Pharmacokinetic Strategies in Deciphering Atypical Drug Absorption Profiles

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Drug absorption is a very complex process that manifests itself through potential interaction with a host of physicochemical and physiological variables. Some factors that may affect the absorption processes include presystemic metabolism/efflux, the "absorption window" along the gastrointestinal tract, disease states, demographics (gender, age, ethnicity), and biopharmaceutical classification of solid dosage forms. Despite the complexity of the absorption processes, the analysis of the absorption kinetic data is mostly empirical, and the assumption of first-order absorption is axiomatic. Nevertheless, we often encounter irregular drug absorption profiles (such as double-peak, absorption window–type absorption profiles, etc.) that cannot be satisfactorily described by a simple first-order absorption process. The selection of an inappropriate absorption model would result in the misspecification of the pharmacokinetic model and subsequent erroneous prediction of the dosing regimen. This article presents several pharmacokinetic strategies in analyzing typical and atypical absorption profiles. The atypical absorption profiles discussed in this article include parallel first-order absorption, mixed zero-order and first-order absorption, Weibull-type absorption, absorption window with or without Michaelis-Menton absorption, time-dependent absorption, and inverse Gaussian density absorption. In any event, intravenous drug concentration-time data are generally needed to avoid the ambiguousness in the absorption analyses.

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Since Teorell[1] published the pioneering paper "Kinetics of Distribution of Substances Administered to the Body" in 1937, pharmacokinetic theory has since been well developed and matured as an independent discipline. However, it has been recognized for a long time that the characterization of drug absorption usually is assumed empirically and lacks physiological relevance.

Oral administration is the predominant route of drug administration. In most cases, drug permeates through the gastrointestinal (GI) epithelium through passive diffusion. Alternatively, passive-facilitated diffusion or active transport may also be operating. Oral drug absorption is a very complex process that manifests itself through potential interaction with a host of physicochemical and physiological variables. Factors that can potentially contribute to the variabilities in drug absorption include presystemic metabolism/efflux, gastric pH/emptying rate, GI motility, luminal contents, formulation effect (pH-solubility/dissolution dependence, permeability, stability in the GI tract, complexation, etc.), and so forth. The mechanistic diagram of oral GI absorption is depicted in Figure 1.

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SEVERAL SELECTED FACTORS AFFECTING THE ABSORPTION PROCESSES

Presystemic Metabolism/Efflux

Recently, the impact of the intestinal mucosa on oral drug bioavailability has become one of the major focuses in pharmaceutical research. Intestinal metabolism may contribute to the considerable inter- and intrasubject variability in the oral bioavailability of many orally administered drugs. The mucosal epithelial cells contain a variety of enzymes mainly involved in phase I and phase II enzymatic reactions. The highest concentration of mucosal enzymes is in the upper small intestine (duodenum and jejunum followed by ileum and colon), after which the content decreases toward the crypts.[2] Of all the enzymes in the intestine re-

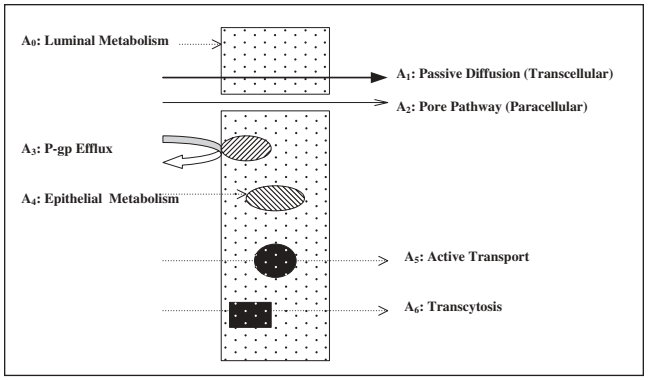

Figure 1. Mechanistic diagram of oral gastrointestinal (GI) absorption (relative contribution of each route may vary from drug to drug).

sponsible for drug metabolism, the CYP superfamily is the most notable. The isoenzymes that have been identified in the human small intestines include CYP1A1, CYP2C, CYP2D6, and CYP3A4 (most populous). CYP3A4 is the predominant drug-metabolizing enzyme observed in both liver and intestine. Unlike CYP2C and CYP2D6, CYP3A4 has been recognized to lack genetic polymorphisms.[3]

Compared to the immense interest in the oxidative biotransformation pathway (phase I), unfortunately, far less attention has been paid to the phase II conjugation reactions because they are classically considered as "detoxification" processes. However, evidence shows that this historical concept of the conjugation reactions as the general detoxification processes is no longer tenable. Some conjugated metabolites, such as glucuronide and hydroxyphenylamide conjugates of retinoic acid, can become more active than the parent compound.[4] The metabolism of oxazepam expresses exclusively the capacity for the glucuronide formation. Severe decompensated liver disease was associated with a significant decrease in the oxazepam clearance.[5] Sulfate conjugation occurring in the GI mucosa has been found to be an important barrier for the oral absorption of isoproterenol, isoetharine, rimiterol, and some steroid hormones.[6,7]

The extent and rate of intestinal metabolism could significantly affect the metabolic contribution of the liver to first-pass metabolism. Arterial blood enters the intestine via the mesenteric artery and leaves via the portal vein, the latter of which contributes to approximately 75% of the total perfusion of the liver. The collective contribution of both gut wall and liver to the oral bioavailability (F) can be described as follows:

$$F = f_{abs} \times (1 - f_g) \times (1 - f_h) \quad (1)$$

where f_{abs} is the fraction of the dose absorbed from the GI lumen, f_g is the fraction of drug metabolized by the gut wall, and f_h is the fraction of drug metabolized by the liver.

Recently, a surge of studies have focused on the identification and the role of molecular transporters, which have helped pharmaceutical scientists to gain more insight into the importance of transporters in modifying drug absorption. As evidenced by drugs that are metabolically inert such as fexofenadine and talinolol, P-glycoprotein (P-gp, a 170-kD transmembrane phosphoglycoprotein from the ATP-binding cassette family) can contribute to the dose-dependent oral bioavailability such that bioavailability can be increased solely due to efflux pump saturation. Intestinal secretion following intravenous administration of P-gp substrates (paclitaxel, vinblastine, digoxin, indinavir, talinolol, etc.[8]) was essentially eliminated in "knockout" mice (mdr1a–/–), while a significant percentage of the dose underwent intestinal secretion in wild-type mice (mdr1a+/+). A similar effect corresponding to the mdr1a–/– genetic variant in mice was also observed in humans, in whom certain variations in the MDR1 gene have been shown to alter both the gut expression of P-gp and the oral absorption of P-gp substrates.[9] P-gp has been shown to recognize and transport a structurally, chemically, and pharmacologically diverse range of compounds. A classic P-gp substrate is usually a hydrophobic, amphipathic molecule with a planar ring system, a molecular weight greater than 400, and a positive charge at pH 7.4.[10]

CYP3A and P-gp are often collocated on the apical surfaces of small intestine villi. They exhibit overlapping substrate specificity and share inducers and inhibitors.[11-13] Efflux of drug substrates by P-gp from intestinal tissue into the lumen side may repeatedly expose drug to metabolizing enzymes (such as CYP3A) in the intestinal mucosa. These combined effects could result in a prolonged absorption process[14] and a shift in the absorption site.[15] Benet et al[16] postulated that the role of P-gp in the intestine extends beyond simply limiting parent drug absorption; it also increases access of the drug to metabolism by CYP3A through repeated cycles of absorption and efflux.

In contrast to CYP3A, P-gp mRNA levels increase longitudinally along the intestine, and the highest levels are located in the colon.[17] Moreover, unseen in CYP3A4, there is considerable genetic variability among membrane transporters (including P-gp).

