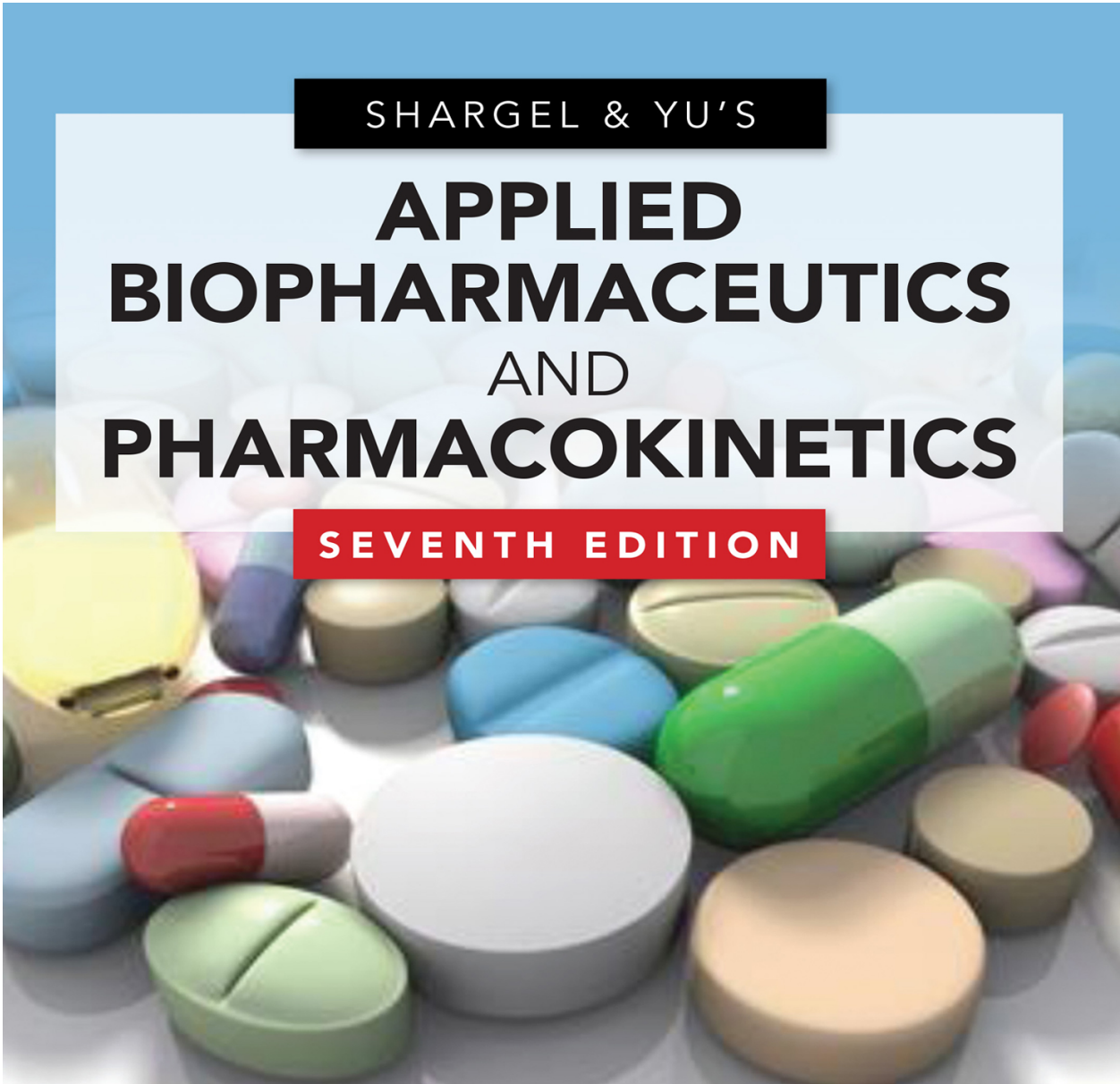




SHARGEL & YU'S

APPLIED BIOPHARMACEUTICS AND PHARMACOKINETICS

SEVENTH EDITION

LEON SHARGEL

ANDREW B.C. YU



Applied Biopharmaceutics & Pharmacokinetics

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Applied Biopharmaceutics & Pharmacokinetics

Seventh Edition

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ISBN: 978-0-07-182964-9

MHID: 0-07-182964-4

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-183093-5,
MHID: 0-07-183093-6.

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1

Introduction to Biopharmaceutics and Pharmacokinetics

Leon Shargel and Andrew B.C. Yu

Chapter Objectives

- ▶ Define drug product performance and biopharmaceutics.
- ▶ Describe how biopharmaceutics affects drug product performance.
- ▶ Define pharmacokinetics and describe how pharmacokinetics is related to pharmacodynamics and drug toxicity.
- ▶ Define the term clinical pharmacokinetics and explain how clinical pharmacokinetics may be used to develop dosage regimens for drugs in patients.
- ▶ Define pharmacokinetic model and list the assumptions that are used in developing a pharmacokinetic model.
- ▶ Explain how the prescribing information or approved labeling for a drug helps the practitioner to recommend an appropriate dosage regimen for a patient.

