Understanding Biopharmaceutics Properties for Pharmaceutical Product Development and Manufacturing I—

Oral Absorption and the Biopharmaceutics Classification System

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“Product and Process Design” discusses scientific and technical principles associated with pharmaceutical product development useful to practitioners in validation and compliance. We intend this column to be a useful resource for daily work applications. The primary objective for this feature: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator Yihong Qiu at qiu.yihong@abbott.com or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS
The following key points are addressed in this article:

• Bioavailability refers to the rate and extent of a therapeutically active drug that reaches the systemic circulation, thereby accessing the site of action
• Bioavailability of an oral dosage form may be understood from three perspectives: Anatomical and physiological features of the gastrointestinal tract, physicochemical properties of the drug molecule, and physicochemical properties of the dosage form
• In vivo dissolution and gut wall permeation are two critical sequential steps before a drug enters the general systemic circulation
• The epithelium in the gastrointestinal tract presents the most significant barrier to drug absorption. It consists of a single layer of enterocyte cells that are joined by tight junctions. The enterocytes in the small intestine are characterized by a large number of micro-villi structures on the lumen side and thus significantly increases the surface area available for absorption.
• Drug molecules can pass through the epithelium by passive diffusion (transcellular or paracellular), active transport, facilitated transport, pinocytosis, or solvent drag
• Small intestine is the major site of drug absorption. Large intestine may also act as an important absorption area for certain drugs
• Physiological and biological factors affecting oral drug absorption include pH, secretions, surface area, permeability, transporters, enzymes, motility, and transit time
• Physicochemical properties that can generally impact oral drug absorption include solubility and solubilization, ionization (pK_a), molecular weight, particle size, dissolution rate, lipophilicity, and chemical stability

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Drug dosage form designs significantly alter how a drug is released and absorbed in the gastrointestinal tract. Pre-systemic elimination by enzymes in the gut wall and liver may further reduce the bioavailability of a drug. Biopharmaceutics classification system (BCS) categorizes drugs based on solubility and permeability, and thus provides a simplified insight into the dissolution and permeation steps of the drug absorption. BCS has gained extensive recognition since its inception in the 1990s because it takes into account three major factors that govern the rate and extent of drug absorption: Dissolution, solubility, and intestinal permeability. The US Food and Drug Administration introduced the BCS guidance in 2000. Regulatory applications of BCS include setting dissolution specification, supporting risk assessment, post-approval changes, and waiver of bioequivalence studies. BCS also provides a framework for drug development from candidate selection to preformulation evaluation, solid form selection, and formulation strategies. A basic understanding of oral drug absorption and the biopharmaceutics classification system is necessary not only for formulation scientists, process engineers, but also for validation and quality unit personnel.

INTRODUCTION
The therapeutic efficacy of a drug is determined by the characteristics of circulating drug levels in the body, which is, in turn, dependent on the ability of a drug product to enable or improve drug absorption into the bloodstream. Bioavailability is generally defined as the extent to and rate at which a drug enters systemic circulation. It is a measure of how much and how fast a drug is actually absorbed from a given dose. Biopharmaceutics concerns the relationships of the physical and chemical properties of a drug and/or its dosage form to the delivery of the drug to the body as related to the onset, duration, and intensity of its action. The bioavailability of an oral dosage form is often influenced by a multitude of factors. The anatomical and physiological features of the human gastrointestinal (GI) tract (1) largely determine how drug molecules are absorbed. The physicochemical properties (for a general review on physicochemical properties, readers can refer to previous articles in drug product design series of this journal [2,3]) of the drug molecule, type and compositions of the dosage form, and the interplay between drug, formulation, and physiology then shape the absorption characteristics of each drug product. Therefore, an understanding of these factors is essential for pharmaceutical scientists to rationally design, develop, and optimize drug products and manufacturing processes for their intended applications. The biopharmaceutics classification system (BCS) takes into account three major factors that govern the rate and extent of drug absorption: solubility, dissolution, and intestinal permeability. It provides a scientific approach for classifying drug substances based on aqueous solubility as related to dose and permeability, as well as for gaining insights to the various rate limiting steps in the oral absorption process. The principles of the BCS have been widely applied to preclinical, clinical drug development, new drug application (NDA), and abbreviated new drug application (ANDA) submissions, and post-approval changes for marketed products.

This article summarizes the fundamental factors affecting oral drug absorption and discusses the concept and applications of BCS. The applications of this information to validation and compliance are discussed.

