15 **Interfacial Phenomena**

Chapter Objectives

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

1. Differentiate among different types of interfaces and describe relevant examples in the pharmaceutical sciences.
2. Understand the terms surface tension and interfacial tension and their application in pharmaceutical sciences.
3. Appreciate the different methods of surface and interface tension measurements.
4. Calculate surface and interface tensions, surface free energy, its changes, work of cohesion and adhesion, and spreading coefficient for different types of interfaces.
5. Understand the mechanisms of adsorption on liquid and solid interfaces.
6. Classify surface-active agents and appreciate their applications in pharmacy.
7. Differentiate between different types of monolayers and recognize basic methods for their characterization.
8. Recognize the electric properties of interfaces and the effects of electrolytes.

Several types of interface can exist, depending on whether the two adjacent phases are in the solid, liquid, or gaseous state (Table 15-1). For convenience, these various combinations are divided into two groups, namely, *liquid interfaces* and *solid interfaces*. In the former group, the association of a liquid phase with a gaseous or another liquid phase will be discussed. The section on solid interfaces will deal with systems containing solid–gas and solid–liquid interfaces. Although solid–solid interfaces have practical significance in pharmacy (e.g., the adhesion between granules, the preparation of layered tablets, and the flow of particles), little information is available to quantify these interactions. This is due, at least in part, to the fact that the surface region of materials in the solid state is quiescent, in sharp contrast to the turbulence that exists at the surfaces of liquids and gases. Accordingly, solid–solid systems will not be discussed here. A final section will outline the electric properties of interfaces.

The term *surface* is customarily used when referring to either a gas–solid or a gas–liquid interface. Although this terminology will be used in this chapter, the reader should appreciate that every surface is an interface. Thus, a tabletop forms a gas–solid interface with the atmosphere above it, and the surface of a raindrop constitutes a gas–liquid interface.

The symbols for the various interfacial tensions are shown in the second column of Table 15-1, where the subscript L stands for liquid, V for vapor or gas, and S for solid. Surface and interfacial tensions are defined later.

Key Concept

Interfaces

When phases exist together, the boundary between two of them is known as an *interface*. The properties of the molecules forming the interface are often sufficiently different from those in the bulk of each phase that they are referred to as forming an *interfacial phase*. If a liquid and its vapors exist together in the same container, the liquid takes the bottom part of the container. The remainder of the container is filled up by the liquid vapor, which, as with any gas, has a tendency to take all available space. Molecules in both the liquid and the gas are in constant motion and can move from the liquid into the vapor and back from the vapor to the liquid. However, the distinct boundary between the vapor and the liquid is preserved under constant temperature, and the exchange of molecules does not destroy the equilibrium between these two phases due to the labile (i.e., dynamic) character of this boundary.

Because every physical entity, be it a cell, a bacterium, a colloid, a granule, or a human, possesses an interface at its boundary with its surroundings, the importance of the present topic is self-evident. Interfacial phenomena in pharmacy and medicine are significant factors that affect adsorption of drugs onto solid adjuncts in dosage forms, penetration of molecules through biologic membranes, emulsion formation and stability, and the dispersion of insoluble particles in liquid media to form suspensions. The interfacial properties of a surface-active agent lining the alveoli of the lung are responsible for the efficient operation of this organ.[1,2,3] Several authors[4,5,6] have reviewed the relationship between surface properties of drugs and their biologic activity.

Liquid Interfaces

Surface and Interfacial Tensions

In the liquid state, the cohesive forces between adjacent molecules are well developed. Molecules in the bulk liquid are surrounded in all directions by other molecules for which they have an equal attraction, as shown in Figure 15-1. On the other hand, molecules at the surface (i.e., at the liquid–air interface) can only develop attractive cohesive forces with other liquid molecules that are situated below and adjacent to them. They can develop adhesive forces of attraction with the molecules constituting the other phase involved in the interface, although, in the case of the liquid–gas interface, this adhesive force of attraction is small. The net effect is that the molecules at the surface of the liquid experience an inward force toward the bulk, as shown in Figure 15-1. Such a force pulls the molecules of the interface together and, as a result, contracts the surface, resulting in a *surface tension*.

Table 15-1 Classification of Interfaces

Phase	Interfacial Tension	Types and Examples of Interfaces
Gas–Gas	—	No interface possible
Gas–liquid	γ_{LV}	Liquid surface, body of water exposed to atmosphere
Gas–solid	γ_{SV}	Solid surface, table top
Liquid–liquid	γ_{LL}	Liquid–liquid interface, emulsion
Liquid–solid	γ_{LS}	Liquid–solid interface, suspension
Solid–solid	γ_{SS}	Solid–solid interface, powder particles in contact

This “tension” in the surface is the force per unit length that must be applied *parallel* to the surface so as to counterbalance the net inward pull. This force, the surface tension, has the units of dynes/cm in the cgs system and of N/m in the SI system. It is similar to the situation that exists when an object dangling over the edge of a cliff on a length of rope is pulled upward by a man holding the rope and walking away from the edge of the top of the cliff. This analogy to surface tension is sketched in Figure 15-2.

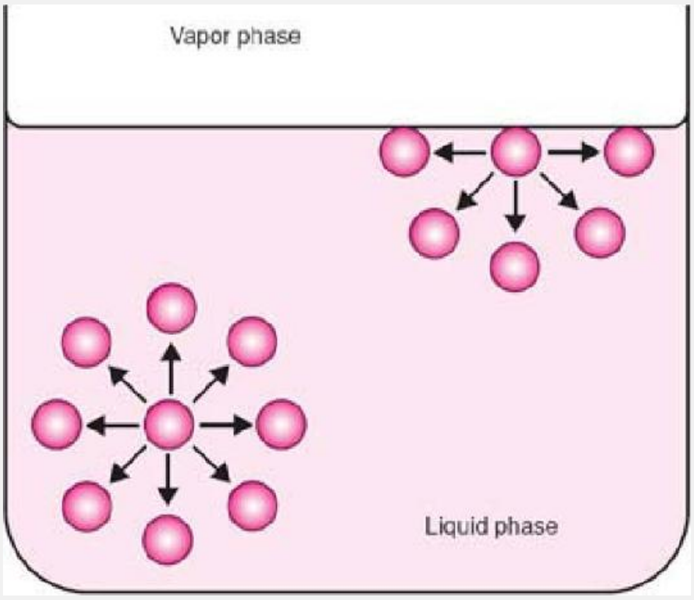

Fig. 15-1. Representation of the unequal attractive forces acting on molecules at the surface of a liquid as compared with molecular forces in the bulk of the liquid.

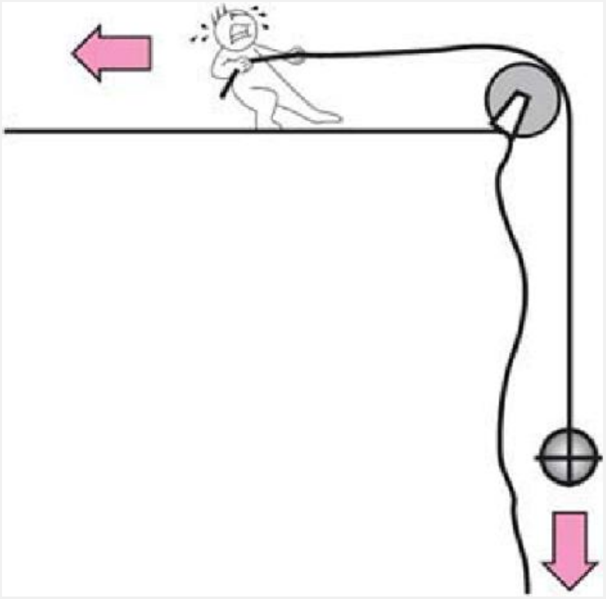

Fig. 15-2. Visualization of surface tension as akin to a person lifting a weight up the side of a cliff by pulling the rope in a horizontal direction.

Interfacial tension is the force per unit length existing at the interface between two immiscible liquid phases and, like surface tension, has the units of dynes/cm. Although, in the general sense, all tensions may be referred to as *interfacial tensions*, this term is most often used for the attractive force between immiscible liquids. Later, we will use the term *interfacial tension* for the force between two liquids, γ_{LL}, between two solids, γ_{SS}, and at a liquid–solid interface,γ_{LS}. The term *surface tension* is reserved for liquid–vapor, γ_{LV}, and solid–vapor, γ_{SV}, tensions. These are often written simply as γ_L andγ_S, respectively. Ordinarily, interfacial tensions are less than surface tensions because the adhesive forces between two liquid phases forming an interface are greater than when a liquid and a gas phase exist together. It follows that if two liquids are completely miscible, no interfacial tension exists between them. Some representative surface and interfacial tensions are listed in Table 15-2.

Surface tension as a force per unit length can also be illustrated by means of a three-sided wire frame across which a movable bar is placed (Fig. 15-3). A soap film is formed over the area ABCD and can be stretched by applying a force *f* (such as a hanging mass) to the movable bar, length *L*, which acts against the surface tension of the soap film. When the mass is removed, the film will contract owing to its surface tension. The surface tension, *γ*, of the solution forming the film is then a function of the force that must be applied to break the film over the length of the movable bar in contact with the film. Because the soap film has two liquid–gas interfaces (one above and one below the plane of the paper), the total length of contact is in fact equal to twice the length of the bar.

Table 15-2 Surface Tension and Interfacial Tension (Against Water) at 20°C*

Substance	Surface Tension (dynes/cm)	Substance	Interfacial Tension (dynes/cm)
Water	72.8	Mercury	375
Glycerin	63.4	*n*-Hexane	51.1
Oleic acid	32.5	Benzene	35.0
Benzene	28.9	Chloroform	32.8
Chloroform	27.1	Oleic acid	15.6
Carbon tetrachloride	26.7	*n*-Octyl alcohol	8.52
Caster oil	39.0	Caprylic acid	8.22
Olive oil	35.8	Olive oil	22.9
Cottonseed oil	35.4	Ethyl ether	10.7
Liquid petrolatum	33.1		

*From P. Becher, *Emulsions: Theory and Practice*, 2nd Ed., Reinhold, New York, 1962, and other sources.

Thus,

$$\gamma = f_b/2L \qquad (15\text{–}1)$$

where f_b is the force required to break the film and L is the length of the movable bar.

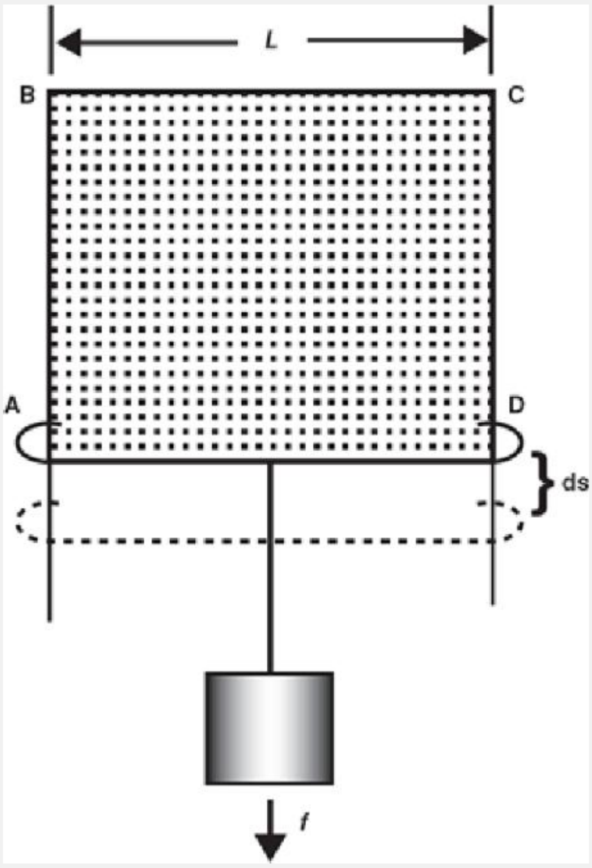

Fig. 15-3. Wire-frame apparatus used to demonstrate the principle of surface tension.

Example 15-1
Calculating the Surface Tension of Water

If the length of the bar, *L*, is 5 cm and the mass required to break a soap film is 0.50 g, what is the surface tension of the soap solution?

Recall that the downward force is equal to the mass multiplied by the acceleration due to gravity. Then

$$\gamma = \frac{0.50\ \text{g} \times 981\ \text{cm/sec}^2}{10\ \text{cm}} = 49\ \text{dynes/cm}$$

Surface Free Energy

To move a molecule from the inner layers to the surface, work needs to be done against the force of surface tension. In other words, each molecule near the surface of liquid possesses a certain excess of potential energy as compared to the molecules in the bulk of the liquid. The higher the surface of the liquid, the more molecules have this excessive potential energy. Therefore, if the surface of the liquid increases (e.g., when water is broken into a fine spray), the energy of the liquid also increases. Because this energy is proportional to the size of the free surface, it is called a surface free energy. Each molecule of the liquid has a tendency to move inside the liquid from the surface; therefore, the liquid takes form with minimal free surface and with minimal surface energy. For example, liquid droplets tend to assume a spherical shape because a sphere has the smallest surface area per unit volume.

To increase the surface of the liquid without any additional changes in the liquid state, in particular without changes in liquid temperature, work must be done against the surface tension. To evaluate the amount of work in increasing the surface area, we can write equation **(**15-1**)** as $\gamma \times 2L = f$. When the bar is at a position AD in Figure 15-3 and a mass is added to extend the surface by a distance ds, the work *dW* (force multiplied by distance) is

$$dW = f \times \text{ds} = \gamma \times 2L \times \text{ds}$$

and, because $2L \times \text{ds}$ is equal to the increase in surface area, *dA*, produced by extending the soap film,

$$dW = \gamma dA$$

For a finite change,

$$W = \gamma \Delta A \qquad (15\text{–}2)$$

where *W* is the work done, or *surface free energy* increase, expressed in ergs, γ is the surface tension in dynes/cm, and ΔA is the increase in area in cm^2. Any form of energy can be divided into an intensity factor and a capacity factor (see Chapter 3). Surface tension is the intensity factor, and a change in area is the capacity factor of surface free energy. Surface tension can be defined as the*surface free energy change per unit area increase* consistent with equation (**15–2**).

Example 15-2

Calculation of Work against Surface Tension

What is the work required in Example 15-1 to pull the wire down 1 cm as shown in Figure 15-3?

Because the area is increased by 10 cm^2, the work done is given by the equation

$$W = 49\ \text{dynes/cm} \times 10\ \text{cm}^2 = 490\ \text{ergs}$$

Repeat the calculations using SI units. We have

$$\begin{aligned}&1\ \text{dyne} = 10^{-5}\ \text{N, or } 49\ \text{dynes} = 49 \times 10^{-5}\ \text{N}\\&49\ \text{dynes/cm} = 49 \times 10^{-3}\ \text{N/m} = 49 \times 10^{-3}\ \text{Nm/m}^2\\&= 49 \times 10^{-3}\text{joule/m}^2\end{aligned}$$

Also, 1 joule = 10^7 ergs. Therefore, $W = 49 \times 10^{-3}\ \text{Nm/m}^2 \times 10^{-3}\ \text{m}^2 = 490 \times 10^{-7}$ joule = 490 ergs.

Equation 15-2 defines surface tension as the work per unit area required to produce a new surface. From thermodynamics, at *T* and*P* constant, the surface tension can also be viewed as the increment in Gibbs free energy per unit area (see Hiemenz7). Thus, equation**(**15-2**)** can be written as

$$\gamma = \left(\frac{dG}{dA}\right)_{T,P} \qquad (15\text{–}3)$$

This definition has the advantage that the path-dependent variable *W*is replaced by a thermodynamic function *G*, which is independent of the path. Many of the general relationships that apply to *G* also serve for *γ*. This fact enables us to compute the enthalpy and entropy of a surface:

$$G^S = \gamma = H^S - TS^S \qquad (15\text{–}4)$$

Key Concept

Surface Free Energy and Surface Tension

The surface layer of a liquid possesses additional energy as compared to the bulk liquid. This energy increases when the surface of the same mass of liquid increases and is therefore called *surface free energy*. Surface free energy per unit of surface of the liquid is defined as *surface tension* and is often denoted as *γ*. This means that for an increase of liquid surface of *S* units without any other changes in the liquid state and without changes in its temperature, the work equal to *γS* must be done.

and

$$\left(\frac{\partial G^S}{\partial T}\right)_P = \left(\frac{\partial \gamma}{\partial T}\right)_P = -S^S \qquad (15\text{–}5)$$

Combining equations **(**15-4**)** and **(**15-5**)**, we obtain

$$\gamma = H^S + T\left(\frac{\partial \gamma}{\partial T}\right)_P \qquad (15\text{–}6)$$

Thus, from a plot of surface tension against absolute temperature, we can obtain the slope of the line, $\partial\gamma/\partial T$, and thus find $-S^s$ from equation **(**15-5**)**. If H^s does not change appreciably over the temperature range considered, the intercept gives the H^s value. It should be noted that the units for S^s and H^s are given in two dimensions, ergs/cm^2 deg for S^s and ergs/cm^2 for H^s in the cgs system. In the SI system, S^s is given in units of joule/m^2 deg and H^sin units of joule/m^2.

Example 15-3

Calculation of S^s and H^s

The surface tension of methanol in water (10% by volume) at 20°C, 30°C, and 50°C (293.15, 303.15, and 323.15 K, respectively) is 59.04, 57.27, and 55.01 dynes/cm (or ergs/cm^2), respectively.8 Compute S^s and H^s over this temperature range.

Using linear regression of *γ* versus *T* according to equation (15-6), we find the slope to be -0.131 erg/cm^2 deg = $(\partial\gamma/\partial T)_p$= $-S^s$; hence, S^s = 0.131 and the intercept is 97.34 erg/cm^2= H^s. The equation is therefore

$$G^S = \gamma = 97.34 + 0.131T$$

If we compute H^s at each temperature from equation (15-6) and if S^s remains constant at -.131, we find

$$\begin{aligned}
&\text{At } 20^\circ\text{C:} \quad H^S = 59.04 + (0.131 \times 293.15) = 97.44 \text{ erg/cm}^2\\
&\text{At } 30^\circ\text{C:} \quad H^S = 57.27 + (0.131 \times 303.15) = 96.98 \text{ erg/cm}^2\\
&\text{At } 50^\circ\text{C:} \quad H^S = 55.01 + (0.131 \times 323.15) = 97.34 \text{ erg/cm}^2
\end{aligned}$$

H^s appears to be practically constant, very similar to the intercept from the regression equation, H^s = 97.34 erg/cm^2= 97.34 mJ/m^2. Note that the numerical value of surface tension in the cgs system, like that for H^s in the cgs system, is the same as that in the SI system when the units mJ are used. Thus, one can convert surface tension readily from cgs to SI units.7 For example, if the surface tension of methanol in water (10% by volume) at 20°C is 59.04 erg/cm^2 in the cgs system, we can write without carrying out the conversion calculation that *γ* for the methanol-in-water mixture at 20°C is 59.04 mJ/m^2 in SI units.

Pressure Differences Across Curved Interfaces

Another way of expressing surface tension is in terms of the pressure difference that exists across a curved interface.

Consider a soap bubble (Fig. 15-4) having a radius *r*. The total surface free energy, *W*, is equal to $4\pi r^2\gamma$, where $4\pi r^2$ is the area of the spherical bubble. (See the formulas, bottom, inside front cover.) Suppose that the bubble is caused to shrink so that its radius decreases by *dr*. The final surface free energy is now

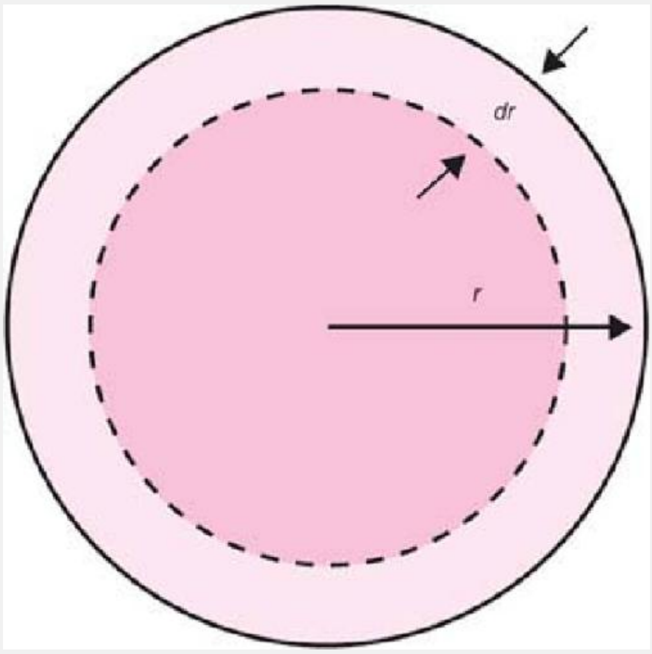

Fig. 15-4. Schematic representation of the pressure difference across the curved surface of a soap bubble.

$$W = 4\pi\gamma(r - dr)^2 \qquad (15\text{–}7)$$

$$W = 4\pi\gamma r^2 - 8\pi\gamma dr + 4\pi\gamma(dr)^2 \qquad (15\text{–}8)$$

Because *dr* is small compared to *r*, the term containing (*dr*)2 in equation **(**15-8**)** can be disregarded. The *change* in surface free energy is therefore $-8\pi\gamma r\, dr$, negative because the surface area has shrunk. Opposing this change is an equal and opposite energy term that depends on the pressure difference, Δ*P*, across the wall of the bubble. Because pressure is a force per unit area, or force = pressure × area, the work change brought about by a decrease in radius *dr* is

$$W = \Delta P \times 4\pi r^2 \times -dr \qquad (15\text{–}9)$$

At equilibrium, this must equal the change in surface free energy, and so

$$-8\pi\gamma r\, dr = -4\, \Delta P r^2 dr \qquad (15\text{–}10)$$

or

$$\Delta P = \frac{2\gamma}{r} \qquad (15\text{–}11)$$

Therefore, as the radius of a bubble decreases, the pressure of the air inside increases relative to that outside. Equation **(**15-11**)** is a simplification of the Young–Laplace equation and can be used to explain capillary rise, as seen in the following section.

