4

Gastrointestinal Absorption—Physicochemical Considerations

Drug absorption is influenced by many physiologic factors, but it also depends on the solubility, particle size, chemical form, and other physicochemical characteristics of the drug itself. Clinically significant differences in the absorption of closely related drugs such as lincomycin and clindamycin, ampicillin and pivampicillin, or secobarbital and sodium secobarbital are the result of differences in physicochemical properties.

ABSORPTION OF DRUGS FROM SOLUTION

The dissociation constant and lipid solubility of a drug, as well as the pH at the absorption site, dictate the absorption characteristics of a drug from solution. The interrelationship among these parameters is known as the pH-partition theory of drug absorption. This theory has been advanced by extensive investigations in laboratory animals[1-5] and in man,[6] and provides a basic framework for the understanding of drug absorption from the gastrointestinal tract and drug transport across biologic barriers in the body.

The pH-partition theory of drug absorption is based on the assumption that the gastrointestinal tract is a simple lipid barrier to the transport of drugs and chemicals. Accordingly, the nonionized form of an acid or basic drug, if sufficiently lipid soluble, is absorbed but the ionized form is not. The larger the fraction of drug in the nonionized form at a specific absorption site, the faster is the absorption. Acid and neutral drugs may be absorbed from the stomach but basic drugs are not. The rate of absorption is related to the oil-water partition coefficient of a drug; the more lipophilic the compound, the faster is its absorption.

Drug pKa and Gastrointestinal pH

The fraction of drug in solution that exists in the nonionized form is a function of both the dissociation constant of the drug and the pH of the solution. The dissociation constant is often expressed for both acids and bases as a pKa (the negative logarithm of the acidic dissociation constant). The pKa values of several drugs and the relative acid or base strengths of these compounds are shown in Figure 4–1. The relationship between pH and pKa, and the extent of ionization is given by the Henderson-Hasselbalch equation:

for an acid

$$pKa - pH = \log (fu/fi)$$

and for a base

$$pKa - pH = \log (fi/fu)$$

where fu and fi are the fractions of the drug present in the un-ionized and ionized forms, respectively.

Most acid drugs are predominantly un-ionized at the low pH of gastric fluids and may be absorbed from the stomach as well as from the intestines. The pH range found in the gastrointestinal tract from the stomach to the colon is about 1 to 8. Very weak acids (pKa > 8) such as phenytoin, theophylline, or glutethimide are essentially un-ionized throughout the gastrointestinal tract. The ionization of weak acids with pKa values ranging from about 2.5 to 7.5 is sensitive to changes in pH. More than 99% of the weak acid aspirin (pKa = 3.5) exist as un-ionized drug in gastric fluids at pH 1. On the other hand, only about 0.1% of aspirin is un-ionized at pH 6.5 in the fluids of the small intestine. Despite this seemingly unfavorable ratio of non-

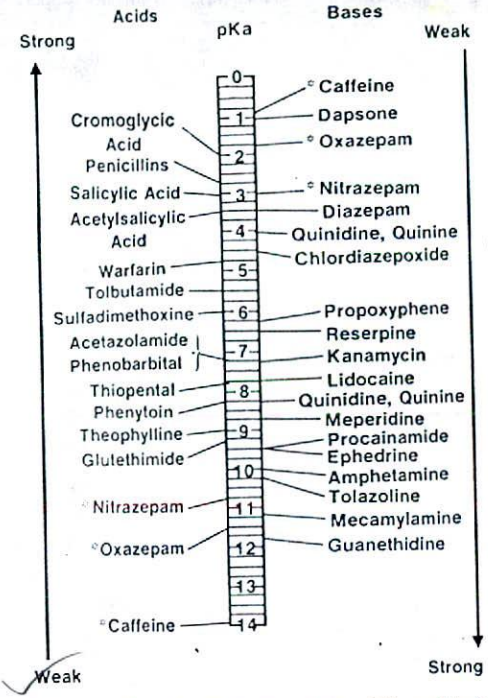

Fig. 4–1. The pKa values of certain acidic and basic drugs. Those drugs denoted with an asterisk* are amphoteric. (From Rowland, M., and Tozer, T.N.[7])

ionized to ionized drug, aspirin and most weak acids are well absorbed in the small intestine. A large surface area and a relatively long residence time in the small intestine are contributing factors. These factors minimize the need for a large fraction of the drug to be in an un-ionized form in the small intestine. Strong acids (e.g., cromolyn) are ionized throughout the gastrointestinal tract and are poorly absorbed.

Table 4–1. Comparison of Gastric Absorption at pH 1 and pH 8 in the Rat*

	pKa	% Absorbed at pH 1	% Absorbed at pH 8
Acids			
5-Sulfosalicylic	<2.0	0	0
5-Nitrosalicylic	2.3	52	16
Salicylic	3.0	61	13
Thiopental	7.6	46	34
Bases			
Aniline	4.6	6	56
p-Toluidine	5.3	0	47
Quinine	8.4	0	18
Dextromethorphan	9.2	0	16

*Data from Schanker, L.S., et al.[3]

Table 4–2. Comparison of Intestinal Absorption in the Rat at Several pH Values*

	pKa	% Absorbed at pH 4	pH 5	pH 7	pH 8
Acids					
5-Nitrosalicylic	2.3	40	27	0	0
Salicylic	3.0	64	35	30	10
Acetylsalicylic	3.5	41	27	—	—
Benzoic	4.2	62	36	35	5
Bases					
Aniline	4.6	40	48	58	61
Amidopyrine	5.0	21	35	48	52
p-Toluidine	5.3	30	42	65	64
Quinine	8.4	9	11	41	54

*Data from Schanker, L.S., et al.[3]

Most weak bases are poorly absorbed, if at all, in the stomach since they are largely ionized at low pH. Codeine, a weak base with a pKa of about 8 will have only 1 of every million molecules in the nonionized form in gastric fluid at pH 1. The pH range of the intestines from the duodenum to the colon is about 5 to 8. Weakly basic drugs (pKa < 5), such as dapsone, diazepam, or chlordiazepoxide, are essentially un-ionized throughout the intestines. Strong bases, those with pKa values of 5 to 11, show pH-dependent absorption. Stronger bases, such as mecamylamine or guanethidine, are ionized throughout the gastrointestinal tract and tend to be poorly absorbed.

Convincing evidence of the importance of dissociation in drug absorption is found in the results of studies in which the pH at the absorption site is changed. According to the Henderson-Hasselbalch equations, an increase in the pH of the stomach should retard the absorption of weak acids but promote the absorption of weak bases; this is evident in Table 4–1. A clinical study has found similar results in healthy subjects. The gastric absorption of aspirin is considerably reduced when the drug is given in a buffered solution (gastric pH about 5) compared to the results following administration of aspirin in an unbuffered solution (gastric pH about 2). The data in Table 4–2 permit a comparison of the intestinal absorption of several drugs from buffered solutions ranging from pH 4 to pH 8. These results are consistent with pH-partition theory.

Lipid Solubility

Certain drugs may be poorly absorbed after oral administration even though they are largely un-ionized in the small intestine; low lipid solubility

Table 4–3. Comparison of Barbiturate Absorption in Rat Colon and Partition Coefficient (Chloroform/Water) of Undissociated Drug*

Barbiturate	Partition coefficient	% Absorbed
Barbital	0.7	12
Aprobarbital	4.9	17
Phenobarbital	4.8	20
Allylbarbituric acid	10.5	23
Butethal	11.7	24
Cyclobarbital	13.9	24
Pentobarbital	28.0	30
Secobarbital	50.7	40
Hexethal	>100	44

*Data from Schanker, L.S.[5]

of the uncharged molecule may be the reason. A guide to the lipophilic nature of a drug is its partition coefficient between a fat-like solvent, such as chloroform or butanol, and water or an aqueous buffer. The effect of lipid solubility on the absorption of a series of barbituric acid derivatives is shown in Table 4–3. Each compound has about the same pKa. In this case, an almost perfect rank correlation exists between partition coefficient and extent of absorption.

The critical role of lipid solubility in drug absorption is a guiding principle in drug development. Polar molecules such as gentamicin, ceftriaxone, heparin, and streptokinase are poorly absorbed after oral administration and must be given by injection. Lipid soluble drugs with favorable partition coefficients are usually well absorbed after oral administration. The selection of a more lipid soluble compound from a series of research compounds often results in improved pharmacologic activity.

Occasionally, the structure of an existing drug can be modified to develop a similar compound with improved absorption. The development of clindamycin, which differs from lincomycin by the single substitution of a chloride for a hydroxyl group, is an example. Even slight molecular modification, however, runs the risk of also changing the efficacy and safety profile of the drug. For this reason, medicinal chemists prefer the development of lipid soluble prodrugs of a drug with poor oral absorption characteristics.

A prodrug is a chemical modification, frequently an ester, of an existing drug that reverts back to the parent compound because of metabolism or chemical reaction in the body. An ideal prodrug is not found in the systemic circulation and has no intrinsic biologic activity. Prodrugs are developed to overcome one or more undesirable characteristics of the parent drug, i.e., bitter taste, poor solubility, pain on injection, poor distribution, or poor absorption.

Prodrugs designed to improve permeability and oral absorption are more lipid soluble than the parent drug and should be rapidly converted to the parent compound during absorption, in the gut wall or the liver. Pivampicillin, the pivaloyloxymethyl ester of ampicillin, is more lipid soluble and efficiently absorbed than the parent compound.[8] The ester appears to undergo rapid and essentially complete hydrolysis to ampicillin during absorption.