In addition to P-gp, several other transporters have been identified to potentially play roles in the drug efflux in the intestines. Multidrug resistance-associated protein (MRP), a 190-kD ABC transport protein, was

the first non-P-gp MDR-conferring transporter identified.[18] MRP1 have been shown to express in the small intestine and its homologues MRP2, MRP3, and MRP6 in the intestine.[19] MRP1 can actively transport a wide range of compounds out of the brain. MRP1 homologues MRP2 to MRP6 have also been shown to mediate drug efflux in vitro. Monocarboxylic acid transporters (MCTs) have been revealed to transport pyruvate, lactate, and other metabolites bidirectionally across membranes.[20] MCT1 and MCTs 4 to 8 have been found to express in intestine tissues. In addition, organic cation transporters (OCT) 1 and 3 have also been found to express in intestine tissues.[19]

Absorption Window

The drug absorption pattern along the GI tract is determined by the interplay between drug physicochemical properties and the physiological conditions, which affect the permeation properties of the drug within the different parts of the GI tract. Once the drug is given orally, GI motility tends to move the drug through the alimentary canal. For drugs that are given orally, an anatomic "absorption window" may exist within the GI tract in which the drug can be efficiently absorbed. The possibility of a "window" effect for digoxin, suggested by Wagner,[21] has been clearly supported by the pharmacological findings that the cardiac glycosides are most rapidly absorbed from the upper intestinal tract.[22]

An acidic drug tends to have low solubility up in the GI tract due to the little ionization in a relatively more acidic environment. It becomes more soluble and less permeable down the tract due to the increasing ionization in a more alkaline condition. As the environment becomes more alkaline down the GI tract, the absorption of acidic drugs may switch from the dissolution control to the membrane control, depending on the pK_a of the drug. In contrast, a basic drug tends to have diminishing solubility transiting down the GI tract and becomes more permeable. Absorption of a basic drug is therefore becoming more dissolution/release controlled. Several physiological factors may vary substantially during the release/absorption of a drug from an extended-release product. These factors include residence time at each site, effective permeability coefficient, pH/buffer capacity of the intestinal fluid, and potential for drug degradation at different sites. The residence time at each site (i.e., the restricted absorption window) may influence the timeframe over which an in vitro–in vivo correlation (IVIVC) can be possibly achieved. Dunne et al[23] proposed an absorption window model to describe the dissolution-limited absorption within an absorption window, assuming first-order dissolution and first-order absorption. Based on the absorption window model, with dissolution-controlled first-order absorption occurring only within the window, the relationship between $F_{rel}\%$ and $t_{80\%}$ can be described by

$$F_{rel}\% = 100 \bullet \left(1 - \frac{k_a}{k_a - k_d} \bullet e^{-k_d \bullet \Delta T} - k_d \bullet e^{-k_a \bullet \Delta T}\right) \quad (2)$$

where $t_{80\%}$ is the time for 80% drug dissolution; $F_{rel}\%$ represents relative bioavailability; k_a and k_d ($k_d = 1.604/t_{80\%}$) are first-order absorption and dissolution rate constants, respectively; and ΔT is the residence time in the absorption window.

Several strategies have been explored to improve the oral bioavailability by prolonging the ΔT in the absorption window. A few modified-release formulations, including the monolithic floating system,[24] nondisintegrating single-unit formulation,[25] and mucoadhesive microspheres,[26] have been designed to prolong their stay in the upper GI tract until all the drug has been released. Terao et al[27] investigated the feasibility of widening the absorption window of furosemide by controlling the pH in distal portions of the GI tract with methacrylate copolymer (Eudragit L100-55). Eudragit L100-55 is a large molecule containing many carboxylate groups that can create an acidic pH in the distal GI tract. Furosemide is a weak acid; therefore, under the influence of Eudragit, the percent un-ionized furosemide in the ileum was significantly increased. A strong positive correlation ($r = 0.9$) was observed between the un-ionized fraction of furosemide distributed in the small intestine and its plasma concentration.[27] The observed increased bioavailability of furosemide was mainly due to the improved absorption in distal portions of the GI tract as a result of the reduction in pH by Eudragit L100-55.

Sawamoto et al[28] proposed a GI-transit-absorption kinetics model to predict the absorption profiles of drugs administered orally as an aqueous solution. This linear GI-transit-absorption kinetic model contains eight segments representing the stomach, duodenum, upper jejunum, lower jejunum, upper ileum, lower ileum, cecum, and colon, respectively, as depicted in Figure 2. This model contains a GI transit process and an absorption process in each segment, where D is the initially administered dose, A_i is the amount of drug in segment i, k_i is the first-order transit rate constant from segment i, ka_i is the first-order absorption rate constant for segment i, k_e is the first-order elimination rate constant from the central compartment, and F is the

bioavailability. Ampicillin was chosen as a model drug with poor absorption from the GI tract, having no first-pass elimination and a restricted absorption window. Therefore, plasma concentrations of this drug after oral administration reflect simply the absorption from the GI tract and the systemic elimination. Predicted by use of the convolution method based on the GI-transit-absorption model, the extent of the bioavailability of ampicillin was increased in rats pretreated with propantheline, an anticholinergic drug that can decrease the GI motility (GI transit rate). The predicted results were in general agreement with the observed data.[29] These results strongly suggest that ΔT of drugs with a restricted absorption window along the GI tract is an important factor in determining the absorption extent for those drugs.

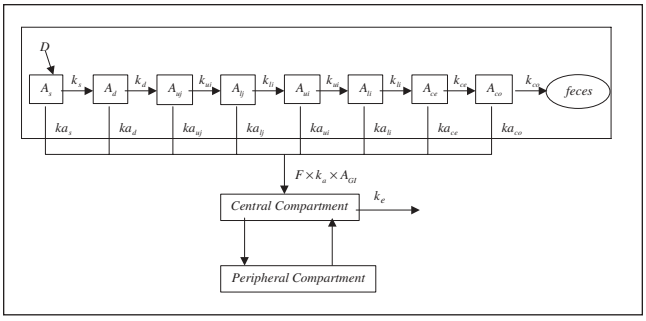

Figure 2. Diagram of GI-transit-absorption model. Adapted from Sawamoto et al.[28] D: initially administered dose. A_s, A_d, A_{uj}, A_{lj}, A_{ui}, A_{li}, A_{ce}, A_{co}, A_{GI}: amount of drug in stomach, duodenum, upper jejunum, lower jejunum, upper ileum, lower ileum, cecum, large intestine, and whole gastrointestinal (GI) tract, respectively. k_s, k_d, k_{uj}, k_{lj}, k_{ui}, k_{li}, k_{ce}, k_{co}: first-order transit rate constant from stomach to duodenum, from duodenum to upper jejunum, from upper jejunum to lower jejunum, from lower jejunum to upper ileum, from upper ileum to lower ileum, from lower ileum to cecum, from cecum to large intestine, and from large intestine to feces, respectively. k_{as}, k_{ad}, k_{auj}, k_{alj}, k_{aui}, k_{ali}, k_{ace}, k_{aco}, k_a: first-order absorption rate constant from stomach, duodenum, upper jejunum, lower jejunum, upper ileum, lower ileum, cecum, large intestine, and whole GI tract, respectively.

Disease State and Demographics

Disease state. The drug absorption in patients with GI disorders is influenced by changes in the gastric and intestine motility, by changes in the surface area available for drug absorption, and by alteration of the physical and chemical properties of the intestinal luminal content. Several diseases or conditions may affect drug absorption. These include Crohn's disease, celiac disease, AIDS enteropathy, drug- and irradiation-induced malabsorption, and so forth.

Age. Drug absorption does not appear to change dramatically with age.[30] However, all the factors that affect drug absorption, including gastric pH, gastric motility, intestinal motility, and so forth, do vary with age. Some physiological changes that occur with aging could potentially influence drug absorption.[31]

A number of factors can alter the absorption of drugs in children. Gastric acidity can enhance or hinder the absorption of drugs in the stomach or affect the dissolution of drugs. In the neonate, a condition of relative achlorhydria persists from 10 days to 1 month of age. In the first 2 years of life, gastric acidity slowly increases, and only after 3 years of age does gastric acid secretion approach the adult level. GI motility and transit time also vary throughout childhood. Neonates and infants have prolonged gastric emptying time; thus, delays may occur in the intestinal absorption of some drugs. Intestinal transit time is also variable in infancy. The pharmacokinetics in pediatrics has been thoroughly reviewed by several authors.[32-35]

Gender. It has been recognized for many years that both gender and estrus cycle influence pharmacokinetics in animals. However, investigation into these differences in humans has only recently been appreciated.