Measurement of Surface and Interfacial Tensions

Of the several methods that exist for obtaining surface and interfacial tensions, only the *capillary rise* and the *DuNoüy ring* methods will be described here. For details of the other methods, such as drop weight, bubble pressure, pendent drop, sessile drop, Wilhelmy plate, and oscillating drop, refer to the treatises by Adamson,9Harkins and Alexander,10 Drost-Hansen,11 Hiemenz,7 and Matsumoto et al.12 It is worth noting, however, that the choice of a particular method often depends on whether surface or interfacial tension is to be determined, the accuracy and convenience desired, the size of sample available, and whether the effect of time on surface tension is to be studied. There is no one best method for all systems.

The surface tensions of most liquids decrease almost linearly with an increase in temperature, that is, with an increase in the kinetic energy of the molecules. In the region of its critical temperature, the surface tension of a liquid becomes zero. The surface tension of water at 0°C is 75.6, at 20°C it is 72.8, and at 75°C it is 63.5 dynes/cm. It is therefore necessary to control the temperature of the system when carrying out surface and interfacial tension determinations.

Capillary Rise Method

When a capillary tube is placed in a liquid contained in a beaker, the liquid generally rises up the tube a certain distance. Because the force of adhesion between the liquid molecules and the capillary wall is greater than the cohesion between the liquid molecules, the liquid is said to *wet* the capillary wall, spreading over it and rising in the tube (spreading is discussed in some detail later). By measuring this rise in a capillary, it is possible to determine the surface tension of the liquid. It is not possible, however, to obtain interfacial tensions using the capillary rise method.

Consider a capillary tube with an inside radius *r* immersed in a liquid that wets its surface, as seen in Figure 15-5a. Because of the surface tension, the liquid continues to rise in the tube, but because of the weight of the liquid, the upward movement is just balanced by the downward force of gravity.

The upward vertical component of the force resulting from the surface tension of the liquid at any point on the circumference is given by

$$a = \gamma\cos(\theta)$$

as seen in the enlarged sketch (Fig. 15-5b). The total upward force around the inside circumference of the tube is

$$2\pi r\gamma\cos(\theta)$$

where θ is the *contact angle* between the surface of the liquid and the capillary wall and $2\pi r$ is the inside circumference of the capillary. For water and other commonly used liquids, the angle θ is insignificant, that is, the liquid wets the capillary wall so that cos θ is taken as unity for practical purposes (see left side of Fig. 15-5b).

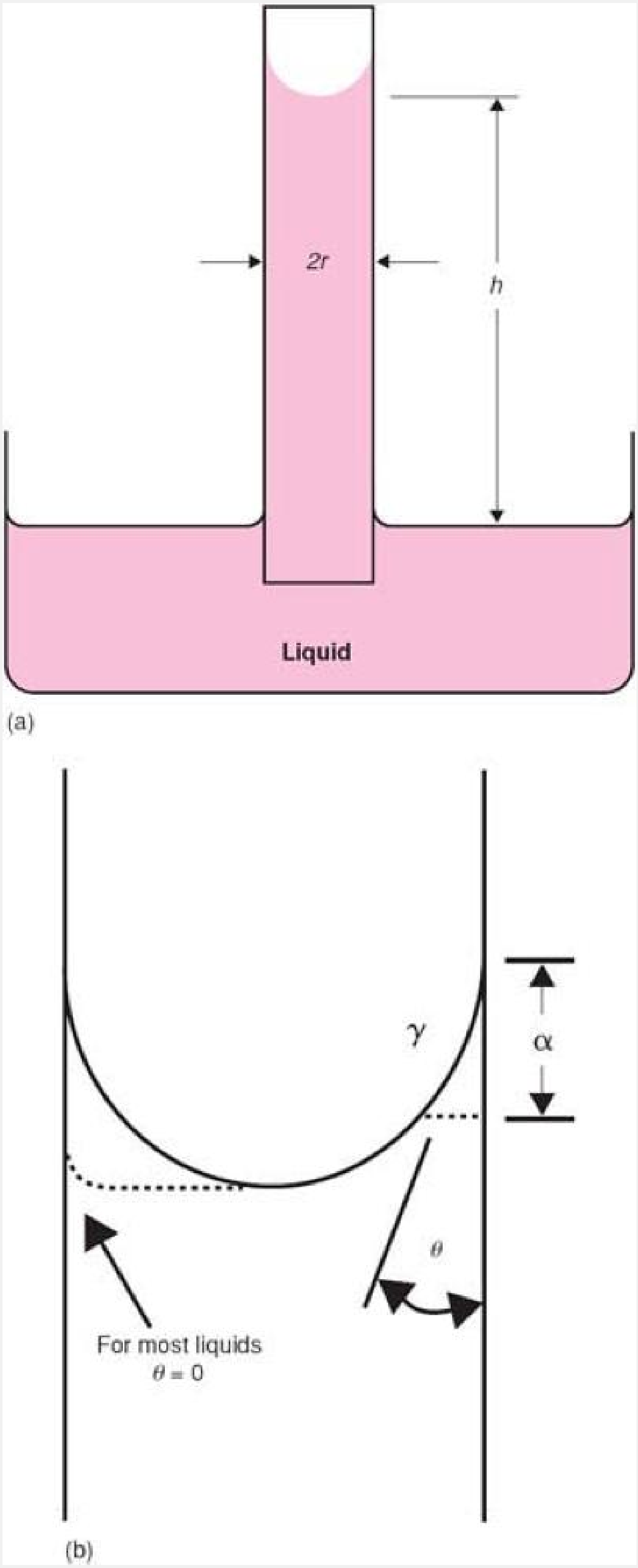

Fig. 15-5. (*a*) Measuring surface tension by means of the capillary-rise principle. (*b*) Enlarged view of the force components and contact angle at the meniscus of a liquid. For many liquids, the contact angle θ (exaggerated in the figure) is nearly zero, as shown on the left-hand side of the diagram.

The counteracting force of gravity (mass × acceleration) is given by the product of the cross-sectional area, πr^2, the height, h, of the liquid column to the lowest point of the meniscus, the difference in the density of the liquid, ρ, and its vapor, ρ_0, and the acceleration of gravity: $\pi r^2 h(\rho - \rho_0)g + w$. The last term, w, is added to account for the weight of liquid above h in the meniscus. When the liquid has risen to its maximum height, which can be read from the calibrations on the capillary tube, the opposing forces are in equilibrium, and accordingly the surface tension can be calculated. The density of the vapor, the contact angle, and w can usually be disregarded; hence,

$$2\pi r\gamma = \pi r^2 h\rho g$$

and finally

$$\gamma = \frac{1}{2} rh\rho g \qquad (15\text{–}12)$$

Example 15-4

Calculation of the Surface Tension of Chloroform by the Capillary Rise Method

A sample of chloroform rose to a height of 3.67 cm at 20°C in a capillary tube having an inside radius of 0.01 cm. What is the surface tension of chloroform at this temperature? The density of chloroform is 1.476 g/cm^3. We write

$$\gamma = \frac{1}{2} \times 0.01\text{ cm} \times 3.67\text{ cm} \times 1.476\text{ g/cm}^3 \times 981\text{ cm/sec}^2$$

$$\gamma = 26.6\text{ g/sec}^2 = 26.6\text{ dynes/cm}$$

Capillary rise can also be explained as being due to the pressure difference across the curved meniscus of the liquid in the capillary. We have already seen in equation **(**15-11**)** that the pressure on the concave side of a curved surface is greater than that on the convex side. This means that the pressure in the liquid immediately below the meniscus will be less than that outside the tube at the same height. As a result, the liquid will move up the capillary until the hydrostatic head produced equals the pressure drop across the curved meniscus.

Using the same symbols as before and neglecting contact angles, we obtain

$$\Delta P = 2\gamma/r = \rho gh \qquad (15\text{–}13)$$

where ρgh is the hydrostatic head. Rearranging equation **(**15-13**)**gives

$$\gamma = r\rho gh/2$$

which is identical with equation **(**15-12**)** derived on the basis of adhesive forces versus cohesive forces.

The DuNoüy Ring Method

The *DuNoüy tensiometer* is widely used for measuring surface and interfacial tensions. The principle of the instrument depends on the fact that the force necessary to detach a platinum–iridium ring immersed at the surface or interface is proportional to the surface or interfacial tension. The force required to detach the ring in this manner is provided by a torsion wire and is recorded in dynes on a calibrated dial.

The surface tension is given by the formula [compare with equation**(**15-1**)**]

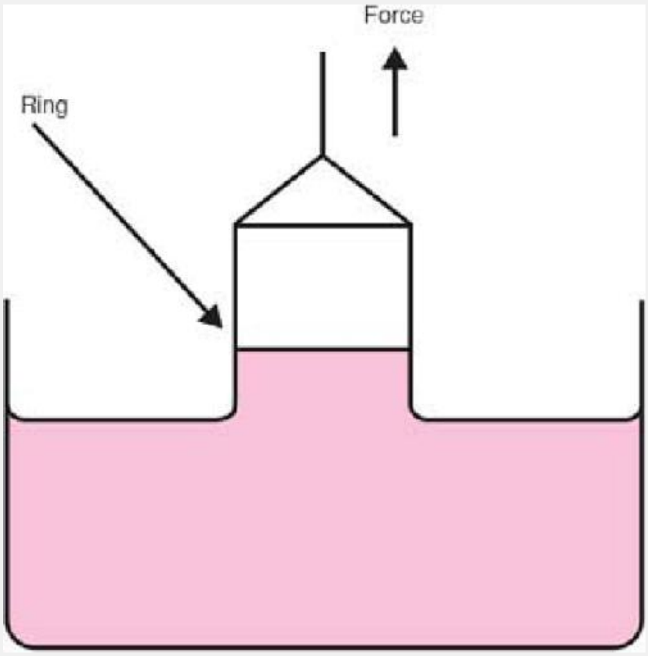

Fig. 15-6. Schematic of the tensiometer ring pulling a column of water above the surface before it brakes away.

$$\gamma = \frac{\text{Dial reading in dynes}}{2 \times \text{Ring circumference}} \times \text{Correction factor, } \beta \qquad (15\text{–}14)$$

In effect, the instrument measures the weight of liquid pulled out of the plane of the interface immediately before the ring becomes detached (Fig. 15-6). A correction factor is necessary in equation**(**15-15**)** because the simple theory does not take into account certain variables such as the radius of the ring, the radius of the wire used to form the ring, and the volume of liquid raised out of the surface. Errors as large as 25% may occur if the correction factor is not calculated and applied. The method of calculating the correction factor has been described13,14; with care, a precision of about 0.25% can be obtained.

Example 15-5

DuNoüy Ring Method

The published surface tension of water at 18°C is 73.05 dynes/cm, and the density, ρ_1, of water at this temperature is 0.99860 g/cm^3. The density, ρ_2, of moist air that is, air saturated with the vapor of the liquid, water, at 18°C is 0.0012130. Therefore, $\rho_1 - \rho_2$, the density of water overlaid with air, is 0.99739 g/cm^3. The dial reading in dynes or newtons on the tensiometer is equal to the mass, *M*, of the liquid lifted by the ring multiplied by the gravity constant, 980.665 cm/sec^2; that is,

$$\text{Dial reading} = M(g) \times 980.665 \text{ cm/sec}^2$$

It is thus possible to obtain the mass *M* of liquid lifted with the ring (*M* = 0.7866 g) before it breaks away from the water surface. The ring must be kept absolutely horizontal for accurate measurement. The volume, *V*, of water lifted above the free surface of water is calculated from the mass of water lifted and the density at 18°C, or

$$V = \frac{M}{\rho_1 - \rho_2} = \frac{0.7866}{0.99739} = 0.78866 \text{ cm}^3$$

Table 15-3 Some Harkins and Jordan β Values*

	β			
R^3 V	$R/r = 30$	$R/r = 40$	$R/r = 50$	$R/r = 60$
0.50	0.9402	0.9687	0.9876	0.9984
1.00	0.8734	0.9047	0.9290	0.9438
2.00	0.8098	0.8539	0.8798	0.9016
3.00	0.7716	0.8200	0.8520	0.8770
3.50	0.7542	0.8057	0.8404	0.8668

*From W. D. Harkins and H. F. Jordan, J. Am. Chem. Soc. **52,** 1751, 1930; H. L. Cupples, J. Phys. Chem. **51,** 1341, 1947.

The ring of the tensiometer has a radius, R, of 0.8078 cm, and $R^3 = 0.527122$ cm^3. The radius, r, of the wire that forms the ring is 0.01877 cm. Two values, R^3/V and R/r, are needed to enter the tables of Harkins and Jordan13 to obtain the correction factor, β, by interpolation. An abbreviated table of R^3/V and R/r values needed to obtain β is given in Table 15-3. In this example $R^3/V = 0.52712/0.78866 = 0.66838$ and $R/r = 0.8078/0.01877 = 43.0368$. Introducing these values into Table VIII-C of Harkins and Jordan13 and by interpolation, one obtains $\beta = 0.9471$ (18°C).

Finally, using equation (15-15), we obtain the surface tension for water at 18°C:

$$\gamma = \frac{M \times g}{4\pi R} \times \beta = \frac{(0.7866\ \text{g})(980.665\ \text{cm/sec}^2)}{4\pi(0.8078\ \text{cm})} \times 0.9471$$
$$= 71.97\ \text{dynes/cm} \quad \text{or} \quad 71.97\ \text{ergs/cm}^2$$

Without the correction factor, β, γ is calculated here to be 75.99 dynes/cm. The value of γ for water at 18°C is recorded in handbooks as approximately 73.05 dynes/cm. The error relative to the published value at 18°C is (73.05 - 71.97/73.05) × 100 = 1.48%.

The correction factor β can be calculated from an equation rather than obtaining it from tabulated values of R/r and R^3/V as done inExample 15-4. Zuidema and Waters15 suggested an equation for calculating β, as discussed by Shaw16:

$$(\beta - \alpha)^2 = \frac{4b}{\pi^2} \cdot \frac{1}{R^2} \cdot \frac{M \times g}{4\pi R(\rho_1 - \rho_2)} + c \quad (15\text{–}15)$$

Example 15-6

Surface Tension Correction Factor Calculation

Use equation (15-15) to calculate β, the surface tension correction at 20°C, for $a = 0.7250$, $b = 0.09075$ m^{-1} sec^2 for all tensiometer rings, and $c = 0.04534 - 1.6790\ r/R$, with $R$the radius of the ring in m, r the radius in m of the wire from which the ring is constructed, M the mass in kg of the liquid lifted above the liquid surface as the ring breaks away from the surface, g the acceleration due to gravity in m/sec^2, $\rho_1$the density of the liquid in kg/m^{-3}, and ρ_2 the density of the air saturated with the liquid in kg/m^3; that is, the upper phase of an interfacial system. With the following data, which must be expressed in SI units for use in equation (15-15), β is calculated and used in equation (15-15) to obtain the corrected surface tension. The terms of equation (15-15) in SI units are R = 0.012185 m, r = 0.0002008 m, M = 0.0012196 kg, g = 9.80665 m/sec, ρ_1 = 998.207 kg/m^3, and ρ_2 = 1.2047 kg/m^3. Finally, c = 0.04534 - 1.6790 r/R = 0.017671. Substituting into equation (15-15), we have

$$
\begin{aligned}
(\beta - \alpha)^2 &= \frac{4(0.09075\ \mathrm{m^{-1}sec^2})}{9.869604} \cdot \frac{1}{0.00014847\ \mathrm{m^2}} \\
&\cdot \frac{(0.0012196\ \mathrm{kg})(9.80665\ \mathrm{m/sec^2})}{4(3.14159)(0.012185\ \mathrm{m})(998.207 - 1.2047\ \mathrm{kg/m^3})} \\
&+ 0.04534 - \frac{(1.6790)(0.0002008\ \mathrm{m})}{0.012185\ \mathrm{m}} = 0.0194077 \\
&+ 0.0176713 = 0.0370790 \\
\beta - 0.7250 &= \sqrt{0.0370790} \\
\beta &= 0.7250 + 0.192559 = 0.918\ \text{(dimensionless) at } 20^\circ\mathrm{C}
\end{aligned}
$$

The literature value of γ for water at 20°C is 72.8 dynes/cm (or ergs/cm^2) in cgs units. Using the uncorrected equation γ= Mg(4πR) and SI units, we obtain for water at 20°C

$$
\begin{aligned}
\gamma &= (0.0012196\ \mathrm{kg} \times 9.80665\ \mathrm{m/sec^2})/(4\pi \times 0.012185\ \mathrm{m}) \\
&= 0.078109\ \mathrm{kg/sec^2}
\end{aligned}
$$

Multiplying numerator and denominator by m^2 yields the result 0.07811 joule/m^2, and expressing the value in mJ/m^2, we have 78.11 mJ/m^2. This is a useful way to express surface tension in SI units because the value 78.11 is numerically the same as that in the cgs system; namely, 78.11 ergs/cm^2 (see Example 15-3). To correct the value γ= Mg(4πR) expressed either in cgs or SI units, we multiply by the Harkins and Jordan13 or the Zuidema and Waters15value for β at a given liquid density and temperature, Mvalue, and ring dimensions. For the particular case in this example,

$$
\begin{aligned}
\gamma = \frac{\mathrm{Mg}}{4\pi R} \times \beta &= 78.11\ \mathrm{ergs/cm^2}\ (\text{or } \mathrm{mJ/m^2}) \times 0.918 \\
&= 71.7\ \mathrm{ergs/cm^2}
\end{aligned}
$$

The error in the Zuidema and Waters15 value of 71.7 mJ/m^{2}relative to the literature value, 72.8 mJ/m^2, at 20°C is (72.8 - 71.7)/72.8 × 100 = 1.51%.

The modern variant of the surface tensiometer, the Sigma 70 Surface Tensiometer from KSV Instruments (Monroe, Conn.), offers advanced, microprocessor-based measurement using either the Wilhelmy plate or DuNoüy ring method. The Wilhelmy plate method is based on the measurement of the force necessary to detach a plate from the surface of a liquid.

Spreading Coefficient

When a substance such as oleic acid is placed on the surface of water, it will spread as a film if the force of adhesion between the oleic acid molecules and the water molecules is greater than the cohesive forces between the oleic acid molecules themselves. The term *film* used here applies to a *duplex film* as opposed to a monomolecular film. Duplex films are sufficiently thick (100 Å or more) so that the surface (boundary between oleic acid and air) and interface (boundary between water and oleic acid) are independent of one another.

The *work of adhesion*, which is the energy required to break the attraction between the unlike molecules, is obtained by reference toFigure 15-7. Figure 15-7a shows a hypothetical cylinder (cross-sectional area 1 cm^2) of the sublayer liquid, S, overlaid with a similar section of the spreading liquid, L.

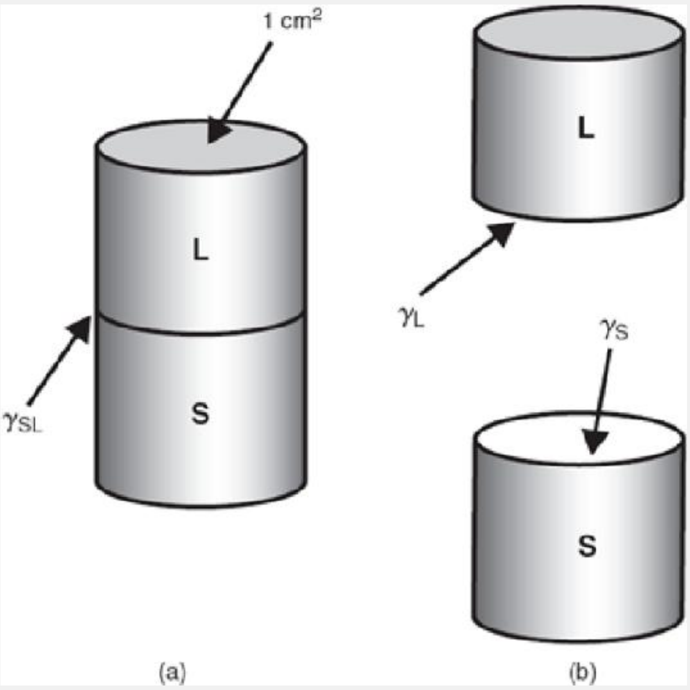

Fig. 15-7. Representation of the work of adhesion involved in separating a substrate and an overlaying liquid.