Another prodrug of ampicillin, bacampicillin, a semisynthetic carbonate ester of ampicillin, has also been introduced in the United States. It is rapidly and completely absorbed after oral administration, and completely hydrolyzed to ampicillin; no bacampicillin is detected in blood or tissues. Peak blood levels of ampicillin after oral administration of the prodrug are reached more quickly and are twice those found after an equivalent oral dose of the parent drug.[9] The poor oral absorption of carbenicillin has also been overcome to some degree by synthesizing a lipid-soluble indanyl ester that, once absorbed, is said to be rapidly hydrolyzed to the parent drug.[10]

Cefuroxime axetil is an oral form of the second-generation parenteral cephalosporin cefuroxime. The oral absorption of cefuroxime is negligible. The axetil form of the drug, an acetoxyethyl ester of cefuroxime, has increased lipid solubility, better gastrointestinal absorption, and sufficient oral bioavailability to be clinically useful. Bioavailability has varied from 35 to 50%. After absorption, it is hydrolyzed to cefuroxime.

Factors affecting the absorption of lipid-soluble prodrugs have been studied by Sommers, et al.,[11] who specifically examined the effect of food and of an increased gastric pH on the bioavailability of bacampicillin and cefuroxime axetil. In one study, healthy subjects received each of the prodrugs alone and after treatment with ranitidine and sodium bicarbonate to elevate gastric pH.

Reduced gastric acidity dramatically decreased the bioavailability of bacampicillin (as ampicillin) and cefuroxime axetil (as cefuroxime). The area under the curve (AUC) for serum levels of cefuroxime decreased from 36 (control) to 13 mg-hr/L (after ranitidine and bicarbonate administration) and urinary recovery decreased from 40 to 12% of the dose. The authors indicated that the most likely

explanation of the results with bacampicillin is that the ester becomes partially hydrolyzed before absorption when the gastric acidity is reduced by pretreatment with an H_2-receptor blocker and antacid. In the case of cefuroxime axetil, the authors suggest that optimum absorption of the prodrug requires a sufficiently low pH level in the stomach to allow the drug to dissolve in gastric juice.

Food also decreased the bioavailability of bacampicillin. In contrast, the gastrointestinal absorption of cefuroxime axetil was enhanced when the prodrug was taken after breakfast. The investigators suggested that the findings with cefuroxime axetil may be rationalized in terms of delayed gastric emptying and gastrointestinal transit allowing more complete dissolution or prolonged residence at optimal absorption sites in the small intestine.

The oral absorption of terbutaline may be improved considerably by administering it in the form of the dibutyrl ester.[12] Levodopa can be used to deliver dopamine in the treatment of heart failure.[13] We are familiar with the use of levodopa in Parkinson's disease, where levodopa crosses the blood-brain barrier and delivers dopamine to the central nervous system. A large amount of dopamine is also formed outside the CNS. Levels are sufficiently high and sustained to produce improvements in cardiac function in patients with severe heart failure.

Enalaprilat is a potent angiotensin-converting enzyme (ACE) inhibitor, effective in the treatment of hypertension, but its use is restricted to iv administration. It is a diacid, fully ionized in the small intestine and poorly absorbed. Enalapril, its inactive prodrug, has one carboxyl group esterified and is well-absorbed after oral administration and converted in the liver to enalaprilat.

DEVIATIONS FROM THE pH-PARTITION THEORY

The pH-partition theory provides a basic framework for understanding drug absorption, but it is an oversimplification of a more complex process. For example, theory indicates that the relationship between pH and permeation or absorption rate is described by an S-shaped curve corresponding to the dissociation curve of the drug (see Fig. 4–2). For a simple acid or base, the inflection point of the pH-absorption curve should occur at a pH equal to the pKa of the drug. This is rarely observed experimentally. In general, pH-absorption curves are less steep than expected and are shifted to higher pH values for acids and to lower pH values for bases. The pH-absorption curves for salicylic acid (a weak acid with a pKa of about 3) and for ephedrine (a weak base with a pKa of about 9.5) have inflection points at about pH 8 and pH 6.5, respectively.[17] Theory predicts little absorption of salicylic acid at pH 8 because at this pH the drug would be almost completely ionized; in fact, the absorption rate of salicylate across the small intestine at pH 8 is about 50% of the maximum absorption rate.

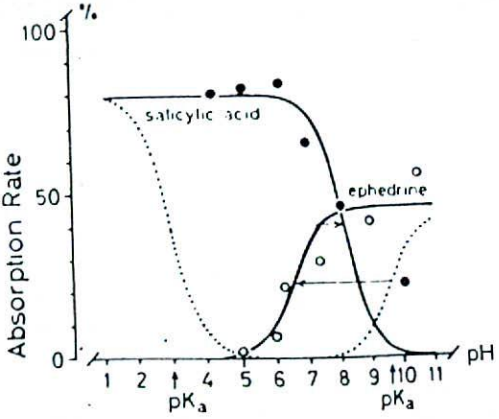

Fig. 4–2. Relationship between absorption rates of salicylic acid and ephedrine and bulk phase pH in the rat small intestine in vivo. Dashed lines indicate curves predicted by the pH-partition theory in the absence of an unstirred layer. (From Winne, D.[17])

Many investigators have attempted to rationalize the experimental deviations from the unmodified pH-partition theory and there is no lack of suggestions. Several of the more interesting factors that may contribute to the deviations are absorption of the ionized form of the drug, the presence of an unstirred diffusion layer adjacent to the cell membrane, and a difference between lumenal pH and the pH at the surface of the cell membrane.

Absorption of the Ionized Form of a Drug

Certain quaternary ammonium drugs elicit systemic pharmacologic effects after oral administration, suggesting that the restriction to ionized forms of a drug by the gastrointestinal barrier may not be absolute. Several in situ and in vivo studies support this idea. It is conceded today that absorption of organic anions and cations does take place in the small intestine but at a much slower rate than the

corresponding un-ionized form of the drug. Crouthamel et al.[14] have estimated that the permeability ratio of un-ionized to ionized drug across the rat small intestine is about 3 for barbital and about 5.5 for sulfaethidole, but these estimates may be low because they do not take into account the presence of a stagnant aqueous diffusion layer or a difference between lumenal and microclimate pH. Hogerle and Winne,[15] using a more comprehensive absorption model, suggest a ratio of about 190 for benzoic acid. The absorption of ionized forms of a drug would cause the pH-absorption curve to shift to the right for a weak acid and to the left for a weak base; the extent of the shift depends on the relative permeability of the ionized form of the drug.

Mucosal Unstirred Layer

The aqueous stagnant layer is now a well-recognized component of the gastrointestinal barrier to drug absorption (see Fig. 4–3). It is found at the villous surface of the mucosa. The thickness of the layer in the small intestine has been estimated at several hundred micrometers. The unstirred layer is particularly important for drugs that penetrate the barrier rapidly; its role in absorption also varies directly with the effective molecular weight of the drug. The unstirred layer is the rate-limiting barrier for the intestinal absorption of lipids from micellar solutions.[17]

The thickness of the unstirred layer can be reduced by, in effect, stirring the drug solution in the intestinal lumen. The absorption rate of butanol, antipyrine, salicylic acid, and urea from rat jejunal loops perfused in vivo is increased significantly if the intraluminal solution is mixed more efficiently by the simultaneous perfusion of air.[18] The increased absorption rate is mainly the result of reducing the effective thickness of the unstirred layer.

The net effect of the unstirred layer on the pH-absorption profile of a weak electrolyte is a reduction in absorption rate, particularly and perhaps exclusively with respect to the un-ionized form of the drug, and a shift in the inflection point of the curve to the right for acids and to the left for bases.[14,19,20]

A similar unstirred layer over the gastric mucosa, estimated to be 800 to 1000 μm thick, may protect the stomach against injury from certain drugs and chemicals. Duane et al.[21] have specifically considered the role of the unstirred layer in protecting the gastric mucosa from bile salt arising from reflux of duodenal contents into the stomach. Some believe that this reflux is a factor in certain forms of gastritis.

Damage to the gastric mucosa by bile salts results from dissolution of mucosal membrane lipids by lumenal micelles. This damage is associated with increased back-diffusion of hydrogen ions. Duane et al. propose that "the presence of an unstirred water layer on the surface of the gastric mucosa could protect against bile salt injury either by creating a concentration gradient of bile salt from lumen to mucosal surface or by slowing diffusion of lipid-laden mixed micelles away from the mucosal surface."

To support this hypothesis, Duane et al. measured the back-diffusion of hydrogen ions across the rat gastric mucosa before and after exposure to a bile salt solution that was either unmixed or mixed by continuous withdrawal and injection. Continuous mixing of gastric contents decreased the thickness of the unstirred water layer by 45%, from 880 to 448 μm. Mixing also increased back-diffusion of hydrogen ions by about 60% and nearly doubled the efflux of mucosal phospholipid and cholesterol in the bile salt solution. These findings provide

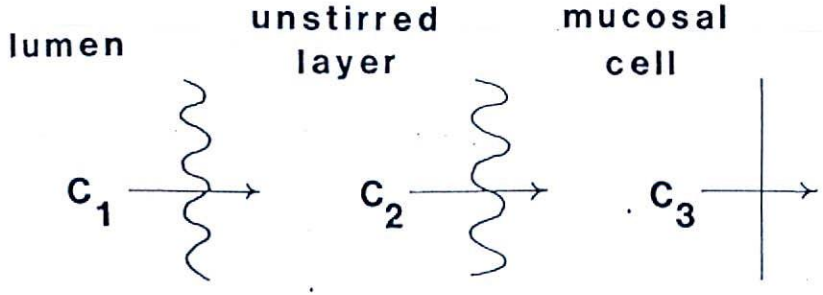

Fig. 4–3. Schematic representation of barriers to gastrointestinal absorption.

evidence that the unstirred water layer helps protect the gastric mucosa from bile-salt injury.