Meager investigations have been conducted to examine gender differences in the absorption of xenobiotics in humans. Gender-related absorption differences were documented for iron and ethanol.[36] Iron was found to be more readily absorbed in preadolescent girls than boys at the same ages, and the gender-related difference in the absorption of iron was hypothesized to be related to hormonal differences.[37] Females were shown to have increased bioavailability of ethanol than males. The difference in ethanol absorption was a result of less gastric "first-pass" metabolism in females because of their less gastric alcohol dehydrogenase activity.[38]

Gastric acid secretion has been reported to be lower in women than in men. Pregnancy can also result in reduced gastric secretion, decreased pepsin activity, and increased intestinal motility.[39] The menstrual cycle variations occur in many systems, including renal, cardiovascular, hematological, and immune systems. Those physiological changes can potentially alter the pharmacokinetics of drugs, including their absorption processes. However, evidence so far has suggested a lack of influence of menstrual cycle on drug absorption. It is still unknown whether hormonal fluctuations within the menstrual cycle would affect the activity of some specific drug-metabolizing enzymes.

Ethnicity. The International Conference on Harmonization (ICH) has put forth a tripartite guideline (ICH-E5) concerning ethnic factors in the acceptability of foreign clinical data. One of the major issues addressed in the guideline is the effect of ethnicity on the drug's pharmacokinetics. Several pharmacokinetic properties that could be potentially sensitive to ethnic factors have been identified in the guideline. These properties include the linearity in pharmacokinetics, metabolism potential, genetic polymorphism, intersubject variation in bioavailability, protein binding, and drug-drug, drug-diet, or drug-disease interactions.

Upon comprehensive literature review, Johnson[40] identified three pharmacokinetic characteristics that would be most likely to cause ethnic differences in pharmacokinetics: high α_1-acid glycoprotein binding, hepatic metabolism as a major route of elimination, and gut or hepatic first-pass effects. Absorption (unless active) would not be expected to exhibit differences between ethnic or racial groups. Although the ethnic differences in genetic polymorphisms of the drug-metabolizing enzymes (e.g., CYP2D6, CYP2C9, CYP2C19, etc.) are well recognized, the ethnic differences in the distribution of genotypes or phenotypes are not necessarily translated into the ethnic differences in metabolism for a single phenotype.

Biopharmaceutical Classification

A biopharmaceutical classification system (BCS) for correlating the in vitro drug product dissolution and in vivo bioavailability for immediate-release (IR) solid oral dosage forms was originally proposed by Amidon et al.[41] The BCS has established the basis for determining the conditions under which IVIVC correlations are expected.[42] The BCS has taken into account three major factors that govern the rate and extent of drug absorption from the IR solid oral dosage forms: dissolution, solubility, and intestinal permeability, as illustrated in Table I.

In developing a classification for IR products, the primary concern is the extent of absorption. The IVIVC is likely to be established for the IR products falling within classes 1 and 2.

Young et al[43] applied a modified BCS to extended-release (ER) oral products containing three classes: high aqueous solubility, low aqueous solubility, and variable solubility under the assumption that all drugs in the ER products have good permeability, as illustrated in Table II.

Metformin is a compound with good aqueous solubility. It is predominantly ionized at intestinal pH ranges. The oral absorption of metformin is slow and incomplete, with an absorption window predominantly present in the small intestine.[44] Thus, it is classified as a high-solubility, low-permeability drug (BCS class 3 for metformin IR products or modified BCS class 1b for metformin ER products). The level A IVIVC models could not be established for drugs such as metformin, which are limited by the absorption rate and the intestinal site of input. The level C IVIVC models were developed for metformin ER formulations, but their usage is only limited in the formulation optimization within the given series of prototypes.[45]

Table I The Biopharmaceutical Classification System for Immediate-Release Drug Products and Expected In Vitro–In Vivo Correlation (IVIVC)

Class	Solubility	Permeability	IVIVC
1	High	High	Likely
2	Low	High	Likely
3	High	Low	Less likely
4	Low	Low	Less likely

The primary concerns in developing a classification for ER products are the time course and variation in input rate. The drugs selected for ER product development should have good GI permeability and an extended site of absorption. The vast majority of the compounds (~60%) used in ER products may be chemically classified as weak bases. The level A type IVIVC are more likely to be obtained for basic compounds than for acidic ones. The alkaline pH environment along the intestinal tract may play a role in the preference of basic compounds in ER products.

TYPES OF ABSORPTION PROFILES

Since oral administration is the most prevailing route of administration, the common procedure for the absorption analysis presented in this article is mainly for oral absorption unless specified. Due to the complexity of the absorption processes, there is no fixed rule and procedure to follow in analyzing the absorption kinetic data. Nevertheless, prior to launching any absorption analysis, it is always recommended to plot the drug plasma (or other biofluid matrices) concentration-time data in both linear-linear and semilogarithmic scales. The oral drug plasma profiles can be generally partitioned into two classes: typical profiles or atypical profiles. To decipher the oral absorption kinetic data accurately, one must have prior knowledge of a drug's "true" disposition kinetics based on its intravenous data.

Table II The Modified Biopharmaceutical Classification System for Extended-Release Drug Products and Expected In Vitro–In Vivo Correlation (IVIVC)

Class	Solubility	Permeability	Site Dependency	IVIVC
1a	High	High	No	Likely
1b	High	Narrow absorption window	Yes	Less likely
2a	Low	High	No	Likely
2b	Low	Narrow absorption window	Yes	Less likely
5a (Bases)	Variable[a]	Variable[b]	Yes	Likely
5b (Acids)	Variable[b]	Variable[a]	Yes	Less likely

a. High in upper gastrointestinal (GI) tract, low in lower one.
b. Low in upper GI tract, high in lower one.

The typical plasma concentration profiles may be classified by two types of absorption: first-order absorption and zero-order absorption. The atypical drug concentration profiles, on the other hand, can be caused by many types of irregular absorption processes, such as parallel first-order absorption, mixed (simultaneous or sequential) first-order and zero-order absorption, Weibull-type absorption, absorption window–type absorption with or without Michaelis-Menten kinetics, time-dependent absorption rate, or inverse Gaussian density absorption. It is beyond the scope of this article to discuss the atypical drug concentration profiles that are caused by reasons other than absorption-origin ones.

Typical Absorption

First-order absorption. It is generally assumed that the oral absorption process follows first-order kinetics. If the absorption process truly follows first-order kinetics, a formal absorption analysis may not be needed. The first-order absorption rate constant can be easily obtained by using a simple compartmental modeling approach. Sometimes the inclusion of the absorption time lag (t_{lag}) may be needed to better characterize the absorption process. In any event, prior knowledge of the disposition nature based on intravenous data is a prerequisite.

Sometimes it is misleading to determine the nature of the absorption by simply basing a drug's disposition characteristics on the visual inspection of the drug concentration-time profile, especially when absorption extends over a long period of time for a drug exhibiting biexponential elimination. Its concentration-time profile may sometimes visually present as a one-compartment model because the distribution part of the curve is actually masked by the absorption portion.[46] Without an intravenous drug concentration-time curve as a reference, the "true" disposition model is rarely known and usually ambiguous.[47,48]

In most cases, the absorption is faster than the elimination (i.e., $k_a > k_e$). Nevertheless, the so-called "flip-flop" phenomenon may arise when $k_a < k_e$. The term *flip-flop* is used to describe the nonuniqueness of the rate constants in a one-compartment pharmacokinetic model, in which the slowest rate constant may be attributed to either absorption or elimination. Consequently, computation difficulties may be encountered when fitting a one-compartment model with first-order absorption in which $k_a \approx k_e$.[49]

The Wagner-Nelson (W-N) method is commonly used for the evaluation of the absorption kinetics of a drug exhibiting one-compartment kinetics with first-order absorption and elimination. The percent bioavailable drug absorbed ($F_a(t)$) can be calculated by the following equation based on the W-N method:

$$\%\ \text{Bioavailable Drug Absorbed} = F_a(t) = \frac{(X_A)_t}{(X_A)_\infty} = \frac{C + k \bullet \int_0^t C \bullet dt}{k \bullet \int_0^\infty C \bullet dt} \quad (3)$$

where $(X_A)_t$ and $(X_A)_\infty$ are the cumulative amount of the drug absorbed up to time t or infinity (the amount of the drug ultimately absorbed), k is the elimination rate constant, and $\int_0^t C \bullet dt$ and $\int_0^\infty C \bullet dt$ are the areas under the plasma concentration versus time curves (AUC) up to time t or infinity, respectively.

The W-N method should only be used for evaluating the oral absorption kinetics of those drugs that demonstrate the monoexponential decay after a bolus intravenous injection.[50] The W-N method or its modification should not be used to analyze oral data with multicompartment disposition characteristics.

The Loo-Riegelman (L-R) method, on the other hand, may be used to quantify the absorption kinetics

when the corresponding intravenous data suggest bi- or triexponential decay in the distribution and elimination profile. The L-R method requires data following both oral and intravenous administration of the drug to the same subject. The percent bioavailable drug absorbed ($F_a(t)$) can be calculated by the following equation based on the L-R method:

$$\%\,\text{Bioavailable Drug Absorbed} = \frac{(X_A)_t}{(X_A)_\infty} = F_a(t) = \frac{C_p + C_t + k_{10} \bullet \int_0^t C_p \bullet dt}{k_{10} \bullet \int_0^\infty C_p \bullet dt} \quad (4)$$

where $(X_A)_t$ and $(X_A)_\infty$ are the cumulative amount of the drug absorbed up to time t or infinity (the amount of the drug ultimately absorbed), respectively; k_{10} is the elimination rate constant from the central compartment; C_p and C_t are the drug plasma concentrations in the central and peripheral (tissue) compartments, respectively; and $\int_0^t C_p \bullet dt$ and $\int_0^\infty C_p \bullet dt$ are the area under the plasma concentration versus time curve (AUC) up to time t or infinity, respectively. Values for C_t can be approximated by the L-R method as follows:

$$(C_t)_{t_n} = \frac{k_{12} \bullet \Delta C_p \bullet \Delta t}{2} + \frac{k_{12}}{k_{21}} \bullet (C_p)_{t_{n-1}} \bullet (1 - e^{-k_{21} \bullet \Delta t}) + (C_t)_{t_{n-1}} \bullet e^{-k_{21} \bullet \Delta t} \quad (5)$$

where t_n and t_{n-1} are the sampling time for samples n and n – 1, respectively; $(C_p)_{t_{n-1}}$ is the drug concentration at the central compartment for sample n – 1; and $(C_t)_{t_n}$ and $(C_t)_{t_{n-1}}$ are the concentrations of the drug at the peripheral (tissue) compartment for samples n and n – 1, respectively. Values of k_{10}, k_{12}, k_{21}, and β are estimated from the intravenous concentration-time data by compartmental modeling.

Zero-order absorption. The assumption of first-order absorption is self-evident in many cases, but there are a number of exceptions. For a typical drug with zero-order absorption, its concentrations after oral administration rise to a sharp peak and then quickly decline with no intermediate plateau. The graphical illustration of the typical zero-order absorption following oral dosing of 300 mg cyclosporin A in healthy subjects is shown in Figure 3.[51] Some of those drugs that exhibit zero-order absorption kinetics include ethanol,[52] sulfisoxazole,[53] griseofulvin,[54] erythromycin,[55] and hydroflumethiazide.[56]

In addition to the aforementioned W-N and L-R methods, several other methods can also be used to estimate zero-order absorption kinetic data. These methods include the area function method,[57,58] the nonlinear regression analysis method, the moment analysis method,[59] the deconvolution method, and the modified residual method.[60] The area function method was found to be far superior to the L-R method and moment analysis method.[57] Assuming that oral absorption follows zero-order kinetics with k_0 (zero-order input rate) over a duration of time, τ, a series of values can be calculated from the following equation:

$$k_0 = \frac{D \bullet C_{PO}(t)}{AUC_{IV}^{0 \to t}} \quad (6)$$

where D is the dose, $C_{PO}(t)$ is the plasma concentration at time t after an oral (PO) dose, and $AUC_{IV}^{0 \to t}$ is the area under the plasma concentration versus time curve following an intravenous (IV) dose measured from time 0 to time t.

The percentage of the amount absorbed ($F_a(t)$) at any time in the absorption phase can be calculated from the following equation:

$$F_a(t) = \frac{t \bullet C_{PO}(t)}{F \bullet AUC_{IV}^{0 \to t}} \bullet 100 \quad (7)$$

where F is the absolute bioavailability.

Since the zero-order absorption process ceases at t_{max}, both k_0 and $F_a(t)$ obtained after t_{max} are no longer meaningful. To apply this method successfully to estimate both k_0 and $F_a(t)$, only those data obtained in the absorption phase ($t \le t_{max}$) will be used.

Nevertheless, an inherent limitation of using the area function method is that one must know that the absorption process is zero-order.[57]

Atypical Absorption

Parallel first-order absorption. In some cases, the oral absorption process can be characterized by parallel first-order absorption kinetics rather than single first-order or single zero-order kinetics. There are many examples of parallel first-order absorption kinetics. For instance, the absorption of ibuprofen effervescent granules was well described by two parallel first-order inputs, while the absorption of ibuprofen suspension was characterized by only one first-order input.[61] The absorption processes of both lidocaine and bupivacaine following epidural administration were studied in surgical patients. Both drugs' absorption could be described by two parallel first-order absorption processes, characterizing both the fast (f: 0.40) and slow (1 – f: 0.60) absorption processes, respectively.[62] The percutaneous absorption of valproic acid was also

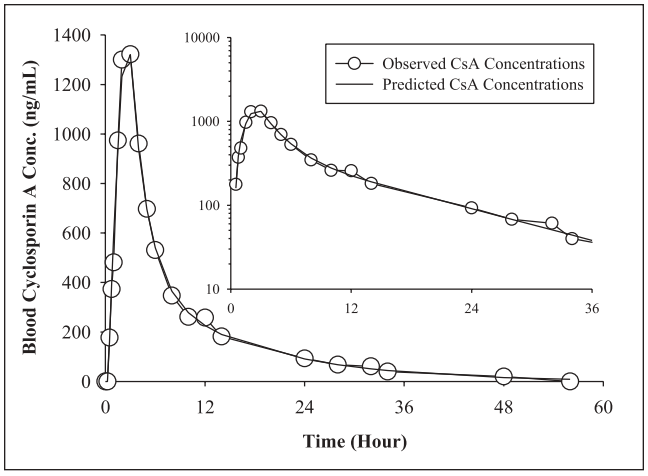

Figure 3. Graphical illustration of typical zero-order absorption following oral dosing of 300 mg cyclosporin A in a healthy subject (insert: semilogarithmic scale). Adapted from Grevel et al.[51]

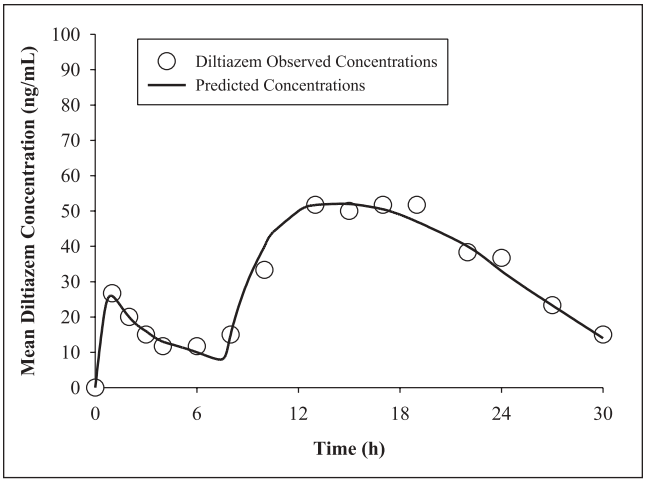

Figure 4. Graphical illustration of a typical two-parallel first-order absorption: mean plasma diltiazem concentration-time profile in dogs after oral administration of 100 mg HER-SR. Adapted from Murata et al.[66]

theorized to comprise two simultaneous absorption processes through the skin: rapid absorption across the water routes (k_{a1} = 2.6 h^{-1}), which accounted for about 70% of the total dose administered, and the remaining absorption via the lipid routes (k_{a2} = 0.11 h^{-1}).[63]