By equation **(**15-2**)**, surface or interfacial work is equal to surface tension multiplied by the area increment. The work required to separate the two sections of liquid in Figure 15-7, each with a cross-sectional area of 1 cm^2, is therefore numerically related to the surface or interfacial tension involved, the area increment being unity:

$$\text{Work} = \text{Surface tension} \times \text{Unit area change}$$

Accordingly, it is seen in Figure 15-7b that the work done is equal to the newly created surface tensions, γ_L and γ_S, minus the interfacial tension, γ_{LS}, that has been destroyed in the process. The work of adhesion is thus

$$W_a = \gamma_L + \gamma_S - \gamma_{LS} \qquad (15\text{–}16)$$

The *work of cohesion*, required to separate the molecules of the spreading liquid so that it can flow over the sublayer, is obtained by reference to Figure 15-8. Obviously, no interfacial tension exists between the like molecules of the liquid, and when the hypothetical 1-cm^2 cylinder in Figure 15-8a is divided, two new surfaces are created in Figure 15-8b, each with a surface tension of γ_L. Therefore, the work of cohesion is

$$W_c = 2\gamma_L \qquad (15\text{–}17)$$

With reference to the spreading of oil on a water surface, spreading occurs if the work of adhesion (a measure of the force of attraction between the oil and the water) is greater than the work of cohesion. The term (W_a - W_c) is known as the *spreading coefficient*, *S*; if it is positive, the oil will spread over a water surface. Equations **(**15-16**)**and **(**15-17**)** can be written as

$$S = W_a - W_c = (\gamma_L + \gamma_S - \gamma_{LS}) - 2\gamma_L \quad (15\text{–}18)$$

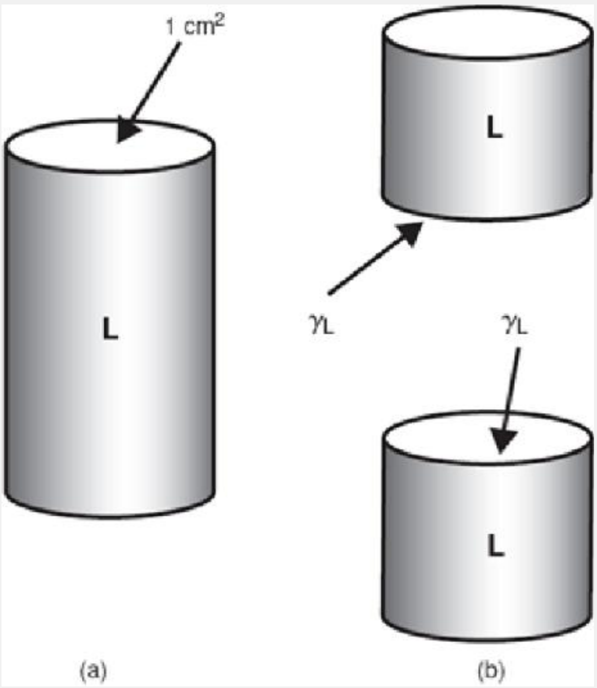

Fig. 15-8. Representation of the work of cohesion involved in separating like molecules in a liquid.

where γ_S is the surface tension of the sublayer liquid, γ_L is the surface tension of the spreading liquid, and γ_{LS} is the interfacial tension between the two liquids. Rearranging equation **(**15-18**)** gives

$$S = \gamma_S - \gamma_L - \gamma_{LS} \qquad \textbf{(15–19)}$$

or

$$S = \gamma_S - (\gamma_S + \gamma_{LS}) \qquad \textbf{(15–20)}$$

Figure 15-9 shows a lens of material placed on a liquid surface (e.g., oleic acid on water). From equation **(**15-20**)**, one sees that spreading occurs (*S* is positive) when the surface tension of the sublayer liquid is greater than the sum of the surface tension of the spreading liquid and the interfacial tension between the sublayer and the spreading liquid. If ($\gamma_L + \gamma_{LS}$) is larger than γ_S, the substance forms globules or a floating lens and fails to spread over the surface. An example of such a case is mineral oil on water.

Spreading can also be thought of in terms of surface free energy. Thus, the added substance will spread if, by so doing, it reduces the surface free energy of the system. Put another way, if the surface free energy of the new surface and the new interface is less than the free energy of the old surface, spreading will take place.

Up to this point, the discussion has been restricted to *initial* spreading. Before equilibrium is reached, however, the water surface becomes saturated with the spreading material, which in turn becomes saturated with water. If we use a prime (′) to denote the values following equilibration (i.e., final rather than initial values), then the new surface tensions are $\gamma_{S'}$ and $\gamma_{L'}$. When mutual saturation has taken place, the spreading coefficient may be reduced or may even become negative. This means that although initial spreading of the material may occur on the liquid substrate, it can be followed by coalescence of the excess material into a lens if *S′* becomes negative in value. This reversal of spreading takes place when $\gamma_{S'}$ becomes less than ($\gamma_{LS} + \gamma_{L'}$). Note that the value of γ_{LS} does not change because the interfacial tension is determined under conditions of mutual saturation.

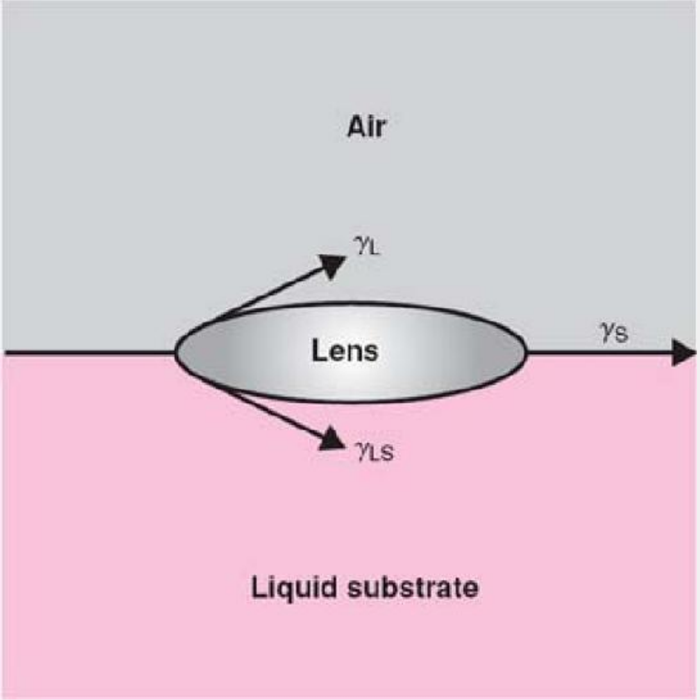

Fig. 15-9. Forces existing at the surface of a lens floating in a substrate liquid.

Example 15-7

Spreading Benzene over Water

If the surface tension of water γ_S is 72.8 dynes/cm at 20°C, the surface tension of benzene, γ_L, is 28.9 dynes/cm, and the interfacial tension between benzene and water, γ_{LS}, is 35.0 dynes/cm, what is the initial spreading coefficient? Following equilibration, $\gamma_{S'}$ is 62.2 dynes/cm and $\gamma_{L'}$ is 28.8 dynes/cm. What is the final spreading coefficient? We have

$$S = 72.8 - (28.9 + 35.0) = 8.9 \text{ dynes/cm (or } 8.9 \text{ ergs/cm}^2\text{)}$$
$$S' = 62.2 - (28.8 + 35.0) = -1.6 \text{ dynes/cm}$$

Therefore, although benzene spreads initially on water, at equilibrium there is formed a saturated monolayer with the excess benzene (saturated with water) forming a lens.

In the case of organic liquids spread on water, it is found that although the initial spreading coefficient may be positive or negative, the final spreading coefficient always has a negative value. Duplex films of this type are unstable and form monolayers with the excess material remaining as a lens on the surface. The initial spreading coefficients of some organic liquids on water at 20°C are listed inTable 15-4.

It is important to consider the types of molecular structures that lead to high spreading coefficients. Oil spreads over water because it contains polar groups such as COOH or OH.

Hence, propionic acid and ethyl alcohol should have high values of*S*, as seen in Table 15-4. As the carbon chain of an acid, oleic acid, for example, increases, the ratio of polar–nonpolar character decreases and the spreading coefficient on water decreases. Many nonpolar substances, such as liquid petrolatum (*S* = -13.4), fail to spread on water. Benzene spreads on water not because it is polar but because the cohesive forces between its molecules are much weaker than the adhesion for water.

Table 15-4 Initial Spreading Coefficient, *S*, at 20°C*

Substance	*S* (dynes/cm)
Ethyl alcohol	50.4
Propionic acid	45.8
Ethyl ether	45.5
Acetic acid	45.2
Acetone	42.4
Undecylenic acid	32 (25°C)
Oleic acid	24.6
Chloroform	13
Benzene	8.9
Hexane	3.4
Octane	0.22
Ethylene dibromide	-3.19
Liquid petrolatum	-13.4

*From W. D. Harkins, *The Physical Chemistry of Surface Films*, Reinhold, New York, 1952, pp. 44–45.

The applications of spreading coefficients in pharmacy should be fairly evident. The surface of the skin is bathed in an aqueous–oily layer having a polar–nonpolar character similar to that of a mixture of fatty acids. For a lotion with a mineral oil base to spread freely and evenly on the skin, its polarity and hence its spreading coefficient should be increased by the addition of a surfactant. The relation between spreading, HLB (*hydrophile–lipophile balance*), and emulsion stability has been studied.17 Surfactant blends of varying HLBs were added to an oil, a drop of which was then placed on water. The HLB of the surfactant blend that caused the oil drop to spread was related to the required HLB of the oil when used in emulsification. (See hydrophile-lipophile classification in this chapter).

Adsorption at Liquid Interfaces

Surface free energy was defined previously as the work that must be done to increase the surface by unit area. As a result of such an expansion, more molecules must be brought from the bulk to the interface. The more work that has to be expended to achieve this, the greater is the surface free energy. Certain molecules and ions, when dispersed in the liquid, move of their own accord to the interface. Their concentration at the interface then exceeds their concentration in the bulk of the liquid. Obviously, the surface free energy and the surface tension of the system are automatically reduced. Such a phenomenon, where the added molecules are partitioned in favor of the interface, is termed*adsorption*, or, more correctly, *positive adsorption*. Other materials (e.g., inorganic electrolytes) are partitioned in favor of the bulk, leading to *negative adsorption* and a corresponding increase in surface free energy and surface tension. Adsorption, as will be seen later, can also occur at solid interfaces. Adsorption should not be confused with *absorption*. The former is solely a surface effect, whereas in absorption, the liquid or gas being absorbed penetrates into the capillary spaces of the absorbing medium. The taking up of water by a sponge is absorption; the concentrating of alkaloid molecules on the surface of clay is adsorption.

Surface-Active Agents

It is the amphiphilic nature of surface-active agents that causes them to be absorbed at interfaces, whether these are liquid–gas or liquid–liquid interfaces. Thus, in an aqueous dispersion of amyl alcohol, the polar alcoholic group is able to associate with the water molecules. The nonpolar portion is rejected, however, because the adhesive forces it can develop with water are small in comparison to the cohesive forces between adjacent water molecules. As a result, the amphiphile is adsorbed at the interface. The situation for a fatty acid at the air–water and oil–water interface is shown in Figure 15-10. At the air–water interface, the lipophilic chains are directed upward into the air; at the oil–water interface, they are associated with the oil phase. For the amphiphile to be concentrated at the interface, it must be balanced with the proper amount of water- and oil-soluble groups. If the molecule is too hydrophilic, it remains within the body of the aqueous phase and exerts no effect at the interface. Likewise, if it is too lipophilic, it dissolves completely in the oil phase and little appears at the interface.

Systems of Hydrophile–Lipophile Classification

Griffin18 devised an arbitrary scale of values to serve as a measure of the hydrophilic–lipophilic balance of surface-active agents. By means of this number system, it is possible to establish an HLB range of optimum efficiency for each class of surfactant, as seen inFigure 15-11. The higher the HLB of an agent, the more hydrophilic it is. The Spans, sorbitan esters manufactured by ICI Americas Inc., are lipophilic and have low HLB values (1.8–8.6); the Tweens, polyoxyethylene derivatives of the Spans, are hydrophilic and have high HLB values (9.6–16.7).

The HLB of a nonionic surfactant whose only hydrophilic portion is polyoxyethylene is calculated by using the formula

$$\text{HLB} = E/5 \qquad (15\text{–}21)$$

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Key Concept

Surfactants

Molecules and ions that are adsorbed at interfaces are termed *surface-active agents* or *surfactants*. An alternative term is *amphiphile*, which suggests that the molecule or ion has a certain affinity for both polar and nonpolar solvents. Depending on the number and nature of the polar and nonpolar groups present, the amphiphile may be predominantly *hydrophilic* (water-loving), *lipophilic* (oil-loving), or reasonably well balanced between these two extremes. For example, straight-chain alcohols, amines, and acids are amphiphiles that change from being predominantly hydrophilic to lipophilic as the number of carbon atoms in the alkyl chain is increased. Thus, ethyl alcohol is miscible with water in all proportions. In comparison, the aqueous solubility of amyl alcohol, $C_5H_{11}OH$, is much reduced, whereas cetyl alcohol, $C_{16}H_{33}OH$, may be said to be strongly lipophilic and insoluble in water.

where *E* is the percentage by weight of ethylene oxide. A number of polyhydric alcohol fatty acid esters, such as glyceryl monostearate, can be estimated by using the formula

$$\mathrm{HLB} = 20\left(1 - \frac{S}{A}\right) \qquad (15\text{–}22)$$

where *S* is the saponification number of the ester and *A* is the acid number of the fatty acid. The HLB of polyoxyethylene sorbitan monolaurate (Tween 20), for which *S* = 45.5 and *A* = 276, is

$$\mathrm{HLB} = 20\left(1 - \frac{45.5}{276}\right) = 16.7$$

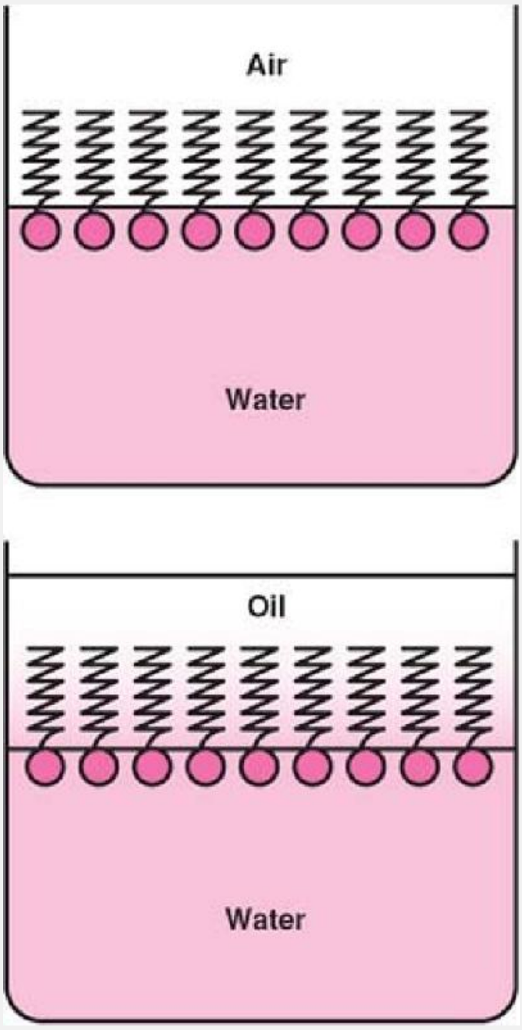

Fig. 15-10. Adsorption of fatty acid molecules at a water–air interface (upper panel) and a water–oil interface (lower panel).

The HLB values of some commonly used amphiphilic agents are given in Table 15-5.

The oil phase of an oil-in-water (O/W) emulsion requires a specific HLB, called the *required hydrophile–lipophile balance* (RHLB). A different RHLB is required to form a water-in-oil (W/O) emulsion from the same oil phase. The RHLB values for both O/W and W/O emulsions have been determined empirically for a number of oils and oil-like substances, some of which are listed in Table 15-6.

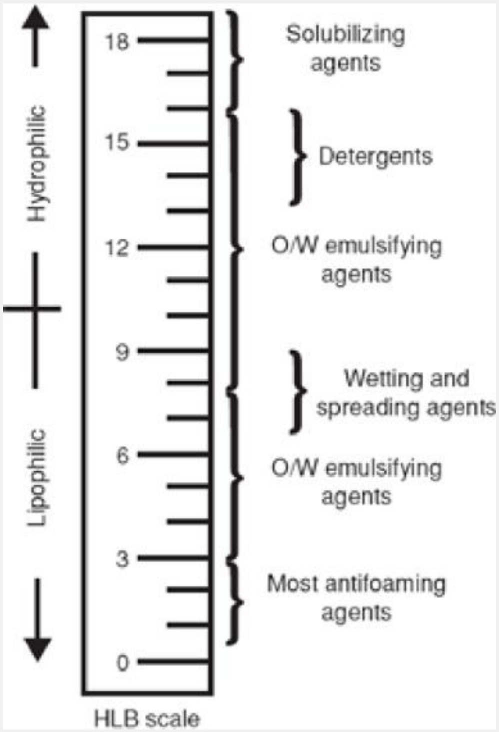

Fig. 15-11. A scale showing surfactant function on the basis of hydrophilic–lipophilic balance (HLB) values. Key: O/W = oil in water.

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Table 15-5 Hydrophilic–Lipophilic Balance (HLB) Values of Some Amphiphilic Agents

Substance	HLB
Oleic acid	1
Polyoxyethylene sorbitol beeswax derivative (G-1706)	2.0
Sorbitan tristearate	2.1
Glyceryl monostearate	3.8
Sorbitan monooleate (Span 80)	4.3
Diethylene glycol monostearate	4.7

Glyceryl monostearate, self-emulsifying (Tegin)	5.5
Diethylene glycol monolaurate	6.1
Sorbitan monolaurate (Span 20)	8.6
Polyethylene lauryl ether (Brij 30)	9.5
Gelatin (Pharmagel B)	9.8
Methyl cellulose (Methocel 15 cps)	10.5
Polyoxyethylene lauryl ether (G-3705)	10.8
Polyoxyethylene monostearate (Myrj 45)	11.1
Triethanolamine oleate	12.0
Polyoxyethylene alkyl phenol (Igepal Ca-630)	12.8
Polyethylene glycol 400 monolaurate	13.1
Polyoxyethylene sorbitan monooleate (Tween 80)	15.0
Polyoxyethylene sorbitan monolaurate (Tween 20)	16.7
Polyoxyethylene lauryl ether (Brij 35)	16.9
Sodium oleate	18.0
Potassium oleate	20
Sodium lauryl sulfate	40

Table 15-6 Required Hydrophilic–Lipophilic Balance (HLB) for Some Oil-Phase

Ingredients for Oil-Inwater (O/W) and Water-in-Oil (W/O) Emulsions*

	O/W	W/O
Cottonseed oil	6–7	—
Petrolatum	8	—
Beeswax	9–11	5
Paraffin wax	10	4
Mineral oil	10–12	5–6
Methyl silicone	11	—
Lanolin, anhydrous	12–14	8
Carnauba wax	12–14	—
Lauryl alcohol	14	—
Caster oil	14	—
Kerosene	12–14	—
Cetyl alcohol	13–16	—
Stearyl alcohol	15–16	—
Carbon tetrachloride	16	—
Lauric acid	16	—
Oleic acid	17	—

Stearic acid	17	—

*From *The Atlas HLB System,* Atlas Chemical Industries, Wilmington, DE; P. Becher, *Emulsions, Theory and Practice*, 2nd Ed., Reinhold, New York, 1966, p. 249.

Example 15-8

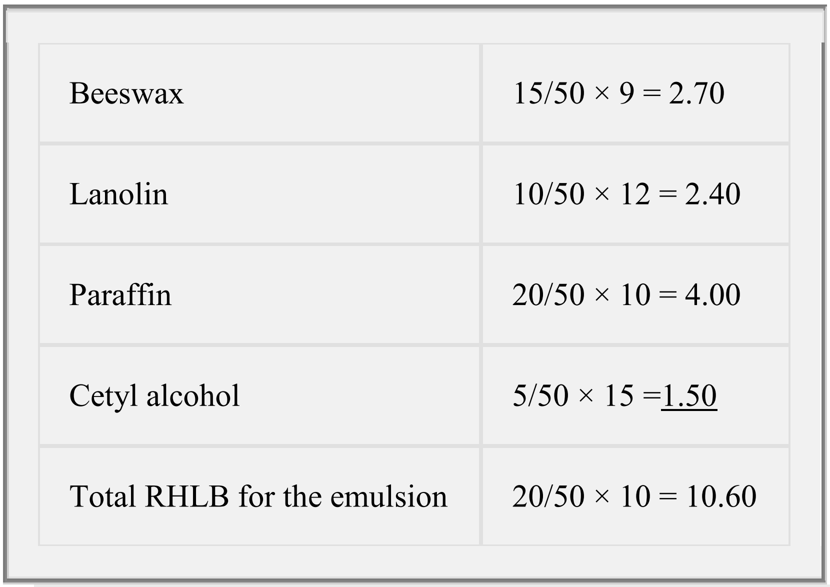
Calculation of HLB Value for Oil-in-Water Emulsions

For the oil-in-water emulsion,

Ingredient	Amount	RHLB (O/W)
1. Beeswax	15 g	9
2. Lanolin	10 g	12
3. Paraffin wax	20 g	10
4. Cetyl alcohol	5 g	15
5. Emulsifier	2 g	
6. Preservative	0.2 g	
7. Color	As required	
8. Water, purified q.s.	100 g	

Key: RHLB = required hydrophilic–lipophilic balance value.