Drug-related gastric injury probably involves mechanisms different from those associated with bile-salt damage. Nevertheless, there is merit in considering the role of the unstirred layer in local adverse effects of drugs. One could imagine that a steep concentration gradient across an unstirred layer could lower drug concentration at the mucosal surface and reduce toxicity.

Microclimate pH

Another factor that can contribute to the deviation of pH-absorption curves from those predicted by the unmodified pH-partition theory is a difference between the lumenal pH and the microclimate or virtual pH at the cell membrane. The microclimate-pH hypothesis is supported by the fact that H^+ ions are secreted into the intestinal lumen.

Hogerle and Winne[15] attempted to characterize the microclimate directly by measuring the pH at the surface of the jejunal mucosa in vivo. The pH of the lumenal solutions was varied over a pH range of 4 to 10.8. In all cases, after lowering the pH electrode down to the tips of the villi, the pH shifted towards neutral. At a lumenal pH of 7, the microclimate pH was 6.4. Microclimate pH varied relatively little with changes in lumenal pH, ranging from about 5.7 to 7.4 over the entire lumenal pH range. The authors proposed the following relationship between microclimate pH and lumenal pH:

$$MpH = A + B\,(LpH - 7) + C\,(LpH - 7)^3, \quad (4\text{–}1)$$

where MpH is the microclimate pH, LpH is the lumenal pH, $A = 6.36$, $B = 12.2 \times 10^{-2}$, and $C = 10.3 \times 10^{-3}$. The authors also proposed that a microclimate pH must be invoked to adequately explain the pH-absorption profile for benzoic acid in the rat jejunum.

A Unifying Hypothesis

Hogerle and Winne[15] have developed a model for intestinal absorption that accounts for the factors discussed above. According to this model, the absorption rate of a drug may be described by the following equation:

$$\text{absorption rate} = (C \times A)/[(T/D) + 1/Pu(fu + fi \times Pi/Pu)] \quad (4\text{–}2)$$

where C is drug concentration in the lumen, A is the absorptive surface area, T is the thickness of the unstirred layer, D is the diffusion coefficient of the drug, *fu* and *fi* are the fractions of the unionized and ionized forms of the drug, and *Pu* and *Pi* are the permeability coefficients for the un-ionized and ionized forms of the drug.

The extent of dissociation is a function of the pKa of the drug and microclimate pH; *fu* and *fi* are calculated from the Henderson-Hasselbalch equation. For a weak acid,

$$pKa - MpH = \log (fu/fi) \quad (4\text{–}3)$$

and for a weak base,

$$pKa - MpH = \log (fi/fu) \quad (4\text{–}4)$$

The microclimate pH (MpH) is a function of lumenal pH (LpH), according to Equation 4–1.

Equation 4–2 has been used to describe the pH-absorption rate profiles for benzoic acid and aminopyrine under stirred and unstirred conditions.[15] The extension of the pH-partition theory to incorporate the effects of the unstirred layer and microclimate pH provides a far more satisfactory rationalization of the experimental data.

ABSORPTION OF DRUGS FROM SOLID DOSAGE FORMS AND SUSPENSIONS

When a drug is given orally in the form of a tablet, capsule, or suspension, the rate of absorption is often controlled by how fast the drug dissolves in the fluids at the absorption site. In other words, dissolution rate is often the *rate-limiting* (slowest) step in the sequence,

Solid drug $\xrightarrow{\text{Dissolution}}$ Drug in solution at absorption site $\xrightarrow{\text{Absorption}}$ Drug in systemic circulation

When dissolution is the controlling step in the overall process, absorption is said to be *dissolution rate limited*. An example of dissolution rate-limited absorption is shown in Figure 4–4, which depicts the absorption of aspirin in man from solution and from two different types of tablets.[22] Absorption from solution proceeds more rapidly than from tablets. Whenever a drug is more rapidly absorbed from solution than from a solid dosage form, it is likely that absorption is rate-limited by dissolution.

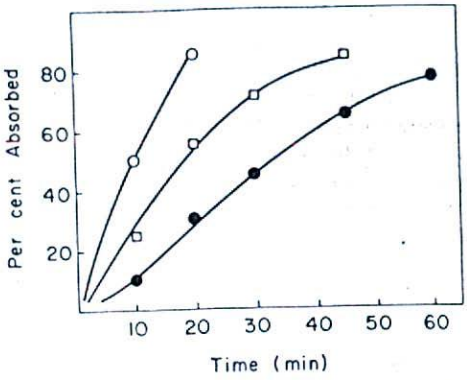

Fig. 4–4. Absorption of aspirin after oral administration of a 650-mg dose in solution (○), in buffered tablets (□), or in regular tablets (●). (Data from Levy, G., Leonards, J.R., and Procknal, J.A.[22])

A general relationship describing the dissolution process was first observed by Noyes and Whitney.[23] The Noyes-Whitney equation states that:

$$dC/dt = kS\ (C_s - C) \qquad (4–5)$$

where dC/dt is the dissolution rate, k is a constant, S is the surface area of the dissolving solid, C_s is the solubility of the drug or chemical in the solvent, and C is the concentration of the material in the solvent at time t. The constant k has been shown to be equal to D/h, where D is the diffusion coefficient of the dissolving material, and h is the thickness of the *diffusion layer*. The diffusion layer, like the unstirred water layer in the intestine, is a thin, stationary film of solution adjacent to the surface of the solid. The layer is saturated with drug; drug concentration in the layer is equal to C_s. The term $(C_s - C)$ in Equation 4–5 represents the concentration gradient between the diffusion layer and the bulk solution. If absorption is dissolution rate-limited, C is negligible compared to C_s. Under these conditions, Equation 4–5 may be written as:

$$dC/dt = DSC_s/h \qquad (4–6)$$

Equation 4–6 describes a diffusion-controlled dissolution process.

It is envisioned that when the solid is introduced to the dissolution medium, the drug rapidly saturates the diffusion layer. Drug molecules diffuse from the saturated layer to the bulk (the slow step in the dissolution process) but are immediately replaced in the diffusion layer from the solid surface.

Equation 4–6 is an oversimplified representation of the dynamics of dissolution; nevertheless, it is qualitatively useful and permits a consideration of the effects of certain important factors on dissolution rate. The solubility (C_s) of many drugs increases with increasing temperature. Therefore, dissolution is temperature-dependent. The diffusion coefficient (D) is inversely related to viscosity; dissolution rate decreases as the viscosity of the solvent increases. The degree of agitation or stirring of the solvent can affect the thickness of the diffusion layer (h). The greater the agitation, the thinner is the layer and the more rapid is the dissolution. Changes in the characteristics of the solvent, such as pH, that affect the solubility of the drug affect the dissolution rate accordingly. Similarly, the use of different salts, or other chemical or physical forms of a drug, which have a solubility or effective solubility different from that of the parent drug, usually affect dissolution rate. Increasing the surface area (S) of drug exposed to the dissolution medium, by reducing the particle size or by attaining more effective wetting of the solid by the solvent, usually increases the dissolution rate. In the discussion that follows, some of the more important factors affecting dissolution are considered in greater detail.

Dissolution and pH

The solubility of a weak acid or base can change considerably as a function of pH. Therefore, differences in dissolution rate are expected in different regions of the gastrointestinal tract.

The total solubility (C_s) of a weak acid is given by:

$$C_s = [HA] + [A^-] \qquad (4–7)$$

where [HA] is the intrinsic solubility of the nonionized acid (denoted as C_o) and $[A^-]$ is the concentration of its anion, which is infinitely soluble. The concentration of the anion can be expressed in terms of the dissociation constant, Ka, and C_o; that is,

$$C_s = C_o + \frac{KaC_o}{[H^+]} \qquad (4–8)$$

In a similar manner, the solubility of a weak base is given by:

$$C_s = C_o + \frac{C_o[H^+]}{Ka} \qquad (4–9)$$

By substituting Equations 4–8 and 4–9 into

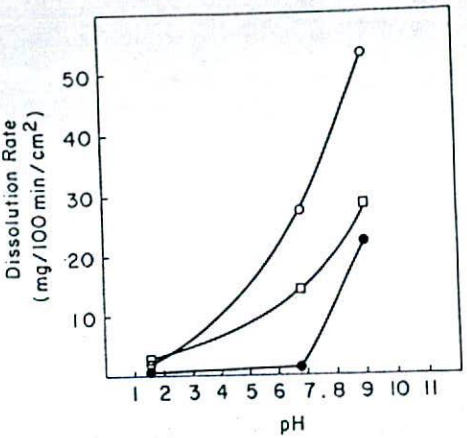

Fig. 4–5. pH-Dependent dissolution of salicylic acid (○), benzoic acid (□), and phenobarbital (●).

