

# ADMET

*for Medicinal Chemists*

## A Practical Guide



*Edited by  
Katya Tsaoun and Steven A. Kates*

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# **ADMET FOR MEDICINAL CHEMISTS**

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## **A Practical Guide**

Edited by

**KATYA TSAIOUN  
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# ***Preface***

Medicinal chemistry and drug development have undergone a rapid evolution since the 1990s due to a much expanded biological and chemical toolbox allowing novel target identification and rapid synthesis of a large number of diverse chemical libraries. Despite this progress, substantial increases in R&D expenditures, and an ever-increasing number of molecules screened and synthesized every year, the pharmaceutical industry has found itself in a productivity paradox. While these improvements should have significantly increased the number of new molecular entities (NMEs) identified each year, the actual numbers in this period remained at a low and constant level with high attrition rates at both the early and the late stages of clinical development.

We believe a number of factors have contributed to this paradox.

One factor is the current system of academic training whose objectives of instructing scientists are not always aligned with the objectives of the pharmaceutical industry. The discovery of novel therapeutics is an inherently complex and interdisciplinary process, requiring close integration of scientists from several disciplines in an environment in which lessons are shared and taught across an organization. Current models of academic training emphasize specialization and insufficiently address the need to understand related subjects.

Not surprisingly, drug-discovery organizations frequently experience difficulties integrating the efforts of chemists, biologists, and preclinical and clinical development specialists. This leaves each discipline producing scientifically valid work that may often have little relevance for developing a commercial product. This

book is a product of a collaborative work of a medicinal chemist and an ADMET scientist; however, the bulk of the content of this book was written by experts in specialized subsegments of these fields. The structure of this book mirrors the most successful organizational model for drug discovery: collaboration and communication among team members comprising a variety of specialties.

While medicinal chemists collaborate among themselves, successful programs depend upon these drug developers to interact with specialists from other disciplines to commercialize therapeutic agents. This is the key insight *ADMET for Medicinal Chemists* provides; the techniques are just a “*how-to*.”

The acronym “ADMET” refers to “absorption, distribution, metabolism, excretion, and toxicity.” These parameters, in addition to efficacy, are critical in determining whether an NME will become a clinical candidate and subsequently a commercially viable product. Depending on context, the acronym can refer either to the properties of a compound, the process of determining those properties, or the discipline that focuses on that process.

“Early ADMET” is a discipline that emerged in the late 1990s. The field has created a unique interdisciplinary interface between medicinal chemists, biologists, formulators, toxicologists, and preclinical development scientists. Consequently, for medicinal chemists, early ADMET is the ideal entry point for expanding the understanding to related disciplines.

The advent of early ADME profiling of drug candidates in a high-throughput fashion in conjunction with proof-of-principle biological efficacy optimization has reduced drug failures in clinical trials due to ADME/DMPK reasons from 40 to <7% during the 1980s-1990s to late 2000s. Even though drug-discovery productivity failed to

improve during this period, the implementation of early ADMET was indisputably a major success. The goal of an ADMET program is to guide candidate selection through the early identification of molecules with suboptimal properties so that their corresponding technical issues could be addressed before large development costs have been incurred. The goal of this book is to guide medicinal chemists in how to implement early ADMET testing in their workflow in order to improve both the speed and efficiency of their efforts.

Many medicinal chemists are unfamiliar with the pharmacological pathway of a drug administered orally. Their chemical innovation can be improved by a better understanding of the digestive system which is provided in Chapter 1. Topics such as enterohepatic circulation, permeability, P-glycoproteins, microsomal stability, first-pass, and glomerular filtration are described.

Structure-based *in silico* ADMET screening models and software approaches are often used to guide medicinal chemistry efforts to design molecules with desired properties. Lipinski, Veber, and Oprea have developed rules that describe the relationship between a compound and its corresponding ADMET properties. These rules have been built into software. Chapter 2 outlines the key computer methods, such as rule-based methods, QSAR, and machine learning approaches. The chapter also discusses and compares the commercially available programs and demonstrates methods for implementation to prepare compound collections.

The physicochemical properties of a new chemical entity (NCE) can impact absorption and pharmacokinetics. Chapter 3 summarizes the strategies for applying *in silico* filters for optimization, and the impact of the solid state of the molecule on



physicochemical properties of NCEs in medicinal chemistry.

