A Mechanistic Approach to Understanding the Factors Affecting Drug Absorption: A Review of Fundamentals

Marilyn N. Martinez, PhD, and Gordon L. Amidon, PhD

This article provides an overview of the patient-specific and drug-specific variables that can affect drug absorption following oral product administration. The oral absorption of any chemical entity reflects a complex spectrum of events. Factors influencing product bioavailability include drug solubility, permeability, and the rate of in vivo dissolution. In this regard, the Biopharmaceutics Classification System has proven to be an important tool for predicting compounds likely to be associated with bioavailability problems. It also helps in identifying those factors that may alter the rate and extent of drug absorption. Product bioavailability can also be markedly influenced by patient attributes such as the integrity of the gastrointestinal tract, physiological status, site of drug absorption, membrane transporters, presystemic drug metabolism (intrinsic variables), and extrinsic variables such as the effect of food or concomitant medication. Through an awareness of a drug's physicochemical properties and the physiological processes affecting drug absorption, the skilled pharmaceutical scientist can develop formulations that will maximize product availability. By appreciating the potential impact of patient physiological status, phenotype, age, gender, and lifestyle, dosing regimens can be tailored to better meet the needs of the individual patient.

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A fundamental premise associated with the use of a therapeutic agent is that for any given patient, the clinical response can be predicted on the basis of the selected drug product, dose, and dosing regimen. This tenet provides the foundation for concepts of prescribability and switchability.[1] Prescribability refers to an assumed relationship between a therapeutic outcome and the rate and extent of drug exposure. A physician will prescribe a particular product in accordance with assumptions pertaining to this relationship.

Generally, the process of drug movement from intake (e.g., oral delivery systems) to its site of action can be schematically presented as follows (Figure 1).

As depicted in Figure 1, the relationship between drug intake and a clinical response is highly complex, potentially affected by a host of intrinsic and extrinsic variables. Accordingly, deviations between drug response within or between individuals may be ascribed either to product bioavailability (i.e., the rate and extent of drug absorption), drug pharmacokinetics (which includes the metabolism, distribution, and elimination of a compound), or the particular concentration-effect relationship.

While product formulation can significantly affect processes leading to drug absorption, once in the circulation, the original formulation is generally considered to no longer affect the ultimate drug response. In other words, it is the concentration of the drug moiety, along with its corresponding effect, that will ultimately determine product safety and effectiveness. For this reason, once a patient is titrated to a particular product and dosing regimen, we assume that a comparable clinical response will be achieved if the patient elects to take a less expensive generic equivalent.

The purpose of this article is to discuss basic principles associated with the process of drug absorption. Special attention will be given to the use of the Biopharmaceutics Classification System (BCS) as a predictive tool for identifying compounds whose absorption characteristics may be sensitive to intrinsic

From the Office of New Animal Drug Evaluation, HFV-130, Center for Veterinary Medicine, Food and Drug Administration, Rockville, Maryland (Dr. Martinez) and the University of Michigan, College of Pharmacy, Ann Arbor, Michigan (Dr. Amidon). Submitted for publication August 15, 2001; revised version accepted February 15, 2002. Address for reprints: Marilyn N. Martinez, Office of New Animal Drug Evaluation, HFV-130, Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