One first calculates the overall RHLB of the emulsion by multiplying the RHLB of each oil-like component (items 1–4) by the weight fraction that each oil-like component contributes to the oil phase. The total weight of the oil phase is 50 g. Therefore,



Beeswax	15/50 × 9 = 2.70
Lanolin	10/50 × 12 = 2.40
Paraffin	20/50 × 10 = 4.00
Cetyl alcohol	5/50 × 15 =1.50
Total RHLB for the emulsion	20/50 × 10 = 10.60

Next, one chooses a blend of two emulsifying agents, one with an HLB above and the other with an HLB below the required HLB of the emulsion (RHLB = 10.6 in this example).

From Table 15-5, we choose Tween 80, with an HLB of 15, and Span 80, with an HLB of 4.3. The formula for calculating the weight percentage of Tween 80 (surfactant with the higher HLB) is

$$\%\ \text{Tween 80} = \frac{\text{RHLB} - \text{HLB low}}{\text{HLB high} - \text{HLB low}} \qquad (15\text{–}23)$$

where HLB high is for the higher value, 15, and HLB low is for the lower value, 4.3. We have

$$\%\ \text{Tween 80} = \frac{10.6 - 4.3}{15.0 - 4.3} = 0.59$$

Two grams of emulsifier has been estimated as proper protection for the O/W emulsion. Therefore, 2.0 g × 0.59 = 1.18 g of Tween 80 is needed and the remainder, 0.82 g, must be supplied by Span 80 for the 100-g emulsion.

The choice of the mixture of emulsifiers and the total amount of the emulsifier phase is left to the formulator, who determines these unknowns over time by preparation and observation of the several formulas chosen.

A mathematical formula for determining the minimum amount of surfactant mixture was suggested by Bonadeo19:

$$Q_s = \frac{6(\rho_s/\rho)}{10 - 0.5 \cdot \text{RHLB}} + \frac{4Q}{1000} \qquad (15\text{–}24)$$

where ρ_s is the density of the surfactant mixture, ρ is the density of the dispersed (internal) phase, and *Q* is the percentage of the dispersant (continuous phase) of the emulsion. The required HLB, written as RHLB, is the HLB of the oil phase needed to form an O/W or W/O emulsion.

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Example 15-9

W/O and O/W Formulations

We wish to formulate two products, (*a*) a W/O and (*b*) an O/W emulsion, containing 40 g of a mixed oil phase and 60 g of water.

(*a*) The oil phase consists of 70% paraffin and 30% beeswax. The density of the oil phase is 0.85 g/cm^3 and the density of the aqueous phase is about 1 g/cm^3 at room temperature. The density of the mixture of surfactants for the W/O emulsion is 0.87 g/cm^3. The required HLB values of paraffin and of beeswax for a W/O emulsion are 4.0 and 5.0, respectively.

The amount Q_s in grams of a mixture of sorbitan tristearate (HLB = 2.1) and diethylene glycol monostearate (HLB = 4.7) to obtain a *water-in-oil emulsion* is obtained by the use of equation (15-24), first calculating the RHLB of the oil phase:

$$\text{RHLB} = (4 \times 0.70) + (5 \times 0.30) = 4.3$$

$$Q_s = \frac{6(0.87/1)}{10 - (0.5 \times 4.3)} + \frac{4 \times 40}{1000} = 0.82\ \text{g}$$

Note that for a W/O emulsion we used the density of the internal phase, ρ_{water} [congruent] 1, and the percentage of dispersant, oil, 40%.

(*b*) The RHLB of the oil phase, 70% paraffin and 30% beeswax, for an O/W emulsion is

$$\text{RHLB} = (0.70 \times 10) + (0.3 \times 9) = 9.7$$

and the total amount of surfactant mixture is

$$Q_s + \frac{6(1.05/0.85)}{10 - (0.5 \times 9.7)} + \frac{4 \times 60}{1000} = 1.68\ \text{g}$$

For an O/W emulsion, we used the density ρ of the oil as the internal phase and the percentage of dispersant as the aqueous phase.

For the amount of surfactant mixture in the W/O emulsion we can raise the value Q_s roughly to 1.0 g and for the O/W emulsion to about 2.0 g. We can then calculate the weights of the two emulsifying agents for each emulsion, using the equation

$$\%\ \text{Surfactant of higher HLB} = \frac{\text{RHLB} - \text{HLB low}}{\text{HLB high} - \text{HLB low}} \qquad (15\text{–}25)$$

For the W/O emulsion, the percentage by weight of diethylene glycol monostearate (HLB = 4.7) combined with sorbitan tristearate (HLB = 2.1) is

$$\%\ \text{Diethylene glycol monostearate} = \frac{4.3 - 6.1}{4.7 - 2.1} = 0.85\ \text{g}$$

$$\text{or} \quad 85\%\ \text{of } 1\ \text{g}$$

The fraction or percentage of sorbitan monostearate is therefore 0.15 g, or 15% of the 1 g of mixed emulsifier.

For the O/W emulsion, the percentage by weight of Tween 80 (HLB = 15) combined with diethylene glycol monolaurate (HLB = 6.1) is

$$\%\ \text{Tween 80} = \frac{9.7 - 6.1}{15 - 6.1} = 0.40 \quad \text{or} \quad 40\%$$

The fraction or percentage of diethylene glycol monolaurate is therefore 0.60, or 60%, and 0.40, or 40%, of a 2-g mixture of emulsifier phase = 0.8 g of Tween 80. The remainder, 1.2 g, is the amount of diethylene glycol monolaurate in the 2-g emulsifier phase.

Other scales of HLB have been developed, although none has gained the acceptance afforded the HLB system of Griffin. A titration method and other techniques for determining the hydrophile–lipophile character of surfactants have been proposed.[20,21,22]

Types of Monolayer at Liquid Surfaces

For convenience of discussion, absorbed materials are divided into two groups: those that form “soluble” monolayers and those that form “insoluble” films. The distinction is made on the basis of the solubility of the adsorbate in the liquid subphase. Thus, amyl alcohol may be said to form a soluble monolayer on water, whereas cetyl alcohol would form an insoluble film on the same sublayer. It must be emphasized that this is really only an arbitrary distinction, for the insoluble films are, in effect, the limiting case of those compounds that form soluble monolayers at liquid interfaces. There are, however, important practical reasons why such a classification is made.

It will become apparent in the following sections that three interrelated parameters are important in studying liquid interfaces: (*a*) surface tension, γ; (*b*) surface excess, Γ, which is the amount of amphiphile per unit area of surface in excess of that in the bulk of the liquid; and (*c*) c, the concentration of amphiphile in the bulk of the liquid. As we shall see, it is relatively easy with soluble monolayers to measure surface tension and c to compute the surface excess. With insoluble monolayers, c is taken to be zero, whereas surface tension and surface excess can be obtained directly. Materials that lie on the borderline between soluble and insoluble systems can be studied by either approach, and, invariably, similar results are obtained.

Data obtained from such studies are of increasing biologic and pharmaceutical interest. For example, emulsions are stabilized by the presence of an interfacial film between the oil and water phases. Knowledge of the area occupied by each amphiphilic molecule at the interface is important in achieving optimum stability of the emulsion. The efficiency of wetting and detergent processes depends on the concentration of material adsorbed. Monolayers of adsorbed amphiphiles can be used as in vitro models for biologic membranes that are thought to consist of two monolayers placed back to back with the hydrocarbon chains intermeshed. Consequently, these model systems are finding increasing application for in vitro studies of drug absorption across biologic membranes. Studies of interfacial adsorption also provide valuable information on the dimensions of molecules because it is possible to calculate the areas occupied by amphiphilic molecules.

Soluble Monolayers and the Gibbs Adsorption Equation

The addition of amphiphiles to a liquid system leads to a reduction in surface tension owing to these molecules or ions being adsorbed as a monolayer. Adsorption of amphiphiles in these binary systems was first expressed quantitatively by Gibbs23 in 1878:

$$\Gamma = -\frac{c}{RT}\frac{d\gamma}{dc} \qquad \textbf{(15–26)}$$

Γ is the surface excess or surface concentration, that is, the amount of the amphiphile per unit area of surface in excess of that in the bulk of the liquid, *c* is the concentration of amphiphile in the liquid bulk, *R* is the gas constant, *T* is the absolute temperature, and *dγ*/*dc* is the change in surface tension of the solution with change of bulk concentration of the substance. The derivation of equation **(**15-26**)** is given in the following paragraphs.

Recall that the free energy change of a bulk phase containing two components is written as

$$dG = -S\,dT + V\,dp + \mu_1\,dn_1 + \mu_2\,dn_2$$

Two immiscible bulk phases can be considered to be separated by an interface or “surface phase” in which the contribution to the volume is ignored, and a new energy term, *γ dA* [equation **(**15-2**)**], is introduced to account for the work involved in altering the surface area, *A*. The surface tension, *γ*, is the work done at a constant temperature and pressure per unit increase of surface area. The new work done on the surface phase is equal to the surface free energy increase, *dG*^{s}. Therefore, we can write

$$dG^S = -S^S\,dT + \gamma\,dA + \mu_1^S\,dn_1^S + \mu_2^S\,dn_2^S \qquad \textbf{(15–27)}$$

At equilibrium, the free energy of the entire system is zero under the conditions of constant temperature, pressure, and surface area. Because no matter passes in or out of the system as a whole, the chemical potential of a component *i* is the same in the two bulk phases as it is in the surface phase, *s*:

$$\mu_{i\alpha} = \mu_{i\beta} = \mu_{is} \qquad \textbf{(15–28)}$$

Such a system consisting of two immiscible liquids, water, *α*, and oleic acid, *β*, separated by the surface phase, *s*, is shown in Figure 15-12a. Equation **(**15-27**)** can be integrated at constant temperature and composition to give the surface free energy,

$$G^S = \gamma A + n_1^S\mu_1^S + n_2^S\mu_2^S \qquad \textbf{(15–29)}$$

Because the surface free energy depends only on the state of the system, *dG*^{s} is an exact differential and can be obtained by general differentiation of equation **(**15-29**)** under the condition of variable composition,

$$dG^S = \gamma\,dA + A\,d\gamma + n_1^S\,d\mu_1^S + n_2^S\,\mu_2^S + \mu_1^S\,dn_1^S + \mu_2^S\,dn_2^S \qquad \textbf{(15–30)}$$

Comparing this result with equation **(**15-27**)** shows that

$$A\,d\gamma + S^S\,dT + n_1^S\,d\mu_1^S + n_2^S\,d\mu_2^S = 0 \qquad \textbf{(15–31)}$$

and at constant temperature,

$$A\,d\gamma + n_1^S\,d\mu_1^S + n_2^S\,d\mu_2^S = 0 \qquad \textbf{(15–32)}$$

When equation (15-32) is divided through by the surface area A, and n_1^s/A and n_2^s/A are given the symbols Γ_1 and Γ_2, respectively, we obtain

$$d\gamma + \Gamma_1 \, d\mu_1^S + \Gamma_2 \, d\mu_2^S = 0 \qquad (15\text{–}33)$$

As expressed by equation (15-33), the chemical potentials of the components in the surface are equal to those in the bulk phases, provided that the system is in equilibrium at constant temperature, pressure, and surface area.

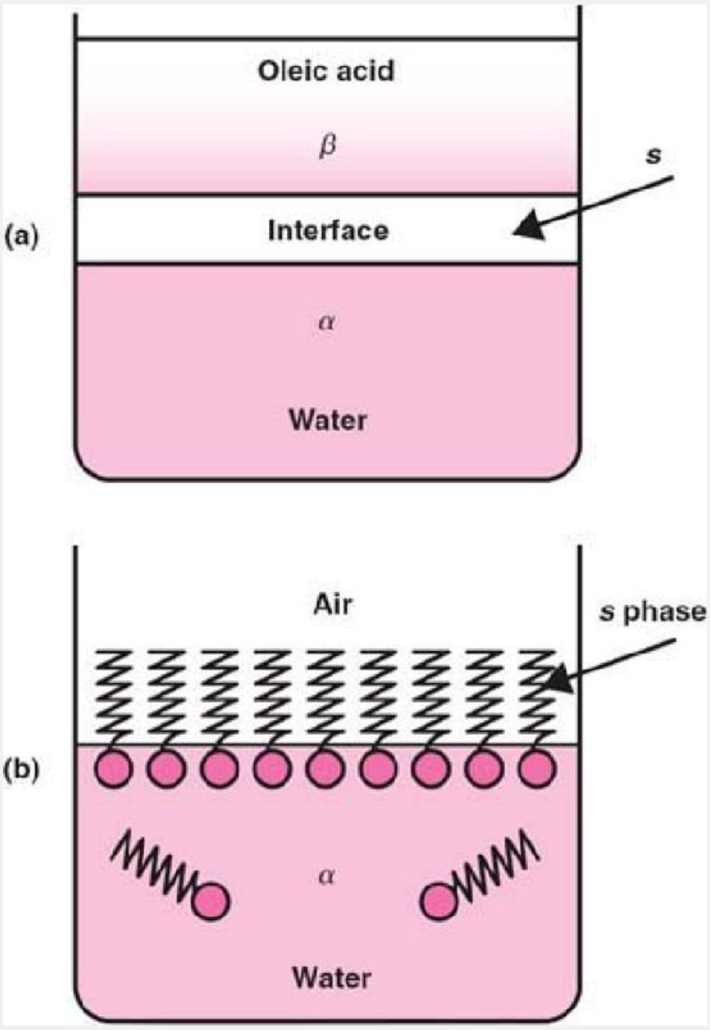

Fig. 15-12. A system consisting of oleic acid and water. (*a*) Graphic description of the two bulk phases, *α* and *β*, and the interface, *s*. (*b*) Condition where only the *α* phase and the surface or *s* phase need to be considered.

Now consider a single-phase solution of oleic acid (solute or component 2) in water (solvent or component 1) as shown in Figure 15-12b. Under these circumstances, it is possible to drop the superscripts on the chemical potentials and write

$$d\gamma + \Gamma_1 \, d\mu_1 + \Gamma_2 \, d\mu_2 = 0 \qquad (15\text{–}34)$$

where Γ_1 and Γ_2 are the number of moles of the components per unit area in the surface and μ_1 and μ_2 are the chemical potentials of the two components in the solution.

It is possible to make an arbitrary choice of the surface, and we do so in a manner that makes Γ_1 equal to zero, that is, we arrange the boundary so that none of the solvent is present in the surface (Fig. 15-12b). Then, equation (15-34) becomes

$$d\gamma + \Gamma_2 \, d\mu_2 = 0 \qquad (15\text{–}35)$$

and

$$\Gamma_2 = -\left(\frac{\partial \gamma}{\partial \mu_2}\right)_T \qquad (15\text{–}36)$$

The chemical potential of the solute can be expressed in terms of the activity using the equation

$$\mu_2 = \mu^\circ + RT \ln \alpha_2$$

By differentiating at constant temperature, one obtains

$$\partial \mu_2 = RT\partial \quad \ln \quad \alpha_2 \qquad (15\text{–}37)$$

Substituting this value in equation **(**15-36**)** produces the result

$$\Gamma_2 = -\frac{1}{RT}\left(\frac{\partial \gamma}{\partial \ln \alpha_2}\right)_T \qquad (15\text{–}38)$$

From differential calculus, if $y = \ln a_2$, then $d \ln a_2 = da_2/a_2$. Substituting this result in equation **(**15-38**)** results in the *Gibbs adsorption equation*,

$$\Gamma_2 = -\frac{\alpha_2}{RT}\left(\frac{\partial \gamma}{\partial \alpha_2}\right)_T \qquad (15\text{–}39)$$

This is equation **(**15-26**)**, which was given in terms of concentration,*c*, instead of activity. If the solution is dilute, a_2 can be replaced by *c*without introducing a significant error.

When the surface tension, γ, of a surfactant is plotted against the logarithm of the surfactant activity or concentration, log c_2, the plot takes on the shape shown in Figure 15-13. The initial curved segment A–B is followed by a linear segment, B–C, along which there is a sharp decrease in surface tension as log c_2 increases. The point C corresponds to the critical micelle concentration (CMC), the concentration at which micelles form in the solution. Beyond the CMC, the line becomes horizontal because further additions of surfactant are no longer being accompanied by a decrease in surface tension. Along the linear segment B–C, the surface excess Γ is constant because from equation **(**15-38**)**, replacing activity with concentration, we find

$$\Gamma_2 = -\frac{1}{RT}\left(\frac{\partial \gamma}{\partial \ln c_2}\right)_T \qquad (15\text{–}40)$$

The slope $\partial\gamma/\partial \ln c_2$ reaches a limiting value and remains constant. Saturation adsorption of the surfactant has been reached at point B; that is, Γ_2 does not increase further as the bulk concentration increases. However, the surface tension decreases greatly until point C is reached. Within the segment B–C of the curve, the surfactant molecules are closely packed at the surface and the surface area occupied per molecule is constant. Both the surface excess Γ_2 and the area per surfactant molecule can be calculated using equation **(**15-40**)**.

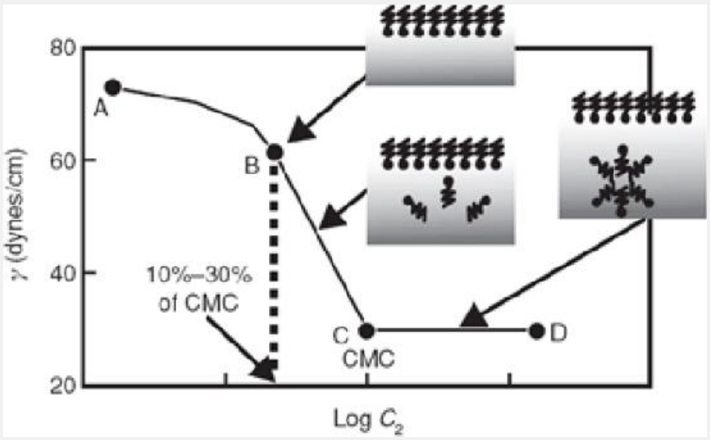

Fig. 15-13. Decrease in the surface tension of water when a strait-chain amphiphile is added. Key: CMC = critical micelle concentration. (Replotted from H. Schott, J. Pharm. Sci. **69,** 852, 1980.)

Example 15-10

Calculation of Area per Molecule of a Surfactant

The limiting slope of a plot of γ versus ln c_2 for a nonionic surfactant, $C_{12}H_{25}O(CH_2CH_2O)_{12}H_2$, is $\partial\gamma/\partial \ln c_2 = -5.2937$ dynes/cm at 23.0°C. Calculate Γ_2 and the area per molecule of this surfactant.

From the Gibbs adsorption equation (15-40),

$$\Gamma_2 = \left(\frac{1}{8.3143 \times 10^7 \text{ ergs/deg mole} \times 296.15 \text{ K}}\right)(-5.2937 \text{ dyne/cm})$$

$$\Gamma_2 = 2.15 \times 10^{-10} \text{ mole/cm}^2$$

The surface excess, 2.15×10^{-10} mole/cm^2, is multiplied by 6.0221×10^{23} mole^{-1}, Avogadro's number, to obtain molecules/cm^2. The reciprocal then gives the area per molecule:

$$\text{Area/molecule} = \frac{1}{6.0221 \times 10^{23} \text{ molecule/mole} \times 2.15 \times 10^{-10} \text{ mole/cm}^2}$$

$$= 7.72 \times 10^{-15} \text{cm}^2\text{/molecule} = 77 \text{ Å}^2\text{/molecule}$$

The validity of the Gibbs equation has been verified experimentally. One of the more ingenious methods is due to McBain and Swain,24who literally fired a small microtome blade across a liquid surface so as to collect the surface layer. Analysis of the liquid scooped up and collected by the speeding blade agreed closely with that predicted by the Gibbs equation. Radioactive techniques using weak beta emitters also have been successfully used.25

Insoluble Monolayers and the Film Balance

Insoluble monolayers have a fascinating history that goes back to before the American Revolution. During a voyage to England in 1757, Benjamin Franklin observed, as had seamen for centuries before him, that when cooking grease was thrown from the ship's galley onto the water, the waves were calmed by the film that formed on the surface of the sea. In 1765, Franklin followed up this observation with an experiment on a half-acre pond in England and found that the application of 1 teaspoonful of oil was just sufficient to cover the pond and calm the waves. In 1899, Lord Rayleigh showed that when small amounts of certain slightly soluble oils were placed on a clean surface of water contained in a trough, they spread to form a layer one molecule thick (monomolecular layer). Prior to Rayleigh's work, a woman named Agnes Pockels, from Lower Saxony, Germany, who had no formal scientific training, developed a “film balance” for studying insoluble monolayers. She carried out a series of experiments, which she summarized in a letter to Lord Rayleigh in January 1881. In fact, she invented the film balance in 1883, more than 30 years before Langmuir, whose name is normally associated with this type of apparatus. These and other early contributions in the area of surface phenomena are described in a series of papers by Giles and Forrester.26

Knowing the area of the film and the volume of the spreading liquid, it should be possible to compute the thickness of such films. The film thickness is equal to the length of the molecules standing in a vertical position on the surface when the molecules are packed in closest arrangement. Furthermore, if the molecular weight and the density of the spreading oil are known, the cross-sectional area available to the molecules should be easily computed.

Example 15-11

Calculation of the Length and the Cross-Sectional Area of a Fatty Acid Molecule

We noted that Benjamin Franklin placed 1 teaspoonful (~5 cm^3) of a fatty acid “oil” on a half-acre (~2×10^7 cm^2) pond. Assume that the acid, having a molecular weight of 300 and a density of 0.90 g/cm^3, was just sufficient to form a condensed monomolecular film over the entire surface. What was the length and the cross-sectional area of the fatty acid molecule?

