Part 1
Introductory Concepts

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Introduction

Overview

- *Drug-like properties confer good ADME/Tox characteristics to a compound.*
- *Medicinal chemists control properties through structure modification.*
- *Biologists use properties to optimize bioassays and interpret biological experiments.*

Drug discovery is an exceedingly complex and demanding enterprise. Discovery scientists must pursue multiple lines of investigation involving diverse disciplines, often with conflicting goals, and integrate the data to achieve a balanced clinical candidate. In recent years there has been considerable discussion of the importance of optimizing the absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) properties (e.g., physicochemical, metabolic, toxicity) of compounds in addition to pharmacology (e.g., efficacy, selectivity) to increase drug discovery success. Christopher A. Lipinski[1] has commented:

> Drug-like is defined as those compounds that have sufficiently acceptable ADME properties and sufficiently acceptable toxicity properties to survive through the completion of human Phase I clinical trials.

Drug properties have always been a prominent component of the *development* phase, after *discovery*, during which detailed studies are performed on formulation, stability, pharmacokinetics (PK), metabolism, and toxicity. However, in recent years it is has become imperative to integrate drug properties into drug discovery research. Ronald T. Borchardt[2] has commented:

> . . . drug-like properties are . . . intrinsic properties of the molecules and it is the responsibility of the medicinal chemists to optimize not only the pharmacological properties but also the drug-like properties of these molecules.

This integration enables optimization of drug discovery leads for ADME/Tox during drug discovery. Comprehensive, simultaneous optimization of in vivo pharmacology, pharmacokinetics, and safety has been an important advance.

Another important advance has been the recognition that properties have a major effect on the performance of drug research biological experiments. Low solubility, permeability, or stability in assay media alters the biological data used to develop structure–activity relationships (SARs), a key aspect of drug discovery. Biologists use property data to optimize bioassays, dosing vehicles, and in vivo routes of administration. Thus, drug-like properties have become important for discovery biological research.

The various drug properties, terminology, and assays can be overwhelming to drug discovery scientists and students without sufficient introduction. Some texts on drug properties are daunting because they are written from the perspective of experts in pharmaceutics or metabolism and contain detail and math that are not useful for discovery scientists. This book is a practical guide for medicinal chemists, biologists, managers, and students. It provides background material and real-world, practical examples for practicing discovery scientists who need to make sense of the data and arrive at informed decisions.

This book provides tools for working with drug-like properties. First, the interactions of drug molecules with the in vivo barriers they encounter after oral administration are described, in order to understand why properties limit drug exposure to the therapeutic target. Next, each key drug property is explored (Figure 1.1) in terms of

1. Fundamentals of each property
2. Effects of each property on ADME/Tox and biological experiments
3. Structure–property relationship (SPR) case studies, to see how structure affects properties
4. Structure modification strategies, to guide property optimization
5. Property method descriptions, for accurate measurement and application of data

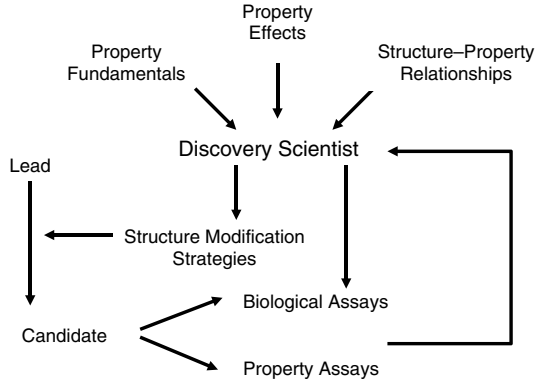

Figure 1.1 ► This book provides discovery scientists and students with a practical understanding of property fundamentals, effects, structure–property relationships, and structure modification strategies that can be applied to improving leads and bioassays. Quality property assays and data are critical for making informed decisions.

Knowledge of these properties equips discovery scientists for increased effectiveness in lead selection, optimization, and enhancement of discovery biology.

Property-related concepts are described with a minimum of math and with emphasis on practical application. Specific property applications in diagnosis of poor pharmacokinetics, design of prodrugs, formulation for in vivo dosing, and strategies for applying property data are discussed.

Drug discovery has diverse elements that must be delicately integrated and balanced. Drug-like properties are important characteristics of quality clinical candidates.

Problems

(Answers can be found in Appendix I.)

1. Define the term *drug-like*.
2. What are two major lead optimization areas in drug discovery?
3. How can understanding compound properties assist discovery biologists?
4. Compound properties can affect which of the following?: (a) pharmacokinetics, (b) bioavailability, (c) IC_{50}, (d) safety.

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Advantages of Good Drug-like Properties

Overview

- *Structural properties determine in vivo pharmacokinetics and toxicity.*
- *Inefficient research, attrition, and costs are reduced if compounds have good properties.*
- *ADME/Tox property assessment and optimization are important aspects of drug discovery.*
- *Optimal clinical candidates have a balance of activity and properties.*

2.1 Drug-like Properties Are an Integral Part of Drug Discovery

Drug discovery is continuously advancing as new fundamental knowledge, methods, technologies, and strategies are introduced. These new capabilities result in changes in the discovery process. For example:

- Pharmacology screening has changed from direct testing in living systems to in vitro high-throughput screening.
- Initial leads (hits) for optimization have changed from natural products and natural ligands to large libraries of diverse structures.
- Compound design has been enhanced from structure–activity relationships by the addition of x-ray crystallography and NMR binding studies and computational modeling.
- Lead optimization chemistry has been enhanced from one-at-a-time synthesis by the addition of parallel synthesis.
- Traditional sequential experiments have been enhanced with parallel experiments, such as microtiter plate formats.

Drug discovery is constantly reevaluating itself in order to advance in speed, efficiency, and quality and thus remain successful.

Drug-like property optimization is another area of drug discovery advancement. It offers significant opportunities for enhancing discovery success. This book focuses on the fundamental knowledge, methods, and strategies of absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) and how structures can be optimized. As background for this information, this chapter describes how optimization of ADME/Tox has progressed.

The term *drug-like* captures the concept that certain properties of compounds are most advantageous in their becoming successful drug products. The term became commonly used following the pivotal work of Lipinski and colleagues.[1] Their work examined the structural properties that affect the physicochemical properties of solubility and permeability and their effect on drug absorption. Since that article, the term *drug-like properties* has expanded and been linked with all properties that affect ADME/Tox.

2.1.1 Many Properties Are of Interest in Discovery

Drug-like properties are an integral element of drug discovery projects. Properties of interest to discovery scientists include the following:

- Structural properties
  - Hydrogen bonding
  - Lipophilicity
  - Molecular weight
  - pK_a
  - Polar surface area
  - Shape
  - Reactivity
- Physicochemical properties
  - Solubility
  - Permeability
  - Chemical stability
- Biochemical properties
  - Metabolism (phases I and II)
  - Protein and tissue binding
  - Transport (uptake, efflux)
- Pharmacokinetics (PK) and toxicity
  - Clearance
  - Half-life
  - Bioavailability
  - Drug–drug interaction
  - LD_{50}

The structure determines the compound's properties (Figure 2.1). When these structural properties interact with the physical environment, they cause physicochemical properties (e.g., solubility). When these structural properties interact with proteins, they cause biochemical properties (e.g., metabolism). At the highest level, when the physicochemical and biochemical properties interact with living systems they cause PK and toxicity. Medicinal chemists control the PK and toxicity properties of the compound by modifying the structure.

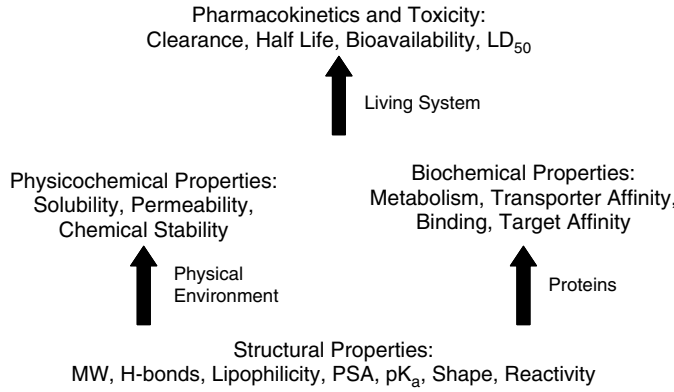

Figure 2.1 ► Compound structure determines the fundamental properties that determine physicochemical and biochemical properties, which ultimately determine pharmacokinetics and toxicity.

2.1.2 Introduction to the Drug Discovery and Development Process

Before exploring how properties affect drug candidates, it is useful to briefly review the process of drug discovery and development. New drug candidates are found during the discovery stage (Figure 2.2). They then enter clinical development and, if approved by the Food and Drug Administration (FDA), become drug products that are used in patient therapy. The major activities in each stage are listed in Figure 2.2. This book focuses on the discovery stage. However, the later stages impose stringent drug-like requirements on the properties of candidates. Thus, it is necessary to anticipate these requirements during drug discovery and promote to development only those compounds that have the highest chances of success.