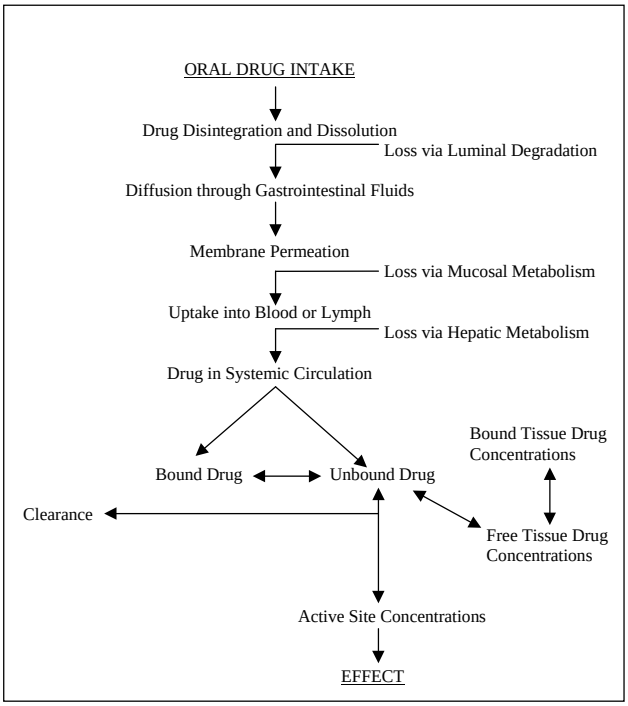

Figure 1. Schematic diagram of the relationship between an oral dose of a drug product and its ultimate effect.

(physiological) and extrinsic (e.g., food and formulation) variables. Accordingly, this review focuses on those factors that can affect drug dissolution, aqueous solubility, membrane permeability, and presystemic drug metabolism.

WHAT IS THE BCS?

One of the most significant prognostic tools created to facilitate product development in recent years has been the BCS.[2] By knowing the solubility and permeability characteristics of specific compounds, we improve our ability to predict those variables (such as formulation, food, dosing regimen, and disease) that will alter oral drug absorption.

Currently, all pharmaceutical compounds are grouped into one of the following categories:

Class I—high solubility, high permeability: generally very well-absorbed compounds
Class II—low solubility, high permeability: exhibit dissolution rate-limited absorption
Class III—high solubility, low permeability: exhibit permeability rate-limited absorption
Class IV—low solubility, low permeability: very poor oral bioavailability

Solubility is calculated on the basis of the largest strength manufactured. It is defined as the minimum solubility of drug across a pH range of 1 to 8 and at a temperature of 37 ± 0.5°C. High-solubility drugs are those with a ratio of dose to solubility volume that is less than or equal to 250 ml. Permeability (P_{eff}, expressed in units of 10^4 cm per second) is defined as the effective human jejunal wall permeability of a drug. High-permeability drugs are generally those with an extent of absorption greater than or equal to 90% and are not generally associated with any documented instability in the gastrointestinal tract.

It is interesting to note that for certain compounds, P_{eff} is not necessarily constant. For example, nonlinear changes in P_{eff} were observed with increasing doses of the surface-active molecule, fluvastatin. This nonlinear increase in P_{eff} was attributed to its effects on membrane surface tension and to a possible decrease in poly-glycoprotein (P-gp) activity associated with an increase in intestinal membrane fluidity.[3]

The application of this system to nonhuman species may require adjustment of these classification parameters based on physiological differences in gastric volume and the pH of the gastrointestinal (GI) fluids. Accordingly, at this time, we cannot be certain that the BCS classification of a compound remains constant across all species. This question is currently being explored by the Food and Drug Administration's (FDA's) Center for Veterinary Medicine.

By understanding the relationship between a drug's absorption, solubility, and dissolution characteristics, it is possible to define situations when in vitro dissolution data can provide a surrogate for in vivo bioequivalence assessments. The use of this surrogate relies on the validity of three fundamental assumptions. First, it must be assumed that a comparison of product in vitro dissolution performance accurately reflects relative differences in product in vivo dissolution behavior. Second, we must assume that if two products present with equivalent in vivo dissolution profiles under all luminal conditions, they will present equivalent drug concentrations at absorptive membrane surfaces. Third, for comparable dissolution profiles to ensure comparable in vivo absorption, the rate and extent of drug presented to absorptive membrane surfaces must determine the absorption characteristics of that drug product.

Lobenberg and Amidon[4] have summarized the relationships between dose, dissolution characteristics, drug solubility, and drug absorption properties. These relationships can be described as follows:

1. Absorption number (An) = $(P_{eff}/R) \bullet \langle Tsi \rangle$,

where R is the gut radius and <Tsi> the residence time of the drug within the intestine.

2. Dissolution number (Dn) = $(3D/r^2) \bullet (C_s/\rho) \bullet \langle Tsi \rangle$,

where D is the diffusivity of the dissolved drug, ρ is the density of the dissolved drug, C_s is the drug solubility, and r is the initial radius of the drug particle.

3. Ratio of dose to dissolved drug $(D_0) = \frac{M / V_0}{C_s}$,

where M is the dose of the drug and V_0 is the volume of fluid consumed with the dose.