ORAL DRUG ABSORPTION
Most drugs are given orally as solid dosage forms primarily for convenience, stability, cost, and patient acceptance. Following oral administration, a drug in the dosage form must dissolve before it crosses the gastrointestinal wall and subsequently enters the bloodstream. Hence, the in vivo dissolution and intestinal permeation are two critical elements in the oral absorption of solid dosage forms. First let’s review how a drug molecule may be transported from the gastrointestinal tract to the systemic circulation.

The Epithelial Barrier to Drug Absorption in the Gastrointestinal Tract
The alimentary canals consist of mouth, esophagus, stomach, small intestine (duodenum, jejunum, ileum), and large intestine (cecum, colon, and rectum). The main function of these digestive tracts is to process and digest food components and to transport water, electrolytes, and nutrients into the body. The absorptive portions of the alimentary canal primarily consist of stomach, small intestine, and all of the large intestine except the distal region, or collectively, the gastrointestinal tract. For most drug molecules, the
small intestine is the major site of absorption in the GI tract because it has the largest surface area available for drug absorption, and its membranes are more permeable than those of the oral mucosa, stomach, and large intestine. However, the large intestine and oral mucosa may also serve as important absorption areas for some drugs.

The digestive tract is lined with a mucous membrane, known as mucosa, which serves as a barrier separating the internal of the body from the external environment. The mucosa consists of an epithelial layer and a thin layer of loose connective tissue called lamina propria. The lamina propria contains blood and lymphatic capillaries and forms the basement against which the epithelium is lined. The absorption of a drug substance from the gastrointestinal lumen requires that drug molecules pass through the epithelium, part of the lamina propria, and the walls of the blood or lymph capillaries. The most significant barrier, however, lies in the epithelium.

The mucosa in the absorptive regions consists of epithelial cells called enterocytes, which are sealed together by tight junctions, and lamia propria that have a rich supply of blood and lymphatic capillaries. The luminal side of an enterocyte in the small intestine (and to a less extent in the large intestine) possesses numerous microscopic cellular membrane protrusions called microvilli that provide significantly increased surface area available for absorption. This area is highly perfused with blood. In addition, the intestinal mucosa is not flat: a variety of modifications, including folds and finger-like projections (villi), exist to further increase the surface area of the mucosa.

**Transport of Drug Molecules Across the Gastrointestinal Membrane**

As mentioned previously, the epithelium presents the most significant barrier to drug absorption in the GI tract. Drug molecules must cross this single layer of cells in order to be absorbed: either by crossing the entire enterocyte or by passing through the tight junctions between them. The mechanisms of drug transport across the intestinal membrane include passive diffusion, carrier-mediated transport including active transport and facilitated diffusion, endocytosis (transcytosis), or solvent drag.

Passive diffusion is generally the most important pathway for drug molecules to cross the gut wall. Passive diffusion is a process by which molecules move from a region of higher concentration to a region of lower concentration (i.e., along the concentration gradient). The rate of diffusion, or amount diffused per unit of time, is related to the area of the membrane, A; the diffusivity, D; the membrane thickness, h; the partition coefficient, K; and the concentration differences between the luminal and the blood sides, based on Fick’s law:

\[
\frac{dM}{dt} = \frac{DAK}{h}(C_{\text{lum}} - C_b) = P(C_{\text{lum}} - C_b)
\]

Parameters D, A, K, and h can be lumped into a single parameter, permeability (P). Because the drug concentration on the blood or basolateral side is much smaller compared to the lumen or apical side and can, therefore, be ignored (i.e., sink condition), the rate of diffusion is proportional to the drug concentration in the lumen. Two types of passive diffusion may exist: transcellular and paracellular. In transcellular route, a drug molecule crosses the entire enterocyte; whereas in paracellular route, it finds a way through intercellular spaces (tight junctions). Transcellular diffusion is the most predominant pathway for drug absorption, while paracellular diffusion is usually absent when molecules are larger than approximately 200 Dalton (4). However, small hydrophilic molecules such as water can cross the intercellular space readily. Disease states may increase the chance of absorption via this route. In addition, a number of previously believed “inert” excipients or the so-called “permeability enhancers” have been shown in the in vitro test to alter the structures of the tight junctions and allow the passage of larger molecules. Their in vitro impact is likely to be minimal considering the effects of dilution and large surface area present in the dynamic environment of the GI tract.