DRUG PRODUCT PERFORMANCE

Drugs are substances intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Drugs are given in a variety of dosage forms or *drug products* such as solids (tablets, capsules), semisolids (ointments, creams), liquids, suspensions, emulsions, etc., for systemic or local therapeutic activity. Drug products can be considered to be drug delivery systems that release and deliver drug to the site of action such that they produce the desired therapeutic effect. In addition, drug products are designed specifically to meet the patient's needs including palatability, convenience, and safety.

Drug product performance is defined as the release of the drug substance from the drug product either for local drug action or for drug absorption into the plasma for systemic therapeutic activity. Advances in pharmaceutical technology and manufacturing have focused on developing quality drug products that are safer, more effective, and more convenient for the patient.

BIOPHARMACEUTICS

Biopharmaceutics examines the interrelationship of the physical/chemical properties of the drug, the dosage form (drug product) in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. The importance of the drug substance and the drug formulation on absorption, and *in vivo* distribution of the drug to the site of action, is described as a sequence of events that precede elicitation of a drug's therapeutic effect. A general scheme describing this dynamic relationship is illustrated in Fig. 1-1.

First, the drug in its dosage form is taken by the patient by an oral, intravenous, subcutaneous, transdermal, etc., route of administration. Next, the drug is released from the dosage form in a predictable and characterizable manner. Then, some fraction of the drug is absorbed from the site of administration into either the surrounding tissue for local action or into the body (as with oral dosage forms), or both. Finally, the drug reaches the site of action. A pharmacodynamic response results when the drug concentration at the site of

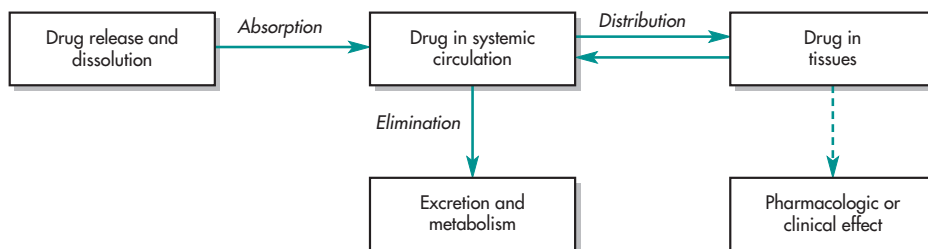


FIGURE 1-1 Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

action reaches or exceeds the *minimum effective concentration* (MEC). The suggested dosing regimen, including starting dose, maintenance dose, dosage form, and dosing interval, is determined in clinical trials to provide the drug concentrations that are therapeutically effective in most patients. This sequence of events is profoundly affected—in fact, sometimes orchestrated—by the design of the dosage form and the physicochemical properties of the drug.

Historically, pharmaceutical scientists have evaluated the relative drug availability to the body *in vivo* after giving a drug product by different routes to an animal or human, and then comparing specific pharmacologic, clinical, or possible toxic responses. For example, a drug such as isoproterenol causes an increase in heart rate when given intravenously but has no observable effect on the heart when given orally at the same dose level. In addition, the *bioavailability* (a measure of systemic availability of a drug) may differ from one drug product to another containing the same drug, even for the same route of administration. This difference in drug bioavailability may be manifested by observing the difference in the therapeutic effectiveness of the drug products. Thus, the nature of the drug molecule, the route of delivery, and the formulation of the dosage form can determine whether an administered drug is therapeutically effective, is toxic, or has no apparent effect at all.

The US Food and Drug Administration (FDA) approves all drug products to be marketed in the United States. The pharmaceutical manufacturers must perform extensive research and development prior to approval. The manufacturer of a new drug product must submit a *New Drug Application* (NDA) to the FDA, whereas a generic drug pharmaceutical manufacturer must submit an *Abbreviated New Drug Application* (ANDA). Both the new and generic drug

product manufacturers must characterize their drug and drug product and demonstrate that the drug product performs appropriately before the products can become available to consumers in the United States.

Biopharmaceutics provides the scientific basis for drug product design and drug product development. Each step in the manufacturing process of a finished dosage form may potentially affect the release of the drug from the drug product and the availability of the drug at the site of action. The most important steps in the manufacturing process are termed *critical manufacturing variables*. Examples of biopharmaceutic considerations in drug product design are listed in Table 1-1. A detailed discussion of drug product design is found in Chapter 15. Knowledge of physiologic factors necessary for designing oral products is discussed in Chapter 14. Finally, drug product quality of drug substance (Chapter 17) and drug product testing is discussed in later chapters (18, 19, 20, and 21). It is important for a pharmacist to know that drug product selection from multisources could be confusing and needs a deep understanding of the testing procedures and manufacturing technology which is included in the chemistry, manufacturing, and control (CMC) of the product involved. The starting material (SM) used to make the API (active pharmaceutical ingredient), the processing method used during chemical synthesis, extraction, and the purification method can result in differences in the API that can then affect drug product performance (Chapter 17). Sometimes a by-product of the synthetic process, residual solvents, or impurities that remain may be harmful or may affect the product's physