

PART I

INTRODUCTION AND BASICS OF ADVANCED DRUG DELIVERY

COPYRIGHTED MATERIAL

PHYSIOLOGICAL BARRIERS IN ADVANCED DRUG DELIVERY: GASTROINTESTINAL BARRIER

D. ALEXANDER OH AND CHI H. LEE

- 1.1 Chapter objectives
- 1.2 Introduction
- 1.3 Physiological factors influencing drug absorption
- 1.4 Physicochemical factors influencing drug absorption
- 1.5 Strategies to overcome gastrointestinal barriers in drug delivery
- 1.6 Summary
- Assessment questions
- References

1.1 CHAPTER OBJECTIVES

- To outline gastrointestinal anatomy and physiology impacting advanced oral drug delivery systems.
- To review key physiological and physicochemical factors influencing drug absorption.
- To illustrate efficient strategies for overcoming gastrointestinal barriers in drug delivery.

1.2 INTRODUCTION

Drug delivery through oral administration is a complicated process: A drug must withstand the digestive processes and penetrate through the gastrointestinal (GI) barrier into the bloodstream. Drugs absorbed from the GI tract travel through portal veins to the liver, and then they are subjected to first-pass metabolism by the hepatic enzymes before entering the systemic circulation [1]. The oral route of drug administration is traditionally known as the most

preferred route for systemic drug delivery, even though there are disadvantages, such as unpredictable and erratic absorption, gastrointestinal intolerance, incomplete absorption, degradation of drug in GI contents, and presystemic metabolism, mostly resulting in reduced bioavailability.

The primary functions of the GI tract are absorption and digestion of food, as well as secretion of various enzymes or fluids [2]. The gastrointestinal mucosa forms a barrier between the body and a luminal environment that contains not only nutrients but also potentially hostile microorganisms and toxins. The normal function of the GI barrier, which is referred to the properties of the gastric and intestinal mucosa, is essential for disease prevention and overall maintenance of health. The major challenge in drug delivery through the GI tract is to achieve efficient transport of nutrients and drugs across the epithelium while rigorously excluding passage of harmful molecules and organisms into the body.

The performance of GI barriers to drug transport may largely depend on the physicochemical characteristics of drugs. Water-soluble small molecules may not be easily absorbed unless a specific transporter to those molecules is present, while lipophilic drugs can be relatively well absorbed through GI barriers. Mucosal transporters include PEPT, OATP, OCT, MCT, ASBT, MDR1, MRP, and BCRP among others [3] as shown in Figure 1.1. Large-molecule drugs, such as antibodies and proteins, may suffer extensive enzymatic degradation in the GI tract [4].

In this chapter, gastrointestinal mucous membranes and gut physiology will be intensively covered from the perspective of physiological barriers, which will lead to thorough understanding of key obstacles to advanced oral drug delivery.

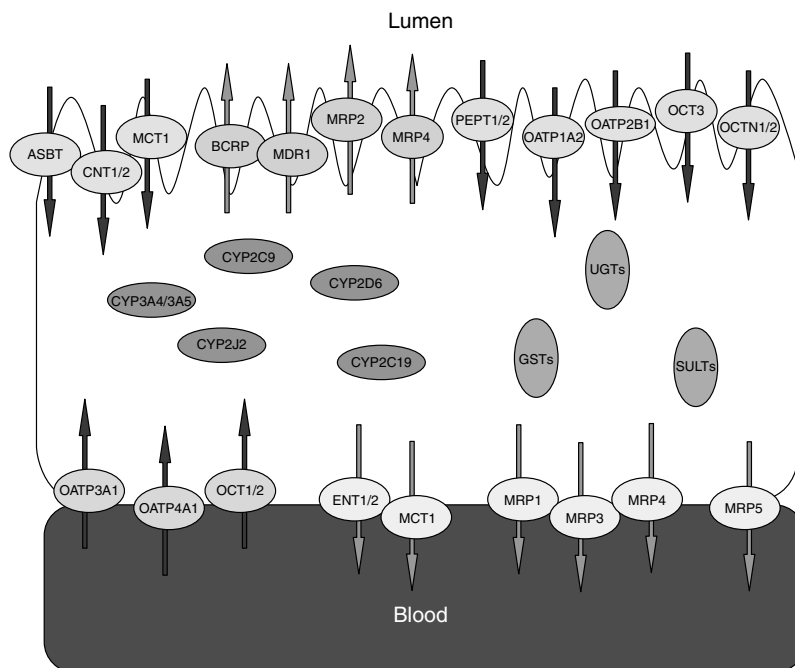


FIGURE 1.1 The intestinal metabolizing enzymes and uptake/efflux transporters [3].

1.2.1 Anatomy of Gastrointestinal Tract

1.2.1.1 Gastrointestinal Anatomy The major components of the gastrointestinal tract are the stomach, small intestine, and large intestine. The small intestine with a length of about 6 m includes the duodenum, jejunum, and ileum [5]. The stomach is a pouch-like structure lined with a relatively smooth epithelial surface. Extensive absorption of numerous weakly acidic or nonionized drugs and certain weakly basic drugs were demonstrated in the stomach under varying experimental conditions [2, 6, 7].

The small intestine is the most important site for drug absorption in the gastrointestinal tract. The epithelial surface area through which absorption of drug takes place in the small intestine is enormously large because of the presence of villi and microvilli, finger-like projections arising from and forming folds in the intestinal mucosa as shown in Figure 1.2 [8]. The surface area decreases sharply from proximal to distal small intestine and was estimated to range from 80-cm²/cm serosal length just beyond the duodeno-jejunal flexure to about 20-cm²/cm serosal length just before the ileo-cecal valve in humans [9]. The total surface area of the human small intestine is about 200 to 500 m² [6, 7]. The small intestine is made up of various types of epithelial cells, i.e., absorptive cells (enterocytes), undifferentiated crypt cells, goblet cells, endocrine cells, paneth cells, and M cells. There is also a progressive decrease in the average size of aqueous pores from proximal to distal small intestine and colon [10, 11].

The small intestine is the most involved region for carrier-mediated transport of endogenous and exogenous compounds. The proximal small intestine is the major area for absorption of dietary constituents including monosaccharides, amino acids, vitamins, and minerals. Both vitamin B₁₂ and bile salts appear to have specific absorption sites in the ileum [2]. The large intestine has a considerably less irregular mucosa than the small intestine.

1.2.1.2 Pores The aqueous pores render the epithelial membranes freely permeable to water, monovalent ions and hydrophilic solutes with a smaller molecular size [2, 6, 7]. It was estimated that the hypothetical pores in the proximal intestine have an average radius of 7.5 Å, and those in distal intestine (ileum) have that of about 3.5 Å [10]. The pore sizes of the aqueous pathway for buccal and sublingual mucosa in pigs were estimated as 18–22 and 30–53 Å, respectively [12]. Since the molecular size of most drug molecules are larger than a pore size in the membrane, drug transport through pores seems to be of minor importance in drug absorption. However, some larger polar compounds with molecular weights up to several hundreds are still absorbed through active participation of the membrane components.

1.2.1.3 Tight Junctions Tight junctions are closely associated areas of two cells whose membranes join together, forming a virtually impermeable barrier to fluid. Tight

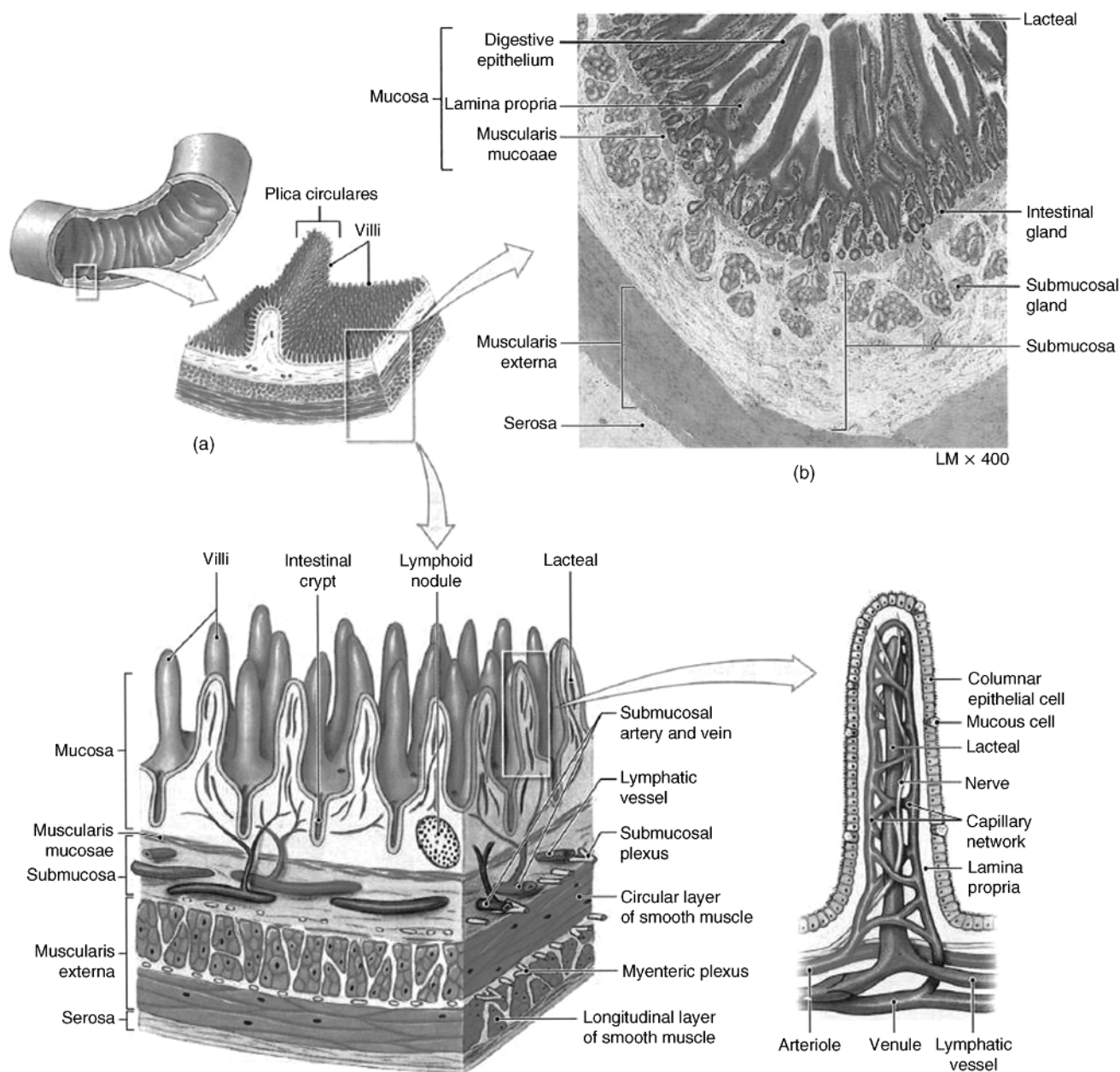


FIGURE 1.2 Gastrointestinal anatomy [8].

junctions are composed of the structural proteins (occludin and claudins), the scaffold proteins (ZO-1, ZO-2, fodrin, cingulin, symplekin, 7H6, and p130), and the actin cytoskeleton [13]. Paracellular transport of drugs mostly occurs via tight junctions (Figure 1.3). The permeability of intestinal epithelium to large molecules or ionized drugs depends on the combination of transcellular transport via adsorptive endocytosis and paracellular transport through tight junctions.