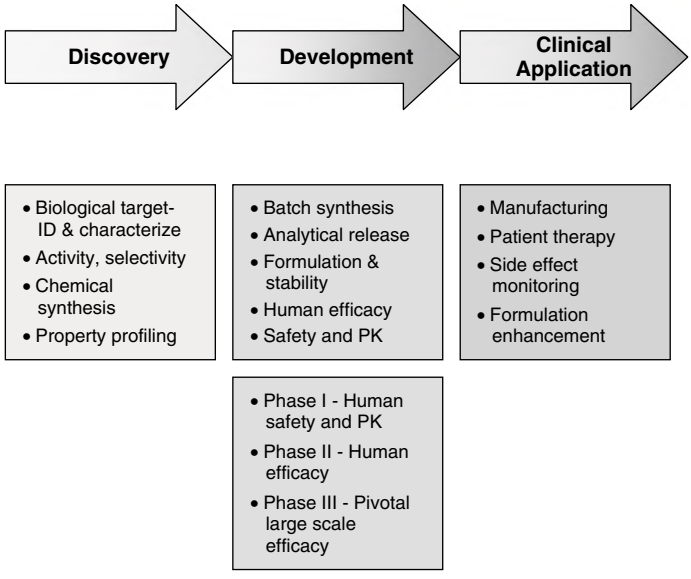

Figure 2.2 ► Overview of drug research and development stages and their major activities.

Drug discovery is diagramed in greater detail in Figure 2.3. In general, successive stages involve increasing depth of study and more stringent advancement criteria. The discovery screening process initially casts a broad net, to explore diverse pharmacophore structural

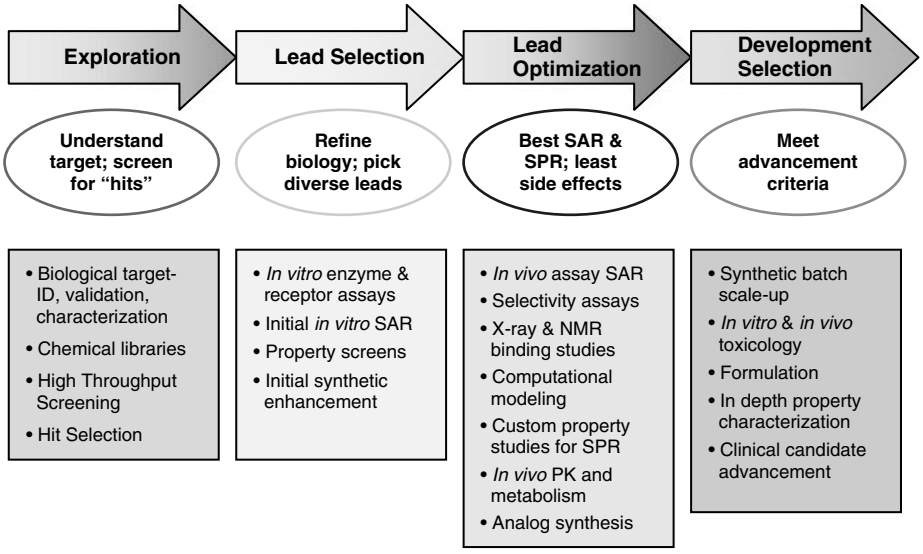

Figure 2.3 ► Stages of drug discovery, primary goals, and major activities.

space. It then narrows these possibilities to select a few lead scaffolds (templates). These are structurally modified to explore SARs, the cornerstone of modern drug discovery, during the lead optimization stage. Finally, candidates for development are subjected to in-depth studies to qualify or disqualify them for development.

2.1.3 Development Attrition is Reduced by Improving Drug Properties

Much of the early history of drug discovery focused on finding active compounds. Issues such as PK, toxicity, solubility, and stability were addressed during the development phase. In 1988 a pivotal paper on the reasons for failure of drugs in development revealed a startling problem.[2] Approximately 39% of drugs were failing in development because of poor biopharmaceutical properties (PK and bioavailability). With the high cost of development, this failure represented a major economic loss for the companies. Furthermore, years of work on discovery and development were lost, and the introduction of a new drug product was delayed.

This great need for enhancement was actively addressed by adding resources to assess biopharmaceutical properties during late discovery. Sorting out the compounds with acceptable properties at this stage did not require the rigorous methods applied during development. Thus, for this task, methods used during development were adapted to use fewer resources and to operate at higher throughput. Criteria were relaxed to reflect the reduced accuracy and precision of the revised methods and the lower level of detail needed for decisions at this stage. The assessment of PK was implemented in the late-discovery/predevelopment stage. This testing succeeded in keeping poor candidates from progressing into development and reduced development attrition.

2.1.4 Poor Drug Properties Also Cause Discovery Inefficiencies

Once late-discovery biopharmaceutical assessment was in place and an attrition burden was lifted from development, another discovery need was revealed. Candidates that were failing in late discovery because of poor properties still caused a great burden on drug discovery. Failure late in discovery meant that the project to discover a new drug had lost valuable

time and resources on the failed candidate and had to start over. This recognition led to the implementation of property assessment even earlier in discovery so that such losses would be reduced. In pharmaceutical companies, implementation has been accomplished by different approaches. In one approach, higher-throughput animal PK capabilities are added earlier in discovery in order to screen more compounds in vivo for PK. This strategy measures the key PK properties that can predict in vivo candidate ADME success. In a second strategy, higher-throughput in vitro property assays are used. These assays measure fundamental physicochemical and biochemical properties, such as solubility, permeability, and metabolic stability, which determine higher-level properties, such as PK. In vitro studies require fewer resources and animals per compound than do PK studies, so more compounds can be assessed using in vitro assays. Also, physicochemical and biochemical properties, determined with in vitro methods, can be more useful to medicinal chemists in deciding how to modify structures to improve properties.[3–5] Medicinal chemists can correlate physicochemical and biochemical properties with structural features more closely than with PK properties. Physicochemical and biochemical methods typically measure a single property (e.g., passive diffusion permeability). On the other hand, PK properties result from multiple variables operating in a dynamic manner, and they do not indicate which discrete structural modifications to make. Most pharmaceutical companies use a combination of these two strategies during discovery.

As a result of these enhancements of discovery, the property-induced failure of compounds in development declined dramatically from 39% in 1988 to 10% in 2000.[6] Figure 2.4 shows that pharmaceutical companies have been successful in improving the biopharmaceutical properties of development candidates. The 2002 study also suggests that other property issues (toxicity, formulation) still are challenges.

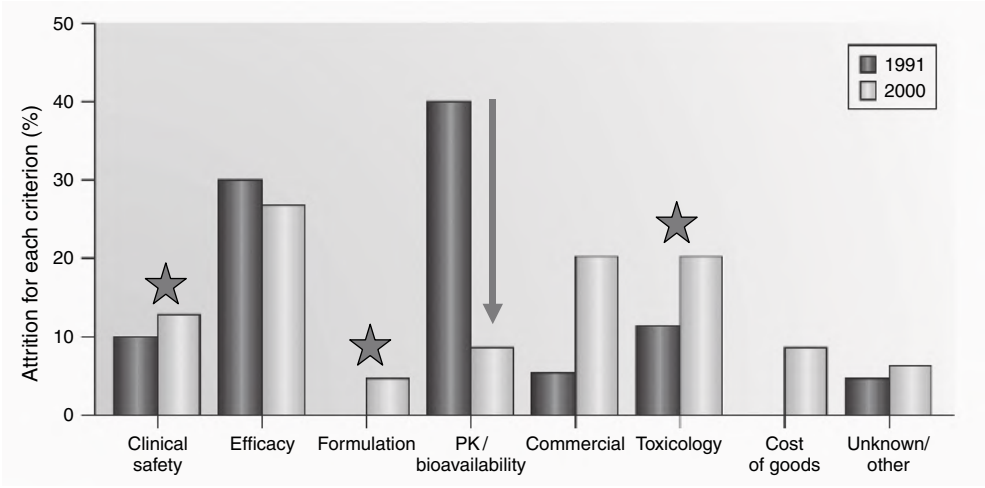

Figure 2.4 ► Between 1991 and 2000, development attrition due to pharmacokinetics (PK) and bioavailability was greatly reduced. Toxicology, clinical safety, and formulation remain significant drug-like property issues. (Reprinted with permission from [6].)

2.1.5 Marginal Drug Properties Cause Inefficiencies During Development

Although the rate of outright candidate failure in development has decreased due to early termination of candidates with inadequate properties, candidates with marginal properties

still progress into development. Even though they might not fail in development, they impose significant inefficiencies on development by increasing development costs and prolonging development time lines.

For example, compounds with poor solubility and stability usually require a longer development time line and more resources, owing to more difficult formulation development, stability testing, and dissolution studies. Sophisticated formulations can improve the dissolution rate and reduce active compound degradation. It is tempting for discovery scientists to shift the burden to development pharmaceutics scientists who will fix the problems by using sophisticated formulations. Although this may be an acceptable choice for new first-in-class therapies, for other drug products it can impose a burden on development resources and delay the introduction of a new drug product.

For a new drug that would produce hundreds of millions of dollars of sales in its first year, $5 to $10 million of sales are potentially lost for each week of delay in discovery or development. Furthermore, if a patent has been filed, each week of delay could result in 1 less week of patent exclusivity during the time of highest sales for the inventing company. Thus, real economic considerations drive enhancement of compound quality.

Another result of poor-to-mediocre properties is that the patient may take on a greater burden. For example, if the drug is poorly absorbed, the dose must be increased to reach therapeutic levels. The dosing regimen might need to be shifted from oral to intravenous, which is not acceptable for dosing among the wide patient population. If the drug has a short half-life in vivo because of metabolic instability, then the drug must be dosed more frequently. Patients are less likely to consistently self-administer drugs that require higher and more frequent daily doses. Once-per-day dosing of a solid dosage form by mouth is preferable. Pharmaceutical companies and academic laboratories have a strong commitment and mission to enhance the quality and length of patient life; thus, patient burdens, needs, and benefits are a primary focus.

In most cases, it is more advantageous to try to improve drug-like properties (e.g., solubility, stability, and permeability) during discovery. This is best accomplished by modifying the chemical structure. Modifications usually are performed at sites in the molecule that are shown by SAR to not be critical for therapeutic target binding. In some cases, the structural requirements for ligand binding to the target do not permit structural modifications to improve properties. Under these conditions, discovery scientists and managers must decide if the drug candidate still has viability as a drug product. Attention to properties and a workflow that includes property optimization during discovery allow for the best chance of discovering a candidate that combines all of the qualities of a successful drug product.