Chapter 4 provides an overview of liver metabolic stability, plasma stability, solution stability, plasma protein binding, intestinal, blood-brain barrier, tissue distribution, permeability models, excretion (biliary and renal), CYP450 inhibition, and efflux and uptake transporters. These parameters are important because physiological phenomena and the properties of drug candidates in biological systems are based upon the disposition and metabolism of a NCE. The chapter also discusses the various preclinical tools that may be used to predict human performance, and strategies for prioritizing and conducting these assays in a lead optimization program.

Pharmacokinetics (PK) describes what the body does to the drug and is dependent on the dose administered, site of administration, and the physiological state of the organism. PK expresses the rates of disposition (movement) of a drug when administered to a living organism such as (A)bsorption, (D)istribution, (M)etabolism, and (E)xcretion (ADME). Chapter 5 provides a brief overview of basic pharmacokinetic principles such as  $T_{max}$ ,  $C_{max}$ ,  $V_d$  (volume of distribution), AUC (area under the curve),  $t_{1/2}$  (half-life), bioavailability, extraction ratio, and metabolic clearance. The inevitable formulas that explicate the concepts are conceptually and pictorially described and explained.

Toxicity assays are the most critical tests of an NCE performed prior to its administration into humans. These tests are designed to ensure the safety of the first human subjects. The FDA requires many different assays for achieving this essential objective. These assays examine how a compound affects different aspects of human pharmacology. Chapter 6 discusses the fundamentals and

mechanisms of cardiac safety including hERG, other ion channels, and nonion channel related cardiac toxicity. Chapter 7 outlines genetic toxicity, including AMES, micronucleus, and GreenScreen. Chapter 8 describes hepatic toxicity, including necrosis, steatosis, cholestasis, reactive metabolites, and covalent binding.

The FDA requires for an NCE *in vivo* toxicological assessment of typically two species: one rodent and one nonrodent. Chapter 9 considers the route of administration for the intended therapeutic (bolus versus infusion and potential inadvertent routes), and the compound requirements for toxicological studies as related to different species. Chapter 9 also covers formulation issues, such as overage, spillage, stability, reactivity/compatibility with glassware, infusion equipment, method validation, and sample analysis. IND-enabling studies and species selection for different therapeutic indications are also reviewed.

Preclinical candidate nomination and development are discussed in Chapter 10, which provides an overview of the late stages of the discovery process, including the process of selecting preclinical candidates, and designing appropriate preclinical studies to support an IND.

Novel approaches to drug design constantly evolve. Chapter 11 addresses fragment-based drug design, such as minimal pharmacophoric elements and fragment hopping, which are recent innovative tools developed for designing drug candidates.

We wish to thank the contributors to this book. They have succeeded in describing the importance for a medicinal chemist to understand ADMET. We are appreciative of their support and substantial effort in providing their expertise and thoughtfulness to this project.

We hope that this book provides readers with an appreciation for the complexity of designing and developing new therapeutic agents for human clinical trials and their subsequent approval into the marketplace. We are privileged to be able to work in a field with such boundless opportunities for reducing human suffering and it is our obligation to create the best of these opportunities.

Color representations of selected figures in this book can be found at [ftp://ftp.wiley.com/public/sci\\_tech\\_med/admet](ftp://ftp.wiley.com/public/sci_tech_med/admet)