Tight junctions were conceptualized a century ago as secreted extracellular cement, forming an absolute and unregulated barrier within the paracellular space [2, 6, 7].

The contribution of the paracellular pathway of the gastrointestinal tract to the general correlation between environment and host molecular interaction was considered to be negligible. It is apparent that tight junctions have extremely dynamic structures engaged with developmental, physiological, and pathological situations.

To date, particular attention has been placed on the role of tight junction dysfunction in the pathogenesis of several diseases, particularly autoimmune diseases with viral etiology [2, 6, 7]. Pathophysiological regulation of tight junctions is influenced by various factors including secretory

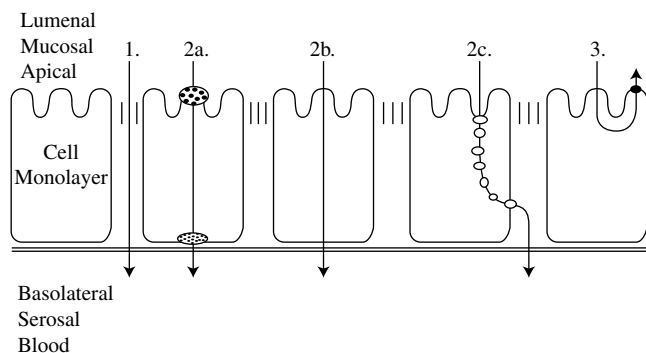


FIGURE 1.3 Mechanism of drug transport through epithelial membranes. 1. Paracellular; 2. Transcellular: 2a. Carrier-mediated; 2b. Passive diffusion; 2c. Receptor-mediated endocytosis; 3. Mediated efflux pathway. (See color figure in color plate section.)

IgA, enzymes, neuropeptides, neurotransmitters, dietary peptides and lectins, yeast, aerobic and anaerobic bacteria, parasites, proinflammatory cytokines, free radicals, and regulatory T-cell dysfunction [2].

1.2.2 Gastrointestinal Physiology

A comprehensive review of the physiological parameters that affect oral absorption in the context of formulation performance and drug dissolution was recently published [14]. This physiologically relevant information to oral human drug delivery could serve as a basis for the design of advanced drug delivery systems.

1.2.2.1 Gastrointestinal Components

- (i) **Bile Salts.** Bile salts are known to enhance the absorption of hydrophobic drugs by enhancing their wettability. The absorption rates of such drugs as griseofulvin can be facilitated when they are taken after meals as a result of the increase of bile salts excretion that promotes their dissolution rates [2]. On the contrary, bile salts reduced the absorption of certain drugs, such as aminoglycosides, neomycin, and nystatin, through the formation of non-absorbable complexes with bile salts [15].
- (ii) **Mucin.** Mucin is a viscous muco-polysaccharaide (glycoprotein) that lines the gastrointestinal mucosa for protection and lubrication purposes [16]. Mucin has a negative anionic charge, so it may form a nonabsorbable complex with some drugs, such as aminoglycosides and quaternary ammonium compounds, subsequently affecting their absorption.
- (iii) **Enzymes.** Since GIT fluid contains high concentrations of enzymes needed for food digestion, some

enzymes may act on drugs. For example, esterases secreted by pancreas affect the metabolic process of ester derivative drugs including aspirin and propoxyphene through the hydrolysis process in the intestine [17]. In epithelial cells, the partial location of the enzyme on the basolateral pole underlies the vectoral transport of salts, water, and organic solutes (e.g., bile salts) across the tissue, whereas in nonepithelial cells, such as fibroblasts, the enzyme is evenly distributed on the cell surface [4].

1.2.2.2 Gastrointestinal Blood Flow About 28% of cardiac output is supplied to the gastrointestinal tract by blood capillaries [2, 6, 7]. The blood perfusion of the gastrointestinal tract plays a critical role in drug absorption by continuously preserving the concentration gradient across the epithelial membrane. Polar molecules that are slowly absorbed exhibit no significant dependence on blood flow, but lipid-soluble molecules and molecules that are small enough to penetrate easily through the aqueous pores are greatly affected by the rate of blood flow. In general, the drug absorption rate is not significantly affected by physiological variability in mesenteric blood flow because blood flow is rarely a rate-limiting step in the drug absorption process through the gastrointestinal tract.

1.2.2.3 Luminal pH The pH of gastric fluid varies considerably according to the sites and contents. Gastric secretions have a pH of less than 1, but the pH of gastric contents is usually between 1 and 3 as a result of dilution and diet [2, 6, 7]. The pH of the stomach contents is briefly but distinctly elevated after a meal; thus, pH values of 5 or even greater are not unusual. Fasting tends to decrease the pH of gastric fluids and subsequently influences the pH of the stomach.

The luminal pH in the small intestine is about 6 to 7 [18], and large intestines have a similar luminal pH as described in Table 1.1. The acidic microclimate pH in the human jejunum was elevated in disease states and contributed to the deviation of the absorption profiles of weak electrolytes from the pH-partition hypothesis [19].

The pH at the absorption site is an integral factor in drug absorption because most drugs are either weak organic acids or bases [2, 6, 7]. Since the gastrointestinal barrier is highly permeable to uncharged and lipid-soluble solutes, a drug may be well absorbed from the segment of the gastrointestinal tract where a favorable pH exists but poorly absorbed from other segments where a less favorable pH exists. Weakly acidic drugs rapidly dissolve in alkaline pH, while basic drugs are more soluble in acidic pH. In addition, disintegration of certain pharmaceutical dosage forms is pH dependent; for example, enteric coated tablets dissolve only in alkaline pH. Luminal pH can influence the stability of some drugs including erythromycin, which is rapidly degraded in the acidic pH [20, 21].

TABLE 1.1 Gastrointestinal Physiology in Humans

GI Region	Length (cm)	Surface Area (cm ²)	Diameter (cm)	pH	Flow Rate (mL/min)	Average Residence Time
Entire GI tract	530–870	2×10^6		1.5–7		Up to 38 h
Mouth cavity	15–20	700				
Esophagus	20	200				
Stomach	25					
Fasted state		65		1.4–2.1		0.5–1.5 h
Fed state		660		2–5		2–6 h
Small intestine	370–630	$2.1\text{--}5.9 \times 10^6$		4.4–7.4		3 ± 1 h
Duodenum	20–30	$1.13\text{--}2.83 \times 10^5$	3.5–6	4.9–6.4		3–10 min
Jejunum	150–260	$2.70\text{--}7.50 \times 10^5$	2.5–4	4.4–6.4	0.73 (fasted); 3.0 (fed)	0.5–2 h
Ileum	200–350	$3.60\text{--}10.50 \times 10^5$	2.3–8	6.5–7.4	0.33 (fasted); 2.35 (fed)	0.5–2.5 h
Large intestine	150	15,000		5.5–7.4		Up to 27 h
Caecum	7	500		5.5–7		
Colon	90–150	15,000		5.5–7.4		
Rectum	11–16	150		7		

Source: Adapted from Refs. 1, 14, 82, and 90.

1.2.2.4 Gastric Emptying and Gastrointestinal Motility

The volume of gastric contents greatly influences the concentration of a drug in the stomach. The rate of gastric emptying is governed by the volume of gastric contents and has a direct impact on the chemical and physical properties of chyme in the duodenum and jejunum [6]. Standard low bulk meals and liquids are transferred from the stomach to the duodenum in an apparent first-order fashion with a half-life of 20 to 60 minutes in healthy adults [6]. In addition, numerous factors as described in Table 1.2 can influence the rate of the gastric emptying process.

Gastric emptying is the major factor that greatly contributes to unusually large intersubject variability in the absorption of drugs released from enteric-coated tablets [22]. Gastric emptying is retarded by fats and fatty acids in the diet, high concentrations of electrolytes or hydrogen ion, high viscosity, mental depression, lying on the left side, and diseases, such as gastroenteritis and gastric ulcer [23]. Gastric emptying of liquids is much faster than that of solid food or solid dosage forms. Gastric emptying is promoted at low stomach pH and retarded at alkaline pH. Various drugs including atropine and narcotic analgesics, amitriptyline, propantheline, and imipramine can also retard gastric emptying [24, 25].

The gastrointestinal tract during the fasting state undergoes the characteristic sequences of motion (i.e., waves of activity) known as the interdigestive myoelectric complex or migrating motility complex [6]. The motility of the small intestine called the small bowel transit time also plays an integral role in drug absorption. The mean transit time of unabsorbed food residues or insoluble granules through the human small intestine is estimated to be about 4 hours [26].

Apart from dissolution of a drug and its permeation through the GI membrane, gastric emptying can also serve as a rate-limiting step in the drug absorption from the intestine. It is generally accepted that fast gastric emptying increases the bioavailability of most drugs. For example, a good correlation was found between stomach emptying time and peak plasma concentration for acetaminophen [27]. The rapid gastric emptying is desirable, when a fast onset of drug action is required (i.e., pain killers), when dissolution of a drug occurs in the intestine, when a drug is not stable in the gastric media, or when a drug is best absorbed from the distal part of the small intestine (e.g., vitamin B₁₂) [2]. Delayed gastric emptying may be preferred, if the food and/or gastric juice promote the disintegration and dissolution of a drug, if

TABLE 1.2 Factors Affecting Gastric Emptying

Gastric Emptying	Influencing Factors	Drugs
Increase	Higher temperature of food, volume of meal (initially), liquid meal, low pH, anxiety and stress, fasting, hyperthyroidism	Cisapride, domperidone, metoclopramide
Decrease	Lying on the left side, type of meal (fatty food > proteins > carbohydrates), solid food, volume of meal, bulky material, higher pH, vigorous exercise, depression	Antacids, anticholinergics (e.g., atropine), narcotic (e.g., morphine), analgesic (e.g., aspirin), tri-cyclic antidepressants, amitriptyline, propantheline, imipramine

a drug like griseofulvin dissolves slowly, if a drug irritates the gastric mucosa (e.g., aspirin), or if a drug is absorbed from the proximal part of the intestines and prolonged duration of action is needed (e.g., vitamin C) [21, 28]. Delayed intestinal transit time may be suitable for enteric coated formulations, sustained release dosage forms, and drugs with site-specific absorption in the intestines.