Active transport is a carrier-mediated, trans-membrane process that shuttles molecules against the concentration gradient (i.e., from low concentration to high concentration). This process requires energy input and the formation of carrier-drug complex. It is usually limited to drugs structurally similar to endogenous substances (e.g., ions, vitamins, sugars, amino acids). These drugs are usually absorbed from specific segments in the small intestine. In addition, due to limited capacity, these carriers can be saturated. However, the capacities often vary with carriers.

Various transporter families exist in the intestinal membranes (5, 6). The absorption of many nutrients and nutrient-like molecules are mediated by the influx transporters. For example, small peptides are
transported by peptide transporters such as PepT1 and PepT2; essential amino acids are transported by the amino acid transporters; nucleoside transporters help the absorption of nucleosides from diet; organic anion transporters such as OATP1/OATP2/OATP3 are involved in the uptake of bile acids; various other transporters are involved in the absorption of vitamins, glucose, and other essential nutrients. These same transporters may be involved in the absorption of many drugs that possess suitable structures. Examples include enalapril, cephradine, valacyclovir, dopa, methyldopa, gabapentin, and many others. On the other hand, the body’s defense mechanism also plays an important role in the absorption process. The efflux transporters in the intestinal epithelia are known to suppress the intracellular accumulation of xenobiotics by preventing the influx and facilitating the efflux out of cells. For example, P-glycoprotein (P-gp) family of transporters limit the intestinal absorption of a variety of structurally and pharmacologically unrelated neutral and positively charged hydrophobic compounds. They are expressed on brush-border membrane that can facilitate the intestinal efflux of substrates dissolved in bloodstream. Multi-drug resistance proteins (MRPs) recognize relatively hydrophilic compounds, including glucuronide, glutathione, and sulfate conjugates of endogenous and exogenous compounds. MRPs such as MRP3 localized on basolateral membrane prevent the influx into intracellular compartment from the bloodstream. The presence of influx and efflux transporters certainly complicates our evaluation and understanding of oral drug absorption. Particularly, the potential food effect is of concern if an influx transporter is involved in the absorption of a drug molecule because the food components might compete for the transporter and drastically influence bioavailability, depending on the capacity of the transporter.

Facilitated diffusion differs from active transport only in that the drug moves along the concentration gradient, and hence does not consume energy. It imposes similar structural requirements and is saturable.

Endocytosis is the process by which cells absorb molecules from outside the cell by engulfing it with their cell membrane. The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior. Energy expenditure is required. Pores may also exist in the membrane of enterocytes; water, urea, and sugar molecules can cross the membrane pore via solvent drag created by osmotic gradient. Endocytosis typically plays a minor role in drug transport, except for large polar molecules, such as proteins, that cannot pass through the hydrophobic cell membrane.

**Factors Affecting Oral Drug Absorption**

The systemic absorption of an oral drug product depends on three aspects: the anatomy and physiological factors of the gastrointestinal tracts, the physicochemical properties of the drug, and the formulation design and properties of the dosage form.

**Physiological Factors.** Secretion, digestion, and absorption are the major physiological processes that may impact the *in vivo* dissolution and absorption of a drug in the GI tract. Fluids, electrolytes, peptides, proteins, and enzymes are secreted in various parts of the gastrointestinal tract. The following is a brief summary of the physiological features in different regions of GI tracts.

pH is a factor that significantly impacts dissolution and absorption of many ionizable drugs. It changes appreciably along the gastrointestinal tracts. Under fasting conditions, gastric pH ranges 2-4, but decreases to 1-2 under fed conditions, due to the increased secretion of hydrochloric acid. Small intestine consists of duodenum, jejunum, and ileum, and pH gradually increases along the intestinal tract. Neutralization of the acidic contents occurs when they are emptied from the stomach by the bicarbonate secreted into the duodenum. The duodenum is short with pH about 6 to 6.5, optimal for many enzymes to break down proteins, peptides, and fats. pH in jejunum, the major site of drug absorption, is around 6.8. The terminal part of small intestine, ileum, has a pH of approximately 7, and can sometimes reach 8 in the distal segment. The colon pH ranges from 5.5 to about 7.

