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Physical Pharmacy

PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES

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Contents

1. Introduction	1
2. States of Matter	22
3. Thermodynamics	53
4. Physical Properties of Drug Molecules	77
5. Solutions of Nonelectrolytes	101
6. Solutions of Electrolytes	125
7. Ionic Equilibria	143
8. Buffered and Isotonic Solutions	169
9. Electromotive Force and Oxidation—Reduction	190
10. Solubility and Distribution Phenomena	212
11. Complexation and Protein Binding	251
12. Kinetics	284
13. Diffusion and Dissolution	324
14. Interfacial Phenomena	362
15. Colloids	393
16. Micromeritics	423
17. Rheology	453
18. Coarse Dispersions	477
19. Drug Product Design	512
20. Polymer Science	556
Appendix: Calculus Review	595
Index	603

TABLE 14-7. Dimensions of Organic Molecules Determined by Means of the Film Balance

Substance	Formula	Length of Molecule (angstroms, Å)	Cross-Sectional Area (sq. angstroms, Å ²)
Stearic acid	C ₁₇ H ₃₅ COOH	25	22
Tristearin	(C ₁₂₈ H ₃₅ O ₂) ₃ C ₃ H ₅	25	66
Cetyl alcohol	C ₁₆ H ₃₃ OH	22	21
Myrcyl alcohol	C ₃₀ H ₆₁ OH	41	27

Equation (14-43), the two-dimensional ideal gas law, may 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 may therefore write that

$$\gamma = bc + \gamma_0 \quad (14-44)$$

in which 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. Since the slope of such a plot is negative, and since $\pi = \gamma_0 - \gamma$, equation (14-44) may be rewritten as

$$\pi = -bc \quad (14-45)$$

The Gibbs adsorption equation (14-26) can be expressed in the following form:

$$-(d\gamma/dc) = -b = \Gamma RT/c \quad (14-46)$$

since $(d\gamma/dc)$ is the slope of the line.

Substituting for equation (14-45) in equation (14-46) and cancelling c , which is common to both sides, we obtain

$$\pi = \Gamma RT \quad (14-47)$$

Surface excess has the dimensions of moles/cm² and can be represented by n/A , in which n is the number of moles and A is the area in cm². Thus:

$$\pi = nRT/A$$

or

$$\pi A = nRT$$

which is equation (14-43).

As with the three-dimensional gas law, equation (14-43) can be used to compute the molecular weights of materials adsorbed as gaseous films at an interface. (See *Problems 14-24* and *14-25*.) 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 (p. 26) for nonideal behavior have been developed.

The relation between the Gibbs adsorption equation and equation (14-43) emphasizes the point made earlier that the distinction between soluble and insoluble films is an arbitrary one, made on the basis of the experi-

mental techniques used rather than any fundamental differences in physical properties.

The variation of the surface pressure π with temperature at the several "phase changes" observed in the two-dimensional isotherm, π -area, (see Fig. 14-18) may be analyzed by a relationship analogous to the Clapeyron equation (p. 68):

$$\frac{d\pi}{dT} = \frac{\Delta H}{T(A_1 - A_2)} \quad (14-48)$$

where A_1 and A_2 are the molar areas (cm² mol⁻¹) of the two phases and T and ΔH are the temperature and enthalpy for the phase change.²⁵ Note that π , ΔH , and $(A_1 - A_2)$ are the two-dimensional equivalents of pressure, enthalpy, and change of volume in the Clapeyron equation.

Example 14-12. Monolayers of insoluble amphiphilic compounds with a polymerizable group serve 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° to 28° C showed two breaks corresponding to phase transitions (changes in state).

Compute ΔH , 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 nm²/molecule. The change of surface pressure with temperature, $d\pi/dt = 0.91$ mN m⁻¹ °K⁻¹, and the temperature of transition is 24.2° C.²⁵

From equation (14-48):

$$\Delta H = T(A_1 - A_2) \frac{d\pi}{dT}$$

$$\Delta H = 297.2^\circ \text{K} (0.357 - 0.265) \times 10^{-18} \text{ m}^2/\text{molecule} \times$$

$$0.91 \times 10^{-3} \frac{\text{N}}{\text{m}^\circ \text{K}} = 2.49 \times 10^{-20} \text{ J/molecule}$$

$$2.49 \times 10^{-20} \times 6.022 \times 10^{23} = 14,995 \text{ J/mol} \approx 15 \text{ kJ/mole}$$

ADSORPTION AT SOLID INTERFACES

Adsorption of material at solid interfaces may take place from either an adjacent liquid or gas phase. The study of adsorption of gases is concerned 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 utilized in decolorizing solutions, adsorption chromatography, detergency, and wetting.