1.2.3 Gastrointestinal Barrier

1.2.3.1 Barrier to Bioavailability Bioavailability is traditionally defined as a ratio of drug amount at the systemic circulation to the amount taken into gut lumen, which is equivalent to an extent of absorption. The whole absorption process is a sequential event and includes dissolution and precipitation in the gut, enzymatic and chemical degradation, permeation through epithelial membrane, and metabolism at both the intestinal wall and the liver. It also includes other physiologic conditions, such as blood flow and transit time as described above, which are all together considered as barriers against complete absorption. The other element of the absorption process is the rate of absorption, which is governed by a series of time-dependent steps, such as dissolution, gastric emptying, intestinal transit time, and membrane permeability, at the brush border epithelial cells [28].

For a drug administered orally, the two most common reasons for its poor bioavailability are the decreased absorption and presystemic first-pass effects [28]. Low solubility and/or less optimal membrane permeability are key parameters for decreased absorption [29]. Before a drug reaches the blood circulation, it has to pass for the first time through organs of elimination, namely, the GI tract and the liver. The loss of drug through biotransformation by such eliminating organs during its passage to systemic circulation is called first-pass or presystemic metabolism. The low drug concentration or complete absence of the drug in plasma after oral administration is indicative of first-pass effects.

The presystemic metabolism of a drug is influenced by luminal, gut wall, bacterial, and hepatic enzymes [28]. Luminal enzymes are the enzymes present in the gut fluids as well as those from intestinal and pancreatic secretions. The enzymes from pancreatic secretions include hydrolases that metabolize ester drugs like choramphenicol and peptides, split the amide linkages through hydrolysis, and ultimately inactivate the protein and polypeptides drugs [2]. Gut wall enzymes also known as mucosal enzymes are mostly present in stomach mucosa. Intestinal mucosa has both phase I and phase II enzymes, e.g., CYP3A4/5, CYP2C9, CYP2C19, CYP2D6, UGT, GST, and SULT as shown in Figure 1.1 [3]. The activity of phase I enzymes in the gut wall is the highest at the duodenum and decreases distally. The highest expression of phase I enzymes was found between villous tips and midvilli. The GI microbes are rich in colon, whereas they are poorly present in stomach

and small intestines [2]. Thus, many orally administered drugs remain unaffected by bacterial enzymes.

The colonic microbes generally render a drug more potent or toxic on biotransformation. For example, sulfasalazine, a drug used in ulcerative colitis, is hydrolyzed to sulfa pyridine and 5-amino-salicylic acid by the microbial enzymes of the colon. Hepatic enzymes play a major role in biotransformation of most drugs going through the first-pass effect before they reach the systemic circulation. Liver has both phase I (oxidation, reduction, hydrolysis) and phase II (glucuronidation, sulfation, methylation, acetylation) enzymes [2, 6]. Among them, cytochrome P450 enzymes are responsible for metabolism and bioactivation of about 75% of all drugs [30].

In the lumen of the small intestine, dietary fat is hydrolyzed to its components, monoacylglycerol (MG) and free fatty acids (FAs), and subsequently dispersed in bile acids. The pH in close proximity to the enterocyte surface is lower than other sites, causing protonation of the fatty acids. Free FAs then dissociate from the bile salt micelles and either passively diffuse or are transported across the brush border membrane by protein-mediated transporters like cluster determinant 36 (CD36), fatty acid binding protein (FABPpm), and fatty acid transport protein family members (FATPs) [31]. Both CD36 and FABPpm are found to reside in specialized microdomains known as lipid rafts [32].

Like dietary fat and cholesterol, lipid-soluble drugs are absorbed by the fat absorption pathways [2]. The oral absorption rates of griseofulvin and vitamin D were enhanced by certain oily formulations including the bile salt micelles that were transferred to blood circulation via the intestinal lymph system. The process of lipid absorption is classified into 3 steps: 1) the uptake, 2) assembled into lipoproteins, and 3) secretion of lipid into the lymphatic circulation. Each step in lipid absorption may be subjected to the pathway-involved regulation.

1.2.3.2 Barrier to Immunity The intestinal epithelium is the largest mucosal surface, providing an interface between the external environment and the mammalian host. The intestinal mucosa is continuously exposed to an immense load of antigens from ingested food, resident bacteria, and invading viruses [33]. The single-cell epithelial layer lining the gut lumen (Table 1.1, surface area ~ 2.1 to $5.9 \times 10^6 \text{ cm}^2$) has biphasic functions, playing a major role in the digestion and absorption of nutrients and simultaneously constituting the organism's most important barrier between the internal and external environments. Epithelial permeability to nutrients depends on the regulation of intercellular tight junctions (TJs) as well as the activity of transcellular transport via endocytosis [13]. Epithelium has its ability to regulate the trafficking of macromolecules between the host organ and its environment through barrier properties. Intact macromolecules can be absorbed either via the

transcellular or the paracellular pathway. For the transcellular pathway, the uptake of macromolecules occurs through the endocytosis process, followed by fusion with lysosomes (phagolysosomes) with potential degradation of the macromolecules before being delivered into the submucosa. In contrast, macromolecules penetrate the intestinal epithelium through the paracellular pathway, reaching the submucosa mostly in an intact form.

Paracellular passage of macromolecules under either physiological or pathological conditions is safeguarded by gut-associated lymphoid tissue (GALT) [34]. GALT serves as a containment system that prevents potentially harmful intestinal antigens from accessing the systemic circulation and induces systemic tolerance against luminal antigens through the processes involved with polymeric Ig A secretion and induction of T-regulatory-cell activity and immune tolerance [34]. Macrophages, leukocytes, and mucosal mast cells (MMC)s release numerous mediators that alter gut function. MMCs release various preformed mediators, such as histamine, serotonin, and mast-cell proteases, as well as newly synthesized mediators including leukotrienes, prostaglandins, platelet-activating factor, interleukin-4, and TNF- α . Most of these mediators affect epithelial permeability, which might explain, in part, enhanced intestinal permeability featured in both T helper 1 (Th1)-mediated and Th2-mediated pathologies [34].

In disease conditions including inflammatory bowel disease, excessive penetration of antigens through the epithelial layer may result in inappropriate immune stimulation, leading to chronic gastrointestinal inflammation [33]. The permeability of substrates through the intestinal epithelium depends on the regulation process of the mucosal immune system and intercellular tight junctions. Serum immunoglobulin to food antigen macromolecules were found in patients with inflammatory bowel disease and celiac disease, indicating that an enhanced amount of these proteins permeate through the intestinal epithelium, and trigger a systemic immune response. The permeability of substrates through the intestinal barrier increased in such disease conditions as food sensitivity, intestinal diseases [35], acute gastroenteritis, chronic intestinal infections, surgery, exercise, stress, extensive burns, malnutrition, secretory IgA deficiency, anti-inflammatory drugs, and viral infections [33].

1.2.3.3 Barrier to Microorganisms The acidic pH of the stomach and the antibacterial activity of pancreatic enzymes, bile, and intestinal secretions have also served as GI tract barriers [36]. Peristalsis and the natural loss of epithelial cells remove microorganisms. If peristalsis is slowed, the removal process of microorganisms is delayed, producing certain infections including symptomatic shigellosis. Compromised GI defense mechanisms may predispose patients to particular infections. Normal bowel microflora

can inhibit pathogens; alteration of this flora with antibiotics allows for overgrowth of inherently pathogenic microorganisms or super infection with ordinarily commensal organisms such as *Candida albicans*.

1.2.4 Absorption Models

The barrier properties of the intestinal epithelium are generally investigated by assessing the permeability to various probe/marker molecules *in vivo* or *in vitro* with intestinal segments mounted in Ussing-type chambers. Although *in vivo* studies are more physiological, the *in vitro* approach makes it feasible to study epithelial permeability to a greater range of probes including proteins, and to determine the mechanisms and routes of passage involved. *In vitro* cell culture models, such as Caco-2, MDCK, or HT-29 cells, are used to measure drug permeability. The *in vivo* quantitative assessment models currently available are human jejunal perfusion technique, intravital microscopy of fluorescent bacteria, and *in vivo* fluorescence microscopic imaging for intestinal mucosa permeability [37, 38].

There are numerous *in vivo*, *in situ*, *in vitro*, and *in silico* models for assessment of absorption/transport-related mechanisms in addition to examining barrier properties [39, 40]. The absorption models and tools for *in silico*, *in vitro*, and *in vivo* experiments/methods used to get various parameters influencing human dosage regimen are shown in Figure 1.4. For example, an intestinal perfusion model allows for estimation of effective permeability (P_{eff}), which enables estimation of bioavailability (F). Similarly, the Ussing chamber or Caco-2 model can provide apparent permeability [40], whereas the parallel artificial membrane permeability assay (PAMPA) enables estimation of passive permeability in a high throughput mode. Other *in vitro* models, such as everted gut sacs, brush border membrane vesicles (BBMV)s, or intestinal rings, can serve as a means to investigate apparent absorption rates of drugs [40].

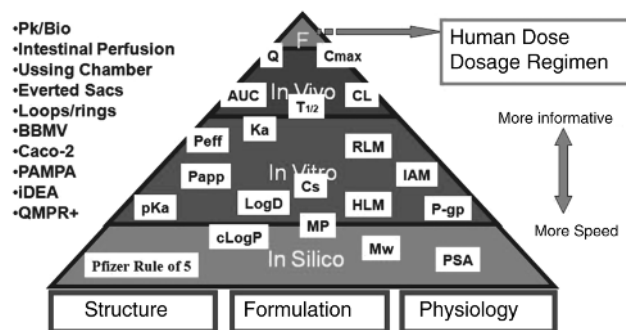


FIGURE 1.4 Absorption models and tools for *in silico*, *in vitro*, and *in vivo* experiments/methods to get various parameters influencing human dosage regimen.