The amounts of fluids and digestive enzymes secreted in the gastrointestinal tracts vary significantly with different regions of GI tract. In the stomach, the output of the gastric juice containing hydrochloric acid, pepsin, mucus, and other regulating factors such as gastrin is 1.5-2 liters per day. In the small intestine, approximately 1-1.5 liter of pancreatic juice containing various digestive enzymes (e.g., amylase, trypsin, chymotrypsin, carboxypeptidase, lipase, esterase, ribonuclease) is secreted into duodenum daily. In addition, 0.5-1 liter of bile salts are produced by the liver, stored and concentrated in the gallbladder, and released into the duodenum each day. Bile salts play an important role in the solubilization and absorption of fats and lipophilic molecules. In the large intestine,
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however, the secretion is much limited. In fact, only a small amount of mucus (~0.2 liter daily) is secreted in the large intestine. In addition, there are bacterial enzymes secreted by the microorganisms residing in this region, which may break down certain food components and xenobiotics.

The surface area available for absorption also varies along the gastrointestinal tracts. The stomach has relatively small surface area (~0.053 m²). The structural features of the small intestine mucosa such as villi, microvilli, and folds, drastically increase the surface area by about 600 folds, comparing it to a cylinder of the same dimensions, to ~200 m². Each enterocyte in the small intestine has 3000-7000 microvilli, while enterocytes in the large intestine have significantly fewer microvilli. As a result, the large intestine only has a surface area of about 0.35 m². Therefore, major absorption occurs in the small intestine, particularly in the duodenum, jejunum, and the proximal portion of the ileum.

Gastrointestinal motility and transit time also affect oral drug absorption. The main purpose of the stomach is to grind food contents into smaller particles. In the fasted state, the stomach undergoes the interdigestive phase: the stomach first experiences a quiet period up to 30-60 minutes, followed by irregular contraction, and ends with high amplitude “house keeper contractions” that empties its entire contents into the small intestine. The quiet period in the stomach is coordinated with an equal resting period in the small intestine. In the fed state, the stomach undergoes a digestive phase with regular and frequent contractions, where the food particles or solids larger than 2 mm are retained but smaller particles are emptied. Gastric emptying time is strongly influenced by the food contents, size, and osmolality. Liquids such as water and particles less than 1 mm usually empty quickly but solids may take 1-4 hours. Generally, gastric retention varies with meal content. Carbohydrates are emptied more rapidly than proteins and fats. In the fasting state, mean stomach residence time of a disintegrating solid dosage form is about 45 minutes. On average, the small intestine transit time is 3-4 hours. The velocity of transport in the small intestine is faster in the proximal portions and slows down in the ileum. The transit time is considerably intestine is faster in the proximal portions and slows down in the ileum. The velocity of transport in the small intestine is faster in the proximal portions and slows down in the ileum. The transit time is considerably longer and variable in large intestine (~8 to >20 hours in healthy human subjects). A drug dosage may be swept quickly into small intestine if administered at the end of the interdigestive phase, but may stay in the stomach for a few hours when administered with high fat foods. The gastrointestinal mobility may also be affected by the pharmacodynamics of the administered drug. For example, anticholinergics and opioid analgesics may significantly reduce the rate of gastric emptying and GI motility, thus significantly increasing their residence time, which should be an important consideration during the product development phase.

Some drugs may be secreted into the bile and eventually released into duodenum along with the bile salts via the gallbladder. These drugs tend to be re-absorbed from the intestinal tract and become systemically available again. This cycle is known as the enterohepatic recycling. Depending on the extent, enterohepatic recycling may cause significant alteration of the pharmacokinetic profile, such as double peaks, particularly for drugs that are concentrated in the bile (e.g., ranitidine).

Physicochemical Properties of Drug Molecules. Drugs given via orally-administered dosage forms must dissolve in vivo before systemic absorption can take place. In evaluating dissolution of a solid particle, a saturated solution is presumably formed at the surface of the solid particle where a stagnant layer between the solid surface and the bulk solution is also assumed. Thus, the concentration at the solid surface is assumed to be its solubility (Cₘ) and a concentration gradient is formed traversing the stagnant layer. According to Fick’s law, the rate of dissolution is proportional to the surface area of the particle, A, the diffusivity, D, the thickness of the stagnant layer, h, and the concentration difference (Cₛ - Cₘ), as represented by the Noyes-Whitney equation:

\[
\frac{dM}{dt} = \frac{DA}{h}(Cₛ - Cₘ) = \frac{DA}{h} Cₛ
\]

Particle size directly affects surface area and, hence, rate of dissolution. For the same dose strength, smaller particles lead to larger surface area and faster dissolution rate. Solubility is a key determinant of drug dissolution. If a drug can dissolve rapidly and completely in the gastrointestinal lumen, typically the absorption will not be limited by the dissolution rate. Thus, solubility has become a key parameter in the pharmaceutical assessments of drug candidates. Many drug candidates fail to produce sufficient systemic exposure required for optimal pharmacological effect due to their low solubility. To overcome this problem, conventional approaches, such as solubility enhancement and micronization, have been routinely utilized. Non-conventional approaches, such
as solid dispersions and nanotechnology, have also emerged in dealing with more challenging insoluble drugs. Despite considerable progresses, poorly soluble compounds will remain a major challenge in the foreseeable future.

Ionization greatly influences the solubility of weak acids or bases in the gastrointestinal tract. The solubility of an acidic drug increases from stomach to small and large intestine (lower pH to higher pH). Its higher solubility in the intestinal tract is favorable to the absorption. On the contrary, a basic drug that has higher solubility at lower pH may first dissolve completely in the stomach and subsequently precipitate in small intestine. The kinetics of precipitation and the properties of the precipitate (e.g., crystallinity, particle size) may affect the dissolution rate of the precipitates and the extent of absorption.

Solubility of poorly soluble lipophilic drugs may be improved in the presence of bile salts. Bile salts are surface-active agents that are secreted from liver into duodenum to aid the solubilization of fat and lipid-like molecules and enhance their absorption. Chemically, these molecules are cholate, deoxycholate, and their conjugates with glycine or taurine. Like other surfactants, they form micelles and mixed micelles that play important roles in the solubilization and absorption of fats and lipid-soluble molecules such as fat-soluble vitamins. It has been demonstrated that these bile salts also greatly influence the solubilization and absorption of many lipophilic drugs (7). Simulated intestinal fluids containing bile salts have been utilized to screen solubility of poorly soluble compounds in the intestinal fluid in an attempt to predict intestinal absorption (8).

It should be noted that the absorption of a drug with adequate solubility may become limited by dissolution rate under certain scenarios where large particle size and small surface area and reduced effective surface area due to poor wetting or poor formulation or process design (e.g., poorly disintegrated tablets) lead to incomplete dissolution within the time frame of intestinal transit.

The octanol-water distribution/partition coefficient (log P or log D) is another property that is related to a drug’s ability to cross the epithelial membrane. The lipid bi-layer structure of the cell membrane requires a passable molecule to have sufficient lipophilicity, which is particularly important for drugs that are absorbed primarily by the passive diffusion. In the absence of carrier mediated absorption, lipophilicity, or log D, of most drugs generally correlates well with their intestinal permeability (9).

Dosage Form Design and Properties. Dosage form design plays an important role in achieving the desired oral absorption of a drug because the design of formulation and dissolution profiles usually determines the rate and total amount of drug absorption. Immediate release (IR) dosage forms are designed to have the entire dose available for absorption immediately. In contrast, modified release (MR) dosage forms are designed such that a drug is delivered at a controlled rate and/or to a certain region of the GI tract to accomplish therapeutic or convenience objectives not offered by IR dosage forms. Modified release dosage forms include extended release (ER) and delayed release (DR) products. Delayed release dosage forms may be developed based on pharmaceutical or biopharmaceutical considerations. For example, aspirin can cause gastric irritation; therefore, it is beneficial to delay the release of the drug till the dosage form reaches the small intestine following gastric emptying. Some drugs may precipitate in the acidic gastric fluid, while other drugs may be chemically susceptible to the low pH in the stomach or the abundant metabolic enzymes (e.g., CYP3A4) in the proximal small intestine (10). Enteric-coated tablets or beads can be used to target drug release in the duodenum or lower part of the small intestine. Most enteric-coated products employ pH-sensitive polymers for their intended applications. For example, Eudragit L30D-55 is a copolymer of ethyl methacrylate and methacrylic acid, which dissolves at pH > 5.5; while Eudragit S 100 is a copolymer of methyl methacrylate and methacrylic acid that is soluble above pH 7. These polymers are suitable for targeting drug release in different regions of the intestinal tract. Because the drug release depends on the pH-sensitivity of the polymers, the variability in gastric emptying time and intestinal pH may influence the in vivo dissolution and absorption.