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# ***Chapter 1***

## ***Introduction***

**Corinne Kay**

### **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.

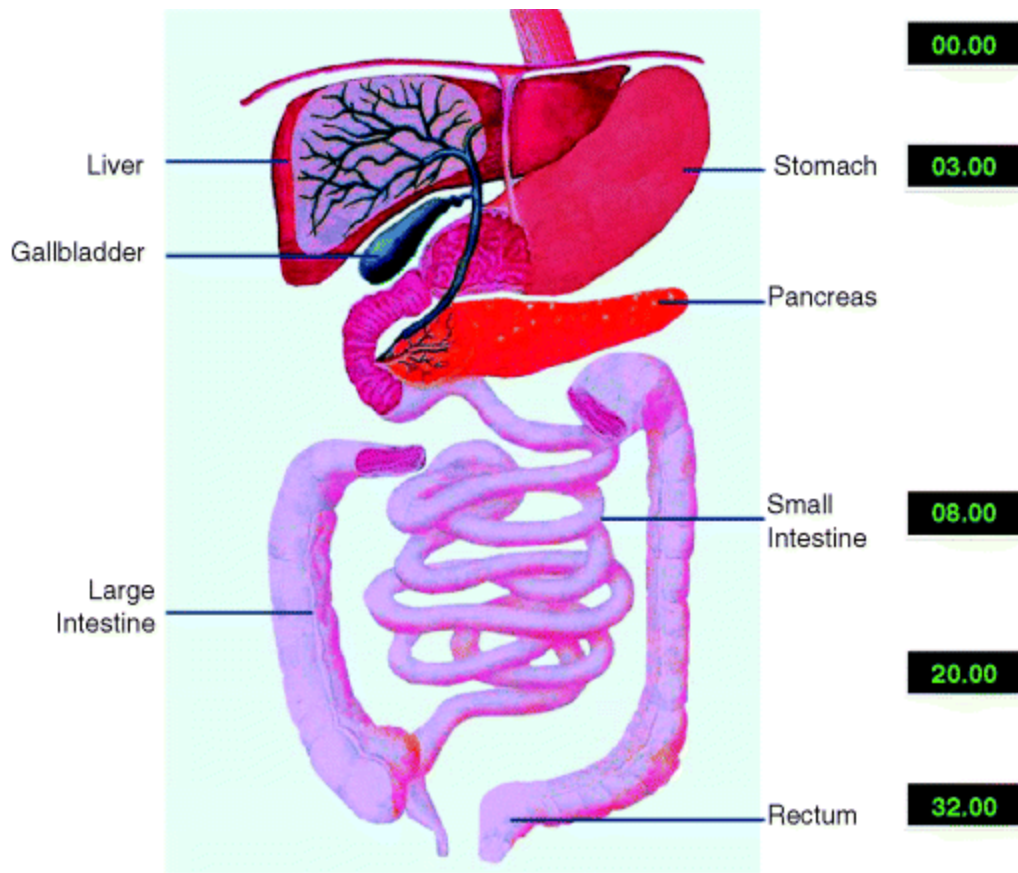
Insight to this process is a key to understanding many drug metabolism concepts. This introduction chapter is not intended to be a physiology textbook. It demonstrates the link between nutrition and drug metabolism and thus provides a framework upon which medicinal chemists can apply their extensive 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  $\text{pH} = 6$  by pancreatic secretions ( $\text{NaHCO}_3$ ), then the 2 m long jejunum ( $\text{pH} = 7-8$ ), 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) ( $\text{pH} = 7.4$ ). 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.

**Figure 1.1** The digestive system. The numbers to the right of the diagram represent the elapsed time.



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

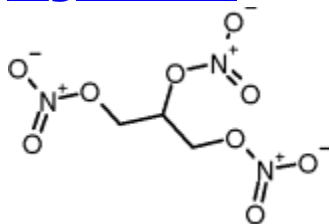
The mouth is the reception center of the digestive system and the place where food is initially processed before being passed onto the stomach via the esophagus. In the mouth, mechanical as well as chemical digestion occurs. On average 1 L of saliva is secreted at various points into the mouth through 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), alanineamino 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 immunoglobulin 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 perfusion 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.

**Figure 1.2** Structure of GTN (glycerin trinitrate).

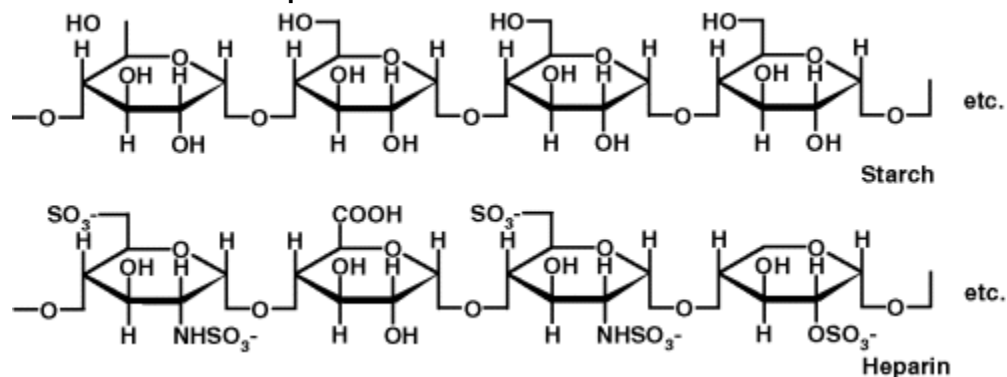


The same route of administration has been exploited by Generex Biotechnology Corporation [1] to develop Oral-lyn™. This formulation delivers insulin as a fine spray in the buccal (i.e., mouth) cavity. The peptide drug is rapidly absorbed through the mucosal lining of the mouth and

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](#)).