The fraction of drug absorbed is closely related to the drug's effective permeability across mucosal cells.[4] If the P_{eff} of a drug is less than $2 \bullet 10^{-4}$ cm/s, then drug absorption will be incomplete, whereas complete absorption can be expected for substances whose P_{eff} exceeds this value. For poorly soluble drugs, critical variables include the volume of the intestinal fluids, GI pH, and GI transit time (where adequate time is needed to dissolve poorly soluble materials). For these lipophilic compounds, food and bile salts may increase drug solubility.

Class I compounds are highly permeable and readily go into solution (Dn > 1). In this case, the fraction absorbed (F) can be expressed as follows:

$$F = 1 - \exp(-2An).$$

For these agents, as "An" increases, the fraction of drug absorbed increases, with 90% absorption (highly permeable compounds) occurring when An = 1.15. Referring back to the equation for An, we see that F can be affected by a change in the compound's membrane permeability, the gut radius of the host, or the intestinal transit time. Based on these factors alone, it is evident that differences in GI physiology due to factors such as disease, age, or animal species can alter the value of An and, therefore, the fraction of drug absorbed.

For Class II drugs (high permeability, low solubility), Dn < 1. In these cases, the relationship between D_0 and Dn is critical for determining the fraction of drug absorbed, and the rate of drug dissolution tends to be the rate-limiting step. Accordingly, anything that increases the rate and extent of in vivo dissolution will also increase the bioavailability of that compound.

SOLUBILITY

Aqueous solubility can be estimated by determining the ability of a drug to partition from lipid to aqueous environments. This partitioning behavior is often a function of solvent pH due to the latter's effects on drug ionization. In general, ionized drugs tend to exhibit far greater aqueous solubility than the un-ionized counterpart. Consequently, the rate of solute dissolution in aqueous media can be markedly affected by the pH of that solvent.

To examine the effect of pH on drug ionization, one can use a rearrangement of the Henderson-Hasselback equation:[5]

Weak acid: % un-ionized = 100/(1 + antilog (pH-pKa)).
Weak base: % un-ionized = 100/(1 + antilog (pKa-pH)).

Weakly basic drugs tend to have a slower dissolution rate at higher pH (when more drug exists in its un-ionized form), whereas weakly acidic drugs dissolve faster at higher pH (when more drug exists in its ionized form). Examples of the relationship between the percentage of drug in its un-ionized form as a function of drug pKa and pH are found in Figures 2 and 3. For this reason, by increasing the proportion of drug existing in its un-ionized state, meals that elevate gastric pH can decrease the dissolution of a weak base. For example, weak bases such as indinavir (with pKa of 3.7 and 5.9) are expected to precipitate when gastric pH is elevated during a meal, resulting in a significant reduction in AUC and C_{max} values in fed versus fasted human subjects.[6] Conversely, the same meal can increase the dissolution rate of a weak acid by increasing the proportion of drug existing in its ionized state, thereby making it more water soluble.[7]

By definition, solubility is the extent to which molecules from a solid are removed from its surface by a solvent. While solubility may be expressed in many ways, some generalizations can be made:[8]

Very soluble: Less than 1 part solvent needed to dissolve 1 part solute
Freely soluble: From 1 to 10 parts solvent needed to dissolve 1 part solute
Soluble: From 10 to 30 parts solvent needed to dissolve 1 part solute
Sparingly soluble: From 30 to 100 parts solvent needed to dissolve 1 part solute
Slightly soluble: From 100 to 1000 parts solvent needed to dissolve 1 part solute
Very slightly soluble: From 1000 to 10,000 parts solvent needed to dissolve 1 part solute
Practically insoluble: More than 10,000 parts solvent needed to dissolve 1 part solute

A compound's aqueous solubility, as measured by its propensity to distribute between octanol and water, is a function of its ability to form hydrogen bonds with the water molecule. Generally, aqueous solubility is directly proportional to the number of hydrogen bonds that can be formed with water.[9] As discussed later,

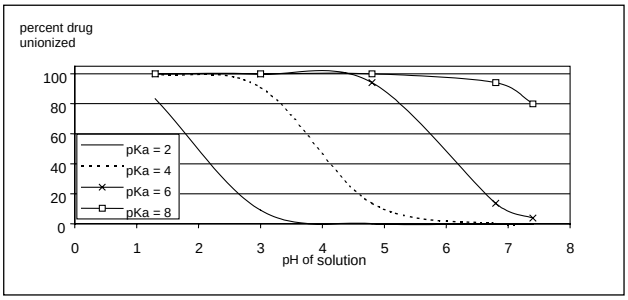

Figure 2. Relationship between percentage of drug un-ionized, and pH and pKa of weak acids.