In many ways, the adsorption of materials from a gas or liquid onto a solid surface is similar to that discussed under liquid surfaces. Thus, adsorption of this type may

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 microsecond, whereas an atom in the surface of a nonvolatile metallic solid may have an average lifetime of 10^{37} seconds.²⁶ 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 may 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.

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 14-20. 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 STP (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 in Figure 14-20a.

One method of obtaining adsorption data is by the use of an apparatus similar to that shown in Figure 14-21, 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 may 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 based on one or more of the following equations.

Freundlich²⁷ suggested a relationship, the *Freundlich isotherm*,

$$y = \frac{x}{m} = kp^{1/n} \quad (14-49)$$

in which 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,

$$\log \frac{x}{m} = \log k + \frac{1}{n} \log p \quad (14-50)$$

which yields a straight line when plotted as seen in Figure 14-20b. The constant, $\log k$, is the intercept on the ordinate, and $1/n$ is the slope of the line.

Langmuir²⁸ 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 by θ , and the fraction of sites not occupied is $1 - \theta$. The rate r_1 of adsorption or condensation of gas molecules on the surface is proportional to the unoccupied spots $1 - \theta$ and to the pressure p , or

$$r_1 = k_1(1 - \theta)p \quad (14-51)$$

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

$$r_2 = k_2\theta \quad (14-52)$$

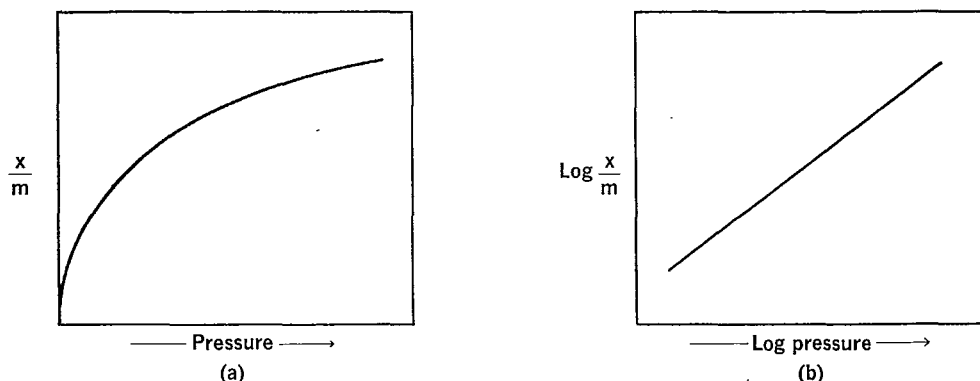


Fig. 14-20. Adsorption isotherms for a gas on a solid. (a) Amount x of gas adsorbed per unit mass m of adsorbent plotted against the equilibrium pressure. (b) Log of the amount of gas adsorbed per unit mass of adsorbent plotted against the log of the pressure.

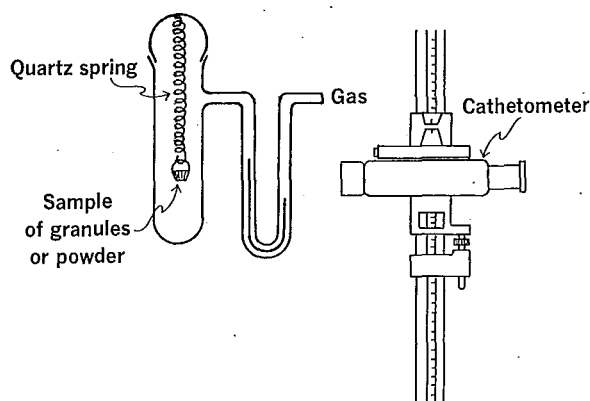


Fig. 14-21. Schematic of apparatus used to measure adsorption of gases on solids.