Some people have commented retrospectively that if properties had been assessed in the past, then some of our current drug products with poor properties would not have become available for clinical therapy. It is true that some current drugs have poor properties and may not have been submitted to the FDA under current criteria. However, it is widely recognized that early property assessment and optimization provide the opportunity for earlier correction of property limitations. If the current property awareness and assessment had been available at the time of discovery of those drugs with poor properties, then better structural analogs having comparable potency without the property limitations may have been discovered. In this way, even better drugs with reduced patient burden and costs may become available sooner.

2.1.6 Poor Properties Can Cause Poor Discovery Research

In addition to development problems, poor properties can cause problems during drug discovery. Once property data became available during discovery, their value to discovery

in ways other than PK began to be recognized. We now know that when discovery project teams encounter unexplained problems, some of the problems are due to poor properties.[3,7,8]

Following are examples of how poor drug properties can reduce the quality of drug discovery biological research:

- Low or inconsistent bioactivity responses for in vitro bioassays can be due to precipitation, owing to low solubility of the compound in the bioassay medium or in dilutions prior to the assay.
- Low activity in bioassays may be due to chemical instability of the compound in the test matrix.
- An unexpectedly high drop in activity can result when transitioning from enzyme or receptor activity assays to cell-based assays. This can be due to poor permeability of the compounds through the cell membrane, which must be penetrated for the compound to reach intracellular targets.
- Compounds may be unstable or insoluble in the DMSO solutions that are stored in microtiter plates and experience freeze–thaw cycles, or they may be exposed to various physicochemical conditions in the laboratory.
- Poor efficacy of a central nervous system (CNS) drug in vivo may be due to poor penetration of the blood–brain barrier.
- Poor efficacy in vivo may be due to low concentrations in the plasma and target tissue because of poor PK, low bioavailability, or instability in the blood.

These effects of poor properties may go unrecognized if discovery scientists are unaware of them and are not vigilant in checking for the effects or ensuring that discovery experiments are designed and interpreted to account for the properties. Poor properties can limit exposure of the compound to the target protein in the discovery biological experiment. This property effect may be misinterpreted as an actual SAR, and a valuable pharmacophore may be overlooked. If the potential effects of poor properties on bioassays are taken into consideration, then the active pharmacophore may be rescued by testing under more appropriate conditions to obtain accurate biological data. Structural modification then can improve the deficient property.

2.2 Changing Emphasis on Properties in Discovery

In the past, the focus on binding to the active site of the target protein has been a strong priority in discovery for medicinal chemistry. Exploration of SAR by synthesis of analogs having systematic modifications of the core structural scaffold has allowed optimization of binding by orders of magnitude. It is so important for discovery project teams to arrive at a potent candidate that other considerations, such as drug-like properties, might be given comparatively less attention.

There is a strong emphasis on driving potency from the micromolar IC_{50} range of high-throughput screening (HTS) hits to the low nanomolar range of good clinical candidates. However, if the focus is solely on activity, the research team can arrive at a candidate with properties that are worse than the original HTS hit. For example, the candidate may be too polar to penetrate the blood–brain barrier and reach the intended CNS target, it may be unstable and rapidly cleared by first-pass metabolism, or it may be too insoluble to be absorbed from the intestine. These findings may hopelessly misdirect a discovery program.

Once nanomolar activity is obtained, it is hard to go back and fix properties by structural modifications because it may be necessary to modify the substructures that were added in order to enhance binding affinity.

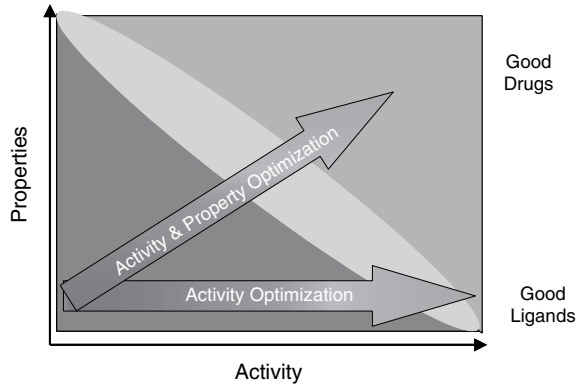

Figure 2.5 ► Changing strategy for drug candidates, from a focus on activity to balanced attention to activity and properties. (Reprinted with permission from [5].)

This situation is demonstrated in Figure 2.5. A primary focus on activity can yield compounds that are very effective as ligands for the target protein, but the properties may be inadequate for the compounds to become successful drugs. For example, increased lipophilicity can enhance target protein binding; however, it also can reduce solubility and metabolic stability. Balanced attention to both activity and properties (holistic approach) yields candidates that can become good drugs. The balanced approach suggested by Figure 2.6 now is common in drug discovery. Good activity and drug-like properties are complementary, and both are necessary for a good drug product. The most active or selective compound may not make the best drug product because of property limitations that cause poor PK or safety. A less potent compound with better properties may produce a better in vivo therapeutic response and be a better drug product for patients. As in the sport decathlon, the candidate is tested by many events/challenges, and it is the combined performance that determines success, not being the best in individual events.

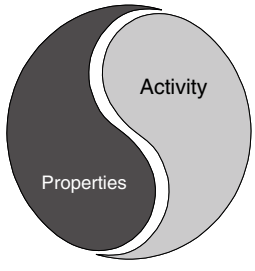

Figure 2.6 ► Pharmaceuticals balance activity and properties. (Reprinted with permission from [11].)

The multitude of challenges faced by discovery scientists has been variously characterized. One useful image is to characterize them as a series of hurdles that a compound must pass.[9] Another useful analogy is juggling (Figure 2.7). A diverse ensemble of crucial elements must be simultaneously monitored and kept in balance in order to achieve success. Neglecting one element can cause the whole ensemble to crash.

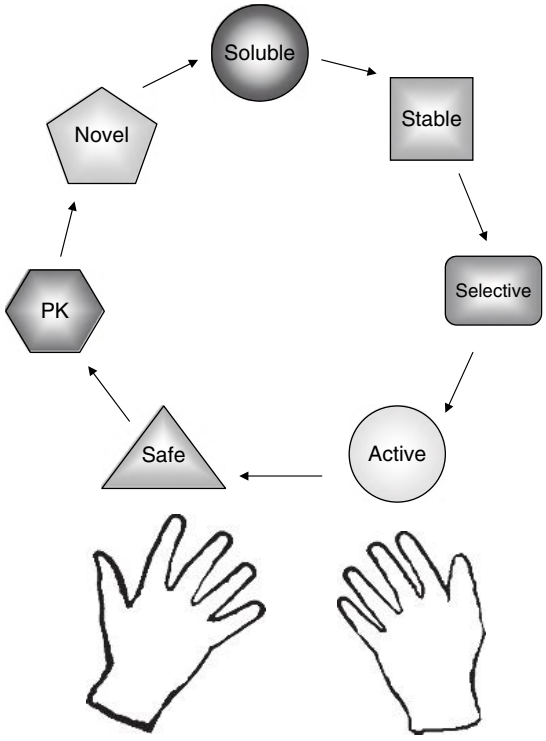

Figure 2.7 ► Success in drug discovery requires simultaneously juggling diverse variables.

2.3 Property Profiling in Discovery

In the past, it was not possible to systematically enhance drug properties during drug discovery because the data were not available. Methods were not in place to provide discovery scientists with the necessary information. If methods were available, they were too slow to provide data on a time schedule that was useful for medicinal chemists. Few resources were devoted to this activity, so data were not available for many compounds. The data were not sufficiently comprehensive for all of the major properties that had to be addressed. If data were available, the data quality either was low or unknown, and discovery scientists did not trust the data for making crucial decisions.

With the increased emphasis on drug-like properties in discovery came an infusion of property knowledge from development colleagues (pharmaceutics, metabolism, toxicology, PK, process, analytical). Experts in these disciplines assisted discovery scientists with understanding and measuring properties. However, discovery applications require distinctly different perspectives and strategies than does development because of the differences in goals and activities of the stages.[9]

Current methods for property prediction and measurement are discussed in Chapters 22 to 37. Those chapters provide information on the various tools available for property assessment. They also provide insight on how data are produced by drug-like property profiling colleagues for project teams. Knowledge of methods and the data they produce leads to better interpretation and application of property data by discovery scientists. The method information also allows chemists to decide on which methods to implement in their organization.

2.4 Drug-like Property Optimization in Discovery

This book provides resource material for medicinal chemists, discovery biologists, managers, and students who are interested in integrating pharmaceutical properties into their selection and optimization of leads and candidates.

A new strategy introduced into discovery is structure–property relationships (SPRs). This is complementary to SAR. The structures of compounds are correlated to their property performance. SPR allows medicinal chemists to understand how structural modifications improve properties for their scaffold. Thus, the established strategy of structure-based design is supplemented with the new strategy of "property-based design" by van de Waterbeemd et al.,[10] the study and modification of structure to achieve property improvement.

There are many reasons for a drug discovery project team to strive toward selecting leads with good drug-like properties and optimizing properties for their compound series during drug discovery. Property optimization can be approached in balance with activity and selectivity optimization. The advantages of good drug-like properties include the following:

- Better planning, execution, and interpretation of discovery experiments
- Reduced discovery time lag from not having to fix property-based problems at a later time
- Faster and more economical pharmaceutical development
- Candidates with lower risk and higher future value
- Longer patent life
- Higher patient acceptance and compliance

Problems

(Answers can be found in Appendix I.)