It is also feasible to calculate various descriptors, such as Lipinski's Rule of Five, molecular weight (MW), polar surface area (PSA), clogP, solubility, and permeability, to a certain extent directly from the structure of a drug [40]. By taking the fundamental complexity of GI physiology and formulation characteristics into further consideration, the advanced absorption model could accurately estimate oral bioavailability and successfully predict an individual dosage regimen, which are crucial in the new drug development process.

Pharmacokinetics and biopharmaceutics are the fundamental areas for development of new drug formulations and evaluation of their clinical efficacy. Pharmacokinetics is divided into drug disposition features including the extent and rate of absorption, distribution, metabolism, and excretion. This is commonly referred to as the ADME scheme [41]. The kinetic approach using a compartment model has been frequently used, and the formation and ADME profiles of each metabolite have been broadly defined [42, 43]. Advanced evaluation and prediction tools for bioavailability/bioequivalence of drugs are also required in every stage of the drug assessment process. The drawbacks of biopharmaceutical estimation have mainly resulted from the physicochemical properties of drugs or the physiological factors of patients. Scientists have been enthusiastic to develop a theoretical model capable of predicting oral drug absorption in humans based on various mechanistic approaches, which can also address intrapatient's variances.

The mechanistic approaches are classified into three categories based on their dependence on spatial and temporal variables [44]: quasi-equilibrium models, steady-state models, and dynamic models. The quasi-equilibrium models are independent of spatial and temporal variables, and they include the pH-partition hypothesis and absorption potential concept. The steady-state models are independent of temporal variables, but they are dependent on spatial variables and include the film model, macroscopic mass balance approach, and microscopic balance approach [45]. The steady-state models are restricted to prediction of the extent rather than the rate of oral drug absorption [44]. The dynamic models deal with the relationship between spatial and temporal variables and include dispersion models and compartmental models [3]. The dynamic models can predict both the rate and extent of oral drug absorption, and thus, they are considered an improvement over the steady-state models.

1.3 PHYSIOLOGICAL FACTORS INFLUENCING DRUG ABSORPTION

Gastrointestinal absorption of orally administered drugs is influenced by various factors including physiological,

physicochemical, and formulation factors [2, 7]. Physiological factors are age, blood flow to the GI tract, gastric emptying and intestinal transit, disease state, first-pass effect, pH of luminal contents, a surface area of absorptive site, digestive enzymes, and microbial flora. Solubility, stability, buffers, complexation, particle size, crystal properties, pKa, and diffusion coefficient are classified as physicochemical factors that can affect drug absorption.

Formulation factors include dosage forms and pharmaceutical excipients that are needed to secure stability, acceptability, bioavailability, or functionality of the drug product [39]. Oral dosage forms, such as solution, suspension, tablet, or capsules, are influenced by these factors. Multiple excipients in a dosage form may cause poor absorption and low bioavailability of drugs [39]. Excipients commonly used are binders, buffers, coatings, diluents, disintegrants, lubricants, suspending agents, sweeteners, colorants, and surfactants [39]. Since drug absorption is concomitantly affected by various factors, it is quite difficult to determine which factors are mainly responsible for the poor bioavailability of specific drugs.

1.3.1 Epithelial Membranes

All cells are bound by membranes [46], which consist of the phospholipids bilayer with embedded proteins as described in Figure 1.5. Cell membranes are involved with a variety of cellular processes, such as cell adhesion, ion conductivity, and cell signaling. Cell membranes serve as the attachment surface for the extracellular glycocalyx, cell wall, and intracellular cytoskeleton. The lipid bilayer of cell membranes is impermeable to most water-soluble molecules.

Membrane transport processes in most biological events occur during the formation process of electrochemical potentials and the uptake process of nutrients, such as sugars and amino acids, removal of wastes, endocytotic internalization of macromolecules, and oxygen transport in respiration [4, 47]. The movement of many ions, nutrients, and metabolites across cellular membranes is catalyzed by specific transport proteins, i. e., transporters that show saturation and substrate specificity [48]. Thus, cell membrane is selectively permeable to ions and organic molecules. The epithelium lies on top of connective tissue, from which it is separated by a basement membrane. It is composed of tightly clustered cells connected by tight junctions and desmosomes. The gastrointestinal barrier that separates the lumen of the stomach and intestines from the systemic circulation has the properties similar to a semipermeable membrane with the complex structure composed of lipids, proteins, lipoproteins, and polysaccharides. Lipid-soluble molecules penetrate the barrier directly through the lipophilic portion of the membrane.

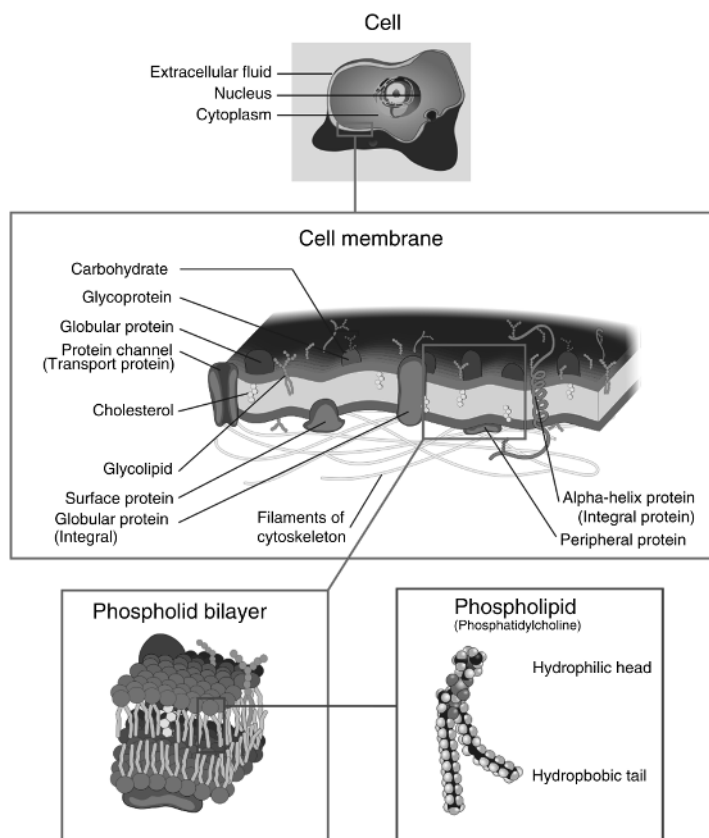


FIGURE 1.5 Illustration of a eukaryotic cell membrane. The cell membrane is a biological membrane that separates the interior of all cells from the outside environment [46].

1.3.2 Absorption Processes

Absorption processes include passive or facilitated diffusion, ion channels, primary and secondary active transporters, and macromolecular and bulk transporters [48]. The characteristics of the absorption processes were summarized in Table 1.3. The mechanisms involved with drug transport through epithelial membranes are shown in Figure 1.3.

1.3.2.1 Passive Diffusion Passive diffusion is the movement of a solute across the membrane down the electrochemical gradient in the absence of the assistance of a transport protein. It does not require any biological energy but follows Fick's law:

$$V = P \cdot A \cdot \Delta C = \left(\frac{D \cdot K}{\delta} \right) \cdot A \cdot \Delta C \quad (1.1)$$

TABLE 1.3 Characteristics of Absorption Processes

Type	Transport Protein	Saturation	Concentration Gradient	Energy Dependence	Examples	Energy Source
Simple diffusion	No	No	No	No	Oxygen, water	
Ion channels	Yes	No	No	No	Na ⁺ channel	
Facilitated diffusion	Yes	Yes	No	No	Glucose transporter	
Primary active transport	Yes	Yes	Yes	Yes	H ⁺ -ATPase, Ca ²⁺ -ATPase, Na ⁺ K ⁺ ATPase, MDR1, BCRP, MRPs	ATP, light, substrate oxidation
Secondary active transport	Yes	Yes	Yes	Yes	Na ⁺ /Ca ²⁺ antiporter, Na ⁺ /amino acid symporters, SGLT, H ⁺ /peptide transporter, OATP, MCT	Ion gradient

Source: Adapted from Ref. 48.

where V is a transport rate, A is the surface area, ΔC is a concentration difference across the membrane, D is the diffusivity of a solute, K is the partition coefficient between membrane and water, and δ is the membrane thickness. The general plot for a simple diffusion is shown in Figure 1.5. As expected from Equation (1.1), the transport rate is proportional to the substrate concentration, displaying a linear relationship (Pattern A). Numerous small lipid-soluble molecules, oxygen, N_2 , CO_2 , and NH_3 , are transported through biological membranes via simple diffusion [4].

1.3.2.2 Ion Channels As ion fluxes are involved with regulation of inorganic ions, such as Na^+ , K^+ , Ca^{2+} , and Cl^- , ion transport across the cell membranes plays a critical role in numerous cell processes, such as cell growth and proliferation [4]. As previously reported, the high concentration of Na^+ ion outside the cell is balanced mainly by extracellular chloride ions [4]. On the other hand, the high concentration of K^+ ion inside the cell is balanced by a variety of negatively charged intracellular ions, such as Cl^- , HCO_3^- , and PO_4^{3-} , or negatively charged organic molecules [4].

Various enzymes and transport mechanisms regulate the pH and the concentrations of Na^+ , K^+ , Ca^{2+} , and Cl^- and other anions in cell, mitochondria, or organelle compartments [49]. Ionic gradients, established at the expense of metabolic energy, e.g., ATP hydrolysis, are used to transfer solutes across the membranes (e.g., amino acids and sugars) into the cell by multitransporters and protons out of the cell by antiporters [4]. The outward K^+ gradient generated across the plasma membrane is a major determinant of the inside negative transmembrane potential of cells [4]. In epithelial tissues, the polarized distribution of enzymes and ion carriers provides the driving force for movement of ions and molecules across the cell interior.

Ion channels have basically two conformations: open or closed. When they are open, ions flow through the channel and reproduce an electric current. For example, the rate of Na^+ movement through the acetylcholine receptor ion channel has a linear relationship with extracellular Na^+ concentration and the process is not saturable (Pattern A in Figure 1.6), which is similar to simple diffusion [48]. The ion channel of the acetylcholine receptor behaves as though it provides a hydrophilic pore within the lipid bilayer through which an ion of the right size, charge, and geometry can diffuse down its electrochemical gradient [48].

1.3.2.3 Facilitated Diffusion Molecules transport through cells according to their electrochemical potential gradient when an energy source is not required [4]. The facilitated diffusion process does not require energy and is accelerated by the specific binding process between a solute and membrane proteins [4].

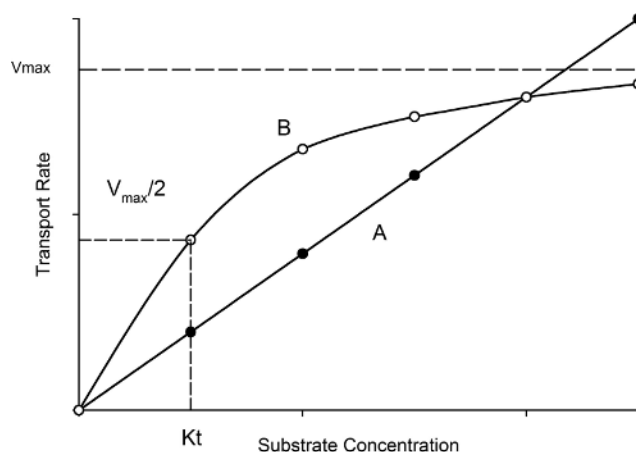


FIGURE 1.6 Concentration dependence of membrane transport: linear (A) and saturable (B) transport processes. Simple diffusion and ion channels obey the linear dependency on the substrate concentration. Facilitated transporter and active transporters follow a saturable pattern [48]. (See color figure in color plate section.)

Some essential features of the facilitated diffusion process can be summarized as follows [50]: 1) The facilitated diffusion process by a mobile transporter system operates such that solute flows from a higher to a lower electrochemical potential; 2) the solute flows at a rate greater than that predicted based on its size or hydrophilicity; 3) the penetration rate does not follow Fick's law except at very low concentrations (at higher concentrations, saturation kinetics are observed as seen in Figure 1.6 (Pattern B)); 4) competitive inhibition occurs between chemically and sterically similar substrates; 5) inhibitory action may be exerted by other compounds, especially those reacting with or ligating reactive groups in proteins; and 6) it is often feasible for the flow of substrate to propel temporarily in the opposite direction against the electrochemical potential gradient of analogs (an overshoot phenomenon) for the accumulation of an analog (or isotope). A well-known example of facilitated diffusion is displayed with erythrocyte glucose transport, in which glucose enters the erythrocyte via a specific transporter that allows for glucose entry into the cell at a rate about 50,000 times greater than its simple diffusion through a lipid bilayer [4].

1.3.2.4 Active Transporters Active transport results in the accumulation of a solute on one side of the membrane and often against its electrochemical gradient. It occurs only when solute accumulation is coupled with the exergonic process directly or indirectly [4]. During the transport process, energy sources, such as adenosine triphosphate (ATP), electron transport, or an electrochemical gradient of another ion, are used to drive ions or molecules against their

electrochemical potential gradients [4]. The active transport process maintains membrane potential and ion gradients, storage of energy for secondary transporters, and pH regulation inside the cell [4].

In primary active transport, solute accumulation is directly coupled with the exergonic reaction (conversion of ATP to adenosine triphosphate (ADP) + Pi) [4]. Secondary active transport occurs when uphill transport of one solute is coupled with the downhill flow of another solute that was originally pumped uphill flow by primary active transport.

An example of the primary active transporter is the $\text{Na}^+\text{K}^+\text{ATPase}$ in the mammalian cells that is energized by ATP [4]. Animal cells maintain a lower concentration of Na^+ and a higher concentration of K^+ intracellularly than are found in extracellular fluid. This concentration difference is established and maintained by primary active transport systems in the plasma membrane. The process is mediated by the enzyme $\text{Na}^+\text{K}^+\text{ATPase}$ that couples the breakdown of ATP with the simultaneous and electrogenic movements of both Na^+ and K^+ against their concentration gradients (i.e., three Na^+ ions move outward for every two K^+ ions that move inward) [4].

In animal cells, the differences in cytosolic and extracellular concentrations of Na^+ and K^+ are maintained by active transport via $\text{Na}^+\text{K}^+\text{ATPase}$, and the generated Na^+ gradient is used as an energy source by a variety of symport and antiport systems [4]. The $\text{Na}^+\text{K}^+\text{ATPase}$ shows specific distribution patterns on the animal cell surface. A few primary active transporters, such as MDR1, MRP2, MRP4, and BCRP in the epithelial membrane, and MRP1, MRP3, MRP4, and MRP5 in the basolateral membrane, are shown in Figure 1.1.

1.3.2.5 Secondary Active Transporters There are a few secondary active transport systems in which the free energy for translocation is not directly provided from metabolic changes but from the energy stored in ionic gradients. In secondary active transport, a single co-transporter couples the flow of one solute (such as H^+ or Na^+) down its concentration gradient with the pumping of a second solute (such as sugar and amino acid) against its concentration gradient [4]. In intestinal epithelial cells, glucose and certain amino acids are accumulated by symport with Na^+ [4]. Peptide transporters in the intestine and kidneys mediate small peptide transport via an inward-directed electrochemical H^+ gradient [51]. A few examples of the secondary active transporters, such as MCT1 and PEPT1 in the epithelial membrane, are shown in Figure 1.1.

Membrane transporters play an integral role in drug entrance and exit from the body. In addition, it is possible to use transporters for drug delivery, e.g., improving oral absorption via the peptide transporter. The identification of the membrane transporters and a better understanding of

their regulation process will allow for development of an efficient drug delivery strategy.

Competition between two similar substances for the same transport system and subsequent reduced absorption of one or both compounds are additional functional properties of the carrier-mediated transport process [52]. The contribution quotient of a carrier-mediated process to the overall absorption rate decreases as the concentration increases, and it is negligibly low at sufficiently high concentrations. The capacity-limited characteristics of a carrier-mediated process indicate that the bioavailability of a drug absorbed through this manner decreases as its dose increases.

1.3.2.6 Macromolecular and Bulk Transport Macromolecules and inert particles are too big to transport across a lipid bilayer. Preformed proteins generally transport through membranes during fusion (secretion) or fission (e.g., pinocytosis) events. For example, during pinocytosis, macromolecules in the extracellular fluid phase are transferred into the cytoplasm via pinocytotic vesicles budding from the plasma membrane [4]. During exocytosis, however, storage vesicles fuse with the plasma membrane and thereby release loaded drugs into the extracellular environment [53]. Adsorptive pinocytosis during the transport process is engaged with transport receptors, such as the LDL receptor, which is a cell-surface integral membrane glycoprotein, recognizing LDL and regulating its endocytosis process [54].

1.3.3 Food

In general, gastrointestinal absorption is favored by an empty stomach. The absorption rate rather than the extent of absorption of drugs, such as sulfonamides and cephadrine, is reduced in the presence of food [55, 56]. The effects of food on the absorption rate of drugs are mainly attributed to the delay in gastric emptying.

It has been frequently observed that administration of certain antibiotics, such as tetracyclines, penicillins [56, 57], lincomycin, captopril [58], and erythromycin [20, 59], right after a meal results in a significant decrease in both the rate and extent of their absorption. The absorption rate of some drugs including riboflavin, griseofulvin, and chlorothiazide is rather elevated when they are administered after a meal [28]. Interactions of drugs with specific food (e.g., grapefruit juice) or nutrients (e.g., calcium supplements) need to be investigated thoroughly to elucidate whether they generally follow theoretical predictions of physicochemical or physiological behaviors [60].

1.3.4 Age

Age is also known to affect the drug absorption through the GI tract. In infants, gastrointestinal pH is higher and intestinal surface and blood flow are lower than those in adults,

resulting in poor drug absorption [2]. Drug absorption is also altered in elderly people as a result of changes in gastric emptying, achlorhydria, and bacterial overgrowth in the small intestine [2]. Accordingly, under current U.S. Food and Drug Administration (FDA) regulation after the Pediatric Research Equity Act enacted in 2003, pediatric assessment of drug products is strongly recommended.

1.3.5 Disease Status

The disease status may influence the rate and extent of drug absorption. It is highly likely that in those with clinical disorders, critical transport processes are either defective at the molecular level or not regulated properly in the physiological situation. The accumulative evidence suggests a role of modulated intestinal permeability in the early stage of the disease pathogenesis. Mutation can also produce defective transporters.

For example, an imbalance of gastric acid secretion causes gastric ulcers and diarrhea by cholera toxin, leading to solute loss and subsequent water loss [2]. Cystic fibrosis, an inherited disorder causing pancreatic, pulmonary, and sinus disease in children and young adults, is characterized with abnormal viscosity of mucous secretions caused by altered electrolyte transport across epithelial cell membranes [2]. The protein encoded by the gene defective in cystic fibrosis is the cystic fibrosis transmembrane conductance regulator (CFTR), which is a chloride channel regulated by cyclic adenosine monophosphate (AMP)-dependent protein kinase phosphorylation and requires binding of ATP for channel opening [61]. Abnormalities associated with celiac disease, which is characterized with loss of intestinal barrier functions [13], produce an increase in GI emptying rate and alteration of intestinal drug metabolism. Crohn's disease has a direct impact on intestinal transit time and lowers intestinal surface area [35]. Hepatic cirrhosis influences the bioavailability of drugs subjected to first-pass effects [62].

An enhanced mucosal permeability is engaged with pathogenesis and onset of pathological complications (e.g., viral and bacterial gastroenteritis, ulcerative colitis, and multiple organ dysfunction syndromes in patients with sepsis and trauma) [33]. The neuro-inflammation with alterations in the function of intestinal barriers is observed in various diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), and certain forms of depression [35, 63, 64].

1.4 PHYSICOCHEMICAL FACTORS INFLUENCING DRUG ABSORPTION

1.4.1 pH-Partition Theory

The dissociation constant and lipid solubility of a drug as well as the pH at the absorption site often define the

absorption characteristics of a drug from the solution. The pH-partition theory of drug absorption is based on the assumption that the gastrointestinal tract is a simple lipid barrier to the transport of drugs and chemicals [65–67]. The nonionized form of an acid or basic drug is readily absorbed at the GI tract if it is sufficiently lipid soluble, whereas the ionized form is not. The fraction of drug in a nonionized form at the specific absorption site can be estimated by the oil–water partition coefficient of a drug; the more lipophilic the compound is, the faster its absorption is [67]. Organic anions or cations are likely absorbed in the small intestine, although they are absorbed at a much slower rate than the corresponding unionized form of the drug [68].