(*a*) The thickness of oil on the pond is approximately equal to the length of the vertically oriented fatty acid molecule:

$$\frac{5\ \text{cm}}{2 \times 10^7\ \text{cm}^2} = 25 \times 10^{-8}\ \text{cm} = 25\ \text{Å}$$

(*b*)

$$\begin{aligned} 5\ \text{cm}^3 \times 0.9\ \text{g/cm}^3 &= 4.5\ \text{g} \\ \frac{4.5\ \text{g}}{300\ \text{g/mole}} &= 0.015\ \text{mole} \\ 0.015\ \text{mole} \times 10^{23}\ \text{molecules/mole} &= 9 \times 10^{21}\ \text{molecules} \\ \frac{2 \times 10^7\ (\text{pond area})}{9 \times 10^{21}\ \text{molecules}} &= 22 \times 10^{16}\ \text{cm}^2/\text{molecule} \\ &= 22\ \text{Å}^2/\text{molecule} \end{aligned}$$

We can readily see from this example that the area of cross section per molecule is given by

$$\text{Cross-sectional area/molecule} = \frac{MS}{V_\rho N} \qquad (15\text{–}41)$$

where *M* is molecular weight of the spreading liquid, *S* is the surface area covered by the film, *V* is the volume of the spreading liquid, ρ is its density, and *N* is Avogadro's number.

Langmuir, Adam, Harkins, and others made quantitative studies of the properties of films that are spread over a clear surface of the substrate liquid (usually water) contained in a trough. The film can be compressed against a horizontal float by means of a movable barrier. The force exerted on the float is measured by a torsion-wire arrangement similar to that employed in the ring tensiometer. This apparatus is called a *film balance*. The compressive force per unit area on the float is known as the *surface* or *film pressure*, π; it is the difference in surface tension between the pure substrate, γ_0, and that with a film spread on it, γ, and is written as

$$\pi = \gamma_0 - \gamma \qquad (15\text{–}42)$$

Surface tension (interfacial tension) is the resistance of the surface (interface) to an expansion in area, and film pressure, π, is the lowering of this resistance to expansion, as expressed quantitatively in equation **(**15-42**)**. Schott27 stated that the film pressure, π, is an expansion pressure exerted on the monolayer that opposes the surface tension, γ_0, or contraction of the clean (water) surface. The surface-active molecules of the monolayer are thought to insert themselves into the surface of the water molecules of a film balance to reduce the resistance of the water surface to expansion. The presence of the surfactant molecules increases the ease of expansion, presumably by breaking or interfering with hydrogen bonding, van der Waals interaction, and other cohesive forces among the water molecules. These attractive forces produce the "springlike" action in the water surface, as measured by the surface tension, γ_0, and the introduction of surfactant molecules into the clean water surface reduces the springiness of the interacting water molecules and decreases the surface tension γ_0 to $\gamma_0 - \gamma$ or π [equation (**15–42**)].

In carrying out an experiment with the film balance, the substance under study is dissolved in a volatile solvent (e.g., hexane) and is placed on the surface of the substrate, which has previously been swept clean by means of a paraffined or Teflon strip. The liquid spreads as a film, and the volatile solvent is permitted to evaporate. A cross-sectional view of the interface after spreading is shown inFigure 15-14. The movable barrier is then moved to various positions in the direction of the float. The area of the trough available to the film at each position is measured, and the corresponding film pressure is read from the torsion dial. The film pressure is then plotted against the area of the film or, more conveniently, against the cross-sectional area per molecule, A^2 [see Example 15-11 and equation **(**15-41**)** for computing the molecule's cross-sectional area from the area of the film]. The results for stearic acid and lecithin are shown in Figure 15-15.

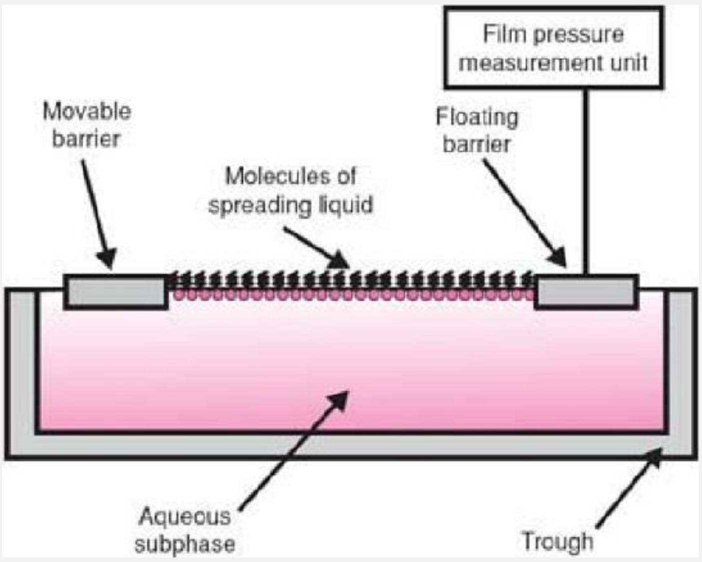

Fig. 15-14. Cross-sectional view of a spreading liquid on the surface of a film balance.

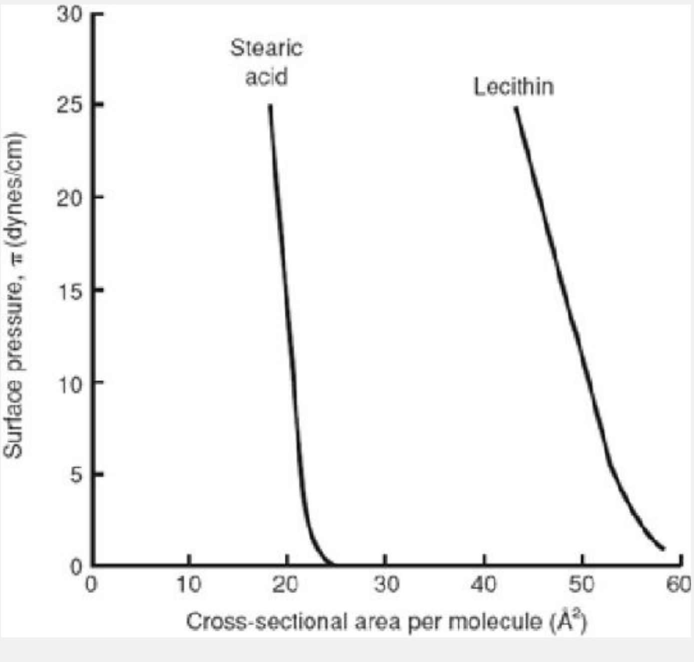

Fig. 15-15. Surface film pressure, π, for stearic acid and lecithin plotted as a function of cross-sectional area per molecule.

Frequently, a variety of phase changes are observed when an insoluble film is spread at an interface and then compressed. A representation of what can occur with a straight-chain saturated aliphatic compound at the air–water interface is shown in Figure 15-16. When the film is spread over an area greater than 50 to 60 Å2/molecule (region G), it exerts little pressure on the floating barrier. The film acts like a gas in two dimensions. As the film begins to be compressed (region L_1 - G), a liquid phase, L_1, appears that coexists in equilibrium with the gas phase. This occurs at a low surface pressure (e.g., 0.2 dyne/cm or less). The liquid expanded state (region L_1) can be thought of as a bulk liquid state, but in two dimensions. Further compression of the film often leads to the appearance of an intermediate phase (region I) and then a less compressible condensed liquid state, region L_2. This then gives way to the least compressible state, region S, where the film can be regarded as being in a two-dimensional solid state. In these latter stages of film compression, the film or surface pressure, $\pi = \gamma_0 - \gamma_1$, rises rapidly as the curve passes through the regions L_2 and S inFigure 15-16. This increase in π with compression of the surfactant film results from surface-active molecules being forcibly inserted and crowded into the surface. This process opposes the natural tendency of the water surface to contract, and the surface tension decreases from γ_0 to γ. Finally, the molecules slip over one another, and the film breaks when it is greatly compressed.

The regions marked along the plot in Figure 15-16 can be represented schematically in terms of the positioning of the spreading molecules in the surface, as shown in Figure 15-17. In region G of Figure 15-16, the molecules in the monolayer lie on the surface with great distances between them, as in a three-dimensional gas. In the part of the curve marked L_1 and L_2 in Figure 15-16, the molecules are forced closer together, and, as shown schematically in Figure 15-17b, are beginning to stand erect and interact with one another, analogous to a three-dimensional liquid. In region S of Figure 15-16, the spreading molecules are held together by strong forces; this condition, analogous to the solid state in three-dimensional chemistry, shows little compressibility relative to that of a gas or a liquid. The S state is shown schematically in Figure 15-17c, where the molecules on the surface of the film balance are compressed together as far as possible. Further compression of the film by a movement from right to left on the horizontal axis of the graph in Figure 15-14, that is, a movement from left to right of the movable barrier, brings about a collapse of the monolayer film, one part sliding over the other, as depicted in Figure 15-16.

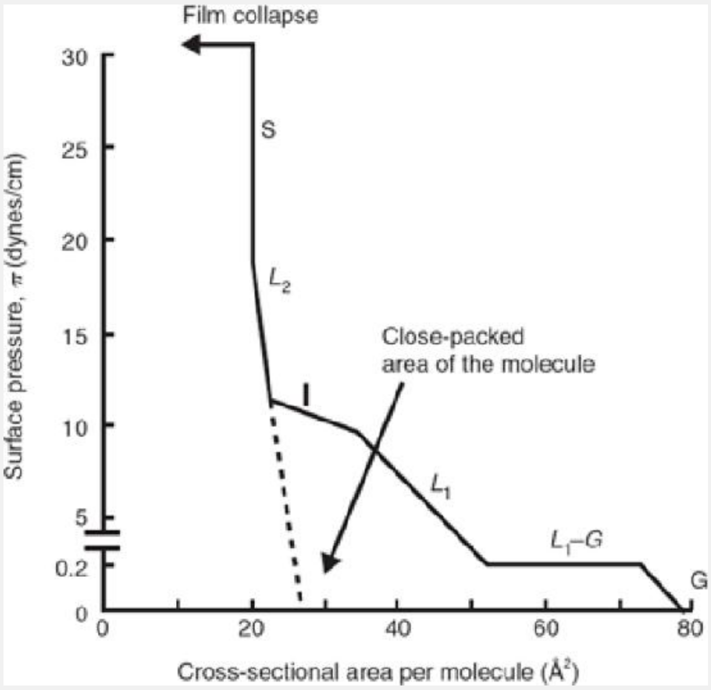

Fig. 15-16. Phase changes that occur when a liquid film is spread at an interface and then compressed. Key: G = two-dimensional gas; L_1 - G = liquid phase in equilibrium with two-dimensional gas; L_1 = liquid expanded or two-dimensional bulk liquid state; I = intermediate state; L_2 = condensed liquid state; S = two-dimensional solid state. When compressed by a force greater than required to form a solid surface, the film collapses, as shown by the arrow at the top of the figure. (Replotted from P. C. Heimenz, *Principles of Colloid and Surface Chemistry*, 2nd Ed., Marcel Dekker, New York, 1986, p. 364.)

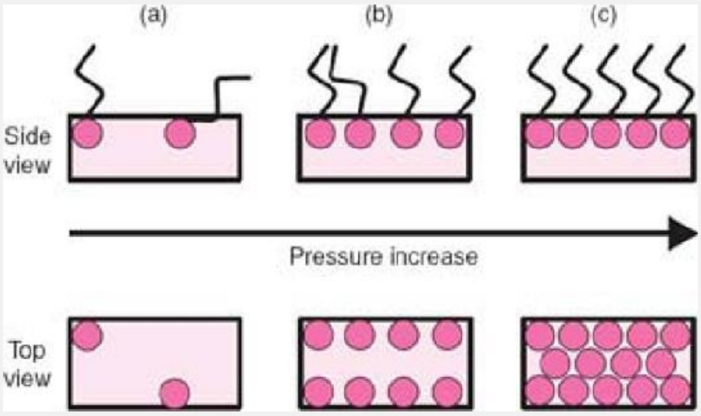

Fig. 15-17. Insoluble monolayers. Insoluble monolayer films exhibit characteristics that can be equated to those of the solid, liquid, and gaseous states of matter. (*a*) Gaseous film. Molecules are apart and have significant surface mobility. The molecules essentially act independently. (*b*) Liquid film. Monolayer is coherent and relatively densely packed but is still compressible. (*c*) Condensed film. Monolayer is coherent, rigid, essentially incompressible, and densely packed, with high surface viscosity. The molecules have little mobility and are oriented perpendicular to the surface.

Table 15-7 Dimensions of Organic Molecules Determined by Means of the Film Balance

Substance	Formula	Length of Molecule (Å)	Cross-Sectional Area ($Å^2$)
Stearic acid	$C_{17}H_{35}COOH$	25	22
Tristearin	$(C_{128}H_{35}O_2)_3C_3H_5$	25	66
Cetyl alcohol	$C_{16}H_{33}OH$	22	21
Myricyl alcohol	$C_{30}H_{61}OH$	41	27

The cross-sectional area per molecule of the close-packed film at zero surface pressure is obtained by extrapolating the linear portion of the curve to the horizontal axis, as seen in Figure 15-16. The values for some organic molecules determined in this way by Langmuir[28] are listed in Table 15-7. It is seen that myricyl alcohol, with 30 carbons in the chain, has a length almost twice that of the other molecules. Its cross-sectional area at the interface is not markedly different from that of other single-chain molecules, however, confirming that it is the cross-sectional area of the alkyl chain, rather than the length, that is being measured. Tristearin, with three fatty acid chains, has a cross-sectional area about three times that of the molecules with only one aliphatic chain.

The electric potential and viscosity of monomolecular films can be studied by means of the film balance, and the molecular weight of high polymers such as proteins can be estimated by its use. The film-balance technique also has considerable significance in the study of biologic systems. Because some protein molecules unfold from a spherical configuration into a flat film when spread on the surface of the film trough, the relationship between unfolding and biologic activity can be studied. The sizes and shapes of molecules of steroids, hormones, and enzymes and their interaction with drugs at interfaces can also be investigated by means of the film balance. The interaction between insulin injected under the surface layer and several lipids spread at constant surface pressure on a film balance was studied by Schwinke et al.[29] The film balance and its applications are discussed in the books of Adam,[30] Harkins,[31] Sobotka,[32] and Gaines.[33]

Mention has been made of the fact that materials forming an insoluble monolayer can be thought of as being in the gaseous, liquid, or solid state, depending on the degree of compression to which the film is subjected. Thus, the surface pressure for molecules in the gaseous state at an interface is comparable to the pressure, *P*, that molecules in three-dimensional gaseous systems exert on the walls of their containers. Just as the equation of state for an ideal gas in three dimensions is *PV* = *nRT* (see the ideal gas law in States of Matter), that for a monolayer is

$$\pi A = nRT \tag{15–43}$$

where π is the surface pressure in dynes/cm and *A* is the area that each mole of amphiphile occupies at the interface.

Equation **(**15-43**)**, the two-dimensional ideal gas law, can be derived as follows. When the concentration of amphiphile at the interface is small, solute–solute interactions are unimportant. Under these conditions, surface tension decreases in a linear fashion with concentration. We can therefore write

$$\gamma = bc + \gamma_0 \tag{15–44}$$

where γ_0 is the surface tension of the pure substrate, γ is the surface tension produced by the addition of *c* moles/liter of adsorbate, and *b*is the slope of the line. Because the slope of such a plot is negative, and because $\pi = \gamma_0 - \gamma$, equation **(**15-44**)** can be rewritten as

$$\pi = -bc \tag{15–45}$$

The Gibbs adsorption equation **(**15-26**)** can be expressed in the following form:

$$-(d\gamma/dc) - b = \Gamma RT/c \qquad (15\text{–}46)$$

because *dγ/dc* is the slope of the line.

Substituting for equation **(**15-45**)** in equation **(**15-46**)** and cancelling*c*, which is common to both sides, we obtain

$$\pi = \Gamma RT \qquad (15\text{–}47)$$

Surface excess has the dimensions of moles/cm^2 and can be represented by *n/A*, where *n* is the number of moles and *A* is the area in cm^2. Thus,

$$\pi = nRT/A$$

or

$$\pi A = nRT$$

which is equation **(**15-43**)**.

As with the three-dimensional gas law, equation **(**15-43**)** can be used to compute the molecular weights of materials adsorbed as gaseous films at an interface. Nonideal behavior also occurs, and plots of *πA* versus π for monolayers give results comparable to those in three-dimensional systems when *PV* is plotted against *P*. Equations similar to van der Waal's equation (see van der Waals Equation for Real Gases in States of Matter) for nonideal behavior have been developed.

The relation between the Gibbs adsorption equation and equation**(**15-43**)** emphasizes the point made earlier that the distinction between soluble and insoluble films is an arbitrary one, made on the basis of the experimental techniques used rather than any fundamental differences in physical properties.

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The variation of the surface pressure, π, with temperature at the several “phase changes” observed in the two-dimensional isotherm*π*-area (see Fig. 15-16) can be analyzed by a relationship analogous to the Clapeyron equation:

$$\frac{d\pi}{dT} = \frac{\Delta H}{T(A_1 - A_2)} \qquad (15\text{–}48)$$

where A_1 and A_2 are the molar areas (cm^2/mole) of the two phases and *T* and Δ*H* are, respectively, the temperature and enthalpy for the phase change.33 Note that π, Δ*H*, and (A_1 - A_2) are the two-dimensional equivalents of pressure, enthalpy, and change of volume, respectively, in the Clapeyron equation.

Example 15-12

Calculation of Enthalpy Change

Consideration of monolayers of insoluble amphiphilic compounds with a polymerizable group serves to investigate the polymerization behavior at the gas–water interface. The π–*A* isotherms resulting from film balance experiments with*n*-hexadecyl acrylate monolayers in the temperature range 13°C to 28°C showed two breaks corresponding to phase transitions (changes in state).

Compute Δ*H*, the enthalpy change of transition from the condensed liquid state, L_2, to the liquid expanded state, L_1. The areas per molecule at L_1 and L_2 are 0.357 and 0.265 nm^2/molecule, respectively. The change of surface pressure with temperature, *dπ*/*dt*, is 0.91 mN/mK, and the temperature of transition is 24.2°C.34

From equation (15-48),

$$\begin{aligned}
\Delta H &= T(A_1 - A_2)\frac{d\pi}{dT}\\
\Delta H &= 297.2\ \mathrm{K}\,(0.357 - 0.265)\\
&\qquad \times 10^{-18}\ \mathrm{m^2/molecule} \times 0.91 \times 10^{-3}\,\frac{\mathrm{N}}{\mathrm{mK}}\\
&= 2.49 \times 10^{-20}\ \mathrm{joule/molecule}\\
&\qquad 2.49 \times 10^{-20} \times 6.022 \times 10^{23}\\
&= 15.995\ \mathrm{joule/mole} \approx 15\ \mathrm{kJ/mole}
\end{aligned}$$

Adsorption at Solid Interfaces

Adsorption of material at solid interfaces can take place from either an adjacent liquid or gas phase. The study of adsorption of gases arises in such diverse applications as the removal of objectionable odors from rooms and food, the operation of gas masks, and the measurement of the dimensions of particles in a powder. The principles of solid–liquid adsorption are used in decolorizing solutions, adsorption chromatography, detergency, and wetting.

In many ways, the adsorption of materials from a gas or a liquid onto a solid surface is similar to that discussed for liquid surfaces. Thus, adsorption of this type can be considered as an attempt to reduce the surface free energy of the solid. The surface tensions of solids are invariably more difficult to obtain, however, than those of liquids. In addition, the solid interface is immobile in comparison to the turbulent liquid interface. The average lifetime of a molecule at the water–gas interface is about 1 μ sec, whereas an atom in the surface of a nonvolatile metallic solid may have an average lifetime of 10^{37} sec.35 Frequently, the surface of a solid may not be homogeneous, in contrast to liquid interfaces.

The Solid–Gas Interface

The degree of adsorption of a gas by a solid depends on the chemical nature of the *adsorbent* (the material used to adsorb the gas) and the *adsorbate* (the substance being adsorbed), the surface area of the adsorbent, the temperature, and the partial pressure of the adsorbed gas. The types of adsorption are generally recognized as physical or van der Waals adsorption and chemical adsorption or chemisorption. *Physical adsorption*, associated with van der Waals forces, is reversible, the removal of the adsorbate from the adsorbent being known as *desorption*. A physically adsorbed gas can be desorbed from a solid by increasing the temperature and reducing the pressure. *Chemisorption*, in which the adsorbate is attached to the adsorbent by primary chemical bonds, is irreversible unless the bonds are broken.

The relationship between the amount of gas physically adsorbed on a solid and the equilibrium pressure or concentration at constant temperature yields an *adsorption isotherm* when plotted as shown in Figure 15-18. The term *isotherm* refers to a plot at constant temperature. The number of moles, grams, or milliliters, *x*, of gas adsorbed on, *m*, grams of adsorbent at standard temperature and pressure is plotted on the vertical axis against the equilibrium pressure of the gas in mm Hg on the horizontal axis, as seen inFigure 15-18a.

One method of obtaining adsorption data is by the use of an apparatus similar to that shown in Figure 15-19, which consists essentially of a balance contained within a vacuum system. The solid, previously degassed, is placed on the pan, and known amounts of gas are allowed to enter. The increase in weight at the corresponding equilibrium gas pressures is recorded. This can be achieved by noting the extension of a calibrated quartz spring used to suspend the pan containing the sample. The data are then used to construct an isotherm on the basis of one or more of the following equations.