1. How do medicinal chemists control compound properties?
2. In addition to structure, what determines physicochemical (e.g., solubility) and biochemical properties?
3. How can drug-like properties be used in each stage of drug discovery (Figure 2.3)?
4. What assays are available to discovery scientists for property assessment and optimization?
5. How do poor properties affect development, clinical application, and product lifetime?
6. How do drug properties affect discovery biological experiments?
7. Define and describe SPR.
8. Which of the following are advantages of optimizing drug-like properties?: (a) better-quality drug product, (b) lower risk of failure, (c) faster and less expensive development, (d) lower cost of goods, (e) more reliable discovery biological data, (f) easier synthesis.

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Barriers to Drug Exposure in Living Systems

Overview

- *Physiological barriers reduce the amount of dosed compound that reaches the target.*
- *Barriers include membranes, pH, metabolic enzymes, and transporters.*
- *Good properties enable good absorption, distribution, low metabolism, reasonable elimination, and low toxicity.*

Drugs encounter many barriers in living systems from the time the dosage form is administered until the time the drug molecules reach the therapeutic target.

The behavior of a drug molecule at each barrier is a direct result of the drug's chemical structure. The combined performance at all the barriers in the body (i.e., the portion that passes the barriers) determines the concentration of drug (exposure) at the therapeutic target. Along with inherent activity at the therapeutic target, this determines the drug's in vivo efficacy. Pharmacokinetics (PK) is often used as a surrogate for exposure. PK parameters are used to determine the dosage form and dosing regimen that are used in clinical practice.

Performance at a particular barrier (e.g., intestinal epithelium) may be due primarily to one or several drug properties (e.g., permeability, efflux transport). For a particular compound, one or two property deficiencies (e.g., metabolic stability, solubility) can greatly limit its PK performance. In discovery, we have the opportunity to make structural modifications that greatly improve the performance of the limiting properties, that is, to create a better drug product.

3.1 Introduction to Barriers

When a drug molecule encounters a barrier, the amount of drug that reaches the other side is diminished. The barrier concept is illustrated in Figure 3.1. Penetration of drug molecules to the therapeutic target is slowed and attenuated by the barrier. The behavior of the molecules at each of the barriers determines the rate at which the molecules progress to the target as well as their target exposure concentration at a particular time after dosing. If we are successful in optimizing the performance of a discovery lead series at these barriers, then we may achieve exposure of drug to the target that is consistent with sustainable efficacy.

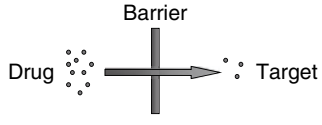

Figure 3.1 ► Model for drug barriers in living systems. Drug delivery to the therapeutic target is attenuated by barriers in the organism. (Reprinted with permission from [4].)

Barriers include a diverse ensemble of physicochemical and biochemical processes that drug molecules encounter. Examples of barriers include cell membranes, metabolic enzymes, solution pH, efflux transporters, and binding proteins.

It is important to remember that efficacy is driven by the inherent activity of the molecule at the target (e.g., IC_{50}) and by exposure (e.g., concentration and duration). In a discovery project, the lead structures are constrained by the substructures and orientations that are needed for binding to the target. If these constraints cause a compound to perform poorly at one or more of the barriers in a living system, then the compound might not achieve sufficient exposure at a safe dose and will not become a drug product.

This is the ying–yang relationship of successful drugs (see Figure 2.6). The process of drug discovery balances a relentless search for molecules that have structural features that produce:

1. Strong target binding using structure-based design and the structure–activity relationship (SAR)
2. High performance at in vivo barriers, using property-based design[1] and the structure–property relationship (SPR)

In the same way that design of structural features using SAR is known as *structure-based design*, the design of structural features using SPR has become known as *property-based design*.[1] How a medicinal chemist goes about balancing these often disparate processes is a matter of experience and strategy.

It is useful to explore the barriers to exposure in living organisms from the standpoint of the drug molecule. Its passage through the various organ systems and the physicochemical and biochemical environment it encounters is a fascinating journey. The molecule's physicochemical properties determine its behavior in solutions and at membrane barriers. Its binding and reactivity at particular enzymes determine its behavior at metabolic barriers. Its binding to various transporters and plasma proteins, as well as nonspecific binding to macromolecules throughout the body, affects its absorption, distribution, and excretion behaviors. The reactivity of the drug and its metabolites affects toxicity.

For the purposes of this introduction to barriers, it is useful to consider barriers in a linear sequence as the drug molecule moves toward the therapeutic target. In living systems, different molecules encounter different barriers at the same time, so the process is very dynamic and interactive. The various barriers also dynamically affect each other. For example, in the intestinal epithelium, efflux transporters remove some compounds from the cell, allowing metabolizing enzymes in the cell to operate in a concentration range of greater efficiency. As another example, a high rate of metabolism limits brain exposure, even if the compound has good blood–brain barrier permeability.

3.2 Drug Dosing

A common goal of pharmaceutical researchers is to develop a drug dosage form that is a low-dose tablet with a dosing regimen of oral administration once per day. Administration by mouth is termed *oral* and is abbreviated PO (*per os*). A drug product of this type has reasonable manufacturing and storage costs and high patient compliance. If a compound has limited performance at one or more in vivo barriers, it may have poor PK performance and will require adjustments to this approach, such as:

- More frequent dosing (if the half-life is short)
- Higher doses (if the bioavailability is low)

- Administration by a different route (if absorption is low)
- A different vehicle or formulation (if solubility is low)

If oral dosing does not produce sufficient exposure, another route of administration, such as intravenous, is necessary (Table 3.1; see Section 41.1). Nonoral routes are also used during discovery before properties are optimized for good absorption after oral dosing.

Formulations can be developed to increase the absorption of molecules. This is accomplished by increasing the solubility or dissolution rate of the drug product (see Chapter 41).

TABLE 3.1 ► Dosing Routes

Administration	Description	Abbreviation
Oral	Swallowed by mouth	PO
Intravenous	Injected directly into the bloodstream as a bolus (rapidly) or by infusion (continuously)	IV
Subcutaneous	Injected under the skin	SC
Transdermal	Applied as a patch or other device and transported through the skin	
Topical	Applied as a solution or suspension onto the skin	
Intramuscular	Injected into the muscle	IM
Epidural	Injected into the epidural space just inside the bone of the lower vertebrae	
Suppository	Placed in the rectum	
Intranasal	Sprayed into the nose	
Buccal	Tablet is held inside the mouth between cheek and gum until dissolved	
Sublingual	Tablet is held underneath the tongue until dissolved	
Intraperitoneal	Injected within the peritoneal (abdominal) cavity	IP

3.3 Barriers in the Mouth and Stomach

In oral dosing, the compound first encounters the mouth. A portion of the drug can be absorbed in the mouth if it stays in the mouth for some time. Buccal and sublingual dosing involve keeping the drug in the mouth. The drug is absorbed through the membranes of the mouth into blood capillaries.

The drug tablet is ingested via the esophagus and arrives at the initial portion of the gastrointestinal (GI) tract, the stomach (Figure 3.2). The drug tablet is broken into smaller particles by the aqueous environment and by movements of the stomach. Here the drug tablet encounters several physicochemical and stability barriers. The first barrier is its *dissolution rate* (see Sections 7.1.2 and 7.5). Another barrier is its solubility at the low pH of the stomach. Molecules must be in solution in order to diffuse to the membrane surface for absorption. Factors that affect solubility are discussed in Chapter 7. As solubility increases, the concentration of compound in solution and at the membrane surface increase. This is favorable for increased absorption. *Permeability* through the membrane is the next barrier for drug molecules in reaching systemic circulation. Higher permeability results in higher drug absorption.

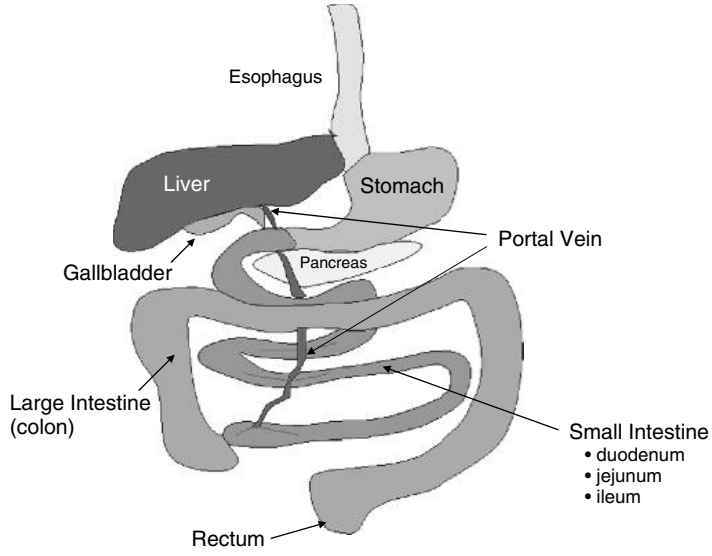

Figure 3.2 ► Diagram of the gastrointestinal tract. (see Plate 1)

For most drugs, absorption from the stomach is limited. This is because the stomach surface area is relatively low (approximately 1 m^2), and blood flow around the stomach (perfusion) is low. In addition, drug material does not stay in the stomach very long. The gastric emptying time varies from 0.5 to 1 hour in the fasted state to several hours after a heavy meal.

Another barrier to drug absorption from the stomach is the acidic solution. In the fasted state, stomach pH is between 1 and 2 and in the fed state is between pH 3 and 7. Compounds that have *chemical instability* at acid pH might be decomposed by hydrolysis reactions. Molecules continue to be exposed to acidic pH and potential acidic decomposition in the upper portions of the small intestine (see Section 3.4). Compounds also encounter *hydrolytic enzymes*. These enzymes naturally catalyze the breakdown of polymeric macromolecules to monomers as nutrients. Some drug molecules can bind to these enzymes and be catalyzed for hydrolysis. Solution stability in enzymatic and varying pH solutions is discussed in Chapter 13.