1.4.2 Drug pKa and Gastrointestinal pH

The relationship among pH, pKa, and the extent of ionization is described by the Henderson–Hasselbalch equation [28]:

for an acid

$$\text{pKa} - \text{pH} = \log (f_u/f_i) \quad (1.2)$$

for a base

$$\text{pKa} - \text{pH} = \log (f_i/f_u) \quad (1.3)$$

where f_u and f_i are the fractions of a drug present in the unionized and ionized forms, respectively.

Most acidic drugs are predominantly unionized at the low pH of gastric fluids and easily absorbed from the stomach as well as from the intestine. However, most weak acids are well absorbed in the small intestine. The major factors, such as a large surface area, a relatively long residence time, and the limited absorption of ionized forms of a drug (a factor not considered by the pH-partition theory), are contributed to the overall absorption rate of weak acids in the intestine. Most weak bases are poorly absorbed, if at all, in the stomach because they are largely ionized at low pH (Equation (1.3)). Strong bases with pKa values of 5 to 11 showed pH-dependent absorption. Stronger bases are ionized throughout the gastrointestinal tract and tend to be poorly absorbed [28].

1.4.3 Lipid Solubility

A basic principle of the lipophilic/hydrophilic nature of a drug is regulated by a property called the partition coefficient between a lipophilic solvent, such as chloroform, butanol, octanol, and water or aqueous buffer. Polar molecules like aminoglycosides and other antibiotics, quaternary ammonium compounds, or polypeptide drugs are poorly absorbed after oral administration as a result of a low partition coefficient [69]. On the other hand, lipid-soluble drugs, such as fentanyl and sufentanil with favorable partition coefficients, are generally well absorbed after oral administration.

Prodrugs designed to improve permeability and oral absorption of parent drugs are more lipid soluble than parent drugs and should be quickly converted to the parent compound during the absorption process in the gut wall or the liver. Ampicillin prodrugs, such as pivampicillin [70] and bacampicillin [71], are more lipid soluble, thus, being absorbed more than the parent compound after oral administration.

1.4.4 Unstirred Water Layer

Experimental evidences show that the pH-absorption profile is often shifted two or more pH units from the curve predicted by the pH-partition theory. This discrepancy can be explained by the experimental theory that an additional barrier to drug transport, called the unstirred or stagnant water layer, exists in parallel with the luminal surface of the intestinal membrane. The unstirred layer, whose thickness ranges from 0.01 to 1 mm [6], shifts the inflection point in the pH-absorption profile to the right for an acid and the left for a basic compound, reducing the absorption rate [72].

1.4.5 Dissolution

When a drug in a solid dosage form is given orally, the rate of its absorption is often controlled by its dissolution rate in the fluids. The solubility of numerous drugs increases as the environmental temperature of the solvent increases [28, 73]. Therefore, it is generally accepted that the dissolution rate is temperature dependent. The diffusion coefficient is inversely related to viscosity so that the dissolution rate could decrease as the viscosity of the solvent increases [73].

The degree of agitation or stirring of the solvent can affect the thickness of the diffusion layer. The greater the agitation is, the thinner the layer becomes and the faster the dissolution rate is. Changes in the solvent properties, such as pH, affect the solubility of the drug and, subsequently, the dissolution rate. Similarly, the use of different salts or other chemicals and physical forms (polymorphism) of a drug whose effective solubility is different from that of the parent drug usually affect the dissolution rate. An enhancement of the surface area of a drug exposed to various dissolution media generally increases the dissolution rate via reducing the particle size or attaining more effective wetting of the solid [28].

1.4.6 Hydrolysis in the Gastrointestinal Tract

The bioconversion through hydrolysis in the gastrointestinal tract is responsible for the poor bioavailability after oral administration [28]. The degradation rate of penicillin G decreases sharply as pH increases [74]. Some penicillins, notably amino-penicillins, are considerably more resistant to acid hydrolysis [73].

1.4.7 Complexation and Adsorption

Complexation of a drug in gastrointestinal fluids may alter the rate, and in some cases, the extent of absorption, because the drug complex usually differs from the free drug with respect to water solubility and lipid–water partition coefficient [28]. The complexing agent could be a substrate in the gastrointestinal tract, a dietary component, or a component of the dosage form. Some insoluble substances, such as charcoal, may adsorb co-administered drugs, often resulting in poor absorption of those drugs [28].

1.4.8 Deviation from pH-Partition Hypothesis

There are various reasons behind deviation of drug absorption from pH-partition hypothesis that is often observed in clinical situations: Some factors, such as variability in pH conditions in humans, unstirred water layer, and ion pair formation, may affect drug absorption through the GI tract.

The pH at membrane surfaces, i.e., microclimate pH, may alter the drug absorption rate based on pH-partition prediction. A more neutral pH in adult celiac disease would cause a smaller percentage of folic acid to be absorbed as a result of less ionized forms available, causing folate malabsorption [72, 75]. The negative charge on the membrane could attract the smaller number of cations toward the surface and subsequently repel the smaller number of anions.

In addition, the movement of water molecules into or out of the GI tract may affect the passage of small molecules across the membrane. The convective water flow can be produced as a result of the difference in osmotic pressure between blood and lumen contents, and the difference in hydrostatic pressure between lumen and perivascular tissues, for instance, derived from muscular contractions [73].

1.5 STRATEGIES TO OVERCOME GASTROINTESTINAL BARRIERS IN DRUG DELIVERY

1.5.1 Alternative Formulations

Various drug delivery strategies based on the physico-dynamic characteristics of a drug can be opted to overcome the poor absorption/bioavailability. In improving the poor absorption/bioavailability, scientists need to deal with complex issues, such as stability in lumen or plasma, solubility, and permeability at the same time. Therefore, it is ideal to find which parameters are of particular importance in each strategy.

If solubility is an underlying problem, dissolution improvement may be a first priority. However, as this approach is not always successful, the chemical modification of a drug can be further considered for the enhancement of solubility. Depending on the lipophilicity of the

compounds, either the water layer or the membrane becomes a limiting barrier to their absorption. For water-insoluble hydrophobic drugs, prodrugs have been synthesized to increase solubility, and later, they are converted back to the parent drugs by intestinal brush border membrane enzymes. For hydrophobic compounds, the diffusion water layer often serves as a barrier to the absorption rate [76]. For example, the solubility of hydrocortisone is only around 0.7 mM and above this concentration there was no significant increase in the uptake rate. The ester prodrugs of hydrocortisone enhanced their uptake rate by 20-fold [76]. Esterase and phosphatase in intestinal mucosal are responsible for reconverting of prodrugs back to parent hydrocortisone.

A popular approach for oral absorption enhancement of hydrophilic drugs is to use ester prodrugs which increase its hydrophobicity. Bacampicillin is a typical example of a prodrug for ampicillin [77]. Parent drugs containing $-OH$ or $-COOH$ groups can often be converted into esters from which the active drugs are regenerated by accountable esterases within the body.

Another strategy for oral absorption enhancement of hydrophilic drugs is to design suitable substrates subjected to a specific intestinal transporter [78]. Schematic representation of a general prodrug strategy to increase intestinal drug absorption is illustrated in Figure 1.7. Even though the parent drug is not a substrate of a particular transporter, when its prodrug becomes a substrate, then it can be taken up into the cells through a transporter-mediated process. Prodrugs need a metabolic process inside cells to be converted back to the parent drug and released into systemic circulation. Also, it would be highly desirable that any brush border or luminal enzymes are not directly involved with the metabolism of prodrugs. As the peptide transport system facilitates the absorption process of small peptides, peptide-like drugs and some β -lactam antibiotics and angiotensin converting enzyme inhibitors [52], a peptide transporter in

the intestine could be used to enhance the bioavailability of poorly absorbed drugs. It has been retrospectively demonstrated that the peptide transporter improved oral absorption of valacyclovir [79] and valganciclovir (i.e., valyl ester of ganciclovir), both of which are a nonpeptidyl prodrug [80]. Ganciclovir has only 5–9% of bioavailability, and its dosing is about 100 mg 3 times daily taken with food. The prodrug valganciclovir has 10 times higher bioavailability than the parent drug, which is about 60%, and the dosing regimen can be improved once a day with a 450-mg dose.

Recently, the promising strategies that are commonly used in practice for long-term administration of drugs without interfering with human physiology have been reviewed [81]. One of the main goals is to replace injection formulations with various noninvasive technologies for simultaneously achieving improvement of safety and enhanced efficacy profiles. Other formulation objectives are modification of bioavailability, stability, permeability, solubility, dissolution rate, residence time, absorption area, and elimination [52]. Modulating barrier properties can be achieved by approaches involved with chemical enhancers, surfactants, iontophoresis, sonophoresis, micro needles, cell-penetrating peptides, ligand/vector-targeted delivery, and prodrugs [81]. Various controlled release formulations and noninvasive delivery technologies have been a main focus of product enhancement and life-cycle management for innovator biopharmaceuticals [82].

1.5.2 Alternative Routes of Administration

The most popular formulations for drug administration are oral dosage forms, such as tablets, capsules, powders, and granules. There are several advantages of oral dosage formulations: ease of accurate dosage, good physicochemical stability, good patient compliance, and cheaper manufacturing costs. However, one of the potential problems of oral medication is poor bioavailability, as the availability of the drug for absorption is affected by both disintegration and dissolution processes. Therefore, they should be stable chemically and/or enzymatically in the gastrointestinal tract during the absorption process.

Among various approaches available for enhancement of the bioavailability of the drug, targeted delivery to the colon via biodegradable polymers seems to be a potentially promising strategy. A wide range of the polysaccharides abundantly available in the market can be used solely for the purpose of colon-specific drug delivery [83]. This family of natural polymers has great appeal to the drug delivery community, as they comprise polymers having a large number of derivable groups, a wide range of molecular weights, varying chemical compositions, and for the most part, low toxicity and biodegradability with high stability [83].