Equation 4–6 (the modified Noyes-Whitney relationship), the following dissolution rate equations are obtained:

for a weak acid

$$\frac{dC}{dt} = K'\left[C_o + \frac{Ka\,C_o}{[H^+]}\right] \qquad (4–10)$$

or

$$\frac{dC}{dt} = K'\,C_o\left[1 + \frac{Ka}{[H^+]}\right] \qquad (4–11)$$

and for a weak base

$$\frac{dC}{dt} = K'\,C_o\left[1 + \frac{[H^+]}{Ka}\right] \qquad (4–12)$$

where K′ is equal to DS/h.

Equations 4–11 and 4–12 indicate that the dissolution rate of weak acids increases with increasing pH (i.e., decreasing $[H^+]$), whereas the dissolution rate of weak bases decreases with increasing pH. The dissolution rate of weak bases is at a maximum in gastric fluids but that of weak acids is at a minimum. The dissolution rate of a weak acid increases as the undissolved drug particles are transported to the more alkaline regions of the gastrointestinal tract. Dissolution rates of some weak acids as a function of pH are shown in Figure 4–5.

It is important for poorly soluble weakly basic drugs to dissolve rapidly in the stomach, since the dissolution rate of undissolved drug in the small intestine may be too low to permit complete absorption. Ketoconazole, a systemic antifungal agent, is a weak base that requires acidity for dissolution and absorption. Patients also being treated with antacids, anticholinergics, or H_2-blockers, which reduce gastric acidity, should take these drugs at least two hours after ketoconazole. This also applies to diazepam and dipyridamole. We are usually less concerned with prompt dissolution of weakly acid drugs in gastric fluids because both dissolution and absorption proceed efficiently in the small intestine.

The relatively poor dissolution of weak acids at the pH of gastric fluids diminishes further the importance of the stomach as a drug absorption site. Although gastric absorption of weak acids may occur from solutions, it is unlikely that much drug dissolves and is absorbed during the limited residence of a solid dosage form in the stomach. Dissolution and gastrointestinal absorption studies with a series of sulfonamides (weak acids) suggest that the importance of gastric absorption is a function of drug solubility at gastric pH.[24] The investigators proposed that the critical value of solubility that distinguishes acid drugs according to their absorption site, stomach or intestine, is about 3 mg/ml in 0.1 N HCl, when 1 g of the drug is given orally to fasted subjects. If the solubility of the drug is less than 3 mg/ml, virtually no absorption occurs in the stomach.

Changes in gastric pH alter the solubility of certain drugs and may affect dissolution and absorption rate. Patients with achlorhydria have a distinctly higher gastric pH and absorb aspirin (pKa = 3.5) more rapidly than healthy subjects.[25] No differences between normal subjects and patients with achlorhydria were found with respect to the absorption rate of acetaminophen, a much weaker acid (pKa = 9.5), whose solubility would be unaffected by changes in gastric pH.

Defective absorption of calcium has been thought to exist in patients with achlorhydria. This has been documented with calcium carbonate.[26] Based on serum and urine levels of calcium, only about 25% of the dose of calcium carbonate was absorbed in patients with achlorhydria compared with that observed in healthy subjects. Curiously, calcium absorption after calcium citrate was twice as effective in patients with achlorhydria than in normal subjects. Both calcium carbonate and citrate were equally well absorbed in normal subjects.

Malabsorption of calcium due to achlorhydria may affect a large population because acid output decreases considerably after the age of 60 years, and calcium carbonate is the most widely used supplement and prophylactic for osteoporosis. Fortunately, the absorption defect is largely overcome when calcium carbonate is given with breakfast.

Differences in gastric and intestinal pH between man and dog have raised questions as to the suitability of a canine model for studying bioavailability. One study found that fasting gastric pH in the dog was significantly higher than in humans (1.8 versus 1.1), and that fasting intestinal pH in dogs was consistently higher than in humans (7.3 versus 6.0).[27]

The pH profiles suggest that absorption of certain drugs would vary between dog and man as a result of pH differences. For example, chlorothiazide (a weak acid, pKa = 6.7) is more efficiently absorbed in the dog than in human subjects. The lower bioavailability in humans may be due to their lower intestinal pH, leading to incomplete dissolution at pH values below the pKa.

Another area of concern in using dogs as an absorption model is the release of drug from enteric-coated products. The polymers used for enteric coating have highly pH-dependent dissolution profiles. An increase in pH of 1 or 2 units could change rapid dissolution to virtually no dissolution. Controlled-release dosage forms sometimes exhibit pH-dependent release profiles, so their performance may also change under different conditions of GI pH.

Diffusion Layer pH

The relationships that have been described between dissolution rate and hydrogen ion concentration (Eqs. 4–11 and 4–12) are approximations because they do not fully account for the influence of the unstirred diffusion layer. These equations tend to overpredict the dissolution rate of weak acids in the small intestine and the dissolution rate of weak bases in the stomach. Strictly speaking, the hydrogen ion concentration of the bulk, $[H^+]$, is not equal to the hydrogen ion concentration of the diffusion layer, $[H^+]_d$. In general:

$$[H^+]_d > [H^+], \text{ for weak acids}$$

and

$$[H^+]_d < [H^+], \text{ for weak bases}$$

The hydrogen ion concentration of the diffusion layer at a given bulk pH may be approximated by determining the pH of an appropriate aqueous buffer solution saturated with the drug. A saturated solution of a weak acid, like that found in the diffusion layer, tends to depress the neutral pH of the intestinal fluids, whereas a saturated solution of a weak base tends to elevate the low pH of gastric fluid.

These differences are probably of limited importance for the absorption of weakly acidic or basic drugs administered as such, but they are important when drugs are given in the form of salts.

Salts

The dissolution rate of a particular salt is usually different from that of the parent compound. Sodium or potassium salts of weak acids dissolve more rapidly than the free acids, regardless of the pH of the dissolution medium.[28] The same is true of the HCl or other strong acid salts of weak bases. Comparative dissolution rates of some weak acids and their sodium salts as a function of pH are shown in Table 4–4.

The effect of salt formation on dissolution rate cannot be explained in terms of solubility and bulk pH, but requires a consideration of the pH of the diffusion layer. At a fixed pH, a drug will have a fixed solubility, irrespective of whether the free acid (or base) or its salt is dissolving. Thus, classical solution theory (see Eqs. 4–8 and 4–9) does not predict the rapid dissolution of salt forms of a drug. In this case, the concept of a diffusion layer becomes helpful.

The pH of the diffusion layer at any given bulk pH is always greater for the sodium or potassium salt of a weak acid than for the corresponding free acid. On the other hand, the pH of the diffusion layer of an HCl or other strong acid salt of a weak base is always smaller than the diffusion layer pH of the corresponding free base. It has been noted that the pH of the diffusion layer may be approximated by determining the pH of an appropriate aqueous buffer saturated with either the drug or its salt. A solution of 0.1 N HCl saturated with sodium salicylate will have a higher pH than the same solution saturated with salicylic acid. It follows that the *effective* solubility and, therefore, the dissolution rate of a soluble salt is always greater than its corresponding free acid or base.

Many examples of the effects of soluble salts on drug absorption can be found. Some studies also report significant differences in clinical response.

Table 4–4. Dissolution Rate of Weak Acids and Their Sodium Salts*

Compound	pKa	Dissolution rate (mg/100 min/cm²) 0.1 N HCl pH 1.5	0.1 M Phosphate pH 6.8	0.1 M Borate pH 9.0
Benzoic acid	4.2	2.1	14	28
Sodium salt		980	1770	1600
Phenobarbital	7.4	0.24	1.2	22
Sodium salt		~200	820	1430
Salicylic acid	3.0	1.7	27	53
Sodium salt		1870	2500	2420
Sulfathiazole	7.3	<0.1	~0.5	8.5
Sodium salt		550	810	1300

*Data from Nelson, E.[28]

Marked differences have been observed in the rate and extent of absorption of novobiocin, a weak acid, when administered as such or in the form of a salt.[29] The bioavailability of the drug after oral administration of the sodium salt was twice that of the calcium salt and 50 times that of the free acid.

The potassium salt of penicillin V yields higher peak concentrations of antibiotic in plasma than does the free acid. Oral administration of the calcium salt yields peak plasma levels intermediary to those of the sodium salt and free acid. Differences in absorption rates are consistent with differences in the dissolution rates of the three forms of the drug.[30]

An example of the difference in pharmacologic response that may result from administering two different chemical forms of the same drug is found in studies with tolbutamide and its sodium salt.[31] The dissolution rate of tolbutamide sodium in 0.1 N HCl is about 5000 times greater than that of the free acid. At pH 7.2 the dissolution rate of the sodium salt is about 275 times greater than that of tolbutamide. Oral administration of the sodium salt results in a rapid and pronounced reduction in blood glucose to about 65 to 70% of control levels. The response is comparable to that observed after intravenous administration. The more slowly dissolving free acid produces a gradual decrease in blood sugar to about 80% of control levels, which is observed about 5 hr after administration. It has been suggested that the sodium salt of tolbutamide would produce an undesirable degree of hypoglycemia and that the free acid is the more useful form of the drug for treatment of diabetes.