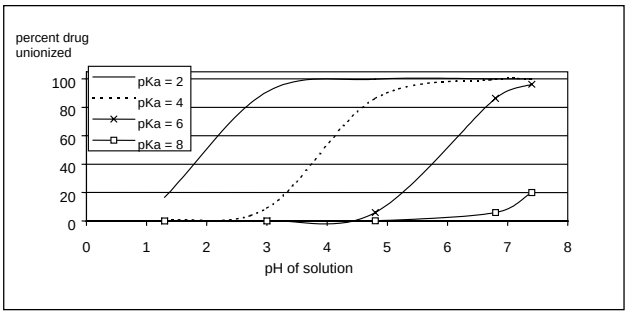

Figure 3. Relationship between percentage of drug un-ionized, and pH and pKa of weak bases.

while very high aqueous solubility is beneficial for drug dissolution in aqueous media, these same compounds often exhibit low permeability due to their high polarity and poor lipophilicity.

Although lipid/water partitioning is often used to describe drug solubility, there is some evidence that solubility may better be described by the compound's dynamic energy properties.[10] The solubility parameter of any compound can be described in terms of the energy required to fragment a molecule into its constituent atoms (its cohesive energy). When described in terms of the square root of its cohesive energy density (energy of vaporization per unit volume), the solubility parameter will lie on a scale from 10 (*nonpolar*) to 48 (*water*). For two materials to be miscible, their solubility parameters must be similar.

When comparing the percent absorbed versus log P (octanol/water partition coefficient), the percent absorbed versus the solubility parameter, and the percent absorbed versus the number of hydrogen bond acceptors, it was noted that a high level of negative correlation was observed for the latter two relationships. Conversely, a large degree of scatter was observed in the relationship between permeability and log P. It was also noted that highly permeable compounds tend to have solubility parameter values almost identical to that of biological membranes (solubility parameter values of 20-26 $MPa^{1/2}$). Accordingly, thermodynamic considerations rather than physicochemical interactions[10] may serve as the best predictors of a compound's membrane permeability.

IN VIVO DRUG ABSORPTION

Efforts are currently under way to identify molecular quantitative structure-bioavailability relationships (QSBR) that predict drug bioavailability.[11] Factors that negatively influence bioavailability include the number of hydrogen bond donors, the presence of heavy atoms, and the inclusion of fragments such as tetrazole, 4-animopyridine, and benzoquinone. Factors that tend to enhance drug bioavailability include the presence of hydrogen acceptors, low molecular weight, and the presence of fragments such as azide, salicylic acid, and amides.

To understand reasons for these structure-bioavailability relationships, it is important to recognize the complex series of events that occur during the process of drug absorption. Molecular movement across lipid bilayers, such as those existing within biological membranes, is extremely complex due to the regional differences in membrane polarity, hydrophobicity, and density. Generally, the bilayer can be divided into four distinct regions.[12] These include the following:

1. The first (outermost) region contains a high proportion of water molecules and may be the region responsible for interactions with other membranes and proteins.
2. The second region has the highest molecular density of all four regions (contains the polar headgroups), contains little or no water, and exerts the greatest barrier to solute *diffusion* (due to its density characteristics).
3. The third region contains the highest density of nonpolar tails. This region serves as the primary barrier to membrane *penetration* and is primarily responsible for the limitations in molecular size and shape associated with membrane transport.
4. The fourth region is the most hydrophobic region of the membrane, serving as a *hydrophobic barrier* in membrane transport.