In addition to oral medication, several alternative methods to the GI tract, such as buccal, sublingual, and rectal

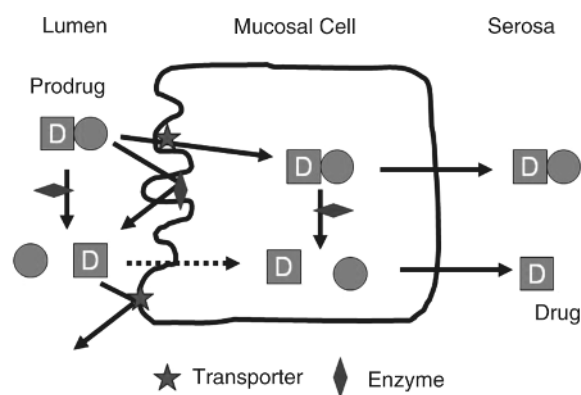


FIGURE 1.7 Schematic representation of transporter-targeted prodrug strategy.

administrations, are available. The absorption of drugs through the oral mucosa provides an alternative route for systemic administration that bypasses the liver metabolism, even though the extent of absorption may be variable. In the oral mucosal cavity, the drug can be delivered by either the sublingual or the buccal route, which are well vascularized with venous blood draining the buccal mucosa, reaching the heart directly via the internal jugular vein [84, 85]. The drug absorption rate via the buccal route is less than that obtained via the sublingual mucosa as a result of the permeability barrier. The low mobility of the buccal musculature as compared with that of the sublingual route makes this site ideally suitable for sustained delivery of drugs [85]. Moreover, this route is convenient, accessible, and generally well complied by patients.

Significantly enhanced absorption through the oral mucosa has been achieved with compounds, such as glyceryl trinitrate, captopril, desoxycortisone acetate, isoprenaline, methacholine chloride, nifedipine, perphenazine, and morphine [85, 86]. The major mechanism of absorption through the sublingual route is simple diffusion. The optimal oil/water partition coefficient was within the range of 40 to 2000 for the sublingual route [73]

Additional routes of drug administration other than per the oral route are topical, inhalation, intramuscular, subcutaneous, intranasal, intraocular, rectal, or vaginal administration [87]. The alternative routes can serve as an efficient means to meet specific requirements in particular patient conditions. For example, rectal administration is an important route for children and old patients. The drugs can be administered as a solution or suppository and can bypass the presystemic hepatic metabolism. Drugs administered by this route include aspirin, acetaminophen [88], and few barbiturates [89].

1.6 SUMMARY

Physiological GI barriers are part of the protection mechanisms for the human body. The thorough understanding of GI barriers in drug delivery makes it possible to identify biopharmaceutical and pharmacokinetic problems on the new drug development process, to suggest alternative approaches to improve bioavailability, and further to predict the clinical efficacies of drugs. Physiological GI barriers include epithelial membrane, tight junctions, mucosa, gastrointestinal blood flow, luminal and microclimate pH, gastric emptying, GI motility, and age. Changes of GI barriers in disease states seem to have a direct impact on new drug development.

Depending on the lipophilicity of a drug, chemical modification, such as prodrug and bioconjugation, would be used for new formulation and drug development. Small-molecule solute or large-molecule transporters are potential

targets, when the passive transmembrane transport is negligible as a result of its charge, size, or hydrophilicity. Prodrugs designed for solubility improvement, such as ester prodrugs, peptidyl drugs, or amino acid ester prodrugs, or designed as an efficient substrate to a specific transporter, are potentially powerful approaches to improving the absorption and intracellular delivery of drugs. Additional routes of drug administration other than per the oral route can serve as an efficient means to meet specific requirements in particular patients.

ASSESSMENT QUESTIONS

- 1.1. Which influencing factor does *not* increase gastric emptying of a drug?
 - a. Higher temperature of food
 - b. Lying on the left side
 - c. Low pH
 - d. Fasting
- 1.2. Which pharmacokinetic parameter will be optimized to develop a once-a-day extended release formulation of a short half-life drug? Explain why.
- 1.3. What are the key influencing factors on oral drug absorption of a drug “product?”
- 1.4. Which drug can be absorbed most from the intestinal tracts at pH 7?
 - a. Quinine (pKa = 8.4)
 - b. Benzoic acid (pKa = 4.2)
 - c. Acetylsalicylic acid (pKa = 3.5)
 - d. Salicylic acid (pKa = 3.0)
- 1.5. What are the biological barriers preventing oral delivery of protein drugs?
- 1.6. Which mechanism of drug transport through epithelial membranes will be the most feasible when nanoparticles are considered a potential delivery method of a vaccine? Which ones will contribute less?
- 1.7. Which mucosal solute transporters are present on the human gastrointestinal tract?
- 1.8. How would the maximal oral absorption be achieved for a drug? (Hint: Use Fick’s law.)
- 1.9. Describe the following terms: (a) passive diffusion, (b) unstirred water layer, (c) tight junction, and (d) luminal pH.
- 1.10. What are the three key barrier functions of the gastrointestinal tract?
- 1.11. What is presystemic metabolism?

REFERENCES

- Li, X., Jasti, B. *Design of Controlled Drug Delivery Systems*, McGraw-Hill, New York, NY, 2006.
- Johnson, L.R. *Physiology of the Gastrointestinal Tract*, 2nd ed., Raven Press, New York, NY, 1987.
- Huang, W., Lee, S.L., Yu, L.X. (2009). Mechanistic approaches to predicting oral drug absorption. *Journal of American Association of Pharmaceutical Scientists*, 11, 217–224.
- Lehninger, A.L. *Principles of Biochemistry*, Worth, New York, NY, 1993.
- Carr, K.E., Toner, P.G. Morphology of the intestinal mucosa, in T.Z. Csaky (ed.), *Pharmacology of Intestinal Permeability I*, Springer-Verlag, Berlin, Germany, 1984, pp. 1–50.
- Davenport, H.W. *Physiology of the Digestive Tract*, 5th ed., Year Book Medical, Chicago, IL, 1982.
- Guyton, A.C. *Textbook of Medical Physiology*, 6th ed., W.B. Saunders, Philadelphia, PA, 1981.
- Wood, M.G. *Laboratory Manual for Anatomy & Physiology. Pig Version*, 4th ed., Pearson Education, San Francisco, CA, 2010, p. 659.
- Wilson, J.P. (1967). Surface area of the small intestine in man. *Gut*, 8, 618–621.
- Fordtran, J.S., Rector, F.C., Ewton, M.F. (1965). Permeability characteristics of the human small intestine. *Journal of Clinical Investigation*, 44, 1935–1944.
- Chadwick, V.S., Phillips, S.F., Hofmann, A.F. (1977). Measurements of intestinal permeability using low molecular weight polyethylene glycols (PEG 400). II. Application to normal and abnormal permeability states in man and animals. *Gastroenterology*, 73, 247–251.
- Goswami, T., Jasti, B.R., Li, X. (2009). Estimation of the theoretical pore sizes of the porcine oral mucosa for permeation of hydrophilic permeants. *Archives of Oral Biology*, 54, 577–582.
- Fasano, A., Schulzke, J.D. The role of the intestinal barrier function in the pathogenesis of Celiac Disease, in A. Fasano, R. Troncone, and D. Branski (eds.), *Frontiers in Celiac Disease*, vol. 12, *Pediatric and Adolescent Medicine*, Basel, Karger AG, 2008, pp. 89–98.
- Mudie, D.M., Amidon, G.L., Amidon, G.E. (2010). Physiological parameters for oral delivery and in vitro testing. *Molecular Pharmaceutics*, 7, 1388–1405.
- Simon, G.L., Gorbach, S.L. (1986). The human intestinal microflora. *Digestive Diseases and Sciences*, 3, 147–162.
- Jany, B.H., et al. (1991). Human bronchus and intestine express the same mucin gene. *Journal of Clinical Investigation*, 87(1), 77–82.
- Rainsford, K.D. (1975). The biochemical pathology of aspirin-induced gastric damage. *Inflammation Research*, 5(4), 326–344.
- Lui, C.Y., et al. (1986). Comparison of gastrointestinal pH in dogs and humans: Implications on the use of the beagle dog as a model for oral absorption in human. *Journal of Pharmacy and Pharmacology*, 75(3), 271–274.
- Lucas, M.L., et al. (1975). Direct measurement by pH-micro-electrode of the pH microclimate in rat proximal jejunum. *Proceedings of the Royal Society of London—Series B: Biological Sciences*, 192, 39–48.
- Welling, P.G., et al. (1978). Bioavailability of erythromycin stearate: Influence of food and fluid volume. *Journal of Pharmacy and Pharmacology*, 67, 764–766.
- Shargel, L., Yu, A.B.C. *Biopharmaceutics, Encyclopedia of Pharmaceutical Technology*, Informa Healthcare USA, New York, NY, 2007, pp. 208–227.
- Blythe, R.H., Grass, G.M., MacDonnell, D.R. (1959). The formulation and evaluation of enteric-coated aspirin tablets. *American Journal of Pharmacy*, 131, 206–216.
- Nimmo, W.S., Prescott, L.F. (1978). The influence of posture on paracetamol absorption. *British Journal of Clinical Pharmacology*, 5, 348–349.
- Hurwitz, A., Robinson, R.G., Herrin, W.F. (1977). Prolongation of gastric emptying by oral propantheline. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 22, 206–210.
- Nimmo, J. (1973). The influence of metoclopramide on drug absorption. *Journal of Postgraduate Medicine*, 49, 25–28.
- Eve, I.S. (1966). A review of the physiology of the gastrointestinal tract in relation to radiation doses of radioactive materials. *Health Physics*, 12, 131–161.
- Heading, R.C., et al. (1973). The dependence of paracetamol absorption on the rate of gastric emptying. *British Journal of Pharmacology*, 47, 415–421.
- Gibaldi, M. *Biopharmaceutics and Clinical Pharmacokinetics*, Lea & Febiger, Philadelphia, PA, 1984.
- Amidon, G.L., et al. (1995). A theoretical basis for a biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Research in Pharmacy*, 12, 413–420.
- Guengerich, F.P. (2008). Cytochrome P450 and chemical toxicology. *Chemical Research in Toxicology*, 21(1), 70.
- Abumrad, N., Coburn, C., Ibrahim, A. (1999). Membrane proteins implicated in long-chain fatty acid uptake by mammalian cells: CD36, FATP and FABPm. *Biochimica et Biophysica Acta*, 1441, 4–13.
- Ehehalt, R., et al. (2006). Translocation of long chain fatty acids across the plasma membrane—lipid rafts and fatty acid transport proteins. *Molecular and Cellular Biochemistry*, 284, 135–140.
- Söderholm, J.D., Perdue, M.H. (2001). Stress and the gastrointestinal tract II. Stress and intestinal barrier function. *American Journal of Physiology—Gastrointestinal and Liver Physiology*, 280, G7–G13.
- Fasano, A., Shea-Donohue, T. (2005). Mechanisms of disease: The role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. *Nature Clinical Practice Gastroenterology & Hepatology*, 2(9), 416–422.
- Turner, J.R. (2009). Intestinal mucosal barrier function in health and disease. *Nature Reviews Immunology*, 9, 799–809.