and at equilibrium $r_1 = r_2$ or

$$k_1(1 - \theta)p = k_2\theta \quad (14-53)$$

By rearrangement, we obtain

$$\theta = \frac{k_1p}{k_2 + k_1p} = \frac{(k_1/k_2)p}{1 + (k_1/k_2)p} \quad (14-54)$$

We can replace k_1/k_2 by b and θ by y/y_m , in which 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 gram of the adsorbent can adsorb when the monolayer is complete. Inserting these terms into equation (14-54) produces the formula

$$y = \frac{y_m b p}{1 + b p} \quad (14-55)$$

which is known as the *Langmuir isotherm*. By inverting equation (14-55) and multiplying through by p , it may be written for plotting as

$$\frac{p}{y} = \frac{1}{b y_m} + \frac{p}{y_m} \quad (14-56)$$

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 (14-49), (14-50), (14-55), and (14-56) are adequate for the description of curves only of the type shown in Figure 14-20a. This is known as the Type I isotherm. Extensive experimentation, however,

has shown that there are four other types of isotherms, as seen in Figure 14-22, 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 Teller and termed for convenience the *BET equation*. This equation may be written as

$$\frac{p}{y(p_0 - p)} = \frac{1}{y_m b} + \frac{b - 1}{y_m b} \frac{p}{p_0} \quad (14-57)$$

in which 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 14-22 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 smaller than 2.0 in the

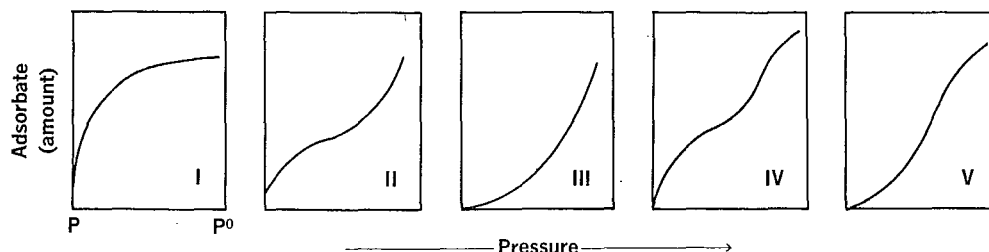


Fig. 14-22. Various types of adsorption isotherms.

BET expression, equation (14-57). Types IV and V frequently involve hysteresis and appear as shown in Figures 14-23 and 14-24, 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 since the dissolution rates of drug particles depend, in part, on their surface area (see p. 331). Other techniques for determining specific surface are discussed in Chapter 16.

The Solid-Liquid Interface. Drugs such as dyes, alkaloids, fatty acids, and even inorganic acids and bases may be absorbed from solution onto solids such as charcoal and alumina. The adsorption of solute molecules from solution may be treated in a manner analogous to the adsorption of molecules at the solid-gas interface. Isotherms, which fit one or more of the equations mentioned previously, may 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 clays²⁹ was capable of being expressed by the Langmuir equation in the form

$$\frac{c}{y} = \frac{1}{by_m} + \frac{c}{y_m} \quad (14-58)$$

in which 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

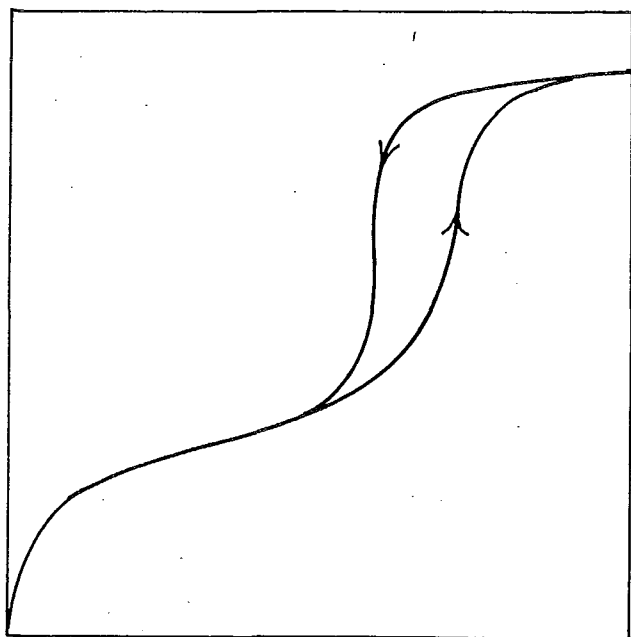


Fig. 14-23. Type IV isotherm showing hysteresis.

