INTRODUCTION

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1.1 INTRODUCTION

Absorption, distribution, metabolism, and excretion (ADME) properties have been and still are a significant reason for attrition in drug discovery. Paradoxically, medicinal chemists have to solve complex ADME issues with a solid organic chemistry background and scant anatomy or physiology training. In reality, drug metabolism is not any different from daily food digestion and understanding of human nutrition demystifies many drug metabolism reactions. Grasping the logical sequence of each step in the digestion process as well as the nature of the chemical reactions that occur in each organ contributes to the understanding of food digestion and drug metabolism.

The human digestive system processes on average 30 tons of food in a lifetime. Food digestion provides nutrients for the body’s function and repair. Useful nutrients are stored in a form that is compatible with existing biological systems (e.g., fat, glycogen). It produces and recycles complex molecules such as bile acids and catabolizes fats. More importantly, the liver is set up to recognize and destroy toxic entities and does so with relentless efficiency.

In order to carry out such a vast array of chemical reactions in a highly compact space, the human body effectively runs the process in set stages corresponding to the various organs of the digestive system. Each organ possesses its own controlled pH. An associated battery of enzymes as well as coenzymes are activated at this pH but denatured at another pH at the next stage. Ingested food will spend from minutes (mouth) to hours (gut) in a single organ where it is effectively mechanically stirred at 37°C in an enzyme bath at a set pH. After all possible chemical transformations
have occurred in that organ, it then moves to the next organ in the digestive tract. Fascinatingly, the associated pH change causes the incoming enzymes to denature, thus exposing the partially processed food to a new set of reaction conditions and enabling new chemical transformations to take place. Little wonder that after meandering for 12–48 h through the 8–9 m length of the digestive track that most complex chemicals have been transformed (or metabolized) to their constituent building blocks. Since the purpose of eating is not to dispose of food waste but to bring nutrients to our body, these chemical building blocks (amino acids, sugars, etc.) are carried to and then stored in appropriate cells in the human body.

Not surprisingly, a drug entering the digestive system will be exposed to the same environment as food and will be subjected to the same battery of chemical reactions. For a patient ingesting a tablet, the constituent chemicals will be exposed to the same mechanical stirring at 37°C, the same pH as well as enzymes. The chemical transformations that occur during food digestion are free to act on the constituents of the drug. Since most drugs are presented to the body as solid or semisolid dosage forms, the drug particles must first be released from that form and dissolved. Furthermore, drug absorption, whether from the gastrointestinal (GI) tract or other sites, requires the passage of the drug in a molecular form across the barrier membrane. The drug will be required to possess the desirable biopharmaceutical properties enabling it to pass from a region of high concentration to a region of low concentration across the membrane into the blood, or general circulation.

Insight to this process is a key to understanding many drug metabolism concepts. This introduction chapter is not intended to be a physiology textbook. It demonstrates the link between nutrition and drug metabolism and thus provides a framework upon which medicinal chemists can apply their extensive organic chemistry knowledge to solve the ever occurring ADME issues. It has been said that “anyone can contribute solutions provided the problem is explained in a language they understand.” Aspiring and even experienced medicinal chemists are encouraged to take basic nutrition and physiology courses to deepen their understanding of developed drugs exposure to these environments.

1.2 VOYAGE THROUGH THE DIGESTIVE SYSTEM

It takes 12–48 h for ingested food to complete its voyage through the digestive system. The food first arrives in the mouth (pH = 7) where it is chewed and exposed to its first set of enzymes, called salivary enzymes. Subsequently, the food travels down the esophagus to the stomach (pH = 1–2), which undergoes receptive relaxation as it fills to a capacity of 2 L or more (Figure 1.1). The next stage in the digestive system is the small intestine where chemical digestion continues and most nutrients are absorbed. The small intestine is made up of three parts: the duodenum where the contents of the stomach are neutralized to pH = 6 by pancreatic secretions (NaHCO₃), then the 2 m long jejunum (pH = 7–8), and finally the ileum (3 m long). Those substances which are not digestible or not absorbed join the large intestine, where leftovers are formed into semisolid masses ready for disposal. When digested nutrients are absorbed
(i.e., exit the gut into the blood stream), they are ducted to the liver via the hepatic-portal vein (HPV) (pH = 7.4). Following metabolism in the liver, molecules can either be ducted back into the digestive system via the bile (enterohepatic cycling) or finally enter the general blood circulation. Finally, approximately 25% of total systemic blood flow is diverted through the kidneys, which act as an on-line filtration unit, and water-soluble waste is concentrated in the urine.

The various events occurring during drug metabolism are more easily understood by visualizing the sequence “mouth—esophagus—stomach—duodenum—gut—liver—kidneys” as well as understanding the chemical reactions taking place in each organ.

1.2.1 The Mouth

The mouth is the reception center of the digestive system and the place where food is initially processed before being passed onto the stomach via the esophagus. In the mouth, mechanical as well as chemical digestion occurs. On average 1 L of saliva is secreted at various points into the mouth through salivary glands. Saliva contains salivary enzymes, which include amylases, which break down complex carbohydrates into simple sugars such as maltose and glucose, and peroxidases. Some
lipases are also present in the saliva, resulting in some of the lipid (i.e., fat or dietary triglycerides) digestion starting to occur in the mouth. Additionally, aspartate aminotransferase (AST), alanine amino transferase (ALT), lactate dehydrogenase (LDH), and acidic and alkaline phosphatase have been reported to be released from the normal and especially damaged cells of periodontal tissues into saliva. Saliva also contains immunoglobin A (IgA), an antibody playing a minor role in human immunity.

Some nutrients are capable of crossing the mucosa and the membranes that line the cavity of the mouth and are captured by the profusion of capillaries to enter the bloodstream. This avenue is used by hypoglycemic patients to quickly deliver glucose to raise their glucose blood levels by placing a glucose tablet under their tongue. The same principle is used when small molecular weight, water-soluble drugs such as glycerin trinitrate, or nitroglycerin (GTN) (Figure 1.2) are given via the sublingual route to patients suffering from angina. This ensures the rapid entry of the drug into the bloodstream as well as bypasses the remainder of the digestive system including the liver where it would otherwise be extensively metabolized.

The same route of administration has been exploited by Generex Biotechnology Corporation [1] to develop Oral-lyn™. This formulation delivers insulin as a fine spray in the buccal (i.e., mouth) cavity. The peptide drug is rapidly absorbed through the mucosal lining of the mouth and enters the bloodstream, where it is reported to produce glucodynamic profiles comparable to that produced by injection of regular human insulin. This drug was first approved for use in Ecuador in 2005 [2] and recently received approval in a number of other countries. The buccal administration of insulin also assures that the drug does not enter the lungs and, therefore, is free of pulmonary side-effect associated with inhaled insulin products.