36. Tunkel, A.R. Host defense mechanisms against infection, in *The Merck Manual for Health Care Professional*, 2009, section 15, chapter 178.
37. Olson, E.S., et al. (2010). Activatable cell penetrating peptides linked to nanoparticles as dual probes for in vivo fluorescence and MR imaging of proteases. *Proceedings of the National Academy of Sciences of the United States of America*, 107(9), 4311–4316.
38. Sumen, C., et al. (2004). Intravital microscopy: Visualizing immunity in context. *Immunity*, 21, 315–329.
39. Dressman J.B., Lennernas, H. (eds.). *Oral Drug Absorption Prediction and Assessment*, Marcel Dekker, New York, NY, 2000.
40. Ehrhardt, C., Kim, K.J. (eds.). *Drug Absorption Studies: In Situ, In Vitro and In Silico Models (Biotechnology: Pharmaceutical Aspects)*, Springer, New York, NY, 2008.
41. Sheiner, L.B., Rosenberg, B., Marathe, V.V. (1977). Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *Journal of Pharmacokinetics and Biopharmaceutics*, 5, 445–479.
42. Sheiner, L.B., et al. (1979). Forecasting individual pharmacokinetics. *International Journal of Clinical Pharmacology, Therapy and Toxicology*, 26(3), 294–305.
43. Bonate, P.L. (2005). Recommended reading in population pharmacokinetic pharmacodynamics (PDF). *Journal of American Association of Pharmaceutical Scientists*, 7(2), E363–E373.
44. Yu, L.X., et al. (1996). Transport approaches to the biopharmaceutical design of oral drug delivery systems: Prediction of intestinal absorption. *Advanced Drug Delivery Reviews*, 19, 359–376.
45. Oh, D.M., Curl, R.L., Amidon, G.L. (1993). Estimating the fraction dose absorbed from suspensions of poorly soluble compounds in humans: A mathematical model. *Pharmaceutical Research*, 10, 264–270.
46. http://en.wikipedia.org/wiki/Cell_membrane. Accessed on January 28, 2012.
47. Lodish, H., et al., *Molecular Cell Biology*, Scientific American Books, New York, NY, 1995.
48. Oh, D.-M., Amidon, G.L. Overview of membrane transport. In G.L. Amidon and W. Sadee (eds.), *Membrane Transporters As Drug Targets*, Kluwer Academic/Plenum, New York, NY, 1999, pp. 1–27.
49. Hopfer, U., Liedtke, C.M. (1987). Proton and bicarbonate transport mechanisms in the intestine. *Annual Review of Physiology*, 49, 51–67.
50. West, I.C. *The Biochemistry of Membrane Transporter*, Chapman and Hall, London and New York, NY, 1983, p. 80.
51. Ganapathy, V., Leibach, F.H. (1996). Peptide transporters. *Current Opinion in Nephrology & Hypertension*, 5, 395–400.
52. Mahato, R.I., Narang, A.S., Thoma, L., Miller, D.D. (2003). Emerging trends in oral delivery of peptide and protein drugs. *Critical Reviews in Therapeutic Drug Carrier Systems*, 20(2–3), 153–214.
53. Petty, H.R. *Molecular Biology of Membranes: Structure and Function*, Plenum, New York, NY, 1993, p. 404.
54. Yamamoto, T., et al. (1984). The human LDL receptor: A cysteine-rich protein with multiple Alu sequences in its mRNA, *Cell*, 39, 27–38.
55. Harvengt, C., et al. (1973). Cephradine absorption and excretion in fasting and nonfasting volunteers. *The Journal of Clinical Pharmacology*, 13, 36–40.
56. Welling, P.G. (1977). Influence of food and diet on gastrointestinal drug absorption: A review. *Journal of Pharmacokinetics and Biopharmaceutics*, 5, 291–334.
57. Klein, J.O., Finland, M.L. (1963). The new penicillins. *New England Journal of Medicine*, 269, 1019–1025.
58. Singhvi, S.M., et al. (1982). Effect of food on the bioavailability of captopril in healthy subjects. *The Journal of Clinical Pharmacology*, 22, 135–140.
59. Welling, P.G., Tse, F.L.S. (1982). The influence of food on the absorption of antimicrobial agents. *Journal of Antimicrobial Chemotherapy*, 9, 7–27.
60. Fleisher, D., Sweet, B.V., Parekh, A. Drug absorption with food, in J.I. Boullata and Vincent T. Armenti (eds.), *Handbook of Drug-Nutrient Interactions*, Humana Press, Totowa, NJ, 2004, pp. 129–154.
61. Schultz, S.G., et al. *Molecular Biology of Membrane Transport Disorders*, Plenum Press, New York, NY, 1996.
62. Regfirdh, C.G., et al. (1989). Pharmacokinetics of felodipine in patients with liver disease, *European Journal of Clinical Pharmacology*, 36, 473–479.
63. Mhatre, M., Floyd, R.A., Hensley, K. (2004). Oxidative stress and neuroinflammation in Alzheimer's disease and amyotrophic lateral sclerosis: Common links and potential therapeutic targets. *Alzheimer's Disease Research Journal*, 6(2), 147–157.
64. Tansey, M.G., Goldberg, M.S. (2010). Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. *Neurobiology of Disease*, 37(3), 510–518.
65. Shore, P.A., Brodie, B.B., Hogben, C.A.M. (1957). The gastric secretion of drugs: A pH partition hypothesis. *Journal of Pharmacology and Experimental Therapeutics*, 119, 361–369.
66. Schanker, L.S., et al. (1958). Absorption of drugs from the rat small intestine. *Journal of Pharmacology and Experimental Therapeutics*, 123, 81–88.
67. Hogben, C.A.M., et al. (1959). On the mechanism of intestinal absorption of drugs. *Journal of Pharmacology and Experimental Therapeutics*, 125, 275–282.
68. Crouthamel, W.G., et al. (1971). Drug absorption IV. Influence of pH on absorption kinetics of weakly acidic drugs. *Journal of Pharmacy & Pharmaceutical Sciences*, 60, 1160–1163.
69. Lin, J.H. (1995). Species similarities and differences in pharmacokinetics. *Drug Metabolism and Disposition*, 23, 1008–1021.
70. Verbist, L. (1974). Triple crossover study on the absorption and excretion of ampicillin, pivampicillin, and amoxicillin. *Antimicrobial Agents and Chemotherapy*, 6, 588–593.
71. Bodin, N.-O., et al. (1975). Bacampicillin, a new orally well-absorbed derivative of ampicillin. *Antimicrobial Agents and Chemotherapy*, 8, 518–525.

72. Winne, D. (1978). Dependence of intestinal absorption *in vivo* on the unstirred layer. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 304, 175–181.
73. Florence, A.T., Attwood, D. *Physicochemical Principles of Pharmacy*, 2nd ed., Macmillan Press, London, 1988.
74. Lu, X.B., et al. (2008). Effect of buffer solution and temperature on the stability of penicillin G. *Journal of Chemical & Engineering Data*, 53, 543–547.
75. Benn, A., et al. (1971). Effect of intraluminal pH on the absorption of pteroylglutamic acid. *British Medical Journal*, 1, 148–150.
76. Amidon, G.L., Stewart, B.H., Pogany, S. (1985). Improving the intestinal mucosal cell uptake of water insoluble compounds, *Journal of Controlled Release*, 2, 13–26.
77. Rautio, J., et al. (eds), *Prodrugs and Targeted Delivery: Towards Better ADME Properties*, Wiley-VCH Verlag GmbH, Weinheim, Germany, 2011.
78. Han, H.-K., Amidon, G.L. (2000). Targeted prodrug design to optimize drug delivery, *Journal of American Association of Pharmaceutical Scientists*, 2(1), article 6.
79. Han, H., et al. (1998). 5'-Amino acid esters of antiviral nucleosides, acyclovir, and AZT are absorbed by the intestinal PEPT1 peptide transporter. *Research in Pharmacy*, 15, 1154–1159.
80. Jung, D., Dorr, A. (1999). Single-dose pharmacokinetics of valganciclovir in HIV- and CMV- seropositive subjects. *The Journal of Clinical Pharmacology*, 39, 800–804.
81. Pint, João F. (2010). Site-specific drug delivery systems within the gastro-intestinal tract: From the mouth to the colon. *International Journal of Pharmaceutics*, 395(1–2), 44–52.
82. Zhang, H., Surian, J.M. Biopharmaceutic consideration and assessment for oral controlled release formulations, in Hong Wen and Kinam Park (eds), *Oral Controlled Release Formulation Design and Drug Delivery Theory to Practice*, Wiley, NJ, 2010, pp. 33–45.
83. Jain, A., Gupta, Y. Jain, S.K. (2007). Perspectives of biodegradable natural polysaccharides for site-specific drug delivery to the colon, *Journal of Pharmacy and Pharmacology*, 10(1), 86–128.
84. McElany, J.C. Buccal Absorption of Drugs. In: *Encyclopedia of Pharmaceutical Technology*, vol. 2, J. Swarbrick, and J.C. Boylan (eds.), Marcel Dekker, Inc., New York, NY, 1990.
85. Shojaei, A.H. (1998). Buccal Mucosa as a route for systemic drug delivery: A review. *Journal of Pharmacy & Pharmaceutical Sciences*, 1(1), 15–30.
86. Turunen, E., et al. (2011). Fast-dissolving sublingual solid dispersion and cyclodextrin complex increase the absorption of perphenazine in rabbits. *Journal of Pharmacy and Pharmacology*, 63(1), 19–25.
87. Lee, C.H., Chien, Y.W. *Drug delivery, Vaginal Route. Encyclopedia of Pharmaceutical Technology*, 3rd ed., Informa Healthcare2, New York, NY, 2011, pp. 961–985.
88. Owczarzak, V., Haddad, J. (2006). Comparison of oral versus rectal administration of acetaminophen with codeine in post-operative pediatric adenotonsillectomy patients. *The Laryngoscope*, 116(8), 1485.
89. Larsson, L.E., et al. (1987). Effects of rectal thiopentone and methohexitone on carbon dioxide tension in infant anaesthesia with spontaneous ventilation. *Acta Anaesthesiologica Scandinavica*, 31(3), 227–230.
90. Davies, B., Morris, T. (1993). Physiological parameters in laboratory animals and humans, *Research in Pharmacy*, 10(7), 1093–1095.