Similarly, the absorption of intramuscular microencapsulated octreotide could also be characterized by k_{IR} and k_{SR}, absorption rate constants for immediate release and sustained release, respectively. The surface, unencapsulated drug was immediately absorbed into the bloodstream with first-order absorption (k_{IR}), while the microencapsulated drug was first released in a zero-order fashion into a depot before being absorbed into the systemic circulation with the first-order absorption (k_{SR}) during a period of ~70 days.[64]

The absorption of a sublingual dose can be described by two-parallel first-order absorption—that is, the rapid first-order absorption from the buccal cavity ($k_{a,BUCCAL}$) and the delayed first-order absorption from the GI tract ($k_{a,GI}$). A portion of the dose (1 – f) escapes absorption from the buccal cavity and is swallowed. This swallowed fraction is then subsequently absorbed from the GI tract.[65]

The graphical illustration of a typical two-parallel first-order absorption is depicted in Figure 4.

Following oral administration of 100 mg HER-SR (a sustained-release diltiazem formulation) in dogs, the plasma diltiazem concentrations exhibited a "double peak,"[66] as shown in Figure 4. The HER-SR preparation was apparently divided into two fractions (14.3% and 85.7%, respectively) in the GI tract. The fractions were absorbed at rate constants of 4.56 h^{-1} and 0.15 h^{-1}, respectively. The lag time of absorption for the slow-release component was 8.3 hours.

Similar to the parallel first-order absorption model, an expanded parallel first-order absorption model, a multifraction (or multisegment) absorption model, may also be adopted in some situations to explain the double or multiple peaks or the discontinuous behavior of some drugs,[67,68] as depicted in Figure 5. The graphical illustration of multifraction absorption following oral administration of diclofenac sodium in man is shown in Figure 6. Three peaks were observed for the representative subject, and those multiple peaks were presumably caused by different absorption rate constants and different lag times from the GI tract.

Some of the double-peak or multiple-peak phenomena can be sufficiently explained by the above parallel first-order absorption model or multisegment absorption model. While numerous other reasons have been implicated in causing double-peak or major shouldering-type behavior, enterohepatic cycling has commonly been suggested in the occurrence of double-peak behavior for many drugs.[69] Enterohepatic cycling as a cause can be easily excluded if no evidence of double-peak behavior is observed following intravenous administration.[70,71] GI transit time or an absorption window effect could also give rise to the double-peak phenomenon.[72] Differential or sequential absorption of unchanged drug and its metabolites or simply of different metabolites could sometimes also result in the occurrence of the double peak.[73] Progressive solubilization along the GI tract and its subsequent intestinal absorption may also contribute to the double-

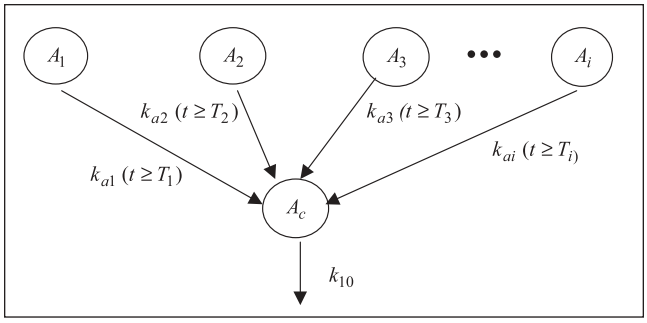

Figure 5. Schematic illustration of multifraction absorption kinetics in a hypothetical one-compartment model. Adapted from Murata et al.[66] *A_1, A_2, A_3, . . . , A_i: amount of drug in the gastrointestinal (GI) tract of the ith fraction. A_c: amount of drug in the central compartment. k_{a1}, k_{a2}, k_{a3}, . . . , k_{ai}: first-order absorption rate constant of the ith fraction. k_{10}: elimination rate constant from the central compartment. T_1, T_2, T_3, . . . , T_i: lag time for the absorption of the ith fraction.*

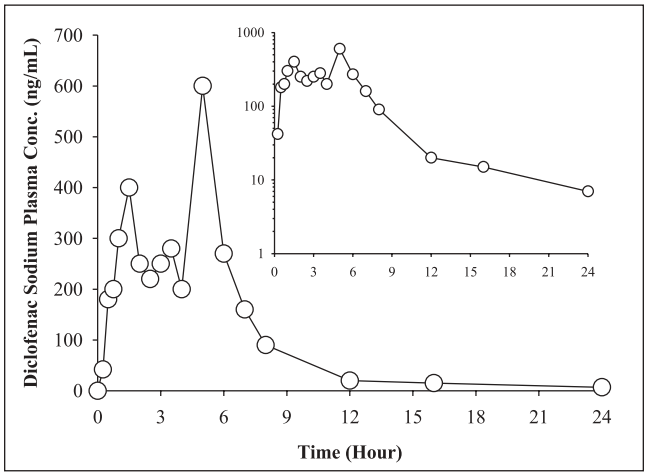

Figure 6. Graphical illustration of multifraction absorption kinetics following oral dosing of 100 mg diclofenac sodium in a representative healthy subject (insert plot: in semilog scale). Adapted from Mahmood.[68]

peak profile.[74] Some authors postulated that the double-peak phenomenon could be accounted for by two distinct absorption sites for the drug, which are separated by a region of relatively low absorption.[75] Gastric emptying–limited absorption could also be responsible for the double-peak behavior.[76-78] Sometimes, the pharmacological effect of the drug of interest could also play a role in the formation of the double peak. Wang et al[79] hypothesized that the double-peak phenomenon of alprazolam following oral administration was due to the reduction in gastric motility caused by the muscle-relaxant effect of alprazolam itself. The utilization of new techniques (such as an imaging approach) in pharmacokinetic studies can help us to better understand the double-peak behavior. The imaging analysis suggested that when gastric emptying was interrupted and resumed, the net result was the formation of the double peak in some plasma concentration profiles.[80] The double-peak phenomenon could also be manifested through a combination of gastric-emptying and bile salt solubilization processes.[81]

Mixed zero-order and first-order absorption. Occasionally, absorption can be described by the mixed zero-order and first-order absorption processes that occur either simultaneously or sequentially. Conceptually, if the first-order rate constant is linked to the zero-order input, the model can be postulated as the consequence of dissolution-limited absorption. Although the oral absorption of cefetamet pivoxil could be described by the sequential zero- and first-order model, the first-order process appeared to be independent of the zero-order input.[82] The zero-order process followed by the first-order absorption of cefadroxil was found to be consistent with its saturable intestinal absorption.[83] To optimize sumatriptan's formulation, nonlinear mixed-effect modeling of sumatriptan's absorption kinetics was performed. Oral absorption of sumatriptan was best described by a first-order input followed by a zero-order input.[84]

The combination of simultaneous first-order and zero-order processes allowed the elegant characterization of the peak concentrations of S20342 observed in the first hour (first-order kinetics) and the representation of the prolonged absorption phase when the dose increased (zero-order kinetics).[85]

The simulated drug concentration versus time profiles following drugs with either simultaneous zero-order and first-order absorption or sequential zero-order followed by first-order absorption are illustrated in Figure 7. The absorption phase of the drug with simultaneous zero-order and first-order kinetics exhibits an "infusion"-type ascent over a duration of τ and then quickly declines with no intermediate plateau. In contrast to the simultaneous type, the absorption phase of the drug with sequential zero-order followed by first-order absorption demonstrates two distinct phases of rise: the first phase manifests itself as zero-order absorption over a duration of τ, while the second phase represents the absorption solely due to a first-order process.