3.4 Gastrointestinal Tract Barriers

The stomach contents empty into the *duodenum*, the first region of the small intestine. Following regions are termed the *jejunum* and *ileum*, in sequence. The pH in the small intestine is higher than in the stomach, varying from pH 4.4 in the duodenum in the fasted state to pH 7.4–8 at the end of the ileum. The pH values of the intestinal regions are listed in Table 3.2. This progression of pH creates a pH gradient from the stomach through the small intestine. The transit time is the amount of time available for drugs to be absorbed in that region.

TABLE 3.2 ► pH Values and Transit Times of Gastrointestinal Tract Regions

GI tract region	Average pH, fasted	Average pH, fed	Transit time (h)
Stomach	1.4–2.1	3–7	0.5–1
Duodenum	4.4–6.6	5.2–6.2	
Jejunum	4.4–6.6	5.2–6.2	2–4
Ileum	6.8–8	6.8–8	

In the small intestine, the solubility of the drug continues to be an absorption barrier. Solubility varies throughout the length of the intestine. The solubility of a compound is a function of the pH and the pK_a of the molecule (see Section 7.1.3). Basic compounds are mostly in the charged cationic (protonated) state throughout the stomach and upper intestine, where the pH is acidic. This favors good solubility because the charged form is more soluble than the neutral form. Acids are neutral in the stomach and upper intestine. Therefore, an acid's solubility in acidic regions is limited. As the pH increases throughout the intestine, the relative amount of the anionic form of the acid increases, resulting in higher solubilities. These behaviors are typical of the solubility differences among compounds in different regions of the intestine. The fundamentals and effects of pK_a on solubility are discussed in Chapter 6.

The material coming from the stomach is mixed with bile in the intestine. Bile enters from the gallbladder. Bile acids enhance the solubility of lipophilic drug molecules. Bile acids work like detergents to enhance solubility. Their natural function is to solubilize food lipids to enhance absorption. Lipophilic drug molecules gain similar benefits in solubility. Bile acids form micelles to which lipophilic molecules adsorb, enhancing their diffusion to the intestinal membrane for absorption.

Pancreatic fluid also is added in the duodenum. It enters from the pancreas and contains hydrolytic enzymes. Major enzymes in pancreatic fluid include amylases, lipases, and proteases. They can catalyze the hydrolysis of some drug molecules that contain hydrolyzable functional groups (see Chapter 13).

Membrane permeability is a major absorption barrier in the intestine. As with solubility, permeability varies with the pH of the intestinal region and the compound's pK_a. A neutral molecule has much greater permeability than does its charged (ionic) form. Conversely, a neutral molecule is less soluble than is its charged form. Thus, permeability and solubility vary inversely with pH.

In the small intestine, drug molecules encounter an anatomy that greatly enhances the absorption of nutrients. The inner surface area of the intestinal lumen is enhanced approximately 400 times by three morphological features. Along the length of the intestinal lumen are folds, which are up and down undulations along the inner surface. Villi add to the surface area by projecting 1 mm into the intestinal lumen (Figure 3.3). A layer of epithelial

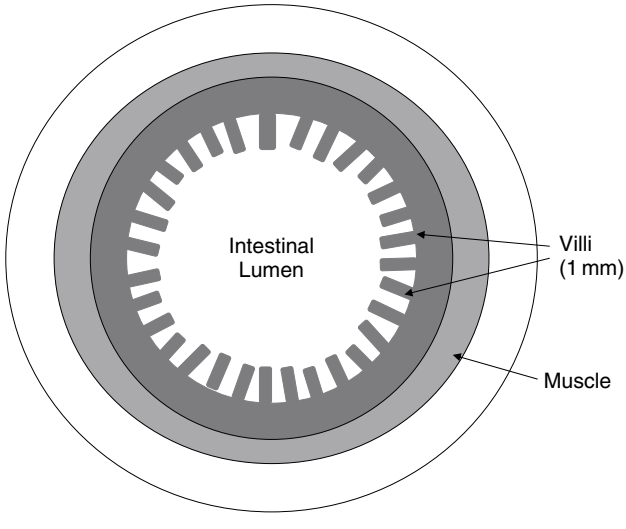

Figure 3.3 ► Diagram of the cross-section of the small intestine.

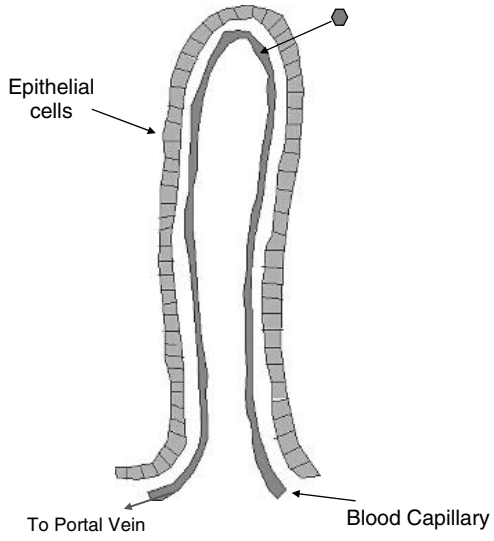

Figure 3.4 ► Diagram of a gastrointestinal villus.

cells cover the surface of the villi (Figure 3.4) and forms the primary permeation barrier to drug molecules. A compound must pass through this cellular membrane to reach the blood capillary and subsequent systemic circulation. Another morphological feature that enhances surface area is the microvilli on the luminal side of the epithelial cells (Figure 3.5). The microvilli extend 1 μm into the lumen and are called the *brush border*.

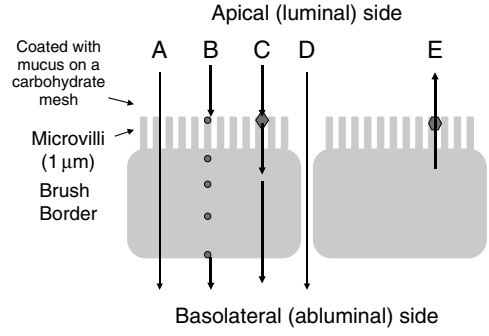

Figure 3.5 ► Permeation mechanisms through the gastrointestinal epithelial cells: (A) passive diffusion, (B) endocytosis, (C) uptake transport, (D) paracellular transport, (E) efflux transport.

3.4.1 Permeation of the Gastrointestinal Cellular Membrane

Compounds permeate through cellular membrane barriers by several different mechanisms (Figure 3.5). In passive diffusion, molecules diffuse through the lipid bilayer membranes and cytoplasm. Some types of transporters in the membrane perform active uptake of compounds that are ligands. Other types of transporters perform efflux of compounds from the cells (see Chapter 9). P-glycoprotein (Pgp) is a well-known efflux transporter. Paracellular permeation between the cells is available to smaller, more polar compounds. In endocytosis, molecules are engulfed by membrane and move through the cell in vesicles. Permeation mechanisms are discussed in greater detail in Chapter 8.

3.4.2 Passive Diffusion at the Molecular Level

Passive diffusion is generally the predominant permeation mechanism for most drugs. The cellular lipid bilayer membrane is shown in Figure 3.6. It consists of phospholipid molecules that self-assemble as a bilayer, with the aliphatic portion on the inside, away from the water molecules, and the polar phosphate and head groups oriented toward the water molecules. Passive diffusion involves movement of drug molecules through the bilayer as follows. The hydrating water molecules around the drug molecule are shed, and hydrogen bonds are broken. The molecule then passes through the region of polar head groups of the phospholipid molecules. It encounters the tightly packed lipid chains around the glycerol backbone and moves to the more disordered lipophilic region of the lipid aliphatic chains in the middle region of the bilayer. Molecules with a larger molecular size (i.e., higher molecular weight [MW]) do not pass through the tightly packed region as readily as smaller molecules. Molecules with higher lipophilicity typically are more permeable than less lipophilic molecules through the highly nonpolar central core of the lipid bilayer membrane. Molecules then move through the side chains and polar head groups of the other leaflet of the bilayer and are rehydrated by water molecules and form hydrogen bonds again. The highest energy barriers for passive diffusion through the bilayer appear to be the tightly packed, highly ordered regions of the phospholipids side chains in the region near the glycerol backbone[2] on both sides of the bilayer.

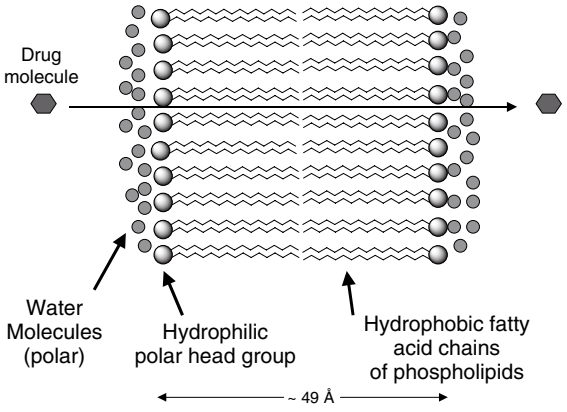

Figure 3.6 ► Passive diffusion of drug molecule through lipid bilayer membrane.