Extended-release dosage form allows a drug to be released over an extended period of time, often resulting in at least a two-fold reduction in dosing frequency and once-daily or twice-daily products. Given that the transit time from mouth to the ileocecal junction ranges from 4 to 8 hours in the fasting state or 6 to 10 hours in the fed state, a significant portion of drug release is expected to occur in the large intestine. Drug absorption in the large intestine is often more challenging and variable because of the limited available fluid, surface area, lower permeability, microbial degradation, and the semi-solid nature of the lumen.
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contents. Generally, it is expected that only drugs with high permeability (11) may be well absorbed in the large intestine, particularly those with high aqueous solubility.

Other special dosage form designs may also offer unique features. The gastric retention technologies have been explored to retain a dosage form in the stomach for an extended period of time for enhanced absorption for drugs that are only well absorbed in the upper small intestine. Because most drugs are released in the stomach, the chemical stability and solubility in the acidic gastric environment could significantly affect drug absorption and bioavailability.

Presystemic Elimination and Lumen Degradation. Chemical and metabolic degradations also impact oral bioavailability. Drug molecules may be metabolized by enzymes (e.g., CYP 3A) in the enterocytes, which is known as gut wall metabolism. As drug molecules cross the enterocytes, they either enter the blood capillary or the lymphatic capillary in the lamina propria. The blood vascular from the stomach, small, and large intestine coalesce into the mesenteric vessels and then to the hepatic portal vein. All blood from the hepatic portal vein flows into the liver prior to its entry into the blood circulation. A portion of the drug is typically metabolized in the liver before reaching the general systemic circulation due to the intimate contact, thus reducing bioavailability. The metabolism of orally administrated drug prior to reaching the systemic circulation is called first-pass effect or presystemic elimination. In contract, the lymphatic route follows the thoracic duct to the venous vessel of the heart and completely bypasses the liver. However, lymphatic route usually plays a very limited role in drug absorption due to its limited capacity and structural requirement. Certain drugs are more prone to presystemic eliminations. For instance, 60 to 80% of absorbed propranolol is eliminated by first-pass effect when administrated orally. The presystemic elimination of nitroglycerin is so high that oral administration becomes infeasible and sublingual or other route is preferred. In addition to the potential breakdown by various enzymes, a drug molecule may also be susceptible to the pH conditions in the gut lumen. For example, the acidic environment and gut enzymes represent significant obstacles to the oral administration of certain antibiotics (e.g., penicillin G) and peptide drugs, respectively.

Determination of Oral Bioavailability

The most commonly used method for assessing bioavailability is through measurement of plasma concentrations after oral administration. The rate of absorption is often estimated using peak drug concentration ($C_{\text{max}}$) and the time for peak drug concentration to occur ($t_{\text{max}}$) is also evaluated. The extent of absorption is determined by area under the plasma concentration-time curve from time zero to time infinity (AUC$_{\text{infty}}$).

Following administration of a drug product, the drug is absorbed into the bloodstream and simultaneously undergoes elimination (excretion and metabolism) from the systemic circulation. In most cases, the elimination process can be approximated by first order kinetics with a rate constant, $K_{10}$, such that,

$$\frac{dX_t}{dt} = K_{10}X_t = CL.C$$

where $X_t$ and $X_c$ are the amounts of drug eliminated and in the systemic circulation at time $t$, respectively; $C$ is the drug concentration in blood at time $t$; $CL$ is the total systemic clearance. Thus, integration of the above equation from time zero to infinity leads to the following equations:

$$\int_0^\infty dX_t = F \cdot D$$

$$CL \cdot Cdt = CI \cdot AUC_{\text{infty}}$$

$$F \cdot D = CI \cdot AUC_{\text{infty}}$$

where $D$ and $F$ are the total dose administered and fraction of the dose absorbed, respectively, because the total amount of drug eliminated equals to the total amount absorbed. Therefore, the extent of absorption is proportional to AUC$_{\text{infty}}$. AUC is normally determined by linear trapezoidal summation or its combination with logarithmic trapezoidal summation.

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The biopharmaceutics classification system (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility as related to dose and intestinal permeability (12). It categorizes drugs into the following four classes:
- BCS 1: high solubility and high permeability
- BCS 2: low solubility and high permeability
- BCS 3: high solubility and low permeability
- BCS 4: low solubility and low permeability.

The BCS provides insight into the most important steps in the oral absorption process of drug substances.
BCS as a Regulatory Tool

BCS was developed to provide a science-based regulatory tool primarily for assessing the equivalence of different drug formulations. When combined with the dissolution of a dosage form, the BCS takes into account three major factors that govern the rate and extent of drug absorption from immediate release solid oral dosage forms: dissolution rate, solubility, and permeability. Within the BCS framework, when certain criteria are met, the in vitro data (e.g., dissolution profiles) of a drug product can be used to justify waivers of clinical bioequivalence studies (i.e., biowaivers), leading to significantly reduced cost and time associated with the human studies as well as regulatory burdens.

