

Simply put, if the work of adhesion exceeds the work of cohesion, wetting will tend to occur. Spreading of a liquid on a solid will occur when the work of

---

Figure 3.12  Prediction of liquid spreading on a particle surface based on particle–liquid contact angle, \( \theta \). If \( \theta - 1 \) = positive values, spontaneous spreading/wetting is predicted. For \( \theta - 1 \) = negative values, wetting is unfavorable.
adhesion exceeds the work of cohesion. That is, spreading is favored when forces between different molecules exceed those between similar molecules.

\[ W_A > W_C \]

\( W_A \) is the spreading coefficient. As stated above, when \( S \) is positive, the liquid will spread on the solid.

\[ S = W_A - W_C \]

Substituting in for the variable, \( S = \gamma_{LS} + \gamma_{SL} - 2\gamma_{LS} \).

\[ S = \gamma_{LS} - \gamma_{LA} - \gamma_{SL} \]

Using either Young’s equation or comparing adhesive and cohesive work, it can be seen that, in order to improve wetting, \( \gamma_{LS} \) and/or \( \gamma_{SL} \) must be reduced. This can be accomplished using surfactants. Surfactants, or ‘surface active agents’, reduce surface tension, allowing particle wetting more easily. Wetting of a solid can be an issue with any liquid dosage form, including solutions (Chapter 4), suspensions, and emulsions (Chapter 7), which will be discussed further. Thus, the wetting of the solute accomplished, the rest of the dissolution process continues – namely, diffusion.

**Diffusion leads to solutions**

**Diffusion**: To illustrate the diffusion process, the diffuse double layer (DDL) model was developed, which helps describe parameters responsible for the rate
The diffuse double layer (DDL) model and diffusion

The DDL model can be utilized to account for characteristics of diffusion, the final step of the dissolution process.

The DDL model is based on the Noyes–Whitney equation (Figure 3.1) and is illustrated in a slightly modified form in Figure 3.14. The model can be described as a solute surface immersed in solvent. When a solid dissolves, the components pass down a diffusion gradient (diffusion layer) until the particle completely dissolves and enters the bulk solution.

The variables in this model are as follows:

- $C_s =$ the concentration of solute in solvent very near the surface of the solute (solid). This is also the saturation concentration for the solute in the solvent;
- $C_t =$ the concentration of solute in the bulk solution;
- $h =$ the concentration gradient, or diffusion layer, through which the solute particles pass, on their way to the bulk solution.

The diffusion layer is thought of as a ‘film’ very near the solid surface. This film forms a thin stagnant layer ($h$) around the particle. At the particle surface the solution is saturated ($C_s$). Molecules first traverse through $h$ almost instantaneously, then diffuse from $h$ into the bulk solution. This diffusion step is slower and often rate limiting. The bulk solution has a concentration ($C_t$) that varies with time, until the dissolution process has been completed. The model illustrates rate of dissolution as an image. The Noyes–Whitney equation describes the model (Figure 3.14) mathematically:

$$\frac{dC_t}{dt} = \frac{Ds}{Vh} (C_s - C_t)$$

where

$$\frac{dC_t}{dt} = \text{Dissolution rate} = \frac{\text{mg}}{\text{mL}} \text{ change in time}$$
Key Point

The Noyes–Whitney equation describes dissolution, which includes diffusion. Diffusion is further described by the Stokes–Einstein equation.

Since diffusion is often rate limiting, it is of special importance within the Noyes–Whitney equation. In addition, the diffusion coefficient \( D \) is dependent on several parameters, including the Boltzmann constant, the absolute temperature, viscosity of the medium and radius of the solute molecule (which should be noted decreases as the solution process proceeds), and is described by the Stokes–Einstein equation:

\[
D = \frac{kT}{6\pi\eta r}
\]

where

\( D \) = diffusion coefficient of the solute in solution
\( k \) = Boltzmann constant
\( T \) = absolute temperature
\( \eta \) = viscosity of the solvent
\( r \) = radius of the solute molecule.

Inspection of the Noyes–Whitney and Stokes–Einstein equations reveals to us the parameters that can affect the dissolution rate of solutes in solvents. Some implications are intuitive. As the solution temperature increases, so does the diffusion coefficient, and so the dissolution rate increases. As the viscosity of the solvent increases, the dissolution rate decreases. As the radius of the solute decreases, total solute surface area increases, and dissolution rate increases. As the solute surface area increases, so does dissolution rate. So what might be some applications? If we can warm solvents, dissolution rate may be increased, depending on the nature of the solute. This ‘if’ is because care must be taken as for the potential for degradation of the solute at higher temperatures, so we must...
not blindly increase temperature without regard to the solute(s). Also, of course, there are some solutes whose solubility is not improved by increasing temperature. With regard to viscosity of the solvent or medium, we should be aware that solutes will tend to dissolve more slowly in more viscous solvents (e.g., syrups rather than water), and so it may be advisable to dissolve solutes in solvents prior to adding excipients that will increase the overall viscosity of the preparation. We cannot always alter the radius of the solute molecules (other than by trituration), but we can anticipate larger solute molecules will dissolve more slowly than smaller ones, and so expect more time for dissolution to go to completion. The thickness of the unstirred layer ($h$) can be decreased \textit{in vitro}, such as by stirring in a beaker, thus increasing dissolution rate. The analogous action \textit{in vivo} is less likely to be accomplished with much success. Perhaps if the patient were required to jump up and down after ingestion of the solute, one could show improved \textit{in vivo} dissolution. Decreasing the solid surface area ($S$) increases dissolution rate, so subdivision/trituration of the solute prior to its addition to the solvent should improve dissolution rate. Regarding the saturation concentration of a solute: one must be careful not to indiscriminately elevate temperatures \textit{in vitro}. Not only may this degrade the solute, as mentioned above, but also a supersaturated solution may be created. When this supersaturated solution is then cooled, the solute(s) may precipitate out of solution. With regard to the solute concentration at time = $t$ ($C_t$), it may be observed that, as the saturation concentration ($C_s$) is approached, dissolution will begin to slow down. The applications include making saturated solutions ahead of time because the last bit of dissolution may take a long time, and it may be advisable to maintain stock bottles of saturated solutions.

If it can be assumed the concentration beyond $h$ is very small (perhaps, for calculations, equal to '0'), then the Noyes–Whitney equation simplifies to:

\[
\frac{dC}{dt} = \frac{DS}{Vh} C_s
\]

This may be the case when there is a large volume of bulk solvent or stirring effectively removes the DDL ($h$ is nearly 0). When these occur, it is said sink conditions exist (i.e., the solute is disappearing as if 'going down a sink drain').

\section*{Summary}

In summary, solubility and dissolution have been discussed. There are several important parameters that dictate a given solute's solubility in a given solvent. Once these parameters are understood and any optimizations made, the solubility of a solute must be understood to be an endpoint. On the other hand, dissolution
is a study of the effects various parameters have on the rate at which a solute reaches its solubility.

**Self-assessment questions**

1. What is a solution?
2. Why do solubility and dissolution mean different things?
3. How can we influence solubility of a substance in a solvent?
4. How can we influence the process of dissolution?
5. Name the three main steps of tablet dissolution.
6. Fine particle dissolution follows what three-step process?
7. What contact angle (θ) is predictive of best – or most spontaneous – wetting?
8. What is a surfactant?
9. What is the DDL model?
10. In order for particle wetting to occur, what is true regarding work of adhesion and work of cohesion?