The chemical structures of representative phospholipid molecules are shown in Figure 3.7. One of the alcohol groups of the glycerol backbone is attached to a phosphate group, which in turn is attached to a head group. Examples of head groups of common phospholipids are shown in Figure 3.7. Phosphatidylcholine is a common phospholipid found in many membranes. The head groups impart a charge and polarity to the outside of the membrane. Membranes also contain other components, such as cholesterol and transmembrane proteins (e.g., channels, transporters, receptors). The membranes in a specific tissue are composed of a specific mixture of phospholipids and other components, which may be different from other tissues. Thus, a compound might have different passive diffusion membrane permeability in different tissues (e.g., GI tract vs blood–brain barrier).

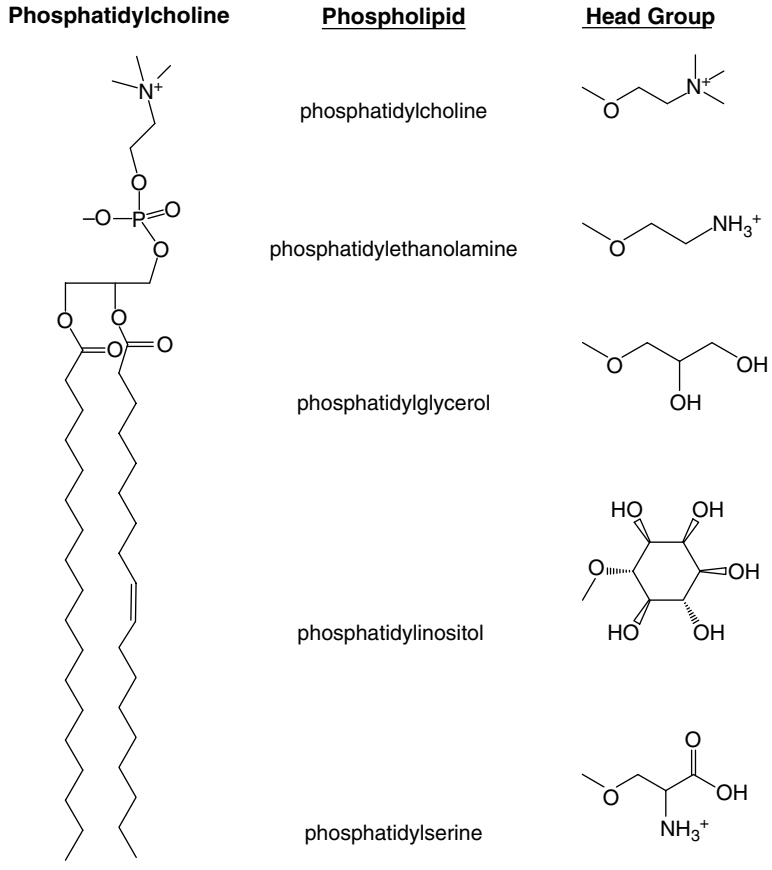

Figure 3.7 ► Structures of some common phospholipids.

3.4.3 Metabolism in the Intestine

Drug molecules can be metabolized in the intestine. Cytochrome P450 3A4 isozyme (CYP3A4) is a major metabolic enzyme in intestinal epithelial cells. This isozyme metabolizes diverse compound structures. Intestinal metabolism is considered part of "first-pass metabolism," which is the initial metabolism of drugs before they reach systemic circulation.

CYP3A4 has similar substrate specificity to Pgp. The two seem to work in concert; Pgp reduces the intracellular concentration of drug in the epithelial cells, which allows CYP3A4 to catalyze drug oxidation in an efficient manner, without being saturated.[1]

3.4.4 Enzymatic Hydrolysis in the Intestine

The natural function of the GI system is the digestion and absorption of nutrients to sustain the living system. Food contains macromolecules that are made up of the monomers that are needed to produce energy and build specific proteins, carbohydrates, lipids and nucleic acids for that organism. Breakdown of the macromolecules is accomplished by a variety of GI enzymes from the pancreas, stomach, and saliva. Protein digestion to amino acids is accomplished by peptidases, such as pepsin, which is secreted into the stomach, and trypsin and chymotrypsin, which are secreted by the pancreas into the small intestine. Fat digestion to fatty acids is performed by esterases, such as lipase, which is secreted by the pancreas into the small intestine. Ribonuclease and deoxyribonuclease digest RNA and DNA, respectively. Phosphatases and phosphodiesterases are other common enzymes.

GI enzymes can also catalyze drug hydrolysis. Drugs that contain derivatives of carboxylic acids, such as esters, amides, and carbamates, are especially susceptible. Enzymes are found in the intestinal lumen and are present in high concentration at the brush border. Thus, drugs can be hydrolyzed before they reach the bilayer membrane. Solution stability is discussed in Chapter 13.

Prodrugs are designed to take advantage of hydrolysis. Compounds that have a desirable pharmacological effect, but lack sufficient solubility for absorption, have been modified to add a substructure that increases solubility in the intestine (e.g., phosphate). The increased solubility allows the modified compound to diffuse to the cell surface. The hydrolytic enzyme cleaves off this substructure, just before it reaches the bilayer membrane. The active drug is released and permeates through the epithelial cells to reach systemic circulation. Prodrugs are the subject of Chapter 39.

The barriers to drug absorption in the GI tract, discussed in this chapter, are summarized in Figure 3.8 and Table 3.3. The dynamic balance of permeation mechanisms (passive, active uptake, efflux), pH and enzyme-induced hydrolysis, CYP metabolism, solubility, and dissolution rate affect the net rate of absorption in the intestine. Medicinal chemists should consider all of these mechanisms when trying to diagnose the causes of poor PK (see Chapter 38).

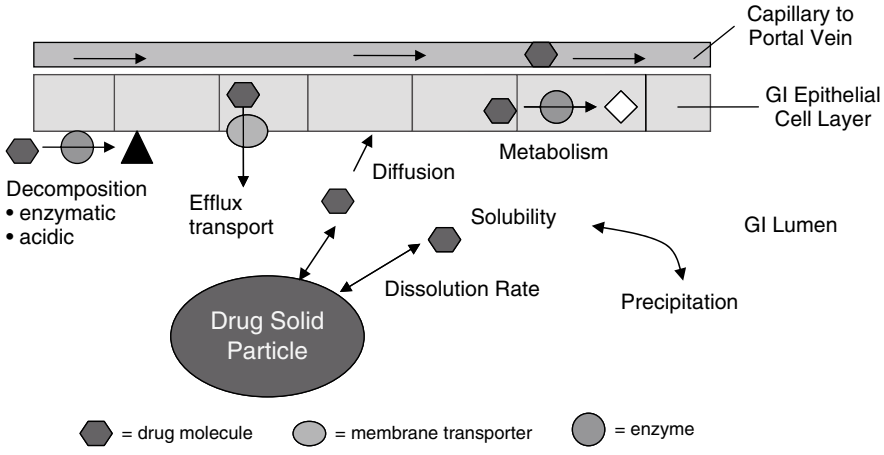

Figure 3.8 ► Composite diagram of barriers to drug absorption in the gastrointestinal tract.

TABLE 3.3 ► Drug Barriers in the Gastrointestinal Tract

Property	Description
Dissolution rate	Rate of transfer of compound from the surface of the particle to aqueous solution
Solubility	Maximum concentration that can be reached under the present conditions
Permeability	Movement from an aqueous solution through a lipid membrane to the aqueous solution on the other side
Chemical instability	Reaction of compound as a result of an environmental condition (e.g., pH, water)
Hydrolyzing enzymes	Naturally occurring enzymes that catalyze hydrolysis of food molecules and can catalyze hydrolysis of some drugs

3.4.5 Absorption Enhancement in the Intestine

A number of factors can enhance absorption of molecules in the intestine (Figure 3.9). One major factor that can be manipulated by discovery scientists is increasing the dissolution rate. This can be accomplished by reducing the particle size, which increases surface area. Particle size is reduced by grinding the solid material or by using techniques that produce nanoparticles. With greater surface area, more of the compound is solubilized in the same time. Salt form also can be manipulated to increase dissolution rate. Several possible counter ions are often screened to select a salt form having a higher dissolution rate. Formulation also is manipulated to enhance dissolution rate. Embedding the compound in excipients that break apart in an aqueous environment can rapidly disperse the compound material in the stomach, thus increasing the dissolution rate (see Chapter 41).

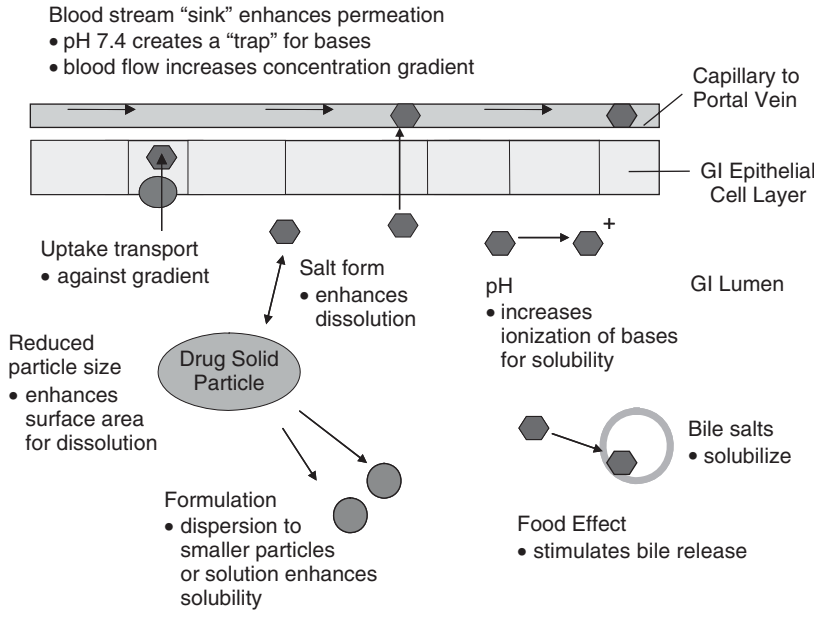

Figure 3.9 ► Composite diagram of factors that enhance drug absorption in the gastrointestinal tract through enhancement of permeation, dissolution, and solubility.