Owing to this membrane structure, it is evident that drug permeability is not a simply two-step process of solubilization and diffusion but rather represents a

spectrum of complex molecular events. Accordingly, intestinal permeability reflects a multifunctional interaction of factors such as molecular size (negatively correlated), lipophilicity (positively correlated), polar van der Walls surface area (negatively correlated), and the molecular flexibility (intramolecular hydrogen bond formation).[13]

In addition to cellular membrane barriers to drug diffusion, significant impedance is also effected by the components of the gastric and intestinal mucous layer.[14] In examining the relative contribution of these various components, it was noted that lipid constituents such as phosphatidyl choline, cholesterol, and linoleic acid significantly retard the diffusion of small lipophilic molecules such as propranolol and hydrocortisone. Conversely, small hydrophilic molecules such as mannitol appear to freely diffuse through this lipoid barrier. Mucous gel-forming components, such as mucin and DNA, exert far less negative effects on the diffusion of lipophilic molecules. However, they may serve to block the diffusion of peptides and proteins.

Molecular flexibility and the corresponding ability to undergo conformation changes can significantly affect the polar surface area of a molecule. The polar surface area and nonpolar surface area are powerful predictors of intestinal permeability, being respectively inversely and directly related to membrane permeability.[15] However, any particular set of descriptors may not adequately predict membrane permeability across nonhomologous compounds.[9] Another important variable is the strength of the hydrogen bonds formed between the molecules of water and solute.[15] It is generally assumed that these bonds must be broken (desolvation) before the solute can traverse the biological membrane. Which of these factors play the dominant role in determining drug permeability may vary across homologous drug series.

Despite these complexities, certain generalizations can be made with regard to drug absorption processes. For example, the vast majority of orally administered drugs are absorbed via passive transcellular transport.[15] This necessitates that the drug traverse through a highly lipophilic membrane. Accordingly, diffusion processes are governed by Fick's laws of diffusion and therefore influenced by the compound's lipophilicity. This ability to diffuse through lipids has been found to be highly correlated with the ability of a drug to partition between water and an organic solvent such as octanol. In fact, when expressed as log P_0 (based on partitioning between n-octanol and water), the optimal partition coefficient for a drug generally falls within the range of 2 to 7.[5] Nevertheless, exceptions do occur, and while transcellular transport generally occurs when the compound is un-ionized, recently, several ionized molecules have been shown to be absorbed via transcellular processes.[16,17] This finding reinforces earlier statements regarding the degree of scatter associated with the relationship between log P and drug absorption.

In addition to passive mechanisms, active transport is important to the absorption of several compounds. Both active and passive transport mechanisms may occur simultaneously for the same molecule. Which of these mechanisms has the dominant role tends to be compound specific and may not be well predicted by in vitro systems.[15] Nevertheless, it must be remembered that even active transport mechanisms require that the drug penetrate the intestinal cells via the transcellular route.

The rate of passive diffusion of any molecule, whether it be absorbed via transport between mucosal cells or through the mucosal membrane, can be described by the following equation:[18]

$$\frac{dM}{dt} = A_m \bullet \frac{D_m}{\lambda} \bullet C_{membrane} + \frac{J_{max}}{K_m + C_{lumen}} + A_p \bullet \frac{D_{aq}}{\lambda_{aq}} \bullet C_{lumen} + J_{fluid} \bullet C_{lumen} \bullet (1-\alpha),$$

where

- dM/dt = the effective rate of passive drug absorption (concentration/time).
- D_{aq} = the diffusion coefficient of the compound in water.
- λ_{aq} = the aqueous diffusion distance.
- J_{fluid} = the fluid flow between epithelial cells.
- α = the ratio of the water flow relative to the solute flux, both under the influence of the existing pressure gradient, and is dependent on molecular size, volume, charge, and hydration number. It may also be influenced by the dynamic width of the tight junction.
- K = the partition coefficient describing the relative tendency of the substance to dissolve in the membrane phase ($C_{membrane}$) as compared to the surrounding aqueous phase (C_{lumen}).
- D_m = the diffusion coefficient of the compound within the membrane, which is dependent on factors such as drug lipophilicity, hydrogen bonding capacity, polar surface area of the molecular, molecular volume, and shape.
- J_{max} = the maximal transport capacity of the carrier-mediated process.
- K_m = the substrate specificity of the membrane transporter (the Michaelis constant).

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