Barbiturates are often available in the form of sodium salts to achieve a rapid onset of sedation. The findings of several studies support this practice. For example, the average sleep induction times in dogs after oral administration of equivalent doses of secobarbital or secobarbital sodium were 23 min and 8 min, respectively. The sodium salt not only produced a more rapid onset of sleep but its effects were also more predictable. The range of induction times in 6 dogs given the sodium salt was 7.5 to 8.5 min, whereas the range in dogs given secobarbital was 12 to 45 min. Peak drug concentrations in the blood were found within 10 min following administration of secobarbital sodium but not until about 80 min after administration of the free acid.[32]

In a double-blind study of 41 healthy subjects, the sodium salts of phenobarbital and secobarbital were found to produce more rapid and more profound impairment of performance on a variety of tests than the corresponding acid forms.[33] The basis for the observed differences between acids and salts in speed of action is presumably more rapid absorption of the salt form from the gastrointestinal tract. Comparison of heptabarbital and heptabarbital sodium in healthy subjects indicates more rapid absorption after giving the salt form of the drug.[34]

The nonsteroidal anti-inflammatory drug naproxen was originally marketed as the free acid for the treatment of rheumatoid- and osteoarthritis. New indications of the drug for the treatment of mild to moderate pain, including dysmenorrhea, prompted the development of naproxen sodium. The sodium salt is absorbed faster and is more effective in postpartum pain than the free acid.[35]

Certain salts have a lower solubility and dissolution rate than the parent drug, e.g., the aluminum salts of weak acids, and the pamoate salts of weak bases. In these particular examples, insoluble films of either aluminum hydroxide or pamoic acid appear to form over the dissolving solids when the

salts are exposed to an alkaline or acidic environment, respectively. These insoluble films further reduce the rate of dissolution.

Use of the relatively insoluble aluminum salt of aspirin has been considered for chewable tablets to minimize the taste of the drug, but aluminum aspirin is more slowly absorbed and less available than aspirin after oral administration.[36]

In general, poorly soluble salts delay the onset of drug effect. Studies with a series of salts of benzphetamine and etryptamine have shown that the median lethal time of death (LT_{50}) of mice following a lethal dose and the median lethal dose (LD_{50}) are inversely related to the dissolution rates of the salts at pH 7.2.[37] The experimental data suggest that salt formation is a potentially useful means of obtaining slow absorption and prolonged effects of certain drugs. The pamoate salt of imipramine has been marketed as a slow-release form of the drug.

Sometimes, problems with chemical stability preclude the use of salts of a drug in a dosage form. Aspirin, for example, is much more prone to hydrolysis in the form of sodium acetylsalicylate than as the free acid. One way to overcome this problem is to form the salt in situ, during dissolution in the gastrointestinal tract. If a mixture of a weakly acidic drug and a nontoxic basic salt is administered, faster dissolution and absorption may be obtained than if the drug were administered alone. When the mixture reaches the gastric fluids, the diffusion layer becomes saturated with both the drug and the basic salt. Accordingly, the pH of the diffusion layer is greater than that for the drug alone. Thus, the solubility of the drug in the diffusion layer and its dissolution rate is increased.

The effects of in situ salt formation on dissolution rate have been demonstrated with benzoic acid.[38] The addition of trisodium phosphate to benzoic acid increases the dissolution rate at pH 1 about 75 times that observed with benzoic acid alone. The principle of in situ salt formation is the basis for the enhanced dissolution and absorption of aspirin from buffered tablets (i.e., tablets of aspirin mixed with small amounts of alkaline materials).[39] Since occult gastrointestinal blood loss produced by therapeutic doses of aspirin is a local effect of the drug,[40] blood losses from aspirin can be reduced by administering the drug in buffered, rapidly dissolving tablets.[41]

Soluble Prodrugs

Most efforts with prodrugs have been directed at improving lipid solubility to increase permeability and absorption after oral adminjstration. The development of a prodrug may also offer an alternative for drugs that show incomplete absorption because of limited water solubility. The minor tranquilizer clorazepate is a prodrug of nordiazepam, an active metabolite of the widely used benzodiazepine diazepam, and is marketed as a dipotassium salt that is freely soluble in water, in contrast to the poorly soluble nordiazepam. Clorazepate, like most prodrugs, has little intrinsic biologic activity, but must be converted to nordiazepam. The prodrug is unstable at low pH; gastric fluid is the principal site of conversion.

A prodrug of the poorly soluble anticonvulsant phenytoin has been described.[42] The sulfate salt of this compound is 9,000 to 15,000 times more soluble in water than phenytoin. The prodrug is unstable at neutral pH and degrades with a half-life of about 7 min.

A general strategy for using soluble prodrugs to improve the gastrointestinal absorption of water-insoluble compounds has been reported.[43] The prodrug is designed to be a substrate for enzymes in the surface coat of the brush border region of the microvillous membrane. Consequently, the properties of the compound are changed from polar to nonpolar, just before reaching the membrane.

The incomplete absorption of acyclovir, an antiherpes drug, when given orally to patients infected with herpesvirus has prompted efforts to develop a water-soluble prodrug that would be better absorbed from the GI tract and then converted to acyclovir. One such compound, desciclovir, lacks the 6-hydroxy group and is also called 6-deoxyacyclovir. Although desciclovir lacks appreciable activity against herpes simplex type 1 virus in vitro, it is readily oxidized in vivo to acyclovir by xanthine oxidase and is far better absorbed than acyclovir after oral administration.

Studies in rats indicate that only about 15% of an orally administered dose of acyclovir is excreted in the urine. When the same rats were given equivalent doses of desciclovir, they excreted 66% of the dose as acyclovir. The urinary excretion of acyclovir in two human volunteers following a 200-mg oral dose of the prodrug was 65% and 68%, respectively. In comparison, about 12% of the dose is recovered in the urine after oral administration

of acyclovir and about 70% after intravenous administration of acyclovir.[44] The area under the acyclovir concentration in plasma-versus-time curve in these two individuals was five to six times greater after oral desciclovir than after oral acyclovir.

Petty et al.[45] gave desciclovir 250 mg orally 3 times daily for 10 days to healthy human subjects. Absorption was at least 75% of the dose and almost two-thirds of the administered dose was recovered in the urine as acyclovir. The levels of acyclovir in plasma were of the same magnitude as those found in subjects given intravenous acyclovir 2.5 mg/kg, and about 10 times higher than levels attained after administration of oral acyclovir 200 mg every 4 hr. The peak ratio of acyclovir to desciclovir in plasma was about 4:1. The mean half-life of desciclovir was 0.85 hr., compared with 2.6 hr. for acyclovir, suggesting rapid conversion of desciclovir to acyclovir.

Surface Area and Particle Size

A drug dissolves more rapidly when its surface area is increased. This is usually accomplished by reducing the particle size of the drug. Many poorly soluble, slowly dissolving drugs are marketed in micronized or microcrystalline form. Particle size reduction usually results in more rapid and complete absorption.

The problems associated with low water solubility were not fully appreciated when certain drugs were first introduced. For example, since the original marketing of spironolactone, the therapeutic dose has been reduced twentyfold (from 500 to 25 mg) by reformulation, including micronization of the drug. A similar situation has occurred with griseofulvin. The currently marketed formulation, containing micronized griseofulvin, requires a daily dose of 0.5 g, which is one half that needed when the drug was originally marketed.

Particle size may also be an important factor in the bioavailability of digoxin.[46] A digoxin powder, widely used in the United Kingdom for tablet manufacture, was found to have a mean particle size diameter of 20 to 30 μm. This material was slowly and incompletely absorbed, compared with a solution of digoxin. Reduction in digoxin particle size by ball milling to a mean diameter of 3.7 μm led to an increase in the rate and extent of absorption of the drug.

Another study examined the influence of both particle size and gastrointestinal motility on the absorption of digoxin.[47] In this study, healthy subjects received 0.5 mg digoxin as standard tablets, or tablets containing micronized digoxin or large particle size digoxin. Tablets were given 30 min after 15 mg propantheline (which increases residence time in the small intestine), 10 mg metoclopramide (which decreases residence time in the small intestine), or placebo, and following an overnight fast. The extent of absorption was estimated by determining the cumulative urinary excretion of digoxin over 4 days. Assigning a value of 100% for the bioavailability of digoxin in subjects who took the micronized tablet, Johnson and associates calculated that the relative bioavailability of digoxin taken with placebo was 94% after the standard tablets, but only 43% after the large particle size tablets.[47] Propantheline improved the absorption of digoxin from these large particle size tablets by an average of about 15%, whereas metoclopramide further reduced bioavailability from 43% to 31%. Neither propantheline nor metoclopramide had an effect on the absorption of digoxin after standard or micronized tablets. A general principle derived from these studies is that the bioavailability of slowly dissolving drugs may be sensitive to normal variation and other changes in gastrointestinal motility.

The gastrointestinal absorption of medroxyprogesterone acetate from tablets containing 10 mg of either micronized or nonmicronized drug was compared in a crossover fashion in healthy subjects.[48] The micronized material had 99.9% of the particles smaller than 10 μm. The specific surface areas of micronized and nonmicronized medroxyprogesterone acetate were 7.4 M^2/g and 1.2 M^2/g, respectively. Micronization led to a twofold increase in the extent of absorption of the steroid.