Another factor that contributes to absorption is solubility. This can be enhanced for a discovery lead compound by structural modifications that introduce a solubilizing functional group (see Chapter 7). Solubility is enhanced by bile salts (e.g., taurocholate, glycocholate) that are released by the gallbladder into the duodenum during stomach emptying and form micelles. Their natural function is the solubilization of lipophilic food components, such as lipids (e.g., triacylglycerols). In the same manner, bile salts serve to solubilize lipophilic drug molecules. This produces a greater concentration of lipophilic drugs in luminal solution. Bile salts carry the lipophilic molecules to the surface of the epithelium for enhanced absorption. Food intake stimulates the release of bile salts.

The pH of the gastric lumen can enhance solubility. For example, the solubility of basic compounds is enhanced at lower pHs values, and the solubility of acidic compounds is enhanced at higher pH values.

Uptake transporters enhance the absorption of some drugs. The natural function of uptake transporters is to enhance nutrient absorption. If the molecule has affinity for a transporter, its absorption might be enhanced (see Chapter 9).

Absorption is facilitated by removal of drug molecules from the intestine by blood flow. Capillary vessels sweep drug molecules into the portal vein and quickly away from the intestine. This creates a concentration gradient that increases passive diffusion in the absorptive direction.

3.5 Barriers in the Bloodstream

In the bloodstream, three barriers affect drugs: enzymatic hydrolysis, plasma protein binding, and red blood cell binding. Each of these barriers can reduce the free unchanged drug in systemic circulation, reducing penetration into the tissues.

3.5.1 Plasma Enzyme Hydrolysis

A large number of enzymes are present in blood for natural functions. They include cholinesterase, aldolase, lipase, dehydropeptidase, alkaline and acid phosphatase, glucuronidase, dehydrogenase, and phenol sulfatase. The substrate specificity and relative amount of these enzymes vary with species, disease state, gender, age, and race. A drug molecule may also be a substrate for an enzyme in the blood. The most common reaction is hydrolysis. Stability in plasma is the subject of Chapter 12.

3.5.2 Plasma Protein Binding

Approximately 6% to 8% of plasma is protein, and a large percentage of this serves as carrier protein for naturally occurring compounds. Drugs often reversibly bind to these proteins as well, which reduces the concentration of free drug in solution. The affinity of binding determines the ratio of bound and unbound ("free") drug in solution. There is high capacity for drug binding in plasma, and it is normally not saturated unless the drug concentration is very high. Protein binding results in a constant fraction of bound and free drug over a wide total drug concentration range. The concentrations of plasma proteins can vary with disease state and age. The three types of binding proteins in plasma are albumin, α_1-acid glycoprotein, and lipoproteins.

Human serum albumin has at least six binding sites with molecular binding specificity. Two sites bind fatty acids and another binds bilirubin. Two sites bind acidic drugs. Warfarin and phenylbutazone bind at one site and diazepam and ibuprofen at another.[3] Other drugs can also bind to sites on human serum albumin.

Basic drugs can bind to α_1-acid glycoprotein. This protein has one binding site. Examples of drugs that bind to α_1-acid glycoprotein include disopyramide and lignocaine. This protein can be saturated at higher drug concentrations.

Lipoproteins occur as particles and serve the natural function of transporting cholesterol and triacylgylcerols (hydrophobic lipids). They consist of nonpolar lipids, surrounded by more polar lipids and protein. Binding of drug molecules involves nonspecific lipophilic interactions.

Protein binding has several effects on drug disposition, which can have complex and counteracting effects. For example:

- Only unbound "free" drug permeates the membranes of the capillary blood vessels to enter the tissues. The drug must reach a therapeutic concentration in the tissues to produce the desired pharmacologic action. The free drug in the tissues reaches equilibrium with the free drug in the plasma. Thus, high binding limits free drug concentration in tissue.

- Only unbound drug permeates into the liver and kidney for clearance. Thus, high binding reduces clearance of a drug from the body and increases PK half-life.
- The kinetics and affinity of binding are important. For some drugs, binding to the plasma protein has a fast "off rate," and free drug depletion from plasma into tissues will result in rapid re-equilibration of the concentration of free drug in the plasma. If a compound is a kidney active secretion transporter substrate (see Section 3.7), its affinity for the transporter likely is higher than its affinity for plasma protein. If re-equilibration is fast from plasma-protein bound to free drug in plasma, re-equilibration can occur within the kidney, thus making formerly bound drug available for extraction in the kidney during the same pass. The result is a high renal extraction rate. Plasma protein binding is discussed in Chapter 14.

3.5.3 Red Blood Cell Binding

Drug molecules can bind to red blood cells. This is primarily a lipophilic interaction with the cell membrane. Drug discovery projects often check for red cell binding of lead compounds.

3.6 Barriers in the Liver

The liver presents two major barriers to drugs: metabolism and biliary extraction. The liver is one of the two major organs of drug clearance from the body.

Within the liver, the portal vein, which carries drug molecules from the intestine, branches into successively smaller vessels. The narrowest are called *venous sinusoid*. A portion of the molecules in solution permeate through the walls of the vessels into the hepatocytes, which form narrow sheets that are highly vascularized by the venous sinusoids (Figure 3.10). A small duct is created where the hepatocytes meet, called the *bile canaliculus*. Within hepatocytes, compounds encounter an array of metabolic enzymes that can modify the structure. Drug molecules and metabolites permeate with bile into the bile canaliculus, from which the fluid moves into the hepatic ductile and into the gallbladder. Bile is released from the gallbladder into the small intestine, resulting in excretion of a significant amount of drug and metabolites in the feces. The fraction of a drug excreted by this route depends on the properties of the compound.

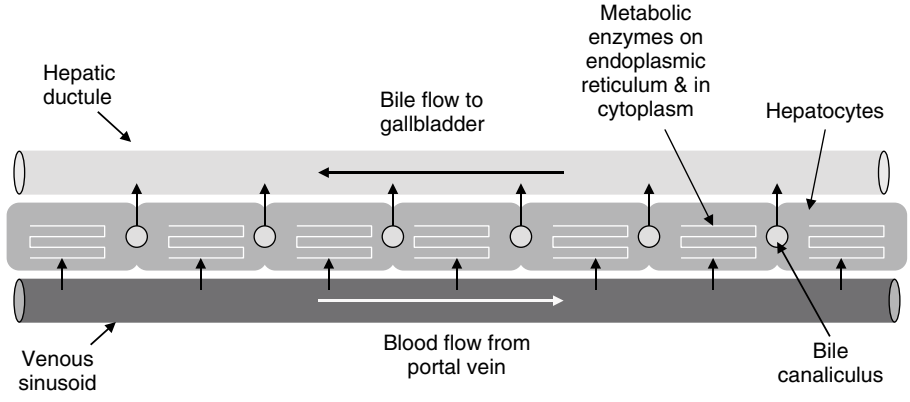

Figure 3.10 ► Diagram of hepatic clearance by metabolism in hepatocytes and extraction into bile.

3.6.1 Metabolism

Two types of metabolic reactions occur in the liver. The first is phase I, which causes changes to the drug molecule (e.g., hydroxylation), which are primarily oxidative. The second type of reaction is phase II, which adds polar groups to these oxidized positions or other substructures of the molecule. Metabolism serves the natural function of making xenobiotic compounds more polar so that they have higher partitioning into the aqueous bile and urine for excretion from the body. A high rate of metabolism results in rapid clearance, low exposure, and low bioavailability. Metabolism is a major route of drug clearance and is discussed in Chapter 11.

3.6.2 Biliary Excretion

A portion of the metabolite and unmetabolized drug molecules move into the bile by passive diffusion and active transport into the bile canaliculus. Transporters such as Pgp are present on the bile canaliculus membrane to actively transport some compounds into the bile. Transporters are discussed in Chapter 9. The distribution of various metabolites and the drug molecules from hepatocytes into the bile and blood depends on their properties (e.g., transporter affinity, passive diffusion, metabolic stability). After the bile is secreted into the intestine, some metabolite and drug molecules are reabsorbed from the intestinal lumen back into systemic circulation in a process called *enterohepatic circulation*. In addition to biliary excretion, some of the metabolite molecules and unmetabolized drug molecules move from the hepatocytes back into systemic circulation. This occurs by passive diffusion and active transport into the venous sinusoid. They eventually are extracted by the kidney.

3.7 Barriers in the Kidney

The liver and kidney are the major organs of elimination for most compounds. In the kidney, molecules of dosed compounds and metabolites permeate from the bloodstream into the urine for excretion. The permeation mechanisms are the same as found in other tissues of the body, primarily passive diffusion, paracellular, active uptake, and efflux.

The primary unit of renal (kidney) elimination is the nephron (Figure 3.11). The kidney contains thousands of nephrons. The first stage of renal elimination is termed *filtration*. Approximately 10% of total renal blood flow passes through the glomerulus, a complex mesh of blood capillaries. These present a high surface area to the Bowman's capsule, which is connected to the urinary system. The membranes of the Bowman's capsule have loose junctions, which allow a high rate of paracellular permeation of water, drug molecules, and other blood components but normally not proteins or cells. Molecules can also permeate passively.

In the proximal tubule, some drug molecules can be actively secreted from the bloodstream by transporters. For example, penicillins and glucuronides are transported by organic anion transporters, morphine and procaine are transported by organic cation transporters, and digoxin is transported by Pgp.[3] Much of the water (99%) and some of the drug molecules are reabsorbed by passive diffusion.