In general, BCS-based biowaivers can be used to address the questions of bioequivalence between a test and a reference product encountered throughout the product development lifecycle, including investigating bioequivalence between early clinical trial products and to-be-marketed products, generic and innovator products, and in the cases of post-approval changes that require bioequivalence testing. Since 2000, the United States Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, and World Health Organization have each published guidances or technical and processing technologies, because it is an inherent biological property. In short, BCS classification allows scientists to anticipate the potential issues, develop strategies, and prioritize resources for pharmaceutical development.

Solid Form Selection. For compounds that have low solubility (BCS 2 or 4), efforts are often directed toward increasing the solubility and dissolution rate. One of the approaches commonly utilized for enhancing solubility or dissolution is the evaluation and selection of solid-state forms that are known to have different apparent solubility. Theoretically, solubility is the concentration of solution in equilibrium with a respective solid-state form. Different forms differ in free energy and, therefore, solubility. For
example, metastable forms have higher solubility. If uncontrolled, it may partially or fully convert to more stable, less soluble solid forms on storage or when in contact with water, resulting in slower and/or variable dissolution. However, if the kinetic of the conversion is slow or can be controlled, the advantage of higher solubility and faster dissolution can be taken by using a metastable solid form. In the case of a rapid phase conversion/precipitation when exposed to GI fluid, fast dissolution may still be possible if the precipitates are of smaller particle size and lower crystallinity. Polymorphism has been shown to significantly influence dissolution rate and bioavailability. A recent example is ritonavir, a BCS class 4 compound (14). Thus, proper selection of a polymorph plays a critical role in new drug development, especially for BCS Class 2 or 4 compounds. Amorphous drug is obtained by destroying the long-range order of the crystalline drug. The disordered phase is highly energetic and exhibits higher solubility. Therefore, solid dispersion that contains amorphous active pharmaceutical ingredients (APIs) with sufficient physical and chemical stability have become a very effective tool for enhancing dissolution and bioavailability of many BCS Class 2 and 4 drug candidates (15).

Salt formation is another effective means to modify the apparent solubility and dissolution rate of a drug molecule. A relatively high percentage of drug candidates are weak organic bases or acids containing ionizable groups such as amines or carboxylic acids. These compounds can form salts with many pharmaceutically inert counter ions. In many cases, an appropriate salt can be used to overcome problems associated with the dissolution-limited absorption of BCS Class 2 or 4 compounds. In addition to higher solubility, salts may also offer other development advantages, such as improved purity, crystallinity, melting point, mechanical properties, and other process-related properties.

**Product Development.** BCS has been widely used to guide product development and assess associated challenges. For BCS Class 1 compounds, achieving adequate systemic exposure is not a major concern in most cases. Problems related to oral absorption are generally not expected in developing IR dosage forms using conventional formulation and processing technologies. With BCS 2 and 4 drugs, slow and/or incomplete dissolution usually represent the most commonly encountered challenges in developing IR products. To overcome the dissolution problems, various strategies and approaches have been utilized in the formulation and process development and shown to be effective. Among them, size reduction is used to increase the surface area thus the dissolution rate. When particle sizes are decreased to nano meters, the solubility may also be increased due to the Kelvin effect. Therefore, use of nano particles can lead to an increase in both the dissolution rate and solubility for poorly soluble drugs. Solubilization using surfactants or complexing agents (e.g., cyclodextrin) can be also effective. Amorphous solid-dispersions taking advantage of the more soluble amorphous drug have been demonstrated in a number of successful commercial products containing BCS Class 2 and 4 drugs. Lipid-based drug delivery systems such as self-emulsion drug delivery systems (SEDDS) that utilize the solubilization power of lipids and surfactant can significantly improve the oral bioavailability. It should be noted that each of these approaches has its own pros and cons. For example, particle agglomeration during or upon size reduction can decrease effective surface area available for dissolution. Physical instability is usually a major concern for amorphous solid dispersion systems, while chemical instability in lipid systems can often be challenging. Many of these problems are drug specific and should be addressed based on the understanding of the properties and required doses of individual drugs. No single formulation technology can be a solution for all.