In a clinical study of pyrvinium pamoate in the treatment of patients infested with pinworms, the cure rate for the suspension form of the drug was significantly higher than the cure rate for the existing tablet form (100% versus 61%). In further studies, the efficacy of a new tablet formulation, with particles less than 10 μm in diameter, in contrast to the 50 to 90 μm particles in the original tablet, was compared with that of the suspension. Cure rates with both the new tablet and suspension were similar and exceeded 90%.[49]

The bioavailability of benoxaprofen, an anti-inflammatory agent withdrawn from the market because of serious side effects, was determined in healthy subjects after oral administration of two capsule formulations containing 200 mg of drug in

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Table 4–5. Maximum Plasma Phenacetin Concentrations and Urinary Recovery of Phenacetin Metabolites Following Oral Administration of Different Suspensions Each Containing 1.5 g Phenacetin to 6 Healthy Subjects*

Preparation	Average maximum plasma phenacetin concentration (μg/ml)	Urinary recovery†
Fine suspension with polysorbate 80	13.5	75
Fine suspension	9.6	51
Medium suspension	3.3	57
Coarse suspension	1.4	48

*Data from Prescott, L.F., Steel, R.F., and Ferrier, W.R.[51]
†Amount recovered in 24 hr, expressed as percent of dose.

the form of either small crystals (mean = 18.5 μm) or large crystals (mean = 610 μm).[50] The percent absorbed relative to an aqueous solution was found to be 94 to 98% for the small crystals and 39 to 43% for the large crystals. A higher dose of the large crystal formulation resulted in still lower bioavailability; an 800 mg dose was only 22% bioavailable.

The effective surface area of hydrophobic drug particles may be increased by the addition of a wetting agent to the formulation. In one investigation, 6 volunteers received 1.5 g of phenacetin as a fine suspension (particle size less than 75 μm) with and without polysorbate 80 (a wetting agent), as a medium suspension (particle size 150 to 180 μm), and as a coarse suspension (particle size greater than 250 μm).[51] Drug absorption was assessed by determining phenacetin concentrations in the plasma and urinary excretion of drug metabolites. The maximum phenacetin concentrations in the plasma and the urinary recovery of phenacetin metabolites, after administration of the different forms of the drug, are presented in Table 4–5. The importance of particle size in phenacetin absorption is evident. Polysorbate 80 significantly enhances the rate and extent of absorption of phenacetin, probably by increasing the wetting and solvent penetration of the particles and by minimizing aggregation of the suspended particles. Physiologic surface active agents, like bile salts and lysolecithin, probably facilitate the dissolution and absorption of poorly water-soluble drugs in the small intestine.[52]

Effective absorption of cyclosporine appears to require the presence of bile in the small intestine. Absorption studies shortly after liver transplantation with bile drained through a T-tube found that the AUC over a dosing interval was only 5.2 ng-hr/ml; blood levels peaked at about 250 ng/ml. Some time later, when bile was returned to the small intestine, AUC was 15.8 ng-hr/ml and peak concentrations exceeded 1500 ng/ml.[53] Bile may increase the solubility of cyclosporine by means of micellar solubilization.

There are instances in which particle size reduction fails to increase the absorption rate of a drug. One reason may be that dissolution is not the rate-limiting step in the absorption process. Weak bases dissolve readily in the acidic gastric fluid; gastric emptying, rather than dissolution, is the slow step in the absorption of these drugs.

Micronization sometimes increases the tendency of a drug powder to aggregate, which may lead to a decrease in effective surface area. This problem may be overcome by adding a wetting agent or other excipients to the formulation.

Another approach to deaglomeration is to intimately mix the hydrophobic drug with an excess of a hydrophillic carrier. This is sometimes called an ordered mixture because we strive to have the fine drug particles distributed fairly evenly on course carrier particles. Micronized griseofulvin mixed with sodium chloride crystals dissolves much more rapidly than micronized griseofulvin alone.[54] Extremely rapid dissolution has also been observed when micronized griseofulvin was mixed with lactose.[55] Under these conditions, drug appears to be delivered as free, well-dispersed primary particles after rapid dissolution of the carrier. Mixing griseofulvin with a hydrophobic carrier (paraffin) results in poorer dissolution than with griseofulvin alone.

The advantages to be derived from the use of micronized particles may be reduced or even eliminated by compaction of the particles during tablet compression. For example, the effect of particle size reduction on the absorption of griseofulvin is much greater when the micronized drug is given in a suspension rather than as a tablet.[56]

Certain drugs such as penicillin G and erythromycin are unstable in gastric fluids. Chemical degradation is minimized if the drug does not dissolve readily in the stomach. Particle size reduction and the attendant increase in dissolution rate may result in more extensive degradation of the drug. It has been shown that the addition of a wetting agent to a formulation of erythromycin propionate results in considerably lower drug levels in the blood.

apparently owing to increased dissolution and degradation of the antibiotic in gastric fluids.[57]

Crystal Form

Many drugs can exist in more than one crystalline form, a property known as *polymorphism*. The drug molecules exhibit different space-lattice arrangements in the crystal from one polymorph to another. Although the drug is chemically indistinguishable in each form, polymorphs may differ substantially with respect to physical properties such as density, melting point, solubility, and dissolution rate. At any one temperature and pressure only one crystal form will be stable. Any other polymorph found under these conditions is metastable and will eventually convert to the stable form, but the conversion may be slow. The metastable polymorph is a higher energy form of the drug and usually has a lower melting point, greater solubility, and greater dissolution rate than the stable crystal form. Accordingly, the absorption rate and clinical efficacy of a drug may depend on which crystal form is administered.

Some drugs also occur in an amorphous form showing little crystallinity. The energy required for a drug molecule to transfer from the lattice of a crystalline solid to a solvated state is much greater than that required from an amorphous solid. For this reason, the amorphous form of a drug is always more soluble than the corresponding crystalline forms.

Two polymorphs of novobiocin have been identified, one of which is crystalline and the other amorphous. The amorphous material is at least 10 times more soluble than the crystalline form. Studies in dogs fail to detect any absorption of novobiocin after oral administration of the crystalline solid, whereas the amorphous form is rapidly absorbed.[58]

Chloramphenicol palmitate exists in four polymorphs: three crystalline forms (A, B, and C) and an amorphous one. Aqueous suspensions of polymorphs A and B yielded average peak chloramphenicol concentrations in blood of 3 and 22 μg/ml, respectively, on oral administration. Similar differences were noted with respect to the extent of absorption of the two polymorphs.[59]

Studies with sulfameter have indicated the occurrence of six polymorphs. Crystalline form II is about twice as soluble as crystalline form III. Studies in normal human subjects show that the rate and extent of absorption of the sulfonamide are about 40% greater after administration of form II than after administration of form III.[60]

MacGregor et al.[61] prepared and evaluated tablets of amorphous chlorthalidone stabilized by the addition of polyvinylpyrollidone (PVP). Studies in the dog indicated that these experimental tablets were bioequivalent in both rate and extent of absorption to an oral solution of the thiazide-related diuretic, and more rapidly and efficiently absorbed than the standard commercial tablet. These differences were also seen in bioavailability studies with normal healthy subjects.[62] The tablet with amorphous chlorthalidone appeared to deliver all the drug, whereas the commercial tablet delivered 80% of the drug.

Vardan et al.[63] compared the efficacy of a 15-mg tablet containing amorphous chlorthalidone with that of a 25-mg commercial tablet in a double-blind placebo-controlled trial in patients with mild hypertension. At the end of 12 weeks, a decrease in standing diastolic blood pressure from baseline of at least 5 mm Hg was seen in 61% of the patients on the 15-mg experimental tablet, 72% of the patients on the 25-mg commercial tablet, and 31% of the patients on placebo. Both active drug groups were significantly different from the placebo group but not from each other.

Fewer adverse events were reported in the placebo and 15-mg groups than in the 25-mg group. The decline in potassium was significantly greater in the 25-mg group than in the 15-mg group. At 12 weeks there were four patients with potassium levels below 3 meq/L in the 25-mg group but none in the 15-mg group. The results demonstrate that 15-mg chlorthalidone administered in a superbioavailable dosage form was as effective as the 25-mg commercial tablet in lowering systolic blood pressure; this was accomplished with a reduced incidence of hypokalemia.

Many drugs can associate with solvents to produce crystalline forms called *solvates*. When the solvent is water, the crystal is termed a *hydrate*. Consistent with theory, the anhydrous forms of caffeine, theophylline, and glutethimide dissolve more rapidly in water than do the hydrous forms of these drugs.[64] The anhydrous form of ampicillin is about 25% more soluble than is the trihydrate. A similar difference has been found with respect to the extent of absorption of ampicillin from the two forms of the drug in man.[65]

Several reports suggest that solvate forms of a drug with organic solvents may dissolve faster than the nonsolvated form. This has been observed with

the n-pentanol and ethyl acetate solvates of fludrocortisone, and with the n-pentanol solvate of succinylsulfathiazole.[66] Studies in man indicate that the rate and extent of absorption of griseofulvin were significantly increased after administration of the chloroform solvate compared to that observed after administration of the nonsolvated form of the drug. These findings are consistent with the greater solubility and dissolution rate of the solvate in simulated intestinal fluid.[67]

DRUG STABILITY AND HYDROLYSIS IN THE GASTROINTESTINAL TRACT

Acid and enzymatic hydrolysis of drugs in the gastrointestinal tract is sometimes the reason for poor bioavailability. The hydrolysis and inactivation of penicillin G in the stomach is one example. The half-life of degradation of penicillin G is less than 1 min at pH 1 and about 9 min at pH 2. The stability of methicillin is equally poor. Other penicillins, notably ampicillin, are considerably more resistant to acid hydrolysis. The degradation rate of penicillin G decreases sharply with increasing pH; the drug is essentially stable in the small intestine. Chemical inactivation in the stomach is responsible in part for the relatively low bioavailability of penicillin G and methicillin.