Weibull-type absorption. Under certain circumstances, when first-order, zero-order, or a combination of both cannot adequately describe the absorption profile, the use of Weibull function(s) in the absorption analysis may be an alternative. The inherent flexibility

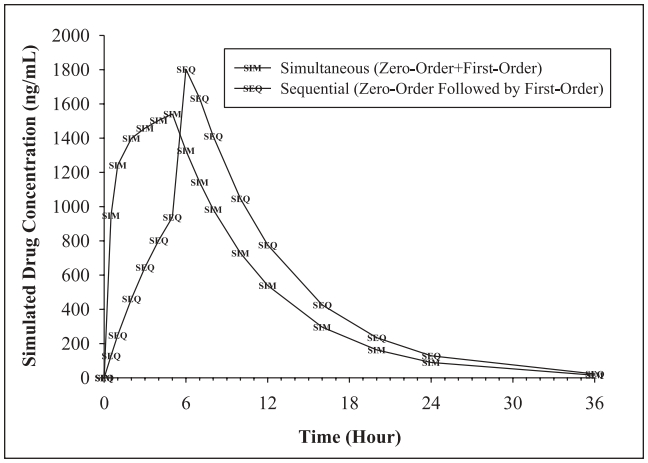

Figure 7. Simulated plasma drug concentration versus time profiles following drugs with simultaneous zero-order and first-order or sequential zero-order followed by first-order absorption.

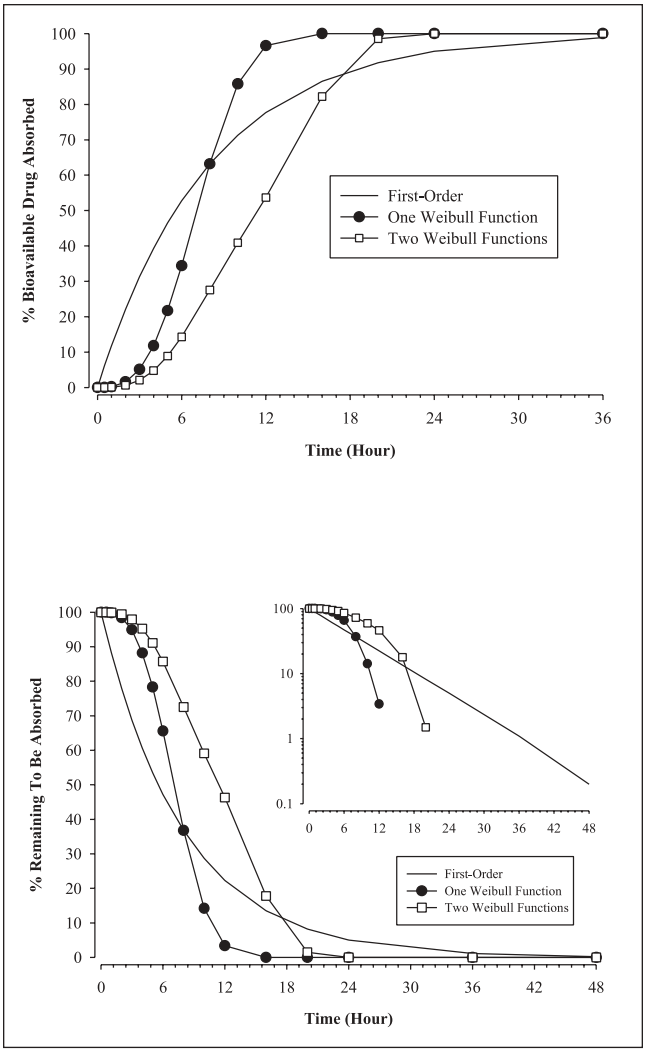

Figure 8. Simulated absorption profiles for compounds with first-order absorption, one Weibull function, or two Weibull functions. Top panel: percent bioavailable drug absorbed versus time profiles; bottom panel: percent remaining to be absorbed versus time profiles; insert: semilogarithmic scale.

of the Weibull functions in the absorption equation may reflect the variable drug input rates along the GI tract.[86]

The Weibull distribution has long been used to describe in vitro dissolution profiles.[87] As in vivo drug absorption is a complex multistage process, it sometimes cannot be adequately described in the framework of simple-order kinetics. Piotrovskii[88] first applied the Weibull function to describe the in vivo absorption data of theophylline and pantothenic acid. The L-R analysis of oral plasma medroxyprogesterone acetate concentration-time profiles indicated that the complex absorption process of medroxyprogesterone can be well characterized by the Weibull input function, but not a simple first-order process.[89] The flexibility of the Weibull model also allowed revealing a longer duration of absorption and a slower rate in amoxicilline's absorption kinetics when amoxicilline was coadministered with SPG (a laxative).[90]

In some cases, two Weibull function inputs are needed to fully characterize the absorption processes of certain drugs.[86,91,92] The simulated absorption profiles for first-order absorption, one Weibull function input, or two Weibull function inputs are illustrated in Figure 8.

The absorption model containing one or two Weibull functions is shown as follows:

$$\% \text{ Absorbed} = F \bullet \left[1 - f \bullet e^{-(k_a \bullet t)^{\gamma}}\right] \quad (8)$$

$$\% \text{ Absorbed} = F \bullet \left[1 - f \bullet e^{-(k_{a1} \bullet t)^{\gamma 1}} - (1-f) \bullet e^{-(k_{a2} \bullet t)^{\gamma 2}}\right] \quad (9)$$

where F represents the absolute bioavailability; k_{a1} and k_{a2} are the apparent absorption rate constants in both rapid and slow absorption phases, respectively; γ_1 and γ_2 are shaping factors; and f and 1 – f are the fractions of drug absorbed in both rapid and slow absorption phases, respectively. Hartmann et al[93] described the absorption profile of vitamin retinyl palmitate in a watermiscible preparation following the ventro-gluteal route by using the Weibull input function (as shown in Figure 9), wherein first-order absorption or zero-order input failed to depict its absorption process.

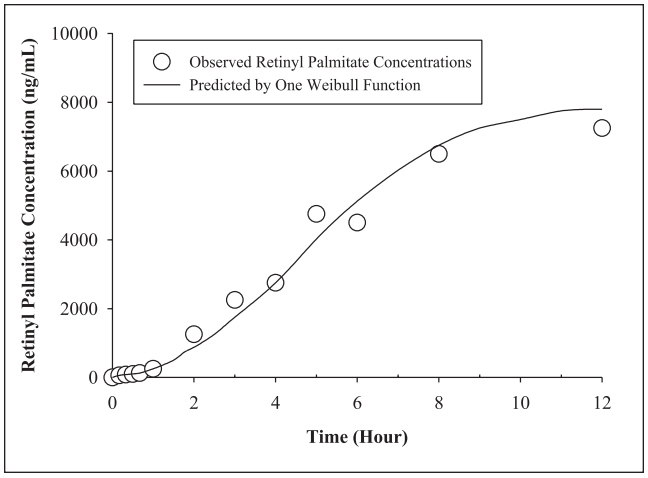

Figure 9. Graphical illustration of absorption phase of plasma profile of retinyl palmitate, which can be described by one Weibull function input. Adapted from Hartmann et al.[93]

The magnitude of shaping factor γ really depends on the degree of steepness in each absorption phase. The effect of shaping factors γ_1 and γ_2 in Weibull function inputs on the absorption profiles is depicted in Figure 10.

The effect of the absorption fraction (f and 1 – f) in each Weibull function input on the absorption profiles is illustrated in Figure 11. The apparent inflection in the absorption profiles discriminates two absorption phases and can facilitate the selection of reasonable initial estimates of f.