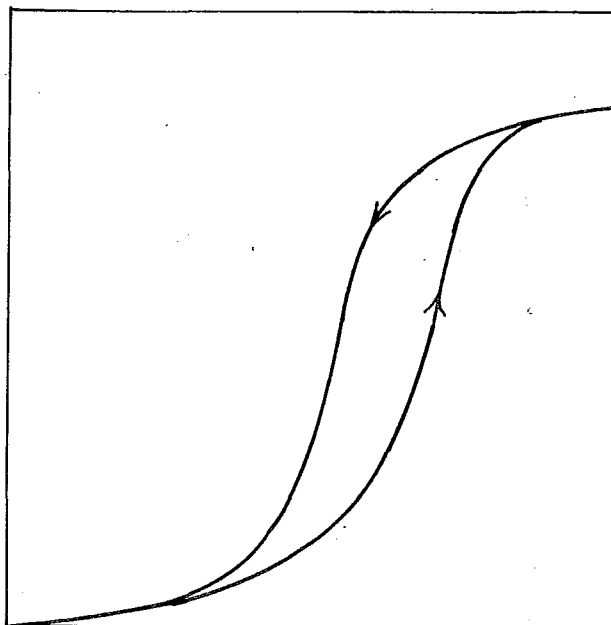


Fig. 14-24. Type V isotherm showing hysteresis.

Arnista³⁰ investigated 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 14-25.

The smaller the slope, the better the adsorption. Thus, it can be calculated from Figure 14-25 that an equilibrium concentration of, say, 400 mg strychnine/100 mL of solution, x/m for the three adsorbents is 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 bioabsorption. The absorption of quinidine salts (an antiarrhythmic agent), for example, is impaired by combining with kaolin, pectin, montmorillonite, and similar adsorbents. Moustafa et al.³¹ found that the adsorption of quinidine sulfate by antacid and antidiarrheal preparations, Kaopectate, Simeco, magnesium trisilicate, and bismuth subnitrate, were well expressed by both Freundlich and Langmuir adsorption isotherms.

Nikolakakis and Newton³² 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

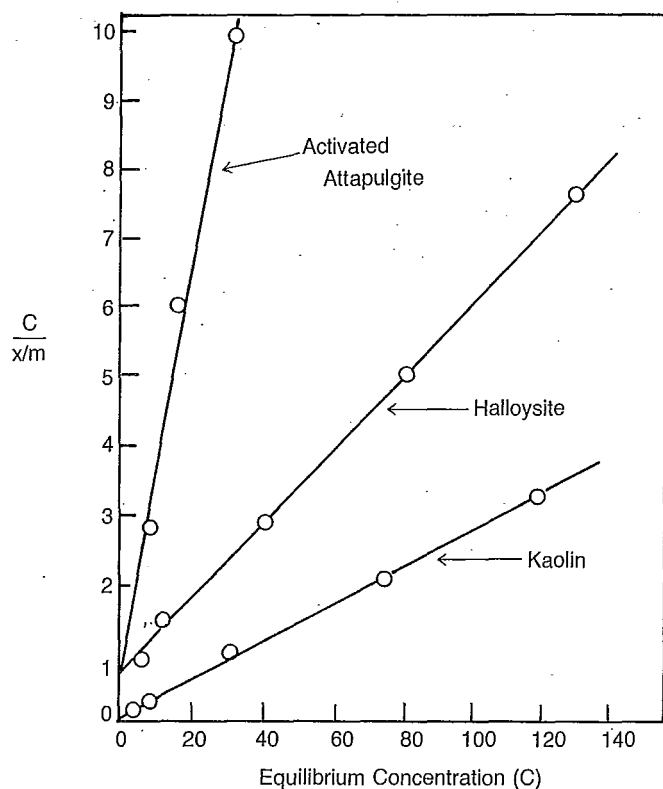


Fig. 14-25. Adsorption of strychnine on various clays. (Modified from M. Barr and S. Arnista, *J. Am. Pharm. Assoc., Sci. Ed.* 46, 486, 488, 1957.)

sucrose-free formulations for diabetic patients. During blending, a fine powder of an antibiotic is adsorbed onto the surface of coarse particles of sorbitol. Nikolakakis and Newton 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 (14-58), the b and y_m values can be computed. 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,⁴ pp. 398-407).