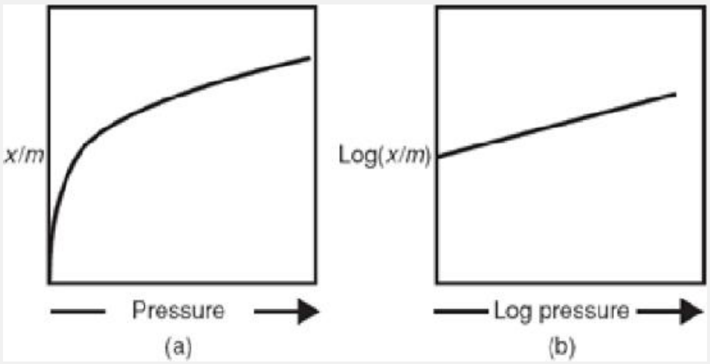


Fig. 15-18. Adsorption isotherms for a gas on a solid. (*a*) Amount, *x*, of gas adsorbed per unit mass, *m*, of adsorbent plotted against the equilibrium pressure. (*b*) Log of the amount of gas adsorbed per unit mass of adsorbent plotted against the log of the pressure.

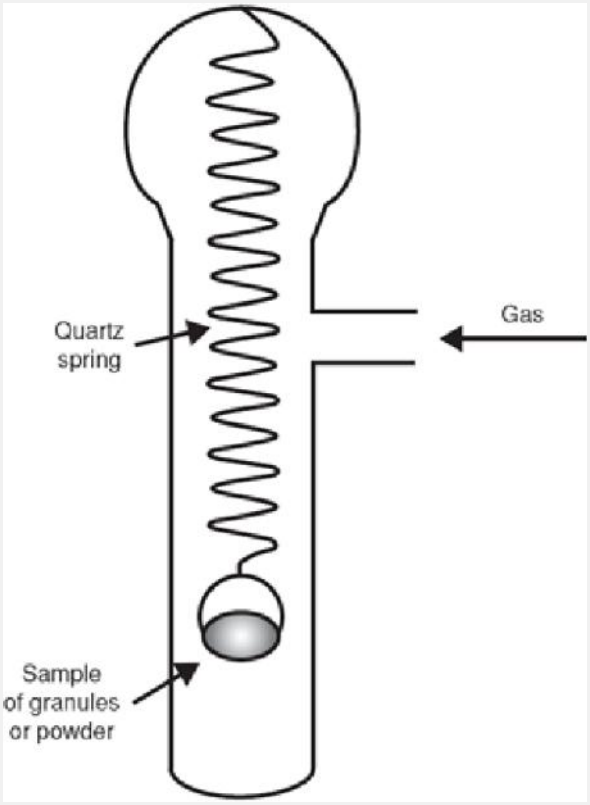


Fig. 15-19. Schematic of apparatus used to measure the absorption of gases on solids.

Freundlich36 suggested a relationship, the *Freundlich isotherm*,

$$y = \frac{x}{m} = kp^{1/n} \qquad (15\text{–}49)$$

where *y* is the mass of gas, *x*, adsorbed per unit mass, *m*, of adsorbent, and *k* and *n* are constants that can be evaluated from the results of the experiment. The equation is handled more conveniently when written in the logarithmic form,

$$\log \frac{x}{m} = \log k + \frac{1}{n} \log p \qquad (15\text{–}50)$$

which yields a straight line when plotted as seen in Figure 15-18b. The constant, log *k*, is the intercept on the ordinate, and 1/*n* is the slope of the line.

Langmuir37 developed an equation based on the theory that the molecules or atoms of gas are adsorbed on active sites of the solid to form a layer one molecule thick (monolayer). The fraction of centers occupied by gas molecules at pressure *p* is represented byθ, and the fraction of sites not occupied is 1 - θ. The rate, r_1, of adsorption or condensation of gas molecules on the surface is proportional to the unoccupied spots, 1 - θ, and to the pressure, *p*, or

$$r_1 = k_1(1 - \theta)p \qquad (15\text{–}51)$$

The rate, r_2, of evaporation of molecules bound on the surface is proportional to the fraction of surface occupied, θ, or

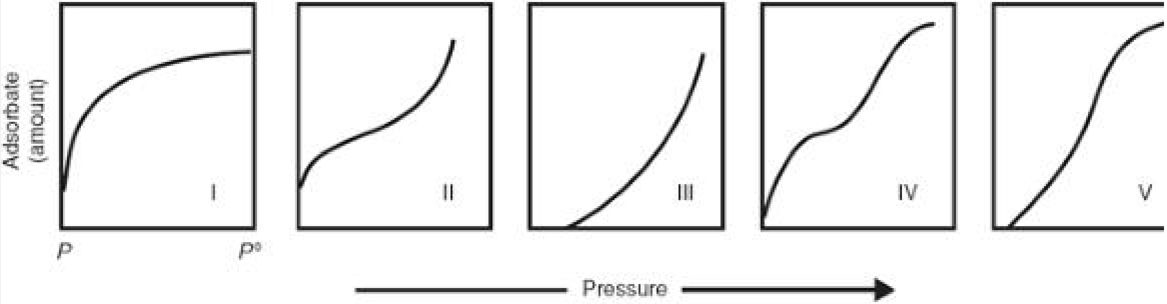


Fig. 15-20. Various types of adsorption isotherms.

$$r_2 = k_2\theta \qquad (15\text{–}52)$$

and at equilibrium $r_1 = r_2$, or

$$k_1(1-\theta) = k_2\theta \qquad (15\text{–}53)$$

By rearrangement, we obtain

$$\theta = \frac{k_1 p}{k_2 + k_1 p} = \frac{(k_1/k_2)p}{1 + (k_1/k_2)p} \qquad (15\text{–}54)$$

We can replace k_1/k_2 by b and θ by y/y_m, where y is the mass of gas adsorbed per gram of adsorbent at pressure p and at constant temperature and y_m is the mass of gas that 1 g of the adsorbent can adsorb when the monolayer is complete. Inserting these terms into equation **(**15-54**)** produces the formula

$$y = \frac{y_m b p}{1 + bp} \qquad (15\text{–}55)$$

which is known as the *Langmuir isotherm*. By inverting equation **(**15-55**)** and multiplying through by p, we can write this for plotting as

$$\frac{p}{y} = \frac{1}{b y_m} + \frac{p}{y_m} \qquad (15\text{–}56)$$

A plot of p/y against p should yield a straight line, and y_m and b can be obtained from the slope and intercept.

Equations **(**15-49**)**, **(**15-50**)**, **(**15-55**)**, and **(**15-56**)** are adequate for the description of curves only of the type shown in Figure 15-18a. This is known as the type I isotherm. Extensive experimentation, however, has shown that there are four other types of isotherms, as seen inFigure 15-20, that are not described by these equations. Type II isotherms are sigmoidal in shape and occur when gases undergo physical adsorption onto nonporous solids to form a monolayer followed

by multilayer formation. The first inflection point represents the formation of a monolayer; the continued adsorption with increasing pressure indicates subsequent multilayer formation. Type II isotherms are best described by an expression derived by Brunauer, Emmett, and Teller23 and termed for convenience the *BET equation*. This equation can be written as

$$\frac{p}{y(p_0 - p)} = \frac{1}{y_m b} + \frac{b-1}{y_m b}\frac{p}{p_0} \qquad (15\text{–}57)$$

where p is the pressure of the adsorbate in mm Hg at which the mass, y, of vapor per gram of adsorbent is adsorbed, p_0 is the vapor pressure when the adsorbent is saturated with adsorbate vapor, $y_m$is the quantity of vapor adsorbed per unit mass of adsorbent when the surface is covered with a monomolecular layer, and b is a constant proportional to the difference between the heat of adsorption of the gas in the first layer and the latent heat of condensation of successive layers. The saturated vapor pressure,p_0, is obtained by bringing excess adsorbate in contact with the adsorbent. For the case of simple monolayer adsorption, the BET equation reduces to the Langmuir isotherm.

Isotherms of the shape shown as IV in Figure 15-20 are typical of adsorption onto porous solids. The first point of inflection, when extrapolated to zero pressure, again represents the amount of gas required to form a monolayer on the surface of the solid. Multilayer formation and condensation within the pores of the solid are thought to be responsible for the further adsorption shown, which reaches a limiting value before the saturation vapor pressure, p_0, is attained. Type III and type V isotherms are produced in a relatively few instances in which the heat of adsorption of the gas in the first layer is *less* than the latent heat of condensation of successive layers. As with type IV isotherms, those of type V show capillary condensation, and adsorption reaches a limiting value before p_0 is attained. The type II isotherm results when b is greater than 2.0 and type III when $b$is less than 2.0 in the BET expression **(**15-57**)**. Types IV and V frequently involve hysteresis and appear as shown in Figures 15-21and 15-22, respectively.

The total surface area of the solid can be determined from those isotherms in which formation of a monolayer can be detected, that is, Types I, II, and IV. This information is obtained by multiplying the total number of molecules in the volume of gas adsorbed by the cross-sectional area of each molecule. The surface area per unit weight of adsorbent, known as the *specific surface*, is important in pharmacy because the dissolution rates of drug particles depend, in part, on their surface area.

The Solid–Liquid Interface

Drugs such as dyes, alkaloids, fatty acids, and even inorganic acids and bases can be absorbed from solution onto solids such as charcoal and alumina. The adsorption of solute molecules from solution can be treated in a manner analogous to the adsorption of molecules at the solid–gas interface. Isotherms that fit one or more of the equations mentioned previously can be obtained by substituting solute concentration for the vapor pressure term used for solid–gas systems. For example, the adsorption of strychnine, atropine, and quinine from aqueous solutions by six different clays38 was capable of being expressed by the Langmuir equation in the form

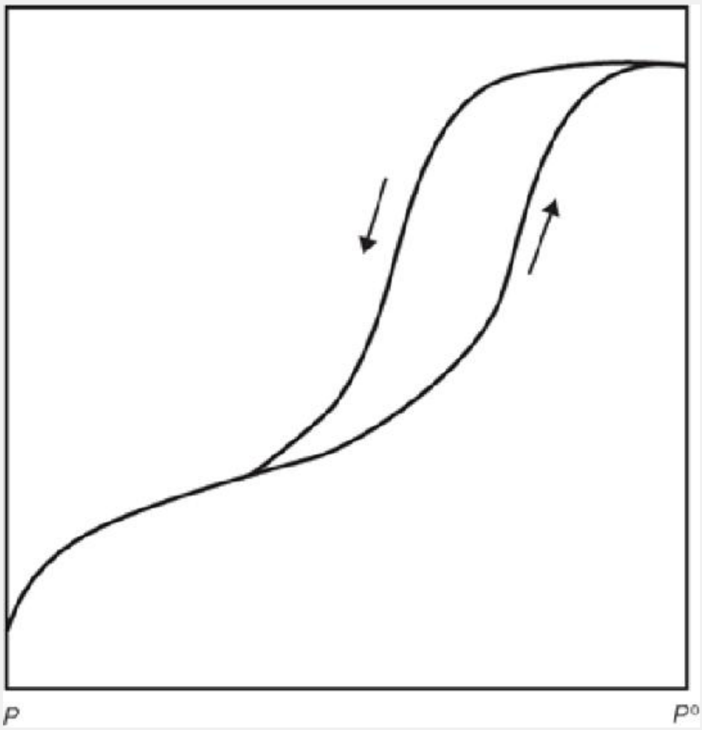


Fig. 15-21. Type IV isotherm showing hysteresis.

$$\frac{c}{y} = \frac{1}{by_{\mathrm{m}}} + \frac{c}{y_{\mathrm{m}}} \qquad \text{(15–58)}$$

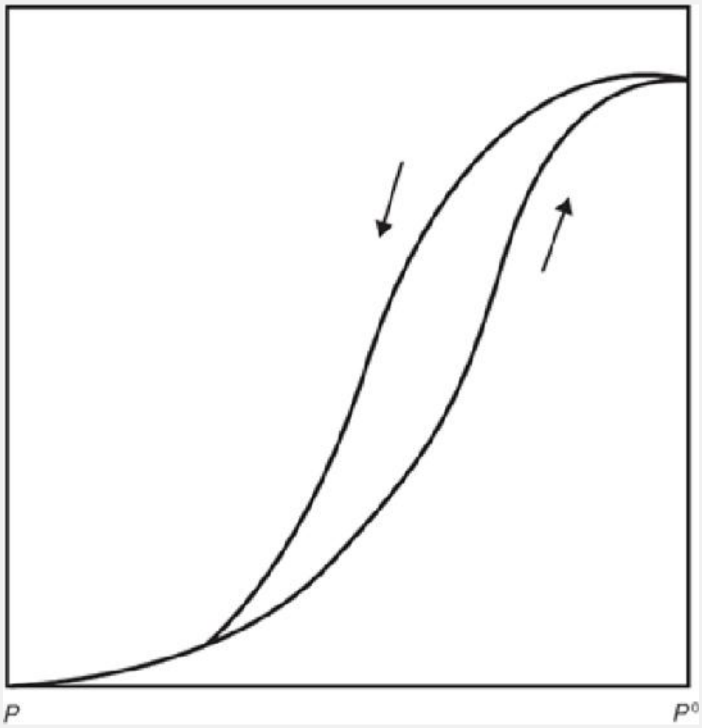


Fig. 15-22. Type V isotherm showing hysteresis.

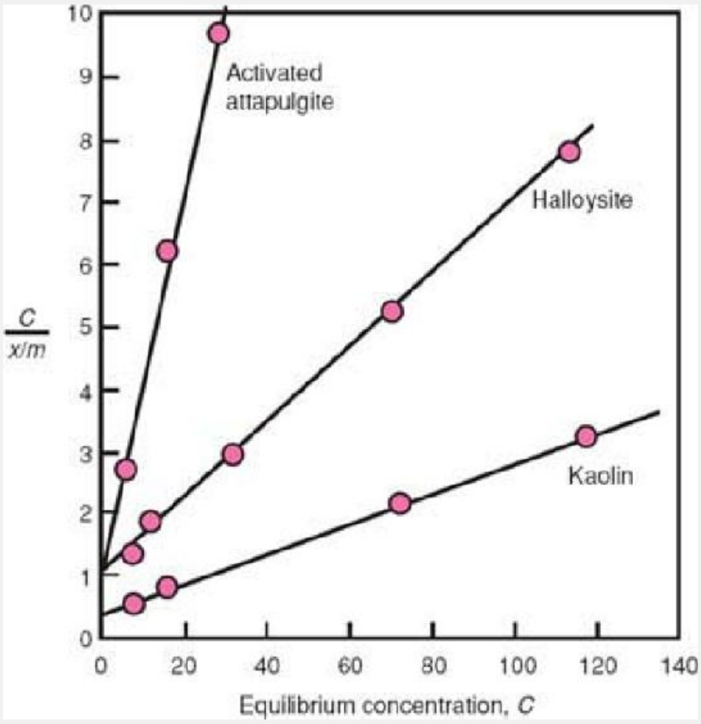


Fig. 15-23. Adsorption of strychnine on various clays. (Modified from M. Barr and S. Arnista, J. Am. Pharm. Assoc. Sci. Ed. **46,** 486–489, 1957.)

where *c* is the equilibrium concentration in milligrams of alkaloidal base per 100 mL of solution, *y* is the amount of alkaloidal base, *x*, in milligrams adsorbed per gram, *m*, of clay (i.e., $y = x/m$), and *b* and $y_m$are constants defined earlier. In later studies, Barr and Arnista39investigated the adsorption of diphtheria toxin and several bacteria by various clays. They concluded that attapulgite, a hydrous magnesium aluminum silicate, was superior to kaolin as an intestinal adsorbent. The results of the adsorption of strychnine on activated attapulgite, halloysite (similar to kaolinite), and kaolin, all washed with gastric juice, are shown in Figure 15-23.

The smaller the slope, the better is the adsorption. Thus, it can be calculated from Figure 15-23 that an equilibrium concentration of, say, 400 mg of strychnine/100 mL of solution, *x/m*, gives approximately 40, 20, and 6.7 mg/g for attapulgite, halloysite, and kaolin, respectively. When an orally administered drug causes gastrointestinal disturbances, commercial adsorbent, antacid, or antidiarrheal preparations are often taken by the patient, and these preparations may interact with the drug to reduce its absorption. The absorption of quinidine salts (an antiarrhythmic agent), for example, is impaired by combining with kaolin, pectin, montmorillonite, and similar adsorbents. Moustafa et al.40 found that the adsorption of quinidine sulfate by antacid and antidiarrheal preparations, loperamide, Kaopectate, Simeco, magnesium trisilicate, and bismuth subnitrate was well expressed by both Freundlich and Langmuir adsorption isotherms.

Nikolakakis and Newton41 studied the solid–solid adsorption of a fine cohesive powder onto the surface of coarse free-flowing particles to form what is called an “ordered” mixture. These systems provide very homogeneous mixtures of powders ordinarily having good physical stability. Examples of “ordered” mixtures are dry blends of sucrose and antibiotics that can be reconstituted with water to provide antibiotic syrup formulations. Sorbitol can replace sucrose to prepare sucrose-free formulations for patients with diabetes. During blending, a fine powder of an antibiotic is adsorbed onto the surface of coarse particles of sorbitol. Nikolakakis and Newton41 obtained an apparent Langmuir or type I isotherm when the weight of drug adsorbed per unit weight of sorbitol, *x/m*, was plotted against the concentration, *c*, of nonadsorbed drug at equilibrium. Thus, using the linear form, equation **(**15-58**)**, one can find the *b* and y_m values. The y_m value is the amount of antibiotic per unit weight of sorbitol required to form a monolayer on the surface of sorbitol particles. This can be considered as a measure of the adsorption capacity or number of binding sites of sorbitol for the antibiotic. The quantity *b* is an empirical affinity or binding constant that is given thermodynamic significance by some workers (see Hiemenz,7 see Fundamentals and Concentration Effects in Chemical Kinetics and Stability).

Example 15-13

Solid–Solid Adsorption of Cephalexin

The values of *c*/*y* against *c* for the solid–solid adsorption of cephalexin monohydrate onto sorbitol are as follows:

Calculate *b* and y_m.

Using a regression analysis of *c*/*y* (*y* axis) against *c* (*x*axis), we find the *c*/*y* = 25.2 + 5.93*c*. Thus,

$$\text{Slope} = \frac{1}{y_m} = 5.93; \qquad y_m = 0.169\,g/g \text{ (dimensionless)}$$

$$\text{Intercept} = \frac{1}{by_m} = 25.2\% \text{ (w/w)}$$

$$b = \frac{1}{25.2\% \text{ (w/w)} \times 0.169\,g/g} = 0.235\% \text{ (w/w)}^{-1}$$

c (% w/w*)	5	10	15	20
c/*y* (% w/w)	54.85	84.5	114.15	143.8
g adsorbate/g adsorbent				

*Note that we express *c* as percent w/w on both the *x*and *y* axes. We express *y* = *x*/*m* as gram adsorbate/gram adsorbent, which is dimensionless. Therefore, the units for *c/y* on the *x* axis are simply% w/w. Like *y*, y_m is dimensionless, and *b* has the units 1 (% w/w).

Activated Charcoal

An example of a substance that can adsorb enormous amounts of gases or liquids is *activated charcoal*, the residue from destructive distillation of various organic materials, treated to increase its adsorptive power. To adsorb more adsorbate, an adsorbent of a given mass should have the greatest possible surface area. This might be achieved by the use of porous or milled adsorbents. Consider the following example: A sphere with a diameter of 1.2 cm has a volume of 1 cm^3 and a surface area of 5 cm^2. If the sphere is divided into two spheres each with a diameter of 1 cm, together they will have the same volume of 1 cm^3 but an increased surface area of 6 cm^2. Particles with a diameter of about 0.01 cm and a summary

volume of 1 cm^3 will have a total surface of about 500 cm^3. If we continue to divide the spheres and finally mill them to particles with diameters of about 10^{-6} cm, the total surface area will increase to hundreds of square meters. Modern activated charcoal has thousands of square meters of active surface area per 1 g of mass. It is used as an antidote for poisonings due to many substances, including drugs (sulfonylureas, acetaminophen, phenobarbital, etc.).

Activated charcoal is made from material burnt in a superheated high-oxygen atmosphere, creating small holes in the range of 100 to 800 Å in diameter throughout the grain of the charcoal. This effectively increases the charcoal's surface area so that the surface area of 1 g of charcoal is approximately 1000 m^2. The usual dose for activated charcoal treatment is 50 to 100 g for adults and 1 to 2 g/kg for children. Activated charcoal is frequently administered to poisoned patients. The assumption is that toxin absorption is prevented and that toxicity (as defined by morbidity and mortality) of the poisoning is decreased. Yet, there is no evidence that activated charcoal improves outcome.42

Sorptive uptake of lignin and tannin from an aqueous phase by activated charcoal was investigated.43 The sorption reaction was found to be of a first order. The influence on the rate of sorption of various factors, such as amount of sorbent and pH of the system, has been investigated. Sorption data fit well into the Langmuir adsorption isotherm, indicating formation of a monolayer over a homogeneous sorbent surface. Desorption studies indicate the irreversible nature of the sorption reaction, whereas interruption studies suggest film diffusion to be rate limiting.43

Shadnia et al.44 described the treatment and successful outcome of a patient who had taken a dose of strychnine that would normally be fatal. A 28-year-old man was admitted 2 hr after ingestion of 1 to 1.5 g of strychnine. He was severely agitated and in mild respiratory distress; blood pressure was 90/60 mm Hg, pulse 110/min, and peripheral pulses weak. He had generalized hyperactive reflexes and had several generalized tonic–clonic convulsions in the emergency department. Treatment consisted of gastric lavage with water, oral administration of activated charcoal and sorbitol solution, continuous intravenous administration of midazolam, and then sodium thiopental, furosemide, sodium bicarbonate, and hemodialysis for acute renal failure. His clinical course included respiratory distress, agitation, generalized tonic–clonic convulsions, hyperactivity, oliguria, and acute tubular necrosis prior to recovery in 23 days.