Absorption window with or without Michaelis-Menten (MM – ΔT). A model that incorporated an absorption window and Michaelis-Menten absorption (MM – ΔT) was first introduced to predict the dose-dependent systemic exposure of cefatrizine following several oral doses of cefatrizine.[94]

Numerous examples show that the absorption of a number of drugs obeys Michaelis-Menten (MM) kinetics, which has implicitly demonstrated capacity-limited absorption. The MM absorption kinetics not only applies to natural substances (such as riboflavin, ascorbic acid, thiamine, β-carotene, amino acids, and α-tocopherol)[95,96] but also to synthetic chemicals (such as tetracycline, fenclozic acid, phenytoin, phenylbutazone, naproxen, chlorothiazide, and β-lactam antibiotics).[97]

Liu et al[98] found that the absorption of cefixime, an amino-β-lactam antibiotic, could be described by MM absorption with an absorption window (MM – ΔT model). The profile of percent unabsorbed versus time after cefixime administration was obtained using the W-N method, as illustrated in Figure 12. The illustrative plot shows a time lag (t_{lag}) before the saturable absorption process begins. The subsequent linear decline reflects zero-order kinetics (over ΔT_1) with a transition toward a first-order process (over ΔT_2). The absorption abruptly stops at an identifiable time, t_{end}.

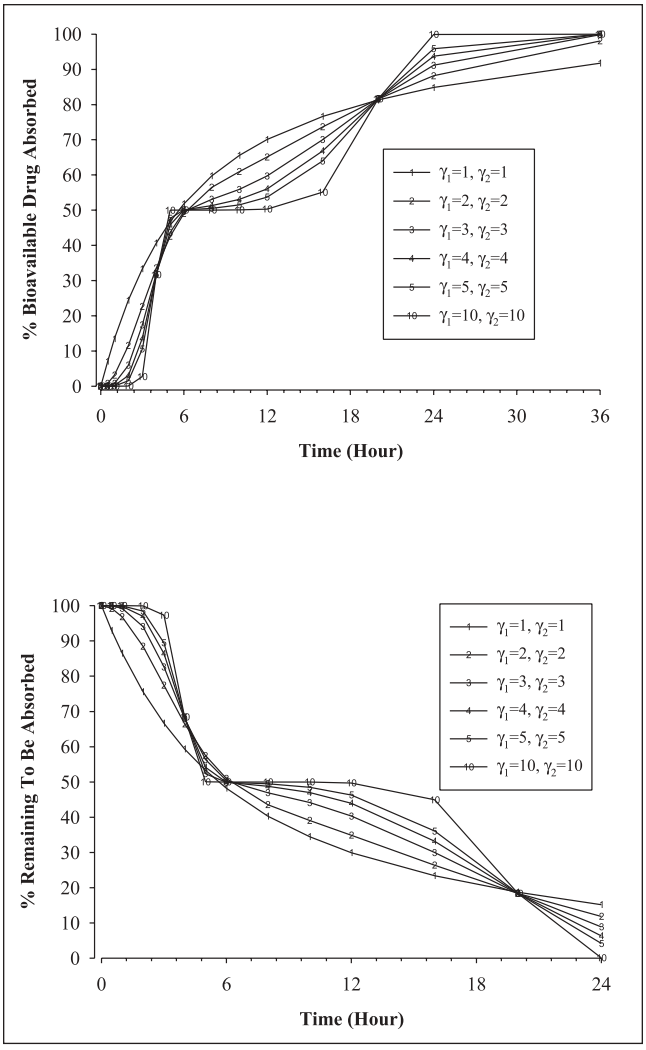

Figure 10. Effect of shaping factors γ_1 and γ_2 in Weibull function inputs on the absorption profiles. Top panel: percent bioavailable drug absorbed; bottom panel: percent remaining to be absorbed.

The mathematical expression of the MM – ΔT model is given as follows:

During absorption ($t_{lag} < t < \Delta T + t_{lag}$):

$$\frac{dC}{dt} = \frac{V'_{max} \times C'_a}{K'_{max} + C'_a} - k \times C \qquad (10)$$

After absorption is over ($t > \Delta T + t_{lag}$):

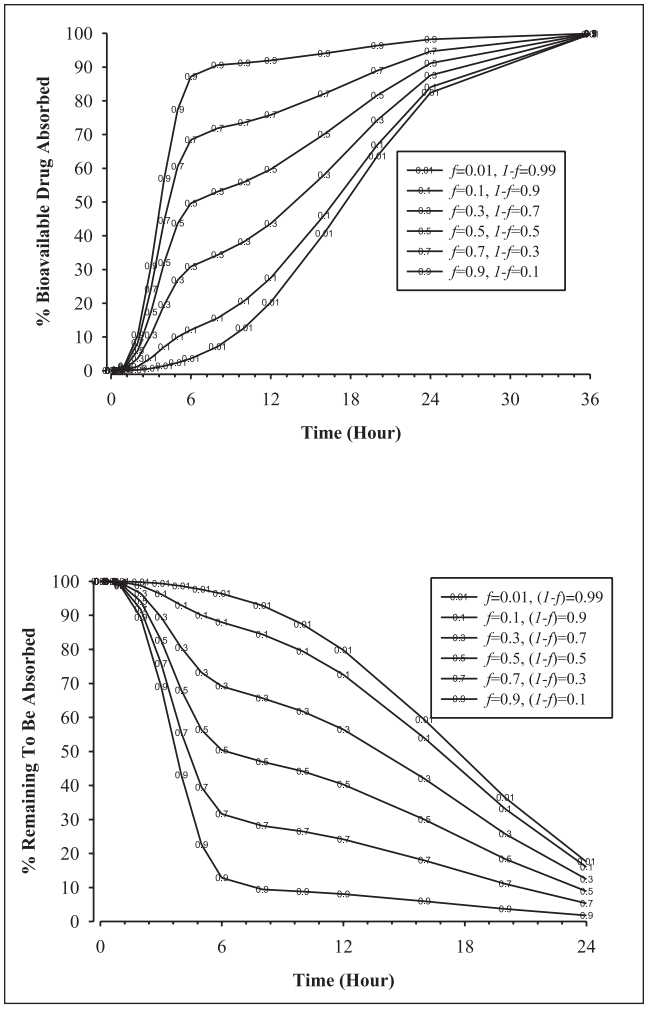

Figure 11. Effect of fraction in each absorption phase, f and 1 – f, in Weibull function inputs on the absorption profiles. Top panel: percent bioavailable drug absorbed; bottom panel: percent remaining to be absorbed.

$$\frac{dC}{dt} = -k \times C \qquad (11)$$

where V'_{max} and K'_{max} are apparent MM constants, respectively; k is the elimination constant; C is the concentration in plasma and C'_a is the apparent concentration at the absorption site; ΔT is the duration of absorption or the absorption window; and t_{lag} is the absorption time lag. Based on the MM – ΔT model, ΔT for cefixime was estimated to be 4.8 hours.

An earlier study investigated the effect of GI motility modifiers, propantheline (decreases motility) and metoclopramide (increases motility), on the bio-

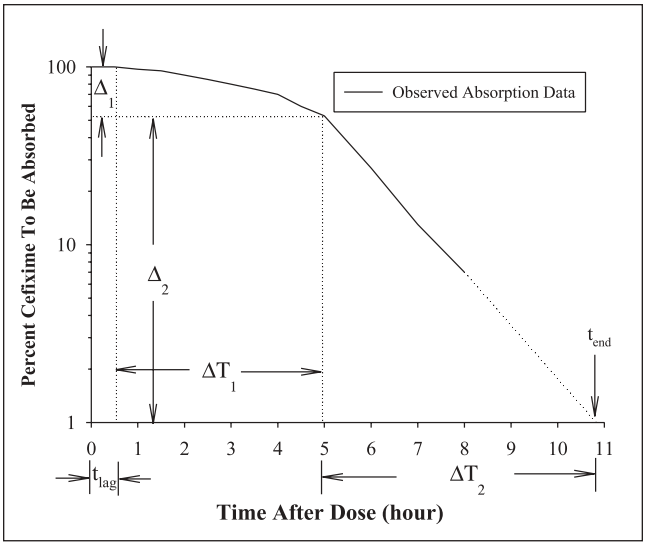

Figure 12. Illustrated plot of percentage of cefixime remaining to be absorbed versus time after dose in 1 representative healthy subject. Adapted from Liu et al.[98]

availability of ciglitazone.[99] The W-N analysis revealed the unusual ciglitazone absorption profiles following coadministration of propantheline, as illustrated in Figure 13.