Example 14-13. The values of c/y against c for the solid-solid adsorption of cephalixin monohydrate onto sorbitol are

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

Calculate b and y_m .

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

Using a regression analysis of c/y (y -axis) against c (x -axis), the equation is $c/y = 25.2 + 5.93c$.

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

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

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

Activated Charcoal. In an investigation of the adsorption of drugs on activated charcoal and its effects on the bioabsorption of drugs in man, Tsuchiya and Levy³³ concluded that reasonable in vivo predictions could be made from in vitro studies concerning the antidotal effectiveness of activated charcoal.

Activated charcoal is used as an antidote in poisonings by sulfonylureas such as tolbutamide, acetohexamide, and other drug and nondrug compounds. Contrary to earlier reports, Kannisto and Neuvonen³⁴ reported that charcoal effectively adsorbs sulfonylureas and can prevent their gastrointestinal absorption and subsequent toxicity in cases of overdose. The data were analyzed by the authors using the Langmuir adsorption isotherm.

In large overdosage, the analgesic acetaminophen (paracetamol) may cause liver damage, renal failure, and death owing to hepatotoxicity and sometimes renal tubular necrosis (15 grams may be fatal). Activated charcoal has been used to adsorb acetaminophen, and acetylcysteine to neutralize the toxic metabolites that deplete hepatic glutathione. However, there has been concern that activated charcoal will absorb the acetylcysteine as well as the acetaminophen and reduce or nullify the effectiveness of acetylcysteine in preventing liver damage and kidney failure. Rybolt et al.³⁵ have shown, however, that acetylcysteine is adsorbed by charcoal in sufficiently small amounts that the concurrent use of acetylcysteine and activated charcoal is a useful treatment for acetaminophen poisoning.

The adsorption of drugs by activated charcoal not only prevents bioabsorption from the gastrointestinal tract but also may increase the diffusion of the drug from the tissues into the gastrointestinal tract and elimination from the body by a process called *gastrointestinal dialysis*. In this process the adsorbing charcoal establishes a gradient between the systemic circulation in the body and the fluids in the gastrointestinal tract.³⁶ A rather thorough list of references to the systemic removal of drugs by charcoal adsorption is given in the 1988 paper by Huang and Tzou.³⁶

Gessner and Hasan³⁷ studied the adsorption of solutes from aqueous solution onto activated charcoal. The adsorption data gave a good fit to the Freundlich isotherm and a poor fit to the Langmuir isotherm, even for published data that were considered earlier to adhere well to the Langmuir isotherm. Furthermore, the Freundlich isotherm accounted better for the effectiveness of activated charcoal to serve as an in vivo antidote against drug overdosing and poisoning.

Kleeman and Bailey³⁸ developed an in vitro approach for quantitatively ranking the affinity of drugs, toxicants, and suspended materials used in the treatment of public water supplies, to activated charcoal using high-performance liquid chromatography as the analytic tool. The authors provide an excellent review of the literature.

The adsorption of phenobarbital from simulated intestinal and gastric fluids by two activated charcoals of different pore size and specific surface area (pp. 440, 393) was investigated by Wurster et al.,³⁹ fitting the data to the linearized Langmuir expression (see equation [14-58]) and to a least-squares regression equation. A new activated charcoal with a specific surface of nearly 3000 m²/g was found to adsorb about three times as much phenobarbital as the charcoal with a specific surface of 1500 m²/g. It was concluded that the poorer adsorption by the older charcoal occurred because the site spacings on its surface were not sufficient for optimum arrangement of the phenobarbital molecules.

Hajratwala⁴⁰ referred to adsorption of drugs on charcoal, talc, and other adsorbents and discussed the manner of obtaining Langmuir and Freundlich constants from adsorption isotherms.

Wetting. Adsorption at solid surfaces is involved in the phenomena of wetting and detergency.