Tanaka et al.45 reported a case of impaired absorption of orally administered phenobarbital associated with the concomitant administration of activated charcoal, and recovery of the absorption after administration of the two drugs was separated by a 1.5-hr interval. A 78-year-old woman weighing 50 kg who had undergone brain surgery was prescribed phenobarbital 120 mg/day for postoperative convulsions. Her serum phenobarbital concentration reached 24.8 µg/mL (therapeutically effective level is 10–30 µg/mL). Thereafter, her renal function worsened, and activated charcoal 6 g/day was started. Four months after the start of activated charcoal, blood analysis revealed that the serum phenobarbital concentration was as low as 4.3 µg/mL. The phenobarbital dose was increased to 150 mg/day. Further evaluation revealed that activated charcoal and phenobarbital had been administered concomitantly. The dosage regimen was altered to separate the administration of the agents by at least 1.5 hr. Subsequently, the patient's serum phenobarbital concentration increased to 11.9 µ/mL within 3 weeks. Her serum phenobarbital concentration was measured monthly thereafter and remained stable in the range of 15.8 to 18.6 µ/mL. The patient's low serum phenobarbital concentration was considered likely to have been due to impaired gastrointestinal absorption of phenobarbital as a result of adsorption of phenobarbital on the activated charcoal. An objective causality assessment showed that the interaction was probable. Therefore, administration of activated charcoal and phenobarbital should be separated by an interval of at least 1.5 hr.

Fourteen adsorbent materials were tested in the pH range of 3 to 8 for deoxynivalenol and nivalenol-binding ability.46 Only activated carbon was effective, with binding capacities of 35.1 and 8.8 µ mole of deoxynivalenol and nivalenol per gram of adsorbent, respectively, calculated from the adsorption isotherms. A dynamic laboratory model simulating the gastrointestinal tract of healthy pigs was used to evaluate the small-intestinal absorption of deoxynivalenol and nivalenol and the efficacy of activated carbon in reducing the relevant absorption. The in vitro intestinal absorptions of deoxynivalenol and nivalenol were 51% and 21%, respectively, as referred to 170 µg of deoxynivalenol and 230 µg of nivalenol ingested through contaminated (spiked) wheat. Most absorption occurred in the jejunal compartment for both mycotoxins. The inclusion of activated carbon produced a significant reduction in the intestinal mycotoxin absorption. At 2% inclusion, the absorption with respect to the intake was lowered from 51% to 28% for deoxynivalenol and from 21% to 12% for nivalenol. The binding activity of activated carbon for these trichothecenes was lower than that observed for zearalenone, a mycotoxin frequently co-occurring with them in naturally contaminated cereals.

The adsorption of three barbiturates—phenobarbital, mephobarbital, and primidone from simulated intestinal fluid, without pancreatin, by activated carbon was studied using the rotating-bottle method.[46] The concentrations of each drug remaining in solution at equilibrium were determined with the aid of a high-performance liquid chromatography system employing a reversed-phase column. The competitive Langmuir-like model, the modified competitive Langmuir-like model, and the LeVan–Vermeulen model were each fit to the data. Excellent agreement was obtained between the experimental and predicted data using the modified competitive Langmuir-like model and the LeVan–Vermeulen model. The agreement obtained from the original competitive Langmuir-like model was less satisfactory. These observations are not surprising because the competitive Langmuir-like model assumes that the capacities of the adsorbates are equal, whereas the other two models take into account the differences in the capacities of the components. The results of these studies indicate that the adsorbates employed are competing for the same binding sites on the activated carbon surface. The results also demonstrate that it is possible to accurately predict multicomponent adsorption isotherms using only single-solute isotherm parameters.[47]

Key Concept

Wetting Agent

A *wetting agent* is a surfactant that, when dissolved in water, lowers the advancing contact angle, aids in displacing an air phase at the surface, and replaces it with a liquid phase. Examples of the application of wetting to pharmacy and medicine include the displacement of air from the surface of sulfur, charcoal, and other powders for the purpose of dispersing these drugs in liquid vehicles; the displacement of air from the matrix of cotton pads and bandages so that medicinal solutions can be absorbed for application to various body areas; the displacement of dirt and debris by the use of detergents in the washing of wounds; and the application of medicinal lotions and sprays to the surface of the skin and mucous membranes.

Hill et al.[48] studied extracorporeal liver support for episodic (acute) type C hepatic encephalopathy (AHE) failing to respond to medical therapy. A series of patients with cirrhosis and AHE failing to respond to at least 24 hr of medical therapy underwent a maximum of three 6-hr charcoal-based hemodiabsorption treatments. It was found that a charcoal-based hemodiabsorption treatment in which a standardized anticoagulation protocol is used is safe and effective treatment for AHE not responding to standard medical therapy.

Although activated charcoal is useful in the management of poisonings, it should not be considered as harmless, especially in children. Donoso et al.[49] reported the case of a patient who developed obstructive laryngitis secondary to aspiration of activated charcoal with a protected airway. This case shows that nasogastric administration of activated charcoal presents a significant degree of risk. Vomiting also frequently complicates the administration of activated charcoal. Little is known about the patient, poison, or procedure-specific factors that contribute to emesis of charcoal. Osterhoudt et al.50 estimated the incidence of vomiting subsequent to therapeutic administration of charcoal to poisoned children 18 years or less of age and examined the relative contributions of several risk factors to the occurrence of vomiting. One of every 5 children given activated charcoal vomited. Children with previous vomiting or nasogastric tube administration were at highest risk, and these factors should be accounted for in future investigation of antiemetic strategies. Sorbitol content of charcoal was not a significant risk factor for emesis.

Wetting

Adsorption at solid surfaces is involved in the phenomena of wetting and detergency. The tendency of molecules of liquids to move from the surface into the bulk and decrease the surface of the liquid–gas interface is explained by the fact that molecules of liquid undergo very weak attraction from the molecules of gas on the interface. There is a limited number of gas molecules in a unit of volume in the gaseous phase as compared with that in liquid phase. When a liquid comes into contact with the solid, the forces of attraction between the liquid and the solid phases begin to play a significant role. In this case, the behavior of the liquid will depend on the balance between the forces of attraction of molecules in the liquid and the forces of attraction between the liquid and the solid phases. In the case of mercury and glass, attractive forces between molecules of mercury and glass are much smaller than the forces of attraction between molecules of mercury themselves. As a result, mercury will come together as a single spherical drop. In contrast, for water and glass (or mercury and zinc), attractive forces between the solid and liquid molecules are greater than the forces between molecules of liquid themselves, and so the liquid is able to wet the surface of the glass.

The most important action of a wetting agent is to lower the *contact angle* between the surface and the wetting liquid. The contact angle is the angle between a liquid droplet and the surface over which it spreads. As shown in Figure 15-24, the contact angle between a liquid and a solid may be 0°, signifying complete wetting, or may approach 180°, at which wetting is insignificant. The contact angle may also have any value between these limits, as illustrated in the Figure. At equilibrium, the surface and interfacial tensions can be resolved into

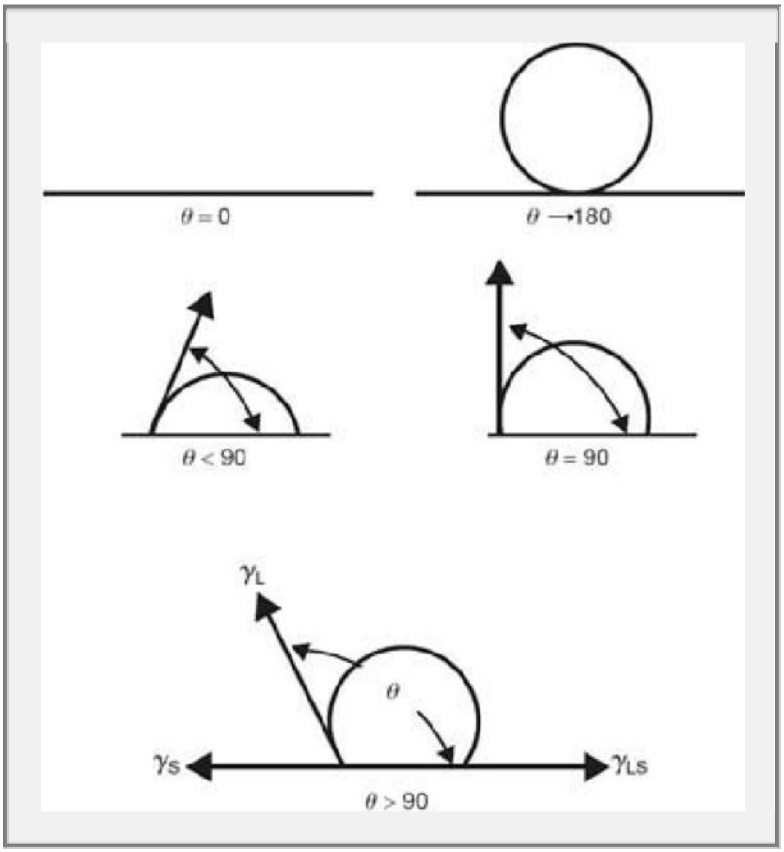


Fig. 15-24. Contact angles from 0° to 180°.

$$\gamma_S = \gamma_{SL} + \gamma_L \cos\theta \qquad (15\text{–}59)$$

which is known as Young's equation.

When γ_S of equation (15-59) is substituted into equation (15-19), we have

$$S = \gamma_L(\cos\theta - 1) \qquad (15\text{–}60)$$

and combining equation (15-59) with equation (15-16) results in

$$W_a = W_{SL} = \gamma_L(1 + \cos\theta) \qquad (15\text{–}61)$$

which is an alternative form of Young's equation. Equations (15-60)and (15-61) are useful expressions because they do not include $\gamma_S$or γ_{SL}, neither of which can be easily or accurately measured. The contact angle between a water droplet and a greasy surface results when the applied liquid, water, wets the greasy surface incompletely. When a drop of water is placed on a scrupulously clean glass surface, it spreads spontaneously and no contact angle exists. This result can be described by assigning to water a high spreading coefficient on clean glass, or by stating that the contact angle between water and glass is zero. If the appropriate wetting agent is added to water, the solution will spread spontaneously on a greasy surface. For a wetting agent to function efficiently—in other words, to exhibit a low contact angle—it should have an HLB of about 6 to 9 (see Fig. 15-11).

Example 15-14

Comparison of Different Tablet Binders

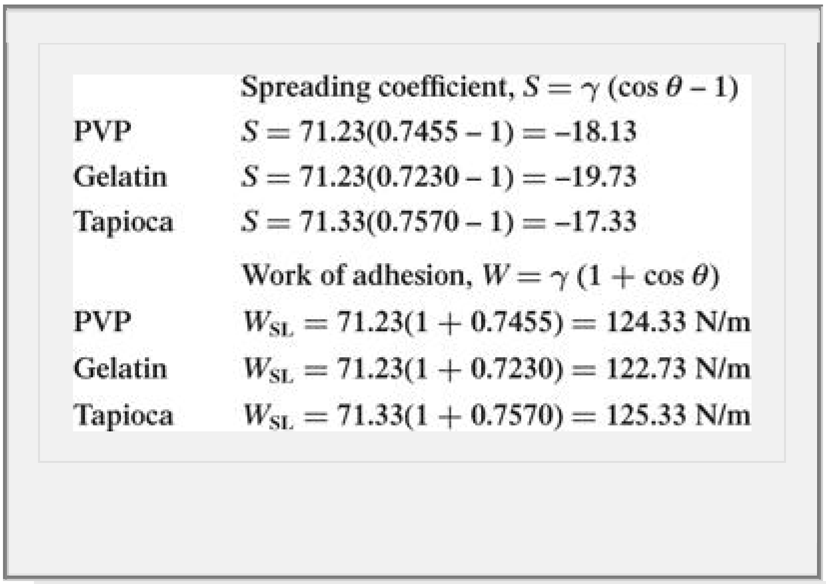
Wettability of tablet surfaces influences disintegration and dissolution and the subsequent release of the active ingredient(s) from the tablet.

A *tablet binder* is a material that contributes cohesiveness to a tablet so that the tablet remains intact after compression. The influence of tablet binders on wettability of acetaminophen tablets was studied by Esezobo et al.51The effect of the contact angle of water on the acetaminophen tablets, the surface tension of the liquid, and the disintegration time of the tablets is given in the following table. The water on the tablet surface is saturated with the basic formulation ingredients excluding the binder. The concentration of the tablet binders, povidone (polyvinylpyrrolidone, PVP), gelatin, and tapioca, is constant at 5% w/w.

Binder	γ (N/m)*	Cos θ	*t* (min)
Povidone	71.23	0.7455	17.0
Gelatin	71.23	0.7230	23.5
Tapioca	71.33	0.7570	2.0

*The surface tension, γ, is given in joules/m, or newtons, the SI force unit, divided by meters. In the cgs system, γ is expressed in the force unit of dynes divided by centimeters, or in ergs/cm^2.

Using equations (15-60) and (15-61), compute *S*, the spreading coefficient, and W_{SL}, the work of adhesion, for water on the tablet surface, comparing the influence of the three binders in the formulation. Observe the disintegration times found in the table and use them to refute or corroborate the *S* and W_{SL} results.



Spreading coefficient, $S = \gamma(\cos\theta - 1)$

PVP $S = 71.23(0.7455 - 1) = -18.13$

Gelatin $S = 71.23(0.7230 - 1) = -19.73$

Tapioca $S = 71.33(0.7570 - 1) = -17.33$

Work of adhesion, $W = \gamma(1 + \cos\theta)$

PVP $W_{SL} = 71.23(1 + 0.7455) = 124.33\ \text{N/m}$

Gelatin $W_{SL} = 71.23(1 + 0.7230) = 122.73\ \text{N/m}$

Tapioca $W_{SL} = 71.33(1 + 0.7570) = 125.33\ \text{N/m}$

The spreading coefficient is negative, but the values are small. Tapioca shows the smallest negative value, $S = -17.33$, followed by PVP and finally gelatin. These results agree with the work of adhesion, tapioca > PVP > gelatin. When the work of adhesion is higher, the bond between water and tablet surface is stronger, and the better is the wetting.

From the table, we observe the tablet disintegration times to be on the order tapioca < PVP < gelatin, which agrees qualitatively with the S and W_{SL} values. That is, the better the wetting, reflected in a larger work of adhesion and a smaller negative spreading coefficient, the shorter is the tablet disintegration time. Other factors, such as tablet porosity, that were not considered in the study cause the relationship to be only qualitative.

Example 15-15

The Influence of Additives on the Spreading Coefficient of a Film Coating Formulation to a Model Tablet Surface

One of the requirements of tablet film coating is that good adhesion of the coat to the tablet must be achieved. The properties of the coating formulation as well as those of the tablet can influence adhesion. The prerequisite for good adhesion is the spreading of the atomized droplets over the surface of the tablet and limited penetration of the coating solution into the pores of the tablet. Both of these are controlled by the surface energetics of the tablet and the coating solution. Khan et al.52 determined the spreading coefficients of hydroxypropyl methylcellulose (HPMC) containing additives on a model tablet surface. Four formulations were studied. The formulations contained (*a*) 9% HPMC, 1% polyethylene glycol 400 (PEG 400); (*b*) 9% HPMC, 1% PEG 400, 2% microcrystalline cellulose (MCC); (*c*) 9% HPMC, 1% PEG 400, 2% MCC, 2% lactose; and (*d*) 9% HPMC, 1% PEG 400, 0.5% Tween 20. Tablets consisted of 75.2% MCC, 24.2% lactose, 0.4% magnesium atearate, and 0.2% colloidal silicon dioxide (all w/w). Two batches of tablets with average breaking loads of 127 and 191 N were produced.

Contact angles (degrees) and spreading coefficients (SC, mJ/m^2) for the coating formulations of the tablets ($N = 10$; means ± SD) are as follows:

Coating Formulations	127-N Tablet Contact Angle	127-N Tablet SC	191-N Tablet Contact Angle	191-N Tablet SC
(*a*) HPMC	43 ± 0.48	41.2	46 ± 0.47	39.6
(*b*) MCC	54 ± 0.34	40.2	54 ± 0.32	38.6
(*c*) Lactose	50 ± 0.37	39.0	51 ± 0.52	37.4
(*d*) Tween	53 ± 0.93	41.8	52 ± 0.47	40.2

The inclusion of additives changes the contact angle of the coating formulations to a limited extent. The spreading coefficients are all high and positive, indicating effective spreading of the coating formulations on the surface of the tablets.

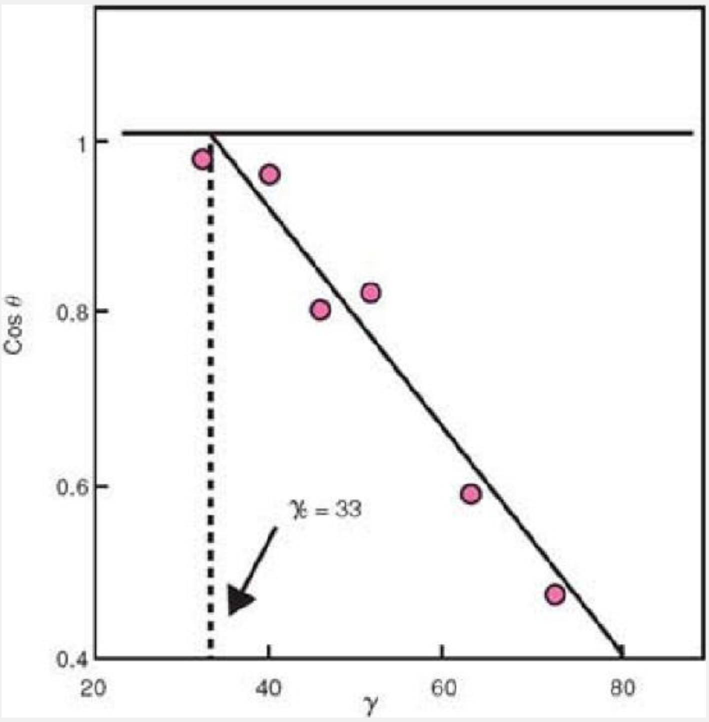


Fig. 15-25. Critical surface tension (Zisman) plot for a model skin. (Replotted from J. C. Charkoudian, J. Soc. Cosmet. Chem. **39,** 225, 1988.)

Zisman and his associates53 found that when the cosine of the contact angle, cos *θ*, was plotted versus the surface tension for a homologous series of liquids spread on a surface such as Teflon (polytetrafluoroethylene), a straight line resulted. The line can be extrapolated to cos *θ* = 1, that is, to a contact angle of zero, signifying complete wetting. The surface tension at cos $\theta = 1$ was given the term *critical surface tension* and the symbol γ_c. Various series of liquids on a given solid surface were all found to have about the same value of γ_c, as observed in Figure 15-25. Zisman concluded that γ_c was characteristic for each solid, Teflon, for example, having a value of about 18 ergs/cm^2. Because the surface of Teflon consists of —CF_2— groups, Zisman reasoned that all surfaces of this nature would have critical surface tensions of about 18 ergs/cm^2, and any liquid with a surface tension less than 18 ergs/cm^2 would wet a surface composed of —CF_2— groups.[54,55]

Example 15-16

Wetting of Model Skin

Charkoudian[56] designed a model skin surface with physical and chemical properties approximating those reported for human skin. The model skin consisted of a protein (cross-linked gelatin), a synthetic lipidlike substance, and water, with the protein and lipid in a ratio of 3 to 1. To further characterize the artificial skin, the surface tensions of several liquids and their contact angles on the model skin surface were determined at 20°C, as given in the following table:

Liquid	Water	Glycerin	Diiodo methane	Ethylene glycol	Benzyl alcohol	Mineral oil
γ(dynes/cm)	72.8	63.4	50.8	48.3	39.2	31.9
Cos θ	0.45	0.56	0.79	0.77	0.96	0.97

Plot cos θ versus γ and compute the critical surface tension, γ_c, for complete wetting of the artificial skin surface. The value of γ_c for in vivo human skin is about 26 to 28 dynes/cm. From the results obtained, which liquid in the table would be expected to best wet the model skin surface?

The plot is shown in Figure 15-25. Although the liquids in the table do not constitute a homologous series, they appear to fit nicely the Zisman[53] principle, producing a straight line that extrapolates to cos θ corresponding to a critical surface tension of γ_c = 33 dynes/cm. Mineral oil, with a surface tension of 31.9 dynes/cm, most closely approximates the critical surface tension, γ_c = 33 dynes/cm, of the model skin surface. For a more exact calculation of γ_c, least squares linear regression analysis can be applied to yield

$$\cos\theta = -0.0137\gamma + 1.450, \qquad r^2 = 0.972$$

For the specific value of cos $\theta = 1$, we obtain γ_c = 33.0 dynes/cm. It is noted that the critical surface tension, γ_c, for the artificial skin used in this study is somewhat higher (γ_c= 33.0 dynes/cm) than values reported elsewhere in the literature for human skin (γ_c = 26–28 dynes/cm). This is believed to be due in part to the absence of sweat and sebaceous secretions, which lower the γ_c value of viable human skin.