The absorption of digoxin is less than complete after oral administration, even when the drug is given in solution. Studies indicate that hydrolysis of digoxin in gastric fluid to digoxigenin and its mono- and bis-digitoxosides contributes to the bioavailability problem.[68-70] Hydrolysis of digoxin at 37°C and pH 3 is minimal after 90 min of incubation but increases with increasing acidity; more than 70% is hydrolyzed at pH 1.2 after 30 min and more than 96% after 90 min incubation.[68] Extensive intragastric hydrolysis and reduced bioavailability of digoxin may occur in man under conditions of maximum acid output.

When a drug is unstable in gastric fluids, rapid dissolution may reduce bioavailability. Investigations with a series of erythromycin esters, unstable in the stomach, have shown that bioavailability is inversely proportional to dissolution rate in simulated gastric fluid (pH 1). The propionyl ester is absorbed to the greatest extent but dissolves most slowly at pH 1. With such drugs it is desirable to have minimal dissolution in the stomach and rapid dissolution in the small intestine.[71]

Certain prodrugs must be hydrolyzed to the parent drug in gastrointestinal fluids to produce clinical effects. Clorazepate is rapidly converted to the anxiolytic nordiazepam at low pH. The only site for effective conversion is gastric fluid. Failure to achieve complete conversion results in absorption of the prodrug itself which has little, if any, tranquilizer activity. Some reports have suggested that the absorption of clorazepate could be adversely affected by giving the drug with antacids, which elevate gastric pH and reduce the rate of conversion to nordiazepam.[72,73] Clinical studies with single oral doses of clorazepate and single or multiple doses of a commercial aluminum-magnesium antacid indicate that although antacids reduce the rate of appearance of nordiazepam in plasma, they have no effect on the extent of conversion of clorazepate to nordiazepam.[74]

Cloramphenicol is sometimes given as the palmitate or stearate ester, particularly in pediatric practice. The low water solubility of the esters minimizes the objectionable taste of the drug and facilitates its use in oral suspensions. However, the esters are poorly absorbed; adequate drug absorption requires conversion of the prodrug to chloramphenicol in the small intestine.[75] Clinical studies in children with serious bacterial infections, who were given the palmitate ester, suggest that conversion is about 70% complete, on the average, and results in satisfactory serum levels of chloramphenicol.[76]

Failure to effectively convert a prodrug to parent drug in the gastrointestinal fluids, gut wall, or liver during absorption results in the prodrug reaching the systemic circulation in relatively large amounts. Chemical or enzymatic conversion of the prodrug to parent drug in blood or tissues may be limited and the prodrug may be metabolized or excreted unchanged. Since the prodrug ordinarily has little or no clinical activity, the net result of these events may be inadequate bioavailability with respect to active drug.

This problem is evident with prodrugs of erythromycin. Erythromycin base is unstable in gastric fluid, which leads to poor bioavailability when the drug is given as such. Various esters of erythromycin have been investigated to find compounds with a low dissolution rate in gastric fluid and high acid stability and lipid solubility. Two prodrugs with these characteristics, the lauryl sulfate salt of the propionate ester of erythromycin (erythromycin estolate) and the ethylsuccinate ester of erythromycin, are marketed in the United States. However, both prodrugs are absorbed directly into the bloodstream; conversion to erythromycin in the

blood and tissues is incomplete. High blood levels of total drug, particularly after the estolate, are misleading because the esters have little antibacterial activity. Certain microbiologic assays for estimating antibacterial activity are misleading, because the assay procedure permits in vitro conversion of the ester to erythromycin during incubation. Despite the incomplete conversion to erythromycin, these prodrugs are clinically effective.

A second important problem that may be encountered when prodrugs reach the systemic circulation in relatively large amounts is the appearance of toxicity distinct from that observed with the parent drug. In general, the safety record of the erythromycins has been good; the only major adverse effect of erythromycin therapy is hepatotoxicity, more frequently associated with the estolate and ethylsuccinate forms of the drug.[77]

Alternatives to ester prodrugs of erythromycin include erythromycin stearate, a salt form of the drug, and enteric-coated products of erythromycin base. The stearate is more resistant to acid degradation than the free base. Prolonged retention in the stomach however may result in breakdown of the drug. Food reduces the bioavailability of erythromycin stearate by more than 50%; when used in this form, the drug should be given 1 hr before or 2 hr after meals to obtain maximum bioavailability. Enteric-coated products of erythromycin base do not dissolve in the stomach but allow rapid absorption of the drug in the small intestine. Administration of these products with meals has no effect on bioavailability.

PHYSICAL-CHEMICAL MODELS OF DRUG ABSORPTION

Clinical effectiveness after oral administration is a decided advantage in the development of new drugs. Principal reasons for inadequate bioavailability are low aqueous solubility, poor lipid solubility, drug degradation in the gut lumen, or presystemic metabolism, and dosage form characteristics that limit the dissolution or release rate of the drug. Dissolution rate considerations are important for poorly water soluble drugs, whereas intestinal wall permeability may be rate controlling for polar drugs. Dosage form characteristics may be important for drugs with low aqueous solubility and for delayed-release and prolonged-release preparations.

The earliest quantitative studies on gastrointestinal (GI) absorption focused on permeability and demonstrated that when drugs were administered in aqueous solution, absorption potential was a function of the pH of GI fluids as well as the pK and partition coefficient of the drug. These principles remain conceptually useful but cannot be applied directly because most drugs are given in solid dosage forms, and dissolution and aqueous solubility play an important role in determining absorption. More recent efforts at predicting drug absorption have attempted to relate in vitro dissolution with in vivo absorption characteristics, assuming that dissolution in the GI fluids is the rate-limiting step in drug absorption. These approaches permit differentiation of dosage forms from which a given drug is absorbed at different rates but are less useful for predicting the extent of absorption of a drug. Dressman et al.[78] have developed an equation for calculating absorption potential that for the first time takes both intestinal permeability and drug solubility into account. The strength of their method of prediction lies in its simplicity; the paradigm is based entirely on easily obtained physical-chemical data.

The investigators assumed that the absorption potential of a drug is a function of the membrane-water partition coefficient, which can be correlated to the octanol/water partition coefficient, P, the intrinsic solubility (i.e., the water solubility of the nonionized species at 37°), S; the dose, D, the fraction in nonionized form at pH 6.5, f; and the volume of the lumenal contents, V. Absorption potential, AP, is defined as follows:

$$AP = \log (PfSV/D) \qquad (4\text{–}13)$$

Several drugs covering a wide range of absorption characteristics were selected to evaluate the ability of the estimated absorption potential to predict bioavailability. The drugs varied widely in their physical-chemical characteristics. Partition coefficients covered the range from 0.018 (acyclovir) to 295 (phenytoin). Acyclovir was also the most soluble (1.3 mg/ml), whereas griseofulvin and phenytoin were the least soluble (< 0.02 mg/ml). Griseofulvin, prednisolone, and digoxin are nonionizable; pKa values for acyclovir, chlorothiazide, hydrochlorothiazide, and phenytoin range from 6.7 to 9.5. The lumenal volume was set at 250 ml for all compounds.

The correlation between absorption potential and fraction of the dose absorbed was excellent and indicates for the compounds chosen that absorption

potential is a good predictor of bioavailability. Negative AP values (acyclovir and hydrochlorothiazide) suggest poor drug absorption; values of 1.0 or above (phenytoin, prednisolone, and digoxin in solution) suggest nearly complete absorption. Compounds with intermediate AP values (micronized griseofulvin and hydrochlorothiazide) show intermediate bioavailability.

Predictions of percent absorption, however, will not correlate with the bioavailability of compounds subject to substantial first-pass metabolism in the intestinal epithelium or liver or degradation in the gut lumen. Under these conditions, the absorption potential may be considerably greater than systemic availability. For example, propranolol is completely absorbed, but bioavailability is less than 30% after a single oral dose.

Absorption potential as described by Dressman et al.[78] is likely to be a useful tool in drug development so long as it is understood that the parameter is exclusively concerned with the physical-chemical characteristics of the drug and that it cannot be used as the sole indicator of bioavailability. Furthermore, the dissolution rate of a drug but not its solubility is affected by characteristics of the dosage form such as particle size; this distinction may be a significant factor in determining the fraction absorbed when drug solubility is in the μg/ml range. Dressman et al. note that for these cases, the absorption potential is an indicator of how well the drug might be absorbed provided dissolution rate limitations are circumvented by micronizing the drug (griseofulvin), using a solid solution formulation, or giving a solution of the drug in a soft gelatin capsule (digoxin).

More recently, Dressman and Fleisher[79] have investigated the role of dissolution in the absorption of very poorly soluble drugs. They simulated absorption profiles based on a theoretical mixing tank model that takes into account dissolution, absorption, and residence time in the small intestine (assumed to be the site of absorption).

Griseofulvin (G) and digoxin (D) were chosen as examples of drugs that exhibit dissolution rate controlled absorption. Both compounds have low aqueous solubilities (G = 15 μg/ml, D = 25 μg/ml) and high partition coefficients (G = 151, D = 56).

Despite the similar physical-chemical characteristics of griseofulvin and digoxin, estimates of their absorption potential (G = 0.36, D = 3.1) indicate that digoxin is potentially completely absorbed, whereas griseofulvin is not. This difference is consistent with the results of bioavailability studies in human subjects and is probably related to the markedly different doses of these drugs (G = 500 mg, D = 0.25 mg). There is a 3000-fold difference between griseofulvin and digoxin in terms of the ratio of dose to solubility.