Similarly, the anticoagulant drug heparin, a polysaccharide not suitable for oral administration, is given to patients via the subcutaneous route. Its similarity to starch makes it an obvious target to amylases (Figure 1.3).

1.2.2 The Stomach

The food bolus is swallowed and enters the stomach where both chemical digestion as well as absorption (from the stomach into the bloodstream) occurs. The wall of the stomach is lined with millions of gastric glands, which together secrete 400–800 mL of gastric juice at each meal. Several types of cells are found in the gastric glands.
including parietal cells, chief cells, mucus-secreting cells, and hormone-secreting (endocrine) cells.

1.2.2.1 Chemical Digestion  Claude Bernard (1813–1878), known as the founder of experimental physiology, demonstrated that contrary to popular belief, little digestion occurs in the stomach. This organ only processes up to half the carbohydrates in a meal, one-tenth of the protein, and hardly any fat while the bulk of the digestion takes place in the intestines. The stomach effectively acts as a food mixer and acid-and-enzyme bath and the breadth of chemical reactions that ensue are of importance to the medicinal chemist. Every few minutes its strong, muscular walls undergo a spasm of squeezing to churn the food into semiliquid state called chyme. Parietal cells secrete hydrochloric acid (HCl) and intrinsic factor. Intrinsic factor is a protein that binds ingested vitamin B12 and enables it to be absorbed by the intestine. A deficiency of intrinsic factor, as a result of an autoimmune attack against parietal cells, causes pernicious anemia. Chief cells synthesize and secrete pepsinogen, the precursor to the proteolytic enzyme pepsin. Pepsin cleaves peptide bonds, favoring those on the C-terminal side of tyrosine, phenylalanine, and tryptophan residues. Its action breaks long polypeptide chains into shorter lengths. Secretion by the gastric glands is stimulated by the hormone gastrin, which is released by endocrine cells in the stomach in response to the arrival of food. Gastrin stimulates the production of hydrochloric acid (HCl), reducing the pH to 1–2, which inactivates amylases, swallowed with the saliva, and denatures ingested proteins, making them more vulnerable to attack by pepsins. Although most of the lipases are secreted from the pancreas into the duodenum, some lipases are present in the stomach and perform an ester bond hydrolysis on a limited range of lipids to produce fatty acids and glycerol.

This panoply of chemical reactions highlights the breadth and variety of the chemical transformations that can occur in the stomach and provide a warning to medicinal chemists attempting to design compounds of peptidic nature or containing multiple amide bonds and unhindered alkyl esters.

1.2.2.2 Absorption  Only a limited range of substances are actually absorbed through the stomach lining into the blood. The stomach can absorb glucose and other
simple sugars, amino acids, and some fat-soluble substances. A number of alcohols, including ethanol, are readily absorbed from the stomach. Water moves freely from the gastric contents across the gastric mucosa into the blood. In tracer experiments [3] using deuterium oxide, about 60% of the isotopic water placed in the stomach was absorbed into the blood in 30 min. The net absorption of water from the stomach is small because water readily moves from the blood across the gastric mucosa to the lumen of the stomach. The absorption of both water and alcohol can be slowed down if the stomach contains food, especially fat, presumably since gastric emptying is delayed and most water is absorbed from the jejunum.

From a medicinal chemistry point of view, the persistent issue associated with the stomach is that of solubility. Only compounds in solution are available for permeation across the gastric membrane and solubility of drug molecules at pH = 2 is often an issue. The following examples illustrate the significance of this problem.

Salicylic acid ($pK_a$ 3.5 and 13.4) is weakly acidic and only 30% is ionized at pH = 2. Its insolubility precludes its absorption in the stomach (Figure 1.4). It is soluble in the intestine (pH = 6.4), but since it is present in its ionized form, it is unable to be effectively absorbed through the gut wall. Given that salicylic acid is also a stomach irritant, it is prepared as an ester prodrug to reduce the amount of acid actually in contact with the gut lining. When it reaches the blood where it is 50–90% plasma bound (depending on the concentration), it is processed by esterases and is converted back to its active form (salicylic acid).

Acid-reducing agents including omeprazole are widely used [4] by patients with HIV to treat acid reflux disease, heartburn, and stomach ulcers. In a recent study [5], 18 HIV-negative volunteers were given ritonavir-boosted saquinavir along with omeprazole for 15 days. Results showed that the addition of omeprazole caused an 82% increase in the levels of saquinavir (invirase) in the blood. It was argued that omeprazole is unlikely to increase saquinavir levels by its weak inhibition of the major liver enzyme CYP3A4 that breaks down saquinavir. However, the most plausible explanation was that saquinavir is dissolving more readily in a less-acidic environment.

The pH of the gastric contents controls the absorption of certain ionizable materials such as aspirin, which is readily absorbed in its unionized form when the stomach is acidic, but more slowly when gastric contents are neutral.

A number of solubility tests are available to assist in identifying this issue prior to drug administration to humans, and these are discussed in subsequent chapters. In addition to the usual solubility tests, many groups [6] have reported the use of the fasted and fed-state simulated gastric fluid (SGF) test [7] due to its more relevance to a physiological environment.

![Figure 1.4 Aspirin—solubility and ionization.](image-url)
1.2.3 The Small Intestine: Duodenum

Following stomach peristalsis and digestion, the pyloric sphincter relaxes and allows the food (and ingested drugs) to enter the first part of the small intestine, the duodenum. The duodenum [8] is a 20 cm long smooth muscle lined tube (Figure 1.5). Two ducts enter the duodenum: one of them drains the gallbladder and hence the liver, and the other drains the exocrine portion of the pancreas. Both organs produce secretions that enable further chemical digestion and have an impact on drug design. The pancreas consists of clusters of endocrine cells (the islets of Langerhans) and exocrine cells whose secretions drain into the duodenum.

1.2.3.1 Pancreatic Juices Since the pHs of the stomach and the intestine are very acidic and nearly neutral, respectively, the pancreas produces 1.5 L/day of alkaline juices (e.g., bicarbonate) to neutralize the partially acidic digested chyme. The neutralization is carried out at a slow, controlled rate and has the additional effect of denaturing incoming stomach enzymes and rendering them inactive. The secretion of pancreatic fluid is controlled by two hormones—secretin and cholecystokinin (CCK). Secretin mainly affects the release of sodium bicarbonate and CCK stimulates the release of the digestive enzymes.

Pancreatic fluid also contains a number of digestive enzymes. Most carbohydrate digestion occurs in the duodenum and is performed by pancreatic amylase, which hydrolyzes starch into a mixture of maltose and glucose. Pancreatic lipase hydrolyzes ingested fats into a mixture of fatty acids and monoglycerides. Its action is enhanced by the detergent effect of bile. In April 1999, the FDA approved orlistat as a treatment for obesity. Orlistat inactivates pancreatic lipase. About one-third of ingested fats fail to be broken down into absorbable fatty acids and monoglycerides and simply passes out in the feces.

The four “zymogens” (proteins that are precursors to active proteases) secreted from the pancreas are trypsin, chymotrypsin, elastase, and carboxypeptidase. These are immediately converted into the active proteolytic enzymes. Trypsin cleaves peptide bonds on the C-terminal side of arginine and lysine. Chymotrypsin cuts amide bonds on the C-terminal side of tyrosine, phenylalanine, and tryptophan.

Figure 1.5 The duodenum receives input from the pancreas and the liver.
residues (the same bonds as pepsin, whose action ceases when NaHCO₃ raises the pH of the intestinal contents). Elastase cuts peptide bonds next to small, uncharged side-chains such as those of alanine and serine. Trypsin, chymotrypsin, and elastase are members of the family of serine proteases. Chymotrypsin precipitates hydrophilic kappa casein in milk by breaking the bond between phenylalanine (105) and methionine (106) to produce two insoluble fragments resulting in the milk curdling, thus slowing down its digestion. Finally, carboxypeptidase removes, one by one, the amino acids at the C-terminal of peptides. Carboxypeptidase A cleaves carboxyl terminal amino acids that have aromatic or aliphatic side-chains, and carboxypeptidase B cleaves carboxyl terminal amino acids that have basic side-chains. It is the presence of this wide array of enzyme proteases, which precludes the oral administration of protein or peptide drugs such as corticotrophin, vasopressin, and insulin. These would be rapidly degraded in the digestive tract and are not generally given orally. Some microencapsulation and nanoparticle formulation studies have been carried out in an attempt to circumvent these issues and are showing promise.

Diarrhea, a side-effect commonly associated with highly active antiretroviral therapy (HAART), has been ascribed to the inhibition of pancreatic lipases by protease inhibitors such as agenerase, norvir, and fortovase. An in vitro study [9] showed that the protease inhibitor agenerase formulated as a solution or a capsule exhibited complete inhibition of pancreatic lipase at physiological concentration. Norvir and fortovase produced 72% and 75% inhibition, respectively, at physiological concentration, as calculated from the plots to determine IC₅₀ values.

Erythromycin stearate USP (ethryl) is the stearic acid salt of erythromycin. It is a crystalline powder that is practically insoluble in water. Similar to erythromycin base, the stearate is acid labile. It is thus film-coated [10] to protect it from acid degradation in the stomach and in the alkaline pH of the duodenum, where the free base is liberated from the stearate and absorbed.

1.2.3.2 Hepatic Bile  The human liver produces 400–800 mL of hepatic bile each day. The bile (pH = 7.8–8.6) is then concentrated fivefold and stored in the gallbladder between meals. When food, especially containing fat, enters the duodenum, the release of the hormone CCK stimulates the gallbladder to contract and discharge its bile into the duodenum. The main constituents of bile are bile salts, bilirubin, bile pigments (end products of hemoglobin breakdown), and electrolytes. Bile salts are amphiphilic steroids, which emulsify ingested fat. The hydrophobic portion of the steroid dissolves in the fat while the negatively charged side-chain interacts with water molecules. The mutual repulsion of these negatively charged droplets keeps them from coalescing. Thus, large globules of fat (liquid at body temperature) are emulsified into tiny droplets (about 1 μm in diameter) that can be more readily digested and absorbed.

The molecules responsible for fat dispersion are bile salts such as glycocholic acid (Figure 1.6). Bile acids are facial amphipathic since they contain both hydrophobic (lipid soluble) and polar (hydrophilic) faces. The cholesterol-derived portion of a bile acid has one face that is hydrophobic (methyl groups) and one that is hydrophilic (hydroxyl groups); the amino acid conjugate is polar and hydrophilic.
Their amphipathic nature enables bile acids to aggregate to form water-soluble micelles, with the hydrophobic and hydrophilic sides toward the center and outside, respectively. In the center of these micelles are dietary triglycerides, which are separated from a larger globule of lipid. Pancreatic lipase is then able to reach the molecules of triglyceride through gaps between the bile salts, providing a largely increased surface area for the digestion of fat.

Glycocholic acid is biosynthesized in the liver starting from cholesterol. Interestingly, the series of synthetic reaction steps are a mimic of the Phases 1 and 2 processes that take place in the metabolism of drug molecules and will be described in Section 1.3. Bile salts promote dissolution of lipophilic drugs and lipophilic drug formulations, enteric coatings, and waxy drug matrices. Bile salts may also promote membrane permeability of lipophilic molecules through micelle formation and solubilization. The brownish color of the bile pigments imparts the characteristic brown color of the feces.

1.2.4 The Small and Large Intestine: Jejunum, Ileum, Colon

Food and ingested drugs exit the duodenum and enter the second part of the small intestine, namely the jejunum. This has the dual role of digestion as well as absorption before food/drugs reach the ileum concerned mainly with absorption.

The actual process of digestion and absorption occurs in the villi, which line the inner surface of the small intestine (Figure 1.7). The crypts at the base of the villi contain stem cells that continuously divide by mitosis producing more stem cells and cells that migrate up the surface of the villus that differentiate into three types:

- Columnar epithelial cells responsible for digestion and absorption (these are the majority of the cells)
- Goblet cells which secrete mucus
- Endocrine cells which secrete a variety of hormones

Finally, Paneth cells secrete antimicrobial peptides that sterilize the contents of the intestine. All these cells replace older cells that continuously die by apoptosis.
The villi increase the surface area of the small intestine by a larger fold than if it were simply a tube with smooth walls. In addition, the apical (exposed) surface of the epithelial cells of each villus is covered with microvilli (also known as a “brush border”). Due to the microvilli, the total surface area of the intestine is almost 200 m\(^2\) \[16\] (about the size of a tennis court) and approximately 100-fold the surface area of the exterior of the body.

Finally, undigested items such as cellulose along with other food wastes are passed into the large intestine (colon) and then the bowel for disposal as feces. The aim of food ingestion is not to produce waste but to provide the body with the nutrients and energy it requires to remain alive and function effectively. The digestive system is therefore equipped with a sophisticated system to ensure both digestion and absorption.

To ensure digestion, nutrients are maintained at 37°C at pH = 6.4–8.0 throughout the small intestine, and exposed to a comprehensive array of new enzymes such as maltase, lactase, intestinal lipases, and nucleases. Optimal exposure is further ensured by the peristaltic action of the gut, which slowly passes food along its 5 m length of convoluted tube while at the same time contracting in short segments to ensure thorough mixing.

Absorption ensures that molecules are transported through the gut wall into the blood circulation. This highly efficient process occurs via the paracellular or the transcellular route (Figure 1.7).

1.2.4.1 Paracellular Route The simplest exit from the gut is via the paracellular route namely through the interstitial space between cells (Figure 1.7). This exit route represents a relatively small area (only 0.01%) compared to the total cell surface area.
The tight junctions are studded with desmosomes (aka macula adherentes or macula adherens), cell structures specialized in cell-to-cell adhesion, limiting the transport of water, small polar molecules, and electrolytes. The restricted diameter of the aqueous pores (typically 3–6 Å in humans) indicates that hydrophilicity and molecular size are important factors in the ability of polar drug molecules to utilize this pathway. Paracellular absorption varies in different regions of the gastrointestinal tract due to varying pore size and frequency. Species differences in absorption have been attributed to variation in pore size, leading to varying efficiency of the paracellular pathway. It has been speculated that absorption of polar drugs are higher in the dog, compared to rat and human due to increased pore size in the dog [11]. Examples of drugs showing this species difference [12] include the α-adrenoceptor antagonists, atenolol, and xamoterol. Atenolol (log $D_{7.4} = -1.9$, molecular weight 266) shows complete absorption (90%) in dog but only about 50% absorption in rat and human [18–20]. In contrast, absorption of the larger molecule xamoterol (log $D_{7.4} = -1.0$, molecular weight 339) is lower overall, but remains higher in dog (about 36%) compared to rat (19%) or human (9%). Rat appears to be a better predictor than dog for paracellular transport regarding animal species modeling absorption in human.

1.2.4.2 Transcellular Route  There are two main modes of transport available to molecules that use the transcellular route.

Active Transport  The transcellular route is served by an array of ATP-powered active transporters for common nutrients such as glucose. Such molecules are absorbed by carrier-mediated cotransport with Na$^+$ ions. In this instance, the concentration difference of sodium ions (high in the intestinal lumen and low in the mucosa cells) drives the import of nutrients against a concentration gradient. Examples of drugs that utilize these transporters include methotrexate and L-DOPA [13]. However, the majority of drug molecules is not recognized by these transporters and has to be passively transported across the membrane causing the panoply of permeability issues that plague the medicinal chemist.

Passive Transport  The more common transcellular route requires a molecule to passively cross the cell membrane, then cytoplasm before emerging at the other side of the enterocyte mucosa. To facilitate this unlikely process, the inside lining of the gut is covered with an extensive array of villi and microvilli. The surface area in the lumen is increased as the cellular surface of each villus is gathered into the “brush border.” The brush borders of the intestinal lining have enzymes anchored into their apical plasma membrane as integral membrane proteins and these are located near the transporters that will then allow absorption.

The transport of a drug through a membrane depends largely on its relative solubility in water and lipids. If the drug is too water soluble, it will not enter the membrane, but if it is too lipid soluble it will enter but not leave the membrane. Good absorption requires that a drug’s hydrophilic–lipophilic nature is in balance. The selection of a suitable carrier can be used to adjust this balance and consequently improve absorption of the drug.
Enalaprilat possesses unfavorable ionization characteristics and is administered intravenously due to its poor oral bioavailability (Figure 1.8). However, esterification of the hydrophilic groups to give enalapril enhanced its transcellular diffusion and bioavailability.

Similarly, pivampicilin [14] and bacampicillin are both prodrugs of ampicillin and result from the esterification of the polar carboxylic group with a lipophilic, enzymatically labile ester. Both prodrugs are more lipid-soluble and absorbed more efficiently across the gut wall than the parent compound ampicillin. The serum levels attained following oral administration of bacampicillin are similar to those obtained after intramuscular injection of an equimolar amount of free ampicillin.

1.2.4.3 P-gp

The surface area of the human gut is estimated to be 200 m² [15]. Unfortunately, such a large surface area is also available for the absorption of molecules that would potentially be harmful to the organism. Consequently, membrane efflux transporters such as P-glycoprotein (P-gp) act as a safety mechanism aimed at preventing toxins and xenobiotics from entering the general circulation by effectively pumping them back into the gut lumen. P-gp, a 170 kDa transmembrane glycoprotein, is a member of the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily. It was discovered in 1976 [16] and was originally identified as a key reason for multidrug resistance in the treatment of certain cancers [17]. It is expressed in intestinal epithelia, hepatocytes, kidney proximal tubules, blood–brain barrier (BBB) endothelia, and placental trophoblast. Vinblastin, verapamil, quinidine, and omeprazole are known P-gp ligands [18], a property which has consequences for their oral absorption. Glibenclamide, a type-2 diabetes drug known to act at the sulfonyl urea receptor (SUR), is both a substrate and an inhibitor [19] of P-gp.

Many authors [20–22] have suggested that gut-wall CYP3A4 and P-glycoprotein act in concert to control the absorption of their substrates. This is based on the large overlap of substrates between the two and the proximity of their expression within the gut wall. It is proposed that P-glycoprotein effectively recycles its substrates allowing CYP3A4 several opportunities to metabolize compounds in the gut. A small amount of CYP3A4 in the gut wall (relative to the liver content) can exert a profound extraction of the compound. A study was conducted [23] with the gastrointestinal
absorption of the HIV protease inhibitor saquinavir mesylate (Invirase®), whose oral bioavailability is low, variable, and significantly increased by coadministration with ritonavir. Both saquinavir and ritonavir were found to be P-gp substrates. Active efflux was temperature dependent, saturable, and inhibited by verapamil and cyclosporin A. Saquinavir and ritonavir decreased each other’s secretory permeability and elevated their net transport by the absorptive pathway. Together with sensitivity to gut-wall metabolism by cytochrome CYP3A, it was proposed that this may partially account for the low and variable oral bioavailability of saquinavir in clinical studies and for its increased bioavailability after coadministration with ritonavir.

It has been shown that P-glycoprotein mRNA levels increase longitudinally along the intestine, with the lowest levels in the stomach and highest in the colon [24]. This observation has implications for controlled release technology.

1.2.5 Hepatic-Portal Vein

Following absorption in the small intestine, amino acids from protein digestion and the sugars from carbohydrates plus vitamins and important minerals such as calcium, iron, and iodine, as well as hydrophilic drugs, are absorbed directly into the blood capillaries in the villi. In contrast, glycerol, fatty acids, and dissolved vitamins enter the lacteals, are carried into the lymphatic system, and then released into the bloodstream at the lymphatic duct. Either way the nutrients (or drugs) exiting the GI tract are captured by the multitude of capillaries and blood vessels that line the outer surface of the digestive system (Figure 1.9). There is an abundance of blood vessels to ensure that all molecules absorbed through the intestinal wall are safely transported into the blood circulation. It has been estimated that a human being possesses 150,000 km of blood-carrying tubes with 98% containing microscopic capillaries for molecules exiting the gut to readily enter the bloodstream via a

![Figure 1.9](image) The hepatic-portal vein carrying nutrients from the gut to the liver.
neighboring capillary. After a meal, blood flow increases by 30–130% of basal flow and the hyperemia is confined to the segment if the intestine is exposed to the chyme. During periods of enhanced absorption or electrolyte secretion, blood is preferentially distributed to the mucosa. Nutrients and drugs do not exit into the general circulation once removed from the gut. The capillary beds of most tissues drain into veins that lead directly back to the heart. For the intestines, however, the draining veins lead to a second set of capillary beds in the liver, which serves as a gatekeeper between the intestines and the general circulation. This additional step ensures that useful substances are stored efficiently and that potentially harmful substances are metabolized for excretion.

The liver screens blood from the hepatic-portal system to ensure that its composition, when it leaves, will be close to normal for the body. This homeostatic mechanism functions in both directions. If the concentration of glucose in blood drops between meals, the liver converts its glycogen stores (glycogenolysis) or certain amino acids (gluconeogenesis) into glucose for release into the blood stream [25] (Figure 1.9). Glucose is removed and converted into glycogen. Other monosaccharides are removed and converted into glucose. Excess amino acids are removed and deaminated. The amino group is converted into urea. The residue can then enter the pathways of cellular respiration and be oxidized for energy.

Many nonnutritive molecules, such as ingested drugs, are removed by the liver and, often, metabolized to be detoxified and excreted through the kidneys. Since the liver is the main store of numerous nutrients and the organ responsible for a significant proportion of drug metabolism, it is not surprising that the multitude of capillaries and blood vessels that drain the digestive system converge into the HPV leading to the liver. The blood in the portal vein is relatively poor in oxygen, but rich in nutrients that have been absorbed from the GI tract. Upon entry into the liver, nutrients can be extracted by the liver cells for further metabolism. A significant proportion of a drug arriving into the liver will partition or be transported into the hepatocyte, where it may be metabolized by hepatic enzymes to inactive chemicals during the initial trip to the liver. This process is known as the first-pass effect.

Understanding the role of the portal vein as well as its position in the digestive system provides a key to diagnosing the plausible causes of “low oral bioavailability” of a compound. The concentration of a drug in the portal vein represents the amount of drug that has already passed the absorption and intestinal metabolism barriers but has not yet reached the liver [26]. A compound with low oral bioavailability and a low HPV level has issues prior to reaching the liver. Conversely, low oral bioavailability and good hepatic portal vein levels may be indicative of high liver metabolism.

This is illustrated in a comprehensive study carried out at Merck [27] on the design of 5HT1D agonists. Compound 1 (Figure 1.10) showed low oral bioavailability and low hepatic portal vein levels (HPV < 5 ng/mL). Rigidification of the amino side chain gave much increased HPV exposure (HPV = 558 ng/mL at 0.5 h) and thus improved oral bioavailability. It was concluded that reducing the conformational mobility may have resulted in the compound being less susceptible to gut-wall metabolism. In addition, rigid analogues are simply more able to pass through the gut wall without conducting many entropically unfavorable conformational changes.
1.3 THE LIVER METABOLISM

Nutrients and drug molecules arrive in the liver via the hepatic portal vein. The liver is a major organ, where nutrient storage, synthesis, and breakdown occur. It stores a multitude of substances, including glucose (in the form of glycogen), vitamin A (1–2 years’ supply), vitamin D (1–4 months’ supply), vitamin B12, iron, and copper. The liver is responsible for immunological effects. The reticuloendothelial system of the liver contains many immunologically active cells, acting as a “sieve” for antigens carried to it via the portal system. The liver produces albumin, the major osmolar component of blood serum. The liver synthesizes angiotensinogen, a hormone that is responsible for raising the blood pressure when activated by renin, a kidney enzyme that is released when the juxtaglomerular apparatus senses low blood pressure.

The liver performs several roles in carbohydrate metabolism including gluconeogenesis (the synthesis of glucose from certain amino acids, lactate or glycerol), glycogenolysis (the breakdown of glycogen into glucose), and glycogenesis (the formation of glycogen from glucose). The latter also occurs in the muscle. The liver is responsible for the mainstay of protein metabolism, synthesis, as well as degradation, and plays a major role in amino acid synthesis. The liver also performs several roles in lipid metabolism: cholesterol synthesis, lipogenesis, and the production of triglycerides (fats). This organ produces coagulation factors I (fibrinogen), II (prothrombin), V, VII, IX, X, and XI, as well as protein C, protein S, and antithrombin. The liver function changes from embryo to adult stage. In the first trimester fetus, the liver is the main site of red blood cell production, but by the 32nd week of gestation, the bone marrow has almost completely taken over that task. The liver produces and excretes bile (a greenish liquid) required for emulsifying fats. Some of the bile drains directly into the duodenum, and some is stored in the gallbladder. The liver also produces insulin-like growth factor 1 (IGF-1), a polypeptide protein hormone that plays an important role in childhood growth and continues to have anabolic effects in adults. The liver is a major site of thrombopoietin production. Thrombopoietin is a glycoprotein hormone that regulates the production of platelets by the bone marrow.

The breakdown of insulin and other hormones occurs in the liver. The liver breaks down hemoglobin, creating metabolites that are added to bile as pigment (bilirubin and biliverdin) and converts ammonia to urea.
Finally, the liver ensures that no toxic entities whether nutrients or drugs are released into the circulation. The process of breakdown of toxic substances and drugs is called drug metabolism and sometimes results in the formation of metabolites that are more toxic than its precursor. This is why understanding of liver metabolism is crucial at the earliest stages of drug discovery.

The metabolism process is best illustrated in the biosynthesis of bile acids from cholesterol, which takes place in the hepatocytes [28]. Cholesterol is ingested as part of the diet and converted into the bile acids chenodeoxycholic acid and cholic acid in a series of Phase 1 oxidation steps (Figure 1.11). The resulting carboxylic acid functionality is then conjugated to glycine or taurine in a Phase 2 conjugation step. The resulting water-soluble product is then actively secreted into tiny bile canaliculi between liver cells that lead into bile duct that connects to duodenum and stored in the gallbladder.

Phase 1 oxidation steps are commonly catalyzed by cytochrome P450 enzymes (CYPs) [29] and introduce polar water-solubilizing groups such as –OH, –COOH, and –SO$_3$H or unmask water-solubilizing groups already present in the molecule. These often provide a point of anchor for further conjugation (Phase 2) with suitable water-soluble fragments. The result is usually an increase in the polarity and a change in the biological activity or toxicity profile of the substance [30].