A *wetting agent* is a surfactant that, when dissolved in water, lowers the advancing contact angle and aids in displacing an air phase at the surface and replacing 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 may 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.

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 14-26, the contact angle between a liquid and a solid may be 0°, signifying complete wetting, or it may approach 180°, at which wetting is insignificant. The contact angle may also have any value between these limits, as illustrated in the sketches. At equilibrium, the surface and interfacial tensions can be resolved into

$$\gamma_s = \gamma_{SL} + \gamma_L \cos \theta \quad (14-59)$$

which is known as Young's equation.

When γ_s of equation (14-59) is substituted into equation (14-19), we have

$$S = \gamma_L (\cos \theta - 1) \quad (14-60)$$

and combining equation (14-59) with equation (14-16) results in

$$W_a = W_{SL} = \gamma_L (1 + \cos \theta) \quad (14-61)$$

which is an alternative form of Young's equation. Equations (14-60) and (14-61) are useful expressions since they do not include γ_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 p. 371).

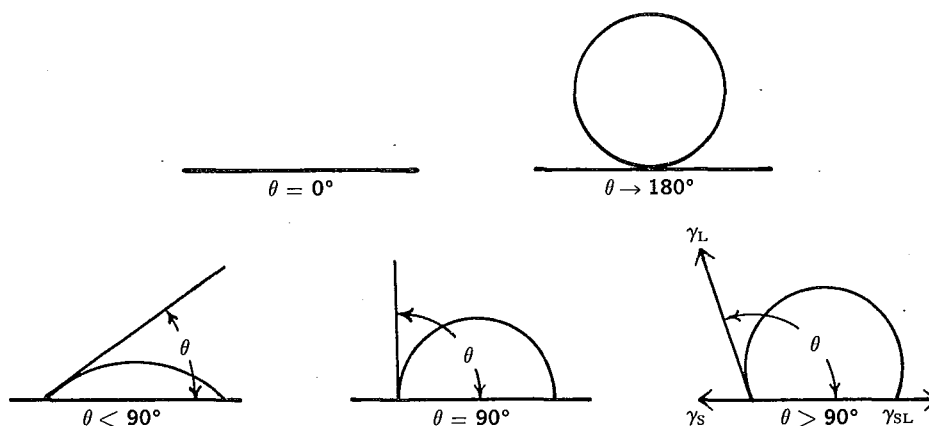


Fig. 14-26. Contact angles from 0° to 180°.

Example 14-14. 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.⁴¹ The contact angle of water on the acetaminophen tablets, the surface tension of the liquid, and the disintegration time of the tablets are found 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	$\gamma(\text{Nm}^{-1})^*$	$\cos \theta$	t (min)
Povidone (PVP)	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 Jm^{-1} or newtons, the SI force unit, divided by meters. In the cgs system γ is expressed in the force unit of dyne divided by cm, or in erg/cm^2 .

Using equations (14-60) and (14-61), 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 $W_{SL} = \gamma (1 + \cos \theta)$
PVP	$W_{SL} = 71.23 (1 + 0.7455) = 124.33 \text{ Nm}^{-1}$
Gelatin	$W_{SL} = 71.23 (1 + 0.7230) = 122.73 \text{ Nm}^{-1}$
Tapioca	$W_{SL} = 71.33 (1 + 0.7570) = 125.33 \text{ Nm}^{-1}$

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. The higher the work of adhesion the stronger is the bond between water and the tablet surface and the better is the wetting.

From the table, we observe the tablet disintegration times to be in 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, which were not considered in the study, cause the relationship to be only qualitative.