In developing modified release (MR) dosage forms discussed previously, understanding solubility and permeability in different regions of the GI tract is critical to the success of product design. For example, in order to achieve the design objectives of extended delivery, a drug candidate must have sufficient solubility and permeability in the large intestine. Generally, BCS class 1 drugs are most suitable for ER dosage form development. Certain BCS class 2 drugs such as felodipine and carbamazepine are also feasible, which can be, in part, attributed to their relatively small doses and high permeability. The rapid permeation of the released drug helps maintain sink conditions in the large intestine and drive the absorption near completion. For BCS class 3 or 4 compounds, absorption in the lower bowel is expected to be limited or absent and thus ER delivery is generally not feasible. A recent survey has indicated that only BCS I drugs are significantly absorbed in the colon in general (11).

Another important role BCS plays in product development is guiding the evaluation and development of an in vivo-in vitro correlation (IVIVC) where the in vitro dissolution is correlated to the in vivo bioavailability. Such a correlation may be possible only when in vivo
dissolution is rate limiting during the absorption process. Therefore, IVIVC is feasible for certain BCS classes of drugs and/or dosage form combinations. For example, IVIVC is not expected for an IR dosage form of BCS 1 or BCS 3 drugs, of which dissolution rates are high and absorption rate is usually controlled by gastric emptying. IVIVC is more likely for BCS 2 drugs, but not expected for BCS 4 drugs. In contrast, IVIVC is often feasible and has been demonstrated in many ER dosage forms of BCS 1 or 2 drugs.

IMPLICATIONS FOR VALIDATION AND COMPLIANCE

The information discussed in this article is fundamental to the rational design and development of an oral drug product and its manufacturing process. Validation and compliance personnel should have a general understanding of the properties of the drug and drug products for which they are responsible. Specifically, they should be aware of the drugs whose properties present high risks to manufacturing processes as well as processes that may potentially impact drug properties and product quality attributes, such as stability, solubility, and dissolution. These risks should be appropriately evaluated and addressed in validation protocols.

Changes to the manufacturing processes for high risk drugs (e.g., BCS class 2 and 4) must be carefully evaluated. Validation protocols developed in response to such changes should require appropriate sampling and testing in support of the changes. The BCS categorization of the active drugs is fundamental to identification of high risk drugs and products. For example, process changes to a dosage form containing a BCS class 2 or 4 drug must be carefully evaluated and would likely require increased testing compared to a BCS class 1 drug. Knowledge of the dosage form complexity must also be considered in determining appropriate validation testing. For example, process changes to an extended release product designed to release drug by diffusion control through a coating membrane must be carefully evaluated to assure no effect on drug release not only in vitro, but also in vivo which is directly linked to the rate and extent of drug absorption. Changes to the manufacturing process for the aforementioned product would likely require more testing than changes to a relatively simple immediate release tablet product.

Manufacturing process changes that have potential to affect drug solubility or rate of dissolution are most likely to impact drug bioavailability. BCS class 2 and class 4 drugs, both of which characterize low solubility drugs, are most susceptible to these changes. Validation and compliance personnel should be especially watchful to changes in granulation, drying, particle size reduction, and other processes with potential to impact the granule structure, granule or particle density, particle size, solid form of drugs and excipients, or other physical properties known to affect dissolution and solubility. Consultation between development scientists and validation and compliance personnel are encouraged to thoroughly evaluate proposed changes of process and/or physical properties of the drug and excipients, and especially for those involving high risk drugs and complex dosage forms.

SUMMARY

Oral drug absorption in the gastrointestinal tract is a very complex process. However, a systematic understanding of the physicochemical and biological properties of the drug substance, characteristics of the dosage forms, physiological features of the gastrointestinal tract, and the interplays among them can provide a more in-depth insight into the challenges and opportunities involved in the absorption of drugs with low solubility and/or permeability. The biopharmaceutics classification system categorizes drug molecules based on their solubility and permeability, thus providing a scientific approach to delineate the rate-limiting step during oral absorption. The BCS has become a useful tool for drug development and for regulatory applications. A basic understanding of oral bioavailability and the BCS is important not only for preformulation investigation, formulation, and process development, but also useful for control of product quality and assessment of risks associated with manufacturing of pharmaceutical products.

REFERENCES

3. Zhou, D., “Understanding Physicochemical Properties for Pharmaceutical Product Development and Manufacturing—Dissociation, Distribution/Partition, and
Product and Process Design.


**GENERAL REFERENCE**


**ARTICLE ACRONYM LISTING**

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