Phase 2 reactions (conjugate formation) couple substrates (bilirubin, metabolites of xenobiotics, drugs, and steroid hormones) to highly polar, water-solubilizing

![Figure 1.11](image-url) The biosynthesis of glycocholic acid in hepatocytes resulting from Phase 1 (oxidation) and Phase 2 (conjugation) processes.
amines (glycine, taurine), or alcohols (glucoronates) taken from the store of the liver. The enzymes involved are transferases.

1.3.1 CYP450 (CYPs)

“CYP” is a host of enzymes that use iron to oxidize xenobiotics, endogenous substances, and nutrients, often as part of the body’s strategy to dispose of potentially harmful substances by making them more water soluble. More than half of known drugs are primarily cleared by CYPs. CYP catalyzes a variety of reactions including epoxidation, N-dealkylation, O-dealkylation, S-oxidation, and hydroxylation. A typical cytochrome P450 catalyzed reaction is

\[ \text{NADPH} + H^+ + O_2 + RH \overset{\text{CYP}}{\rightleftharpoons} \text{NADP}^+ + H_2O + R-OH \]

The main organ in humans involved in drug and toxin removal is the small intestine even though most of the CYPs are found in the liver. CYP is usually found in the “microsomal” part of the cytoplasm (endoplasmic reticulum). Metabolic clearance of drugs is not the only function of CYP. Recently, it has been found that CYP is intimately involved in vascular autoregulation, particularly in the brain. CYP is vital to the formation of cholesterol, steroids, and arachidonic acid metabolites. There are over a thousand different CYPs, although the number in man is only about 50 (49 genes and 15 pseudogenes have been sequenced). It is likely that most of the human CYPs have already been discovered.

What’s in a name?

Cytochrome P450 chemistry is fascinating. All chemists appreciate that the bond between the two atoms in an oxygen molecule is rather strong. This implies that a substantial amount of energy is required to break the bond. The energy is supplied by the addition of electrons to the iron atom of heme. These electrons come from the last protein in an “electron transfer chain.” There are two such chains in cells that end up at P450. The first is in the endoplasmic reticulum (ER), and the protein involved is called NADPH cytochrome P450 reductase. Electrons pass from NADPH to FAD to FMN and finally to heme. The second chain is located within mitochondria. A complex chain of proteins transfers the electrons to heme. NADPH passes electrons to ferredoxin reductase, thence to ferredoxin (which itself has an iron–sulfur cluster), and finally to CYP.

1.3.1.1 CYP Isoforms  How do we classify CYP since there are numerous isoforms of cytochrome P450? An isoform is a CYP enzyme variant that derives from one particular gene. They are classified according to the similarities of their amino acid sequences. Such classification allows division of CYP isoforms into families. CYP families contain genes that have at least 40% sequence homology. There are at least 74 CYP families, but only about 17 of these have been described in man. Families are numbered such as CYP2 and CYP21. Families are further subdivided into subfamilies in which members must have at least 55% identity. About 30 subfamilies are well characterized in man. Subfamilies are identified by a letter
such as CYP3A and CYP2D. Finally, there are individual CYP genes. There are approximately 50 genes important in man. Individual genes are identified by a number such as CYP2D6.

Among the diverse human genes, several have been identified as particularly important in oxidative metabolism including

- CYP3A4 (by far the most important, metabolizing ~40% of xenobiotics)
- CYP2D6
- CYP2C9
- CYP2C19

Other notable CYPs are CYP2E1, CYP2A6, and CYP1A2. On exposure to appropriate substrates, enzyme induction occurs with all of these CYPs, apart from CYP2D6.

What is polymorphism and why is it significant? The activity of CYP oxidases differs in different people and different populations. Genetic variation in a population is termed “polymorphism” when both gene variants exist with a frequency of at least 1%. Such differences in activity may have profound clinical consequences, especially when multiple drugs are given to a patient. There are profound racial differences in the distribution of various alleles. Data on a drug that behaves in one way in one population group cannot necessarily be extrapolated to another group. The explanations for the various polymorphisms are thought to be complex, but perhaps the most interesting is the high expression of CYP2D6 in many persons of Ethiopian and Saudi Arabian origin. 2D6 is not inducible, so these people have developed a different strategy to cope with the presumably high load of toxic alkaloids in their diet—multiple copies of the gene. These CYPs break down a variety of drugs such as many antidepressants and neuroleptics, thus making them ineffective. Conversely, prodrugs such as codeine will be extensively activated and will be largely converted into morphine.

In contrast, many individuals lack functional 2D6. These subjects will be predisposed to drug toxicity caused by antidepressants or neuroleptics, but will find codeine and tramadol to be inefficacious due to lack of activation. Other drugs that have caused problems in those lacking 2D6 include dextenfluramine, propafenone, mexiletine, and perhexilone. Perhexilone was withdrawn from the market due to the neuropathy it caused in those 2D6-inactive patients.

Another potentially disastrous polymorphism is the deficient activity of CYP2C9. Patients possessing this enzyme variant are ineffective in clearing (S)-warfarin to an extent that a 0.5 mg dose in a day results in full anticoagulation. Additionally, the same CYP is important in removal of phenytoin and tolbutamide, both potentially very toxic drugs in excess. Alternatively, the prodrug losartan will be poorly activated and inefficacious with 2C9 deficiency. Azole antifungals, sulphinpyrazone, and even amiodarone may cause a similar effect by inhibiting the enzyme.

Occasionally benefits are derived from an unusual CYP phenotype. Cure rates for peptic ulcer treated with omeprazole are substantially greater in individuals with defective CYP2C19 due to sustained, high plasma levels of the drug.
CYP induction is another important concept. Most of the CYPs can be induced with CYP3A4 the most important and CYP2D6 the most notable exception. CYP3A4 is the most prevalent CYP in the body and metabolizes many substrates. The most important inducers of 3A4 are antimicrobials such as rifampicin, and anticonvulsants such as carbamazepine and phenytoin. Potent steroids such as dexamethasone may also induce 3A4. The long list of agents metabolized by the enzyme includes opioids, benzodiazeines, and local anesthetics, as well as erythromycin, cyclosporine, haloperidol, calcium-channel blockers, cisapride, and pimozide. Oral contraceptives are also metabolized, and their efficacy may be impaired when an inducer such as rifampicin is administered.

The inhibitors of 3A4 are even more important than the inducers of 3A4 and include azole antifungals, HIV protease inhibitors, calcium-channel blockers, some macrolides such as troleandromycin and erythromycin, and the commonly used “SSRI” antidepressants. Lethal clinical consequences can result from combining 3A4 inhibitors with drugs that are metabolized by this cytochrome. Non-sedating antihistamines have resulted in fatal arrhythmias, as has occurred with cisapride administration in combination with an inhibitor. Erythromycin in combination with theophylline may cause toxicity due to the latter.

There is an interesting association between some CYPs and the important transmembrane pump protein, P-glycoprotein (the product of the \textit{MDR1} gene). Generally, if P-glycoprotein is present, then CYP3A4 is also found. This presumably is due to a concerted strategy by the body to eliminate xenobiotics. The P-glycoprotein pumps out as much xenobiotics as possible and CYP3A removes the remainder! This association contributes to even more interesting drug interactions such as calcium-channel blockers and drugs as diverse as azole antifungals, immunosuppressants, and macrolides interacting with the membrane pump and the CYP.

CYP metabolism is so critical that predominant degradation of a drug by one of the polymorphic CYPs is often enough to terminate further research on that compound during discovery.

Although most of the CYP metabolism occurs in the liver, with a minor contribution from the intestine, some isoforms are found throughout the body such as CYP51. Other isoforms are limited to one specific tissue such as CYP11B2, found mainly if not exclusively in the glomerulosa zone of the adrenal gland. Differential expression of some CYPs in different organs may also have clinical consequences, especially where the unfortunate side-effect of “degradation” of a drug produces a more toxic product. The degradation of paracetamol by CYP2E1 results in a highly active intermediate product, which in sufficient quantities can result in fulminant liver failure. Antioxidants protect against this catastrophe. In contrast, chronic ethanol consumption induces CYP2E1 and may increase the likelihood of toxicity.

Drug molecules that are not recognized by liver enzymes and considered toxic are subjected to a similar reaction sequence as illustrated in the liver metabolism of aspirin [31] (Figure 1.12). Phase 1 oxidation introduces a number of solubilizing hydroxyl groups. In the Phase 2 steps, the hydroxyl moiety is glucoronidated, while the carboxylic acid functionality is conjugated with the amine group in glycine. This produces a range of water-soluble products suitable for elimination.
The metabolism of aromatic carboxylic acids involves the conjugation of the acid with glycine (a Phase 2 conjugation reaction) via an acetyl coenzyme-A intermediate. The resulting hippuric acid (Figure 1.13) conjugate is very water soluble and readily excreted through the kidneys. Thus a reduced concentration of hippuric acid in the urine indicates the possibility of liver damage and this formed the basis of a test for checking [32] the detoxification function of the liver.

Many factors may affect liver metabolism. Dietary factors such as lack of vitamins or a low protein diet can cause decreased oxidative drug metabolism. Drugs and some foods (e.g., grapefruit juice) that are known inhibitors, inducers, or substrates for

**Figure 1.12** The metabolism of aspirin in hepatocytes with Phase 1 (oxidation) and Phase 2 (conjugation) resulting in water-soluble products.

**Figure 1.13** Hippuric acid produced in the liver from a Phase 2 conjugation reaction with glycine.
CYPs can potentially interact with the metabolism of coadministered drugs affecting its AUC and rate of clearance.

Variable expression of CYP has substantial clinical consequences, not only in different people and different race groups, but also in individuals as they progress from infancy to old age. Age affects the expression of metabolizing enzymes leading to potentially fatal situations. The antibacterial drug chloramphenicol, which is no longer used for premature babies, relies on the presence of Phase 2 glucoronol transferase to eliminate the oxamyl chloride intermediate produced from Phase 1 as its soluble glucoronide conjugate [33]. Since infants lack this Phase 2 enzyme, the highly reactive oxamyl chloride is free to produce an N-nitroso-derivative, which causes fatal aplastic anemia in neonates. CYP1A2 is not expressed in neonates and so they are particularly susceptible to toxicity from substance such as caffeine.

Some disease states cause patients to develop impaired liver function, liver cirrhosis, or hepatoma, which can present altered hepatic blood flow and decreased number of functional hepatocytes (CYPs). This has serious consequences for the administration of drugs that display or rely on high liver clearance.

Understanding CYP metabolism has been used productively in AIDS therapy. As discussed previously, saquinavir (Invirase®) is a potent HIV protease inhibitor with oral bioavailability limited by extensive first-pass metabolism mediated primarily by CYP3A4 [34]. While saquinavir is a weak CYP3A4 inhibitor [35], its exposure is enhanced [36] when combined with a low (subtherapeutic) dose of ritonavir [37], a potent inhibitor of CYP3A4.

In summary, once a drug has completed a route from the mouth through the stomach, duodenum, jejunum, ileum, hepatic portal vein and the liver, first pass metabolism is complete. During this process, a portion of the drug is lost before it reaches the systemic circulation.

Not all the drug substances that have been processed in the liver reach the blood circulation. Some drugs such as steroid hormones, digoxin, and some cancer chemotherapeutic agents are secreted from the liver back into the bile and reenter the digestive system via the bile duct. The secretion is effected [38] by members of ABC superfamily of transporters, which include seven families of proteins such as the multidrug resistance (MDR) family. In many cases, these drugs undergo enterohepatic circulation, in which they are reabsorbed in the small intestine and reenter the liver via the hepatic portal vein.

1.4 THE KIDNEYS

The final filters in the voyage of a drug are the kidneys and 25% of cardiac output is directed to these organs. The kidneys act as an “on-line filtration unit” and provide the primary route of excretion for many drugs such as vancomycin, atenolol, and ampicillin. These drugs can accumulate to toxic levels in patients with compromised renal function and in elderly patients. Blood has a cellular (45% organic) and plasma (55% aqueous) component. Cellular blood component consists of red blood cells (erythrocytes), monocytes, white blood cells, etc. The plasma is composed of water,
small solutes, and proteins such as albumin and α1 acid glycoprotein that adsorb acidic and basic molecules, respectively. An initial liquid–liquid separation takes the aqueous part of the blood in the nephron where it is filtered, cleansed, and its composition readjusted. It is then gradually reunited with the organic phase and the resulting reconstituted “cleansed” blood emerges in the afferent vein while the waste products are excreted in the urine. From the 1100–2000 L of blood that flows through the human kidneys each day, the nephron processes about 180 L of filtrate, but excretes only about 1.5 L of urine. The rest of the filtrate, including about 99% of the water, is reabsorbed into the blood.

The renal medulla is studded with an excess of one million nephrons, which are the basic functional filtering units. Blood arrives into the Bowman capsule via a cluster of porous capillaries called the glomerulus (Figure 1.14). The high hydrostatic pressure inside the capillaries causes the aqueous part to separate from the blood and enter the proximal tubule through the pores. This process is known as glomerular filtration. Most drug particles pass easily through the spaces of the capillary walls into the urine in the proximal tubule. Large particles, such as cells, proteins, or drug molecules bound to protein remain in the capillaries and exit the renal corpuscle via afferent arterioles.