Although one frequently desires to determine the relative efficiencies of wetting agents, it is difficult to measure the contact angle. Nor are spreading coefficients usually available, because no convenient method is known for directly measuring the surface tension of a solid surface. As a result of these difficulties, empirical tests are used in industry, one of the best-known wetting tests being that of Draves23. The *Draves test* involves measuring the time for a weighted skein of cotton yarn to sink through the wetting solution contained in a 500-mL graduate. No method has been suggested for estimating the ability of a wetting agent to promote spreading of a lotion on the surface of the skin, and the application properties of such products are ordinarily determined by subjective evaluation.

Detergents are surfactants that are used for the removal of dirt. Detergency is a complex process involving the removal of foreign matter from surfaces. The process includes many of the actions characteristic of specific surfactants: initial wetting of the dirt and of the surface to be cleaned; deflocculation and suspension; emulsification or solubilization of the dirt particles; and sometimes foaming of the agent for entrainment and washing away of the particles. Because the detergent must possess a combination of properties, its efficiency is best ascertained by actual tests with the material to be cleaned.

Other dispersion stabilizers, including deflocculating, suspending, and emulsifying agents, are considered in Chapter 17.

Applications of Surface-Active Agents

In addition to the use of surfactants as emulsifying agents, detergents, wetting agents, and solubilizing agents, they find application as antibacterial and other protective agents and as aids to the absorption of drugs in the body.

A surfactant may affect the activity of a drug or may itself exert drug action. As an example of the first case, the penetration of hexylresorcinol into the pinworm, *Ascaris*, is increased by the presence of a low concentration of surfactant. This potentiation of activity is due to a reduction in interfacial tension between the liquid phase and the cell wall of the organism. As a result, the adsorption and spreading of hexylresorcinol over the surface of the organism is facilitated. When the concentration of surface-active agent present exceeds that required to form micelles, however, the rate of penetration of the anthelmintic decreases nearly to zero. This is because the drug is now partitioned between the micelles and the aqueous phase, resulting in a reduction in the effective concentration. Quaternary ammonium compounds are examples of surface-active agents that in themselves possess antibacterial activity.55 This may depend in part on interfacial phenomena, but other factors are also important. The agents are adsorbed on the cell surface and supposedly bring about destruction by increasing the permeability or “leakiness” of the lipid cell membrane. Death then occurs through a loss of essential materials from the cell. Both gram-negative and gram-positive organisms are susceptible to the action of the cationic quaternary compounds, whereas anionic agents attack gram-positive organisms more easily than gram-negative bacteria. Nonionic surfactants are least effective as antibacterial agents. In fact, they often aid rather than inhibit the growth of bacteria, presumably by providing long-chain fatty acids in a form that is easily metabolized by the organism.

Miyamoto et al.58 studied the effects of surfactants and bile salts on the gastrointestinal absorption of antibiotics using an in situ rat-gut perfusion technique. Polyoxyethylene lauryl ether reduced the absorption of propicillin in the stomach and increased it in the small intestine. Some surfactants increase the rate of intestinal absorption, whereas others decrease it. Some of these effects may result from alteration of the membrane by the surfactant. The effects of surfactants on the solubility of drugs and their bioabsorption have been reviewed by Mulley59 and Gibaldi and Feldman.60

Foams and Antifoaming Agents

Any solutions containing surface-active materials produce stable foams when mixed intimately with air. A foam is a relatively stable structure consisting of air pockets enclosed within thin films of liquid, the gas-in-liquid dispersion being stabilized by a *foaming agent*. The foam dissipates as the liquid drains away from the area surrounding the air globules, and the film finally collapses. *Agents*such as alcohol, ether, castor oil, and some surfactants can be used to break the foam and are known as *antifoaming agents*. Foams are sometimes useful in pharmacy (e.g., vaginal contraceptive or antimicrobial formulations) but are usually a nuisance and are prevented or destroyed when possible. The undesirable foaming of solubilized liquid preparations poses a problem in formulation.

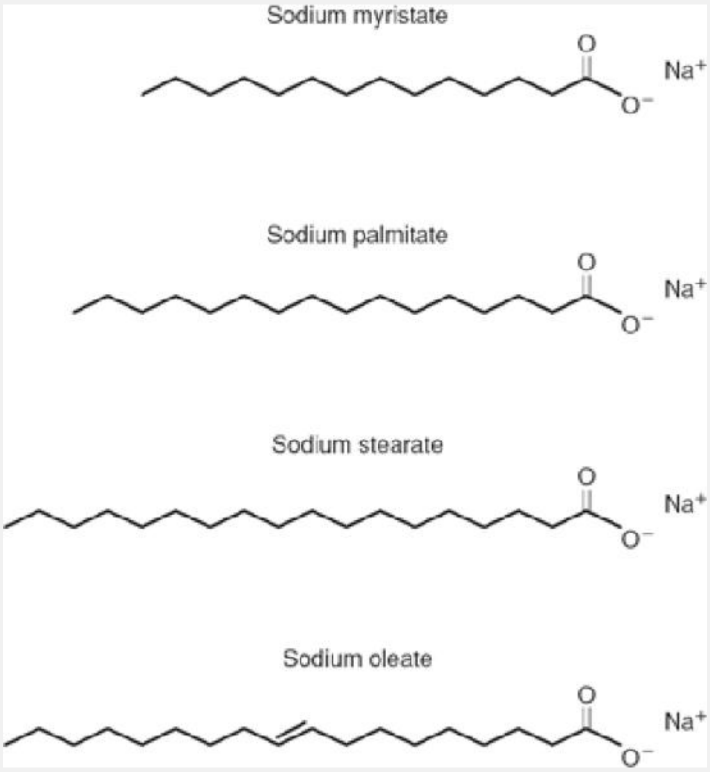


Fig. 15-26. Common soaps.

All of the *soaps* (sodium oleate, etc.) are fatty acid salts (anionic surfactant). They are characterized by (*a*) a long hydrocarbon chain, which may be monounsaturated (i.e., have one double bond, like sodium oleate), polyunsaturated (i.e., have more than one double bond), or saturated (i.e., no double bonds), and (*b*) a carboxylate group at the end (Fig. 15-26). Any surfactant that is not a soap is a*detergent*. The cleaning action of soaps and detergents is based on the property known as detergency. Possibly, the most important industrial role for surfactants is the formation of emulsions. An emulsion is a dispersion of one liquid in a second, immiscible liquid. Salad dressings, milk, and cream are emulsions, as are medicinal creams such as moisturizers. Emulsions are multiphase systems, even though they often look like they are just one phase. The phases in an emulsion are normally called the continuous phase and the dispersed phase. Detergency is a complex process involving the removal of foreign matter from surfaces. The process includes the following main steps (Fig. 15-27): (*a*) The hydrocarbon tails of the detergent anions dissolve in the grease; (*b*) the grease spot gradually breaks up and becomes pincushioned by the detergent anions; and (*c*) small bits of grease are held in colloidal suspension by the detergent. The anionic heads keep the grease from coalescing because the particles carry the same electric charge.

Lung Surfactant

Lung surfactant is surface-active agent that covers the surface of alveoli contacted with air. It decreases the surface tension at the air–alveoli interface almost to zero and therefore

accomplishes two main tasks. First, it prevents the collapse of alveoli. Second, main surfactant function is to decrease the pressure inside the alveoli. Thus, lung surfactant allows us to breathe and prevents pulmonary edema. Lung surfactant is a complex mixture of proteins and lipids but the major component is phosphatidylcholine. Some pathologic conditions were found to decrease the activity of lung surfactant. In the United States, 40,000 premature infants per year are born without enough lung surfactant, resulting in thousands of deaths. The typical premature infant has only 1/20 of the lung surfactant needed to breathe. Fortunately, additional artificial lung surfactant can be administered. Calfactant (Infasurf; Forest Pharmaceuticals, St. Louis, MO) is one of the available artificial surfactants. Infasurf (calfactant) Intratracheal Suspension is a sterile, nonpyrogenic lung surfactant intended for intratracheal instillation only. It is an extract of natural surfactant from calf lungs and includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C). It contains no preservatives. Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 to 6.0. Each milliliter of Infasurf contains 35 mg of total phospholipids (including 26 mg of phosphatidylcholine, of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg of proteins, including 0.26 mg of SP-B. Treatment with calfactant often rapidly improves oxygenation and lung compliance.

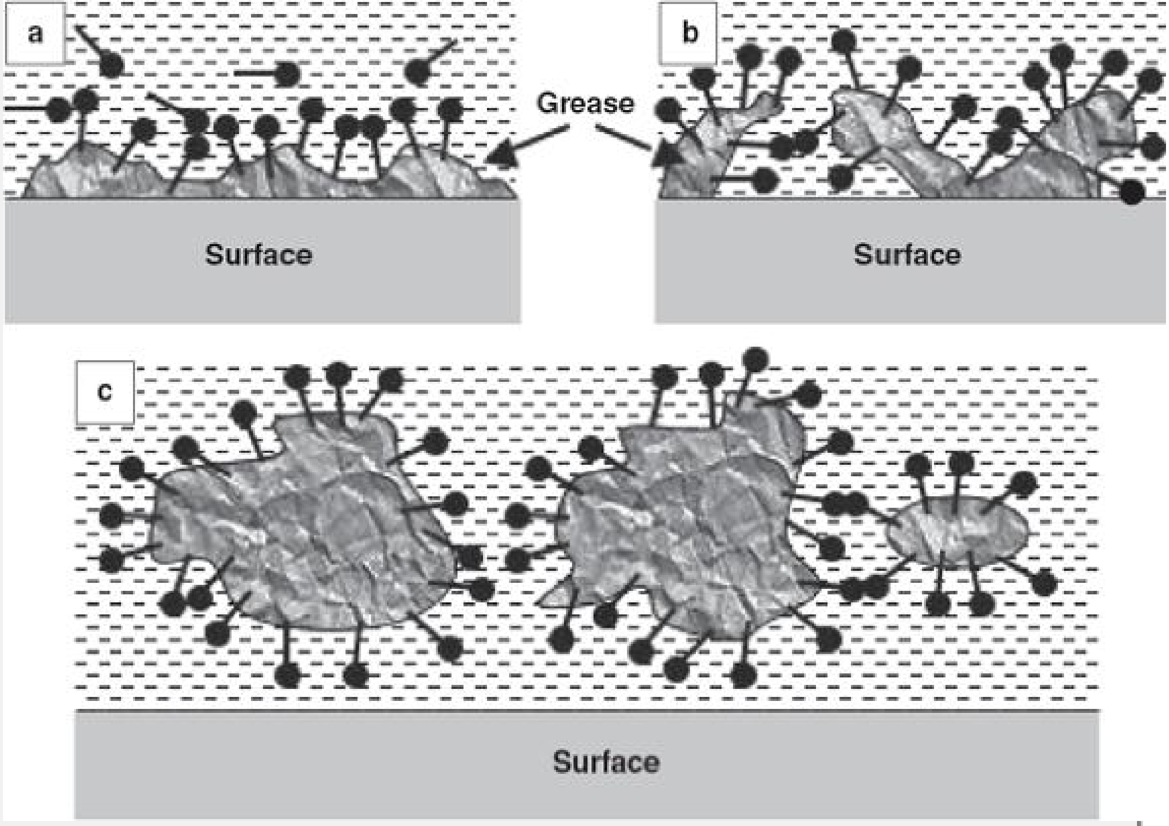


Fig. 15-27. Mechanism of detergent action. (*a*) The hydrocarbon tails of the detergent anions dissolve in the grease; (*b*) the grease spot gradually breaks up and becomes pincushioned by the detergent anions, and (*c*) small bits of grease are held in colloidal suspension by the detergent.

Electric Properties of Interfaces

This section deals with some of the principles involved with surfaces that are charged in relation to their surrounding liquid environment. Discussion of the applications arising from this phenomenon is given in the chapters dealing with colloidal systems (Chapter 16) and suspensions (Chapter 17).

Particles dispersed in liquid media may become charged mainly in one of two ways. The first involves the selective adsorption of a particular ionic species present in solution. This may be an ion added to the solution or, in the case of pure water, it may be the hydronium or hydroxyl ion. The majority of particles dispersed in water acquire a negative charge due to preferential adsorption of the hydroxyl ion. Second, charges on particles arise from ionization of groups (such as COOH) that may be situated at the surface of the particle. In these cases, the charge is a function of p*K* and pH. A third, less common origin for the charge on a particle surface is thought to arise when there is a difference in dielectric constant between the particle and its dispersion medium.

The Electric Double Layer

Consider a solid surface in contact with a polar solution containing ions, for example, an aqueous solution of an electrolyte. Furthermore, let us suppose that some of the cations

are adsorbed onto the surface, giving it a positive charge. Remaining in solution are the rest of the cations plus the total number of anions added. These anions are attracted to the positively charged surface by electric forces that also serve to repel the approach of any further cations once the initial adsorption is complete. In addition to these electric forces, thermal motion tends to produce an equal distribution of all the ions in solution. As a result, an equilibrium situation is set up in which *some* of the excess anions approach the surface, whereas the remainder are distributed in decreasing amounts as one proceeds away from the charged surface. At a particular distance from the surface, the concentrations of anions and cations are equal, that is, conditions of electric neutrality prevail. It is important to remember that the system *as a whole* is electrically neutral, even though there are regions of unequal distribution of anions and cations.

Such a situation is shown in Figure 15-28, where *aa*′ is the surface of the solid. The adsorbed ions that give the surface its positive charge are referred to as the *potential-determining ions*. Immediately adjacent to this surface layer is a region of tightly bound solvent molecules, together with some negative ions, also tightly bound to the surface. The limit of this region is given by the line *bb*′ inFigure 15-28. These ions, having a charge opposite to that of the potential-determining ions, are known as *counterions* or *gegenions*. The degree of attraction of the solvent molecules and counterions is such that if the surface is moved relative to the liquid, the shear plane is *bb*′ rather than *aa*′, the true surface. In the region bounded by the lines *bb*′ and *cc*′, there is an excess of negative ions. The potential at *bb*′ is still positive because, as previously mentioned, there are fewer anions in the tightly bound layer than cations adsorbed onto the surface of the solid. Beyond *cc*′, the distribution of ions is uniform and electric neutrality is obtained.

Thus, the electric distribution at the interface is equivalent to a double layer of charge, the first layer (extending from *aa*′ to *bb*′) tightly bound and a second layer (from *bb*′ to *cc*′) that is more diffuse. The so-called diffuse double layer therefore extends from *aa*′ to *cc*′.

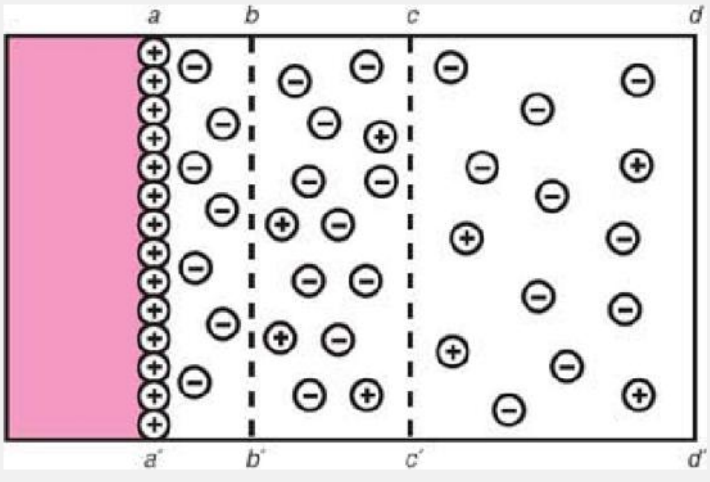


Fig. 15-28. The electric double layer at the surface of separation between two phases, showing distribution of ions. The system as a whole is electrically neutral.

Two situations other than that represented by Figure 15-28 are possible: (*a*) If the counterions in the tightly bound, solvated layer equal the positive charge on the solid surface, then electric neutrality occurs at the plane *bb*′ rather than *cc*′. (*b*) Should the total charge of the counterions in the region *aa*′–*bb*′ exceed the charge due to the potential-determining ions, then the net charge at *bb*′ will be negative rather than less positive, as shown in Figure 15-28. This means that, in this instance, for electric neutrality to be obtained at *cc*′, an excess of positive ions must be present in the region *bb*′–*cc*′.

The student should appreciate that if the potential-determining ion is negative, the arguments just given still apply, although now positive ions will be present in the tightly bound layer.

Nernst and Zeta Potentials

The changes in potential with distance from the surface for the various situations discussed in the previous section can be represented as shown in Figure 15-29. The potential at the solid surface *aa*′ due to the potential-determining ion is the *electrothermodynamic* (*Nernst*) *potential*, *E*, and is defined as the difference in potential between the actual surface and the

electroneutral region of the solution. The potential located at the shear plane *bb*′ is known as the *electrokinetic*, or *zeta, potential*, *ζ*. The zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electroneutral region of the solution. As shown in Figure 15-29, the potential initially drops off rapidly, followed by a more gradual decrease as the distance from the surface increases. This is because the counterions close to the surface act as a screen that reduces the electrostatic attraction between the charged surface and those counterions further away from the surface.

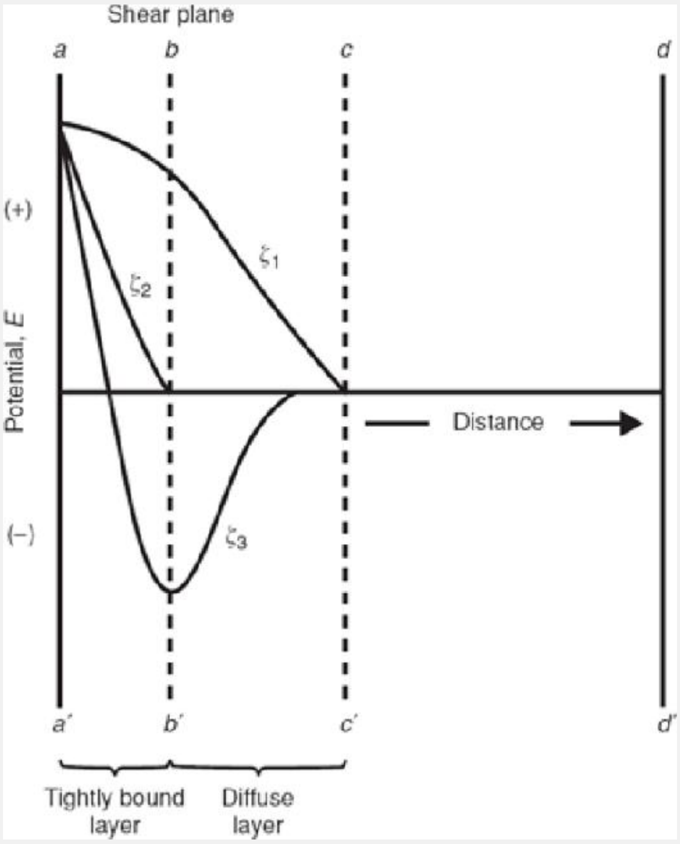


Fig. 15-29. Electrokinetic potential, E, at solid–liquid boundaries. Curves are shown for three cases characteristic of the ions or molecules in the liquid phase. Note that although E is the same in all three cases, the zeta potentials are positive (ζ_1), zero (ζ_2), and negative (ζ_3).

The zeta potential has practical application in the stability of systems containing dispersed particles because this potential, rather than the Nernst potential, governs the degree of repulsion between adjacent, similarly charged, dispersed particles. If the zeta potential is reduced below a certain value (which depends on the particular system being used), the attractive forces exceed the repulsive forces, and the particles come together. This phenomenon is known as *flocculation* and is discussed in the chapters dealing with colloidal and coarse dispersions.

Effect of Electrolytes

As the concentration of electrolyte present in the system is increased, the screening effect of the counterions is also increased. As a result, the potential falls off more rapidly with distance because the thickness of the double layer shrinks. A similar situation occurs when the valency of the counterion is increased while the total concentration of electrolyte is held constant. The overall effect frequently causes a reduction in zeta potential.

Chapter Summary

Several types of interface can exist, depending on whether the two adjacent phases are in the solid, liquid, or gaseous state. For convenience, this chapter divided these various combinations into two groups, namely, *liquid interfaces* and*solid interfaces*. In the former group, the association of a liquid phase with a gaseous or another liquid phase was discussed. The section on solid interfaces dealt with systems containing solid–gas and solid–liquid interfaces. Although solid–solid interfaces have practical significance in pharmacy (e.g., the adhesion between granules, the preparation of layered tablets, and the flow of particles), little information is available to quantify these interactions. This is due, at least in part, to the fact that the surface region of materials in the solid state is quiescent, in sharp contrast to the turbulence that exists at the surfaces of liquids and gases. Accordingly, solid–solid systems were not discussed. Finally, the electric properties of interfaces were outlined. By the conclusion of this chapter you should understand the terms surface tension and interfacial tension and their application in pharmaceutical sciences as well as appreciate the various methods of measuring surface and interface tensions. The student should also be able to classify surface-active agents and appreciate their applications in pharmacy.

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

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Recommended Reading

C. A. Miller and P. Neogi (Eds.), *Interfacial Phenomena: Equilibrium and Dynamic Effects*, 2nd Ed., CRC Press, Boca Raton, FL, 2007.

Chapter Legacy

Fifth Edition: published as Chapter 16 (Interfacial Phenomena). Updated by Tamara Minko.

Sixth Edition: published as Chapter 15 (Interfacial Phenomena). Updated by Patrick Sinko.