Reabsorption of molecules back into the bloodstream also occurs by passive and active transport mechanisms. The behavior of a particular drug is dependent on the same physicochemical properties (e.g., pK_a, lipophilicity) and transporter affinity as permeation in other tissues. The physiological factors affecting transport include blood flow, surface area, pH of the fluids, and transporter expression. Generally, metabolites in the blood are more readily eliminated by the kidney than their parent molecules because increasing polarity enhances extraction by the nephron. Urine flows through the ureter to the bladder from which it is excreted.

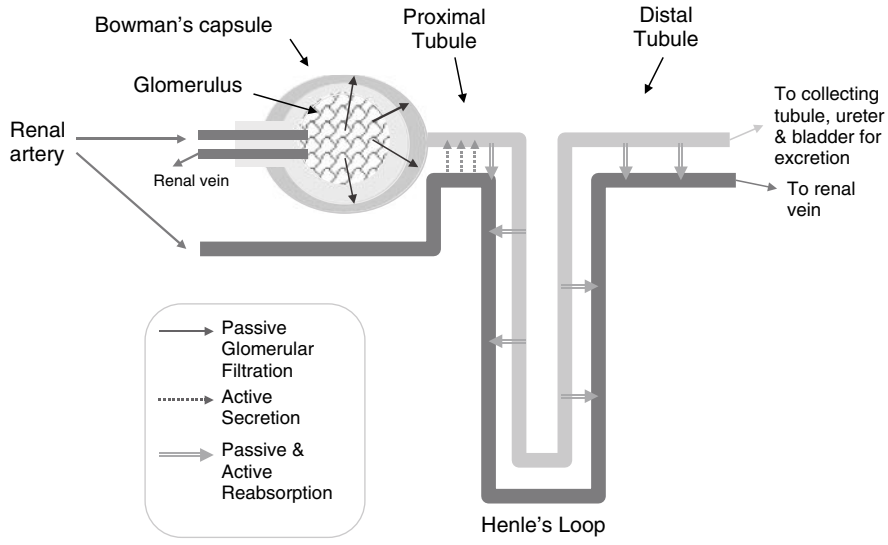

Figure 3.11 ► Diagram of drug extraction in the kidney nephrons.

3.8 Blood–Tissue Barriers

Some organs have barriers that reduce the penetration of drugs into the organ tissue. Such barriers exist at the placenta, testes, and brain. The barrier consists of a cellular layer that has properties that attenuate permeation. These barriers can include tight intercellular junctions that reduce paracellular permeation, efflux transporters that actively remove compound molecules from inside the cells or membrane, and a different lipid composition with different passive diffusion characteristics than the GI tract. A major issue in discovering drugs for neurological disorders is permeation of the blood–brain barrier, which is discussed in Chapter 10.

3.9 Tissue Distribution

The bloodstream carries compound molecules throughout all the tissues of the body. Distribution of drug into nontarget tissues effectively keeps it away from the target disease tissue. Compounds may depot in some tissues. For example, lipophilic compounds tend to accumulate in adipose tissues. Acidic compounds accumulate in muscle, which has a pH of approximately 6. The pH values of various physiological fluids and organs are listed in Table 3.4.

TABLE 3.4 ► pH Values of Physiological Fluids and Organs

Physiological fluid	pH
Blood	7.4
Stomach	1–3
Small intestine	5.5–7
Saliva	6.4
Cerebrospinal fluid	7.4
Muscle	6
Urine	5.8

Blood flow to an organ affects the time needed for the organ tissue drug concentration to equilibrate with the blood. High cardiac output (blood flow) to heart, lungs, kidney, and brain allows rapid equilibration of drugs with those organs. Cardiac output is lower to skin, bone, and fat, resulting in slower equilibration in these tissues.

3.10 Consequences of Chirality on Barriers and Properties

Chirality can have a significant effect on the behavior of compounds in vivo. It affects many properties owing to the different interaction of enantiomers with proteins in vivo. This affects the compound's PK and pharmacodynamics. Examples of properties affected by chirality and the causes (in parentheses) are as follows:

- Solubility (crystal forms of enantiomers are different)
- Efflux and uptake transport (binding to transporter)
- Metabolism (binding, orientation of molecule's positions to the reactive moiety)
- Plasma protein binding (binding)
- Toxicity, such as CYP inhibition, hERG blocking (binding)

An example is shown in Table 3.5. These drugs have differences in renal clearance owing to chirality. These differences likely are caused by differences in active transport in the nephrons (secretion or reabsorption) or by plasma protein binding. Additional discussion on the effects of chirality is found in chapters on specific properties.

TABLE 3.5 ► Stereoselectivity of Renal Clearance

Drug	Renal clearance enantiomeric ratio[a]
Quinidine	4.0
Disopyramide	1.8
Terbutaline	1.8
Chloroquine	1.6
Pindolol	1.2
Metoprolol	1.2

[a] ratio of renal clearances of the two enantiomers

3.11 Overview of In Vivo Barriers

The effects of individual barriers on in vivo delivery of compound to the therapeutic target are discussed in greater detail in following chapters. Poor delivery of the compound to the target results in reduced in vivo efficacy for a given dose. In vivo barriers are summarized in Figure 3.12. It is important for discovery project teams to assess how in vivo barriers affect their lead compounds. This is accomplished by assaying the compounds in vitro for key properties that predict performance at these barriers and making structural modifications to improve these properties.

There is often a tradeoff between structural features that enhance therapeutic target binding and structural features that enhance delivery to the target through optimal performance

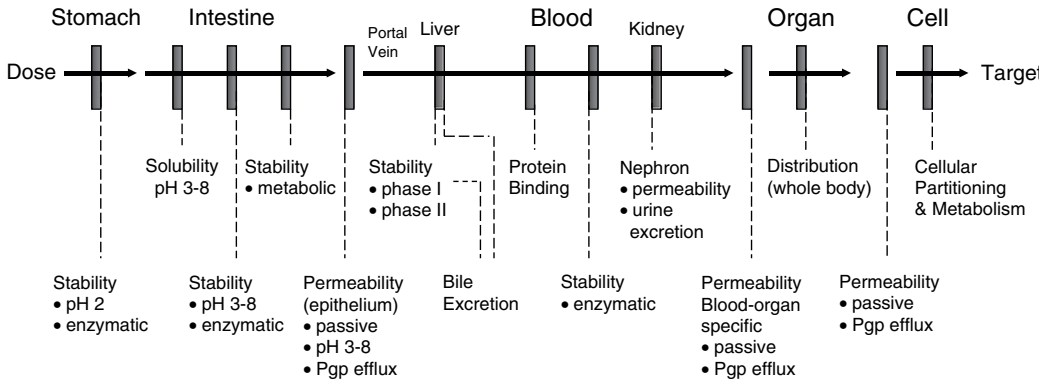

Figure 3.12 ► Overview of in vivo barriers to drug delivery to the target. (Reprinted with permission from [4].)

at in vivo barriers. If the sole focus of a drug discovery program is activity optimization, poor properties can result, leading to:

- ► Low absorption, owing to low solubility or permeability
- ► High clearance, owing to metabolism
- ► Clearance by hydrolysis in the GI tract or blood
- ► Efflux that opposes uptake in many membranes and enhances extraction in the liver and kidney
- ► High protein binding that limits free drug at the target
- ► Poor penetration of a blood–organ barrier at the target organ
- ► High volume of distribution due to lipophilicity

Each of these factors usually can be improved by medicinal chemists through structural modification.

Problems

(Answers can be found in Appendix I at the end of the book.)

1. List two factors that affect drug efficacy in vivo.
2. What is the preferred drug dosage form and regimen?
3. List some physicochemical and metabolic property limitations that reduce drug exposure in vivo.
4. What is the relationship of solubility to absorption?
5. What is the relationship of permeability to absorption?
6. What factors make drugs have lower absorption in the stomach than in the small intestine?
7. Is the pH higher or lower in the fasted state than in the fed state?

8. A greater portion of molecules of a basic compound is neutral in the: (a) upper intestine or (b) lower intestine? A greater portion of molecules of an acidic compound is ionized in the: (a) upper intestine or (b) lower intestine?
9. What is mixed with stomach contents as it enters the intestine, and what are the effects on drugs?
10. Charged versus neutral molecules are: (a) more permeable, (b) less permeable, (c) more soluble, or (d) less soluble?
11. Passive diffusion across lipid bilayer membranes is generally higher for molecules with: (a) lower lipophilicity or (b) higher lipophilicity?
12. List three barriers in the bloodstream.
13. For most drugs, the organs primarily involved in elimination are: (a) stomach, (b) large intestine, (c) portal vein, (d) small intestine, (e) liver, (f) kidney?
14. List two clearance mechanisms in the liver.
15. What barrier limits drug penetration to brain tissue?
16. Why are metabolites that are circulating in the blood generally more readily extracted by the kidney than the drug from which they were formed?
17. For most drugs, absorption occurs primarily in the: (a) stomach, (b) large intestine, (c) portal vein, (d) small intestine, (e) liver, (f) kidney.
18. Total absorption from the intestinal lumen into the bloodstream can be affected by which of the following properties of the compound?: (a) solubility, (b) permeability, (c) pK_a, (d) Pgp efflux, (e) metabolic stability, (f) molecular size, (g) enzymatic hydrolysis, (h) blood–brain barrier permeation.
19. Which of the following are effects of high plasma protein binding in vivo?: (a) reduced distribution to tissues, (b) increased metabolism, (c) reduced clearance.
20. Which of the following can be improved by structural modification of the lead?: (a) phase I metabolism, (b) efflux, (c) enzymatic decomposition, (d) solubility, (e) passive diffusion permeability.

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