The simulations predict that about 40% of a 500-mg dose of micronized griseofulvin (particles 4 μm in diameter) will be absorbed over a 5-hr period, whereas about 20% of the same dose of "regular" griseofulvin (30 μm mean diameter) will be absorbed over the same period. These estimates are in good agreement with values in the literature from studies in human subjects. The results indicate that even with small particles, the absorption of griseofulvin does not approach 100%. "This suggests that the dose-to-solubility ratio as well as the dissolution rate is a significant limitation to griseofulvin absorption."[79]

The model also predicts that the absorption of micronized griseofulvin is dose-dependent. The fraction absorbed increases from about 40 to 80% as the dose is decreased from 500 to 100 mg. This finding implies that small doses of micronized griseofulvin given more frequently may result in higher drug levels in blood and greater effectiveness.

In summary, the model adequately simulates the gastrointestinal absorption of griseofulvin over a wide range of particle sizes and other conditions. The results indicate that the large dose-to-solubility ratio for this drug restricts the fraction absorbed, even when dissolution rate effects are minimized by administering very fine particles of the drug. "At usual doses of griseofulvin, reducing the particle size below the compendial requirement for the micronized form is not predicted to result in significantly better bioavailability."[79]

Simulations of digoxin absorption present a different picture, principally because of the much smaller doses that are required. As with griseofulvin, the absorption of digoxin is strongly dependent on particle size, but the model predicts that a particle diameter of 5 μm or less will result in complete absorption.

Mean residence time in the small intestine also has a substantial effect on digoxin absorption. With the usual range of residence times (100 to 250 min), the percentage absorbed can vary from 60 to 90%. These predictions are consistent with the effects of metoclopramide and propantheline, drugs that modify gastric emptying and intestinal transit, on

the bioavailability of digoxin from certain preparations.

The theoretical considerations proposed by Dressman et al.[78,79] are a substantial contribution to our understanding of drug absorption from the gastrointestinal tract. It appears that quantitative estimates of drug absorption may be made, based solely on certain physical-chemical properties of the drug and several assumptions as to the characteristics of the gut. These advances, however, do not minimize the need for continued improvements in our ability to predict drug absorption after oral administration of solid dosage forms, particularly controlled-release forms.

COMPLEXATION

Complexation of a drug in gastrointestinal fluids may alter the rate and, in some cases, the extent of absorption. The complexing agent may be a substance normal to the gastrointestinal tract, a dietary component, or a component of the dosage form. Intestinal mucus, which contains the polysaccharide mucin, can avidly bind streptomycin and dihydrostreptomycin.[63] This binding may contribute to the poor absorption of these antibiotics. Bile salts in the small intestine interact with certain drugs, including tubocurarine, neomycin, and kanamycin, to form insoluble, nonabsorbable complexes.[81,82]

Tetracyclines form insoluble complexes with calcium. Absorption of these antibiotics is substantially reduced if they are taken with milk, certain foods, or other sources of calcium such as antacids. Similar effects are observed with aluminum antacids. Incorporation of dicalcium phosphate as a filler in a tetracycline dosage form substantially reduces the bioavailability of the drug.

Complexation probably occurs often in pharmaceutical dosage forms. Complex formation between drugs and gums, cellulose derivatives, polyols, or surfactants is common. Such complexes have a much higher molecular weight and are usually considerably more polar than the drug itself. The physicochemical properties of these complexes suggest poor absorption characteristics. Fortunately, most complexes are freely soluble in the fluids of the gastrointestinal tract and dissociate rapidly. Therefore, little or no effect on absorption is noted. There are, however, some exceptions. Amphetamine interacts with carboxymethylcellulose to form a poorly soluble complex that leads to reduced absorption of the drug.[83] Phenobarbital forms an insoluble complex with polyethylene glycol 4000. The dissolution and absorption rates of phenobarbital from tablets containing this polyol are markedly reduced.[84]

Drug complexes usually differ appreciably from the free drug with respect to water solubility and lipid-water partition coefficient. Many investigators have pursued the possibility that certain polar drugs, which are poorly absorbed, may be made more permeable by forming lipid-soluble complexes. For example, certain dialkylamides can enhance the intestinal absorption of prednisone in the rat. These amides presumably form well-absorbed lipid-soluble complexes with the steroid.[85] The usefulness of this approach to increasing the absorption of certain drugs may be seriously limited by the residence time of the complexing agent in the gastrointestinal tract. If the complexing agent is more rapidly absorbed than the complex, the concentration of complex at the absorption site decreases rapidly and enhanced absorption of the drug may be short-lived.

Perhaps a more rewarding application of complex formation is the administration of water-soluble complexes of drugs that are incompletely absorbed because of poor water solubility. For example, inclusion complex formation of a drug with cyclodextrin is known to increase solubility and dissolution rate.[86]

Hydroquinone forms a water-soluble, rapidly dissolving complex with digoxin.[87] The complex is quickly and completely dissociated when dissolved. An oral tablet formulation containing the complex resulted in significantly faster absorption of digoxin than did a standard tablet of digoxin, but only small differences were found with respect to the extent of absorption.[88] Relative to an intravenous injection of digoxin, the bioavailability of the complex was 70% whereas that of the standard tablet was 65%. In the same subjects, the bioavailability of digoxin from an elixir was about 80%.

ADSORPTION

Certain insoluble substances may adsorb coadministered drugs. This often leads to poor absorption. Studies of the effects of attapulgite or charcoal on promazine absorption in man are illustrative. Attapulgite is used as an active component in antidiarrheal mixtures. Charcoal has been used for various gastrointestinal disorders and is considered to be an efficient antidote in drug intoxication.

Promazine was administered to healthy subjects as a solution in water or as a mixture containing either charcoal or attapulgite. About 80% of the drug was adsorbed initially in the attapulgite preparation and about 50% in the charcoal preparation. Attapulgite decreased the rate but not the extent of absorption of promazine. Charcoal significantly reduced both the rate and extent of drug absorption. In vitro studies indicated that the promazine-charcoal adsorbate had little tendency to dissociate. Apparently, only the fraction of the dose that is initially unadsorbed in the mixture is available for absorption. On the other hand, dissociation of drug from the promazine-attapulgite adsorbate is rapid. Therefore, the extent of adsorption in a dosage form may not be related directly to the effect on absorption. The ease with which the adsorbate dissociates may be the more important factor.[89]

In another investigation, serum concentrations and urinary excretion of lincomycin were determined under the following conditions: (1) 0.5 g in a capsule taken orally with 3 fl oz of water; (2) 3 fl oz of a commercial kaolin-pectin mixture taken 2 hr *before* the capsule; (3) 3 fl oz of the antidiarrheal mixture taken 2 hr *after* the capsule; and (4) 3 fl oz of the mixture taken *with* the capsule. The relative bioavailabilities were 1.00, 0.71, 0.69, and 0.20 for conditions (1), (2), (3), and (4), respectively.[90] Parallel in vitro studies showed that the mixture strongly binds lincomycin. The effect of the antidiarrheal mixture on lincomycin absorption is reduced by administering the drug and the mixture several hours apart.

Cholestyramine and colestipol are insoluble anionic exchange resins used to lower serum cholesterol levels in patients with hypercholesterolemia. These agents bind cholesterol metabolites and bile salts in the intestinal lumen and prevent enterohepatic cycling. They also bind and reduce the absorption of many drugs.

Clinical studies show that fecal radioactivity after oral administration of thyroxine I-131 is markedly increased in patients receiving cholestyramine. Absorption, as determined by whole-body retention and cumulative urinary radioactivity, is correspondingly reduced. If a 4- to 5-hr period exists between the ingestion of cholestyramine and the ingestion of thyroxine, the absorption of the hormone approaches normal in most subjects. Hypothyroid patients receiving thyroxine and cholestyramine, at the same time, should be examined periodically for evidence of lack of efficacy. Adjustments in thyroxine dose and in the time interval between the two drugs should be made, if appropriate.[91]

Single-dose studies in adult subjects have shown that cholestyramine significantly reduces the absorption of the anticoagulants warfarin[92] and phenprocoumon.[93] Cholestyramine also affects the bioavailability of digoxin.

Brown et al.[94] studied the effect of continuous treatment with cholestyramine on steady-state levels of digoxin resulting from either two 0.25-mg digoxin tablets or two 0.2-mg digoxin capsules (containing a solution of the drug) once a day for 2 weeks. Bioavailability was determined from the steady-state 24-hr area under the serum concentration-time curve (AUC, ng × hr/ml).

The AUC values for tablets alone and with the resin were 32.8 and 22.4, a decrease of about 32%. For the capsules alone and with cholestyramine, AUC values were 31.7 and 24.7, a decrease of about 22%. The results show that the 0.2-mg capsule of digoxin is bioequivalent to the 0.25-mg tablet with respect to AUC. The results also suggest that cholestyramine may have a greater effect on the more slowly dissolving tablets than on the capsules of digoxin.

Unlike cholestyramine, colestipol had no apparent effect on phenprocoumon absorption.[95] On the other hand, colestipol has been found to decrease chlorothiazide absorption by 50% even when the drug was taken 1 hr after the resin.[96] Doses of cholestyramine (8 g) and colestipol (10 g), equieffective in lipid lowering, produce similar reductions in the bioavailability of propranolol when given with the drug.[97] Additional examples of drug-drug interactions affecting absorption are described in Chapter 14.

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