Zisman and his associates⁴² found that when the cosine of the contact angle, $\cos \theta$, 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 may be extrapolated to $\cos \theta = 1$; 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*

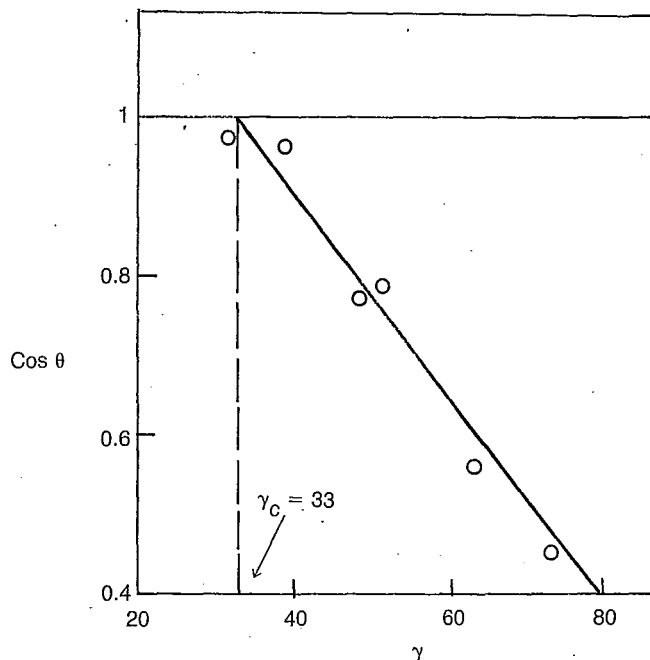


Fig. 14-27. Critical surface tension (Zisman) plot for a model skin. (From J. C. Charkoudian, J. Soc. Cosmet. Chem. 39, 225, 1988, reproduced with permission of the copyright owner.)

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 14-27. Zisman concluded that γ_c was characteristic for each solid, Teflon, for example, having a value of about 18 erg/cm^2 . Since the surface of Teflon consists of $-\text{CF}_2-$ groups, Zisman reasoned that all surfaces of this nature would have critical surface tensions of about 18 erg/cm^2 , and any liquid with a surface tension less than 18 erg/cm^2 would wet a surface composed of $-\text{CF}_2-$ groups.^{43,44}

Example 14-15. Charkoudian⁴⁵ 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 lipid-like 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.

Plot the $\cos \theta$ versus γ and compute the critical surface tension γ_c for complete wetting of the artificial skin surface. The values of γ_c for in vivo human skin are about 26 to 28 dyne/cm .

From the results obtained, which liquid in the table below would be expected to best wet the model skin surface?

The plot is shown in Figure 14-27. Although the liquids in the table do not constitute a homologous series, they appear to fit nicely the Zisman principle, producing a straight line that extrapolates to $\cos \theta$ corresponding to a critical surface tension of $\gamma_c = 33 \text{ dyne/cm}$.

Mineral oil, with a surface tension of 31.9 dyne/cm , most closely approximates the critical surface tension $\gamma_c = 33 \text{ dyne/cm}$ of the

Liquid	Water	Glycerin	Diiodomethane	Ethylene glycol	Benzyl alcohol	Mineral oil
γ (dyne/cm)	72.8	63.4	50.8	48.3	39.2	31.9
$\cos \theta$	0.45	0.56	0.79	0.77	0.96	0.97

model skin surface. For a more exact calculation of γ_c , least-squares linear regression analysis may be applied to yield

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

For the specific value of $\cos \theta = 1$, we obtain $\gamma_c = 33.0$ dyne/cm. It is noted that the critical surface tension γ_c for the artificial skin used in this study is somewhat higher ($\gamma_c = 33.0$ dyne/cm) than values reported elsewhere in the literature for human skin ($\gamma_c = 26$ – 28 dyne/cm). According to the author, this is 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, since no convenient method is known for directly measuring the surface tension of a solid surface. As a result of these difficulties, empiric tests are used in industry, one of the best known wetting tests being that of Draves. 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 yet 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. However, see *Problems 14-11* and *14-14*.

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. Since 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 18.

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. 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 gram-positive organisms are attacked more easily by anionic agents than are 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.⁴⁶ 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. It is a well-known fact that some surfactants increase the rate of intestinal absorption, while 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 has been reviewed by Mulley⁴⁷ and by Gibaldi and Feldman.⁴⁸

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 may be used to break the foam and are known as *antifoaming agents*. Foams are sometimes useful in pharmacy but are usually a nuisance and are prevented or destroyed when possible. The undesirable foaming of solubilized liquid preparations poses a problem in formulation.

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 will be reserved for the chapters dealing with colloidal systems (Chapter 15) and suspensions (Chapter 18).

Particles dispersed in liquid media. *Dr. Ind. Pharm. Ex.* 1055
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