**Figure 1.3** The similarities between the structures of starch and heparin.



## 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**

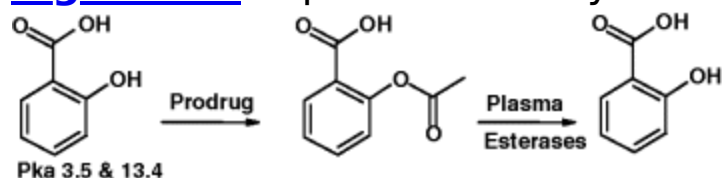
Only a limited range of substances are actually absorbed through the stomach lining into the blood. The stomach can absorb glucose and other simple sugars, amino acids, and some fat-soluble substances. A number of alcohols, including ethanol, are readily absorbed from the stomach. Water moves freely 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  $\text{pH} = 2$  is often an issue. The following examples illustrate the significance of this problem.

Salicylic acid ( $\text{p}K_a$  3.5 and 13.4) is weakly acidic and only 30% is ionized at  $\text{pH} = 2$ . Its insolubility precludes its absorption in the stomach ([Figure 1.4](#)). It is soluble in the intestine ( $\text{pH} = 6.4$ ), 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).

**Figure 1.4** Aspirin—solubility and ionization.



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 (inivirase) 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.

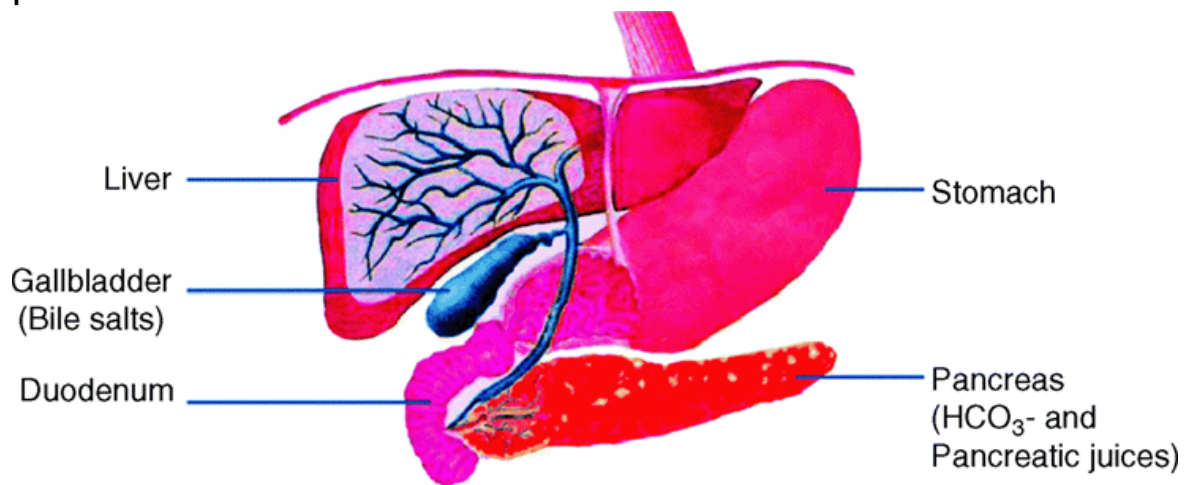
A number of solubility tests are available to assist in identifying this issue prior to drug administration to humans, and these are discussed in subsequent chapters. In addition to the usual solubility tests, many groups [6] have reported the use of the fasted and fed-state

simulated gastric fluid (SGF) test [7] due to its more relevance to a physiological environment.

### **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.

**Figure 1.5** The duodenum receives input from the pancreas and the liver.



#### **1.2.3.1 Pancreatic Juices**

Since the pHs of the stomach and the intestine are very acidic and nearly neutral, respectively, the pancreas