Ciglitazone's absorption exhibited a first-order process for about ΔT_1 (around 6-7 h) followed by a period ΔT_2 with a higher absorption rate. The rate-limiting step in ciglitazone absorption became the slow gastric emptying induced by propantheline. It was hypothesized that the response to propantheline diminished after 6 to 7 hours (ΔT_1). Then an increased rate of gastric emptying could have allowed the transit of the remaining unabsorbed drug into the small intestine and increased the rate of absorption (during ΔT_2) due to the higher concentrations of ciglitazone at the absorption sites. The 20% increase in ciglitazone absorption in the presence of propantheline may be related to an increased residence time in the small intestine. An increase in the residence time may have allowed more of the drug to dissolve at absorption sites.

Time-dependent absorption. Higaki et al[100] postulated that irregular plasma concentration-time profiles following oral administration that could not be interpreted easily with typical absorption kinetics could be adequately described by introducing a time-dependent absorption rate constant, $k_a(t)$. The time dependency was varied to account for the changes in dynamic processes such as fluid absorption or secretion, absorption surface area, and motility in the GI tract. The time de-

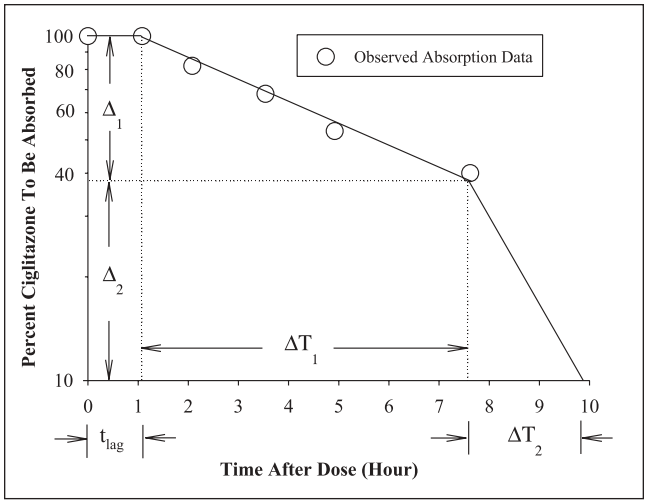

Figure 13. Semilog plot of percent ciglitazone remaining to be absorbed versus time following a treatment of a ciglitazone tablet and propantheline bromide. Adapted from Cox et al.[99]

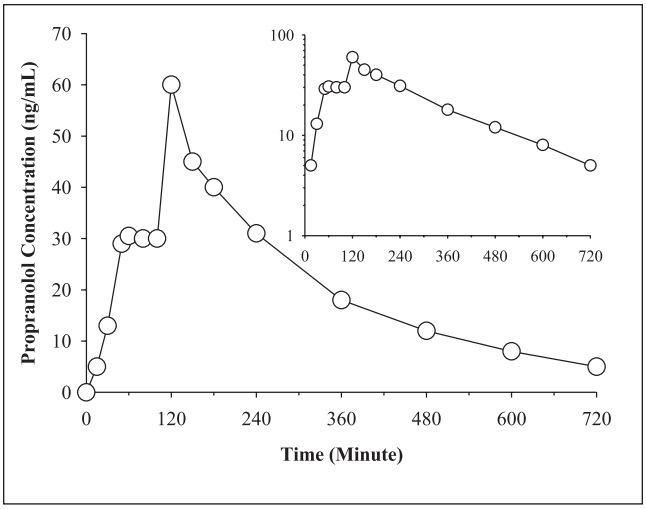

Figure 14. Plasma propranolol concentration versus time profile in 1 representative subject following time-dependent absorption (two-phase absorption with lag times). Adapted from Higaki et al.[100]

pendency of the absorption rate constant was defined in a conceptual manner rather than on a physiological basis.

One of the time-dependent absorption models, the two-phase model including lag time (TPLAG model), incorporated the variability in gastric emptying. This model successfully described the irregular propranolol plasma concentration profiles following oral dosing of propranolol. The TPLAG model constituted two different first-order absorption processes representing two phases of gastric emptying or motility. The first phase was characterized by one set of absorption rate constants (k_{a1}), bioavailability (F_1), and lag time (T_1). The second phase was characterized by another set of absorption rate constants (k_{a2}), bioavailability (F_2), and lag time (T_2).

$$\begin{aligned} &\%\ \text{Absorbed} = F \bullet e^{[-k_a \bullet (t - T_1)]} && T_1 < t < T_2 \\ &\%\ \text{Absorbed} = F_1 \bullet e^{[-k_{a1} \bullet (t - T_1)]} + F_2 \bullet e^{[-k_{a2} \bullet (t - T_2)]} && t > T_2 \end{aligned} \quad (12)$$

The plasma propranolol concentration versus time profiles, which follow time-dependent absorption (TPLAG model), are shown in Figure 14.

Inverse Gaussian density absorption. The absorption model using inverse Gaussian density has been used in many areas of pharmacokinetics, such as the examination of bioavailability for an extended-release dosage,[101] the description of a minimum circulatory model comprising both pulmonary and systemic subsystems,[102] the approximation of the transit time density of intravascular indicators,[103] and the analysis of organ distribution kinetics.[104]

Zhang et al[105] used the inverse Gaussian density function-input model to describe the complex enfuvirtide absorption profiles following the subcutaneous administration of enfuvirtide to patients with HIV infection.

The functions for the absorption model with the inverse Gaussian density function are given in the following equation:

$$\text{Input}(t) = \text{Dose} \bullet F \bullet \sqrt{\frac{\text{MAT}}{2\pi \bullet \text{NV}^2 \bullet t^3}} \bullet e^{-\frac{(t - \text{MAT})^2}{2 \bullet \text{NV}^2 \bullet \text{MAT} \bullet t}} \quad (13)$$

where F is the fraction of drug absorbed, MAT is the mean absorption time, t is the time postdosing, and NV^2 is the normalized variance of the Gaussian density function. MAT is an independent term and can be easily derived from the difference between the subcutaneous MRT and the intravenous MRT. NV^2 represents the relative dispersion of MAT by way of the squared coefficient of variation:

$$NV^2 = (\text{Variance of MAT}/\text{MAT})^2 \quad (14)$$

The fraction of the total bioavailable dose (F • Dose) absorbed at any time can be calculated from

$$\text{Fraction}(t) = \int_0^t \left(\frac{\text{Input}(t)}{F \bullet \text{Dose}} \right) \bullet dt \quad (15)$$

The virtues of the inverse Gaussian density function in the absorption analysis lie in its simplicity in the time domain and its flexibility in describing the complex absorption processes. However, its value in analyzing absorption kinetic data still awaits further examination.

CONCLUSION

Absorption analysis can separate the absorption process of a drug from its disposition. It is a very useful tool to decipher the atypical absorption profiles. Some drugs, such as cimetidine, molsidomine,[106] colchicine,[107] and dipyridamole, can exhibit significant double-peak or multiple-peak phenomena following oral dosing. Many potential causes could attribute to those phenomena. Elaborate absorption analyses would be needed to better understand the underlying mechanism of those atypical concentration-time profiles. The phenomenon of the absorption window can also be interpreted using the absorption principle along with other techniques or modeling strategies. The importance of absorption analysis is again reflected in the "flip-flop" situation when the absorption instead of the elimination rate becomes the rate-limiting step.

Pharmacokinetics is an ever-changing science. It can be envisioned that as the science evolves and new research gains more insight into the absorption processes, the absorption analysis may move toward more mechanism-based rather than simply abstract number crunching. It may also be expected that more and more novel research techniques and computational tools will be used to greatly facilitate the in-depth understanding of absorption processes.

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