Efferent arterioles wrap themselves around the structure of the nephron and will collect cleansed water and ions as they are produced by the remainder of the nephron apparatus. Next, the proximal tubule actively reabsorbs up to two-thirds of the valuable substances such as glucose, vitamins chloride ions via ATP-powered pumps, which use Na⁺ as the cotransporter (Figure 1.14). Water follows by osmosis and together they enter blood vessels near the tubule and are thus returned to the body. The filtrate that emerges from the proximal tubule, which is high in wastes and low in nutrients, now enters a U-shaped region of the nephron named the
loop of Henle. The wall of the descending limb is impermeable to solutes but permeable to water, which is removed by osmosis into the tissue fluid surrounding this section of the loop. The thick region of the ascending limb of the loop of Henle is highly permeable to $\text{Na}^+$ and $\text{Cl}^-$ but impermeable to water and contains chloride pumps, which remove sodium and chloride ions from the fluid in the lumen by active transport. The fluid in the two limbs of the loop of Henle flows in opposite directions, and the active removal of ions from the ascending limb and their constant inflow in the descending limb create an osmotic gradient along the length of the loop of Henle, which is known as a counter current multiplier system. The peritubular capillaries that surround the loop of Henle passively absorb the water and the ions that have been removed. The filtrate enters the distal tubule where electrolytes and water are reabsorbed under hormonal control (aldosterone and arginine vasopressin (AVP), also known as vasopressin, argipressin or antidiuretic hormone (ADH)). Urea, uric acid, creatinine, and other substances are finally collected as waste and released in the urine.

Urinary excretion occurs through glomerular filtration, active tubular secretion, and passive tubular reabsorption. The glomeruli filter unbound xenobiotics in a manner that is not saturable and at a rate that depends on renal blood flow [39]. Most drugs are filtered from blood in the glomerular unless they are tightly plasma protein bound or have been incorporated into red blood cells. From a medicinal chemistry point of view, the overall renal excretion is controlled by what happens in the tubules, namely, active tubular secretion and passive tubular reabsorption.

### 1.4.1 Active Tubular Secretion

Active transport systems in the renal tubule move some drugs from the blood to urine. The secretory mechanisms are not generally specific to drugs. Drug secretion takes advantage of molecular similarities between the drug and naturally occurring substances such as organic anions (transported by OAT family proteins) and cations (transported by OCT family proteins). Penicillin (Figure 1.15) is an example of a drug that is eliminated largely by active transport in the proximal tubule [40]. The extent of plasma protein binding appears to have a relatively small effect on drug secretion into the proximal tubule, because the highly efficient transporters that mediate active tubular secretion rapidly remove free (unbound) drug from the peritubular capillaries, thereby altering the equilibrium between free and protein-bound drug at these sites.

Since tubular secretion is an active process, it may be subject to saturation and drug interactions. The clearance of penicillin G [41] in normal individuals occurs predominantly via the kidney. It is extremely rapid and is the result of glomerular filtration and active tubular transport, with the latter route predominating [42]. Urinary recovery is reported to be 58–85% of the administered dose. Coadministration of probenecid, a drug normally administered to treat gout, competes with the same acid transporter and blocks the renal tubular secretion of penicillin resulting in slower rate of excretion of penicillin G and increased serum concentrations. It has been shown that probenecid also alters the distribution of penicillins to various
tissues causing more drug to distribute out of plasma, causing even less to be eliminated.

The topoisomerase 1 inhibitor topotecan (Hycamtin®) is an antineoplastic chemotherapy drug. It is primarily eliminated by the kidneys, with 60–70% of the dose recovered as topotecan total in the urine. Coadministration of topotecan lactone or hydroxy acid in combination with probenecid resulted in decreased topotecan lactone, total, and hydroxy acid systemic clearance, and total renal clearance. By inhibiting renal tubular secretion, probenecid decreased renal and systemic clearance, which led to an increase in topotecan systemic exposure.

1.4.2 Passive Tubular Reabsorption

Passive tubular reabsorption accounts for the reabsorption of noncharged, lipid-soluble xenobiotics. A concentration gradient exists with more drug particle in the urinary tubule than in the bloodstream because much of the water in the filtrate has been reabsorbed. The concentration gradient is in the direction of reabsorption. Drugs in the renal tubules have a tendency to transfer back into the blood by passive reabsorption. Like other passive diffusion processes, passive reabsorption is controlled by the drug’s lipid solubility, degree of ionization, and pH of both the blocked and tubular filtrate. If the compound is nonionized, it will have a greater tendency to be reabsorbed. If the compound is charged, it will tend to be excreted. These changes can be quite significant as urine pH can vary from 4.5 to 8.0 depending on the diet (meat can cause a more acidic urine) or drugs (which can increase or decrease urine pH). The pH of the renal tubules can be therapeutically manipulated to increase the

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**Figure 1.15** Structures of penicillin, probenecid, and topotecan. Three acidic molecules competing for the acid transporter.
excretion of drugs. In the case of an overdose from the weak acid phenobarbital [44], increasing the pH of the urine will cause an increase in the rate of excretion of the drug. This process is called forced alkaline diuresis. In addition, changing the rate of urine flow through the tubules can also modify the rate of drug reabsorption, since an increased rate of urine output tends to dilute the drug concentration in the tubule and to decrease the amount of time during which facilitated diffusion can occur. Aspirin is a weak acid that is excreted by the kidney. Aspirin overdose is treated [45] by administering sodium bicarbonate to alkalinate the urine (and trap aspirin in the tubule) and by increasing the urine flow rate (and thus dilute the tubular concentration of the drug). Both of these clinical maneuvers result in faster elimination of the drug. Conversely, the excretion of weak bases can sometimes be increased by acidification of the urine using ammonium chloride.

1.5 CONCLUSIONS

Understanding the process of digestion allows for the appreciation of the various routes of administration. Although drugs administered by intravenous by-pass the digestive system, they are still exposed to the liver or kidneys and metabolized. While the suppository route of administration relies on permeability through the large intestine, this part of the gut is not normally involved in absorption and can lead to low plasma levels. Oral administration of salbutamol alleviates symptoms associated with asthma, whereas intravenous administration delivers a muscle relaxant systematically and is used to avert premature labor. Finally, administration of local anesthetic to the bone can lead to temporary tachycardia, as adrenaline (vasoconstrictant used to reduce bleeding) can leak into a neighboring blood vessel.

Drugs undergo the same metabolic processes as food. The most important issue that medicinal chemists encounter is that of solubility, followed by the intricacies of permeability, which are complicated by the intervention of P-gp efflux. Finally, the perennial issues of metabolism in the liver and other organs (mainly by the CYPs) often plague drug development. Diagnosing drug metabolism issues will assist medicinal chemists in solving recurrent problems encountered in the course of drug development.

REFERENCES


REFERENCES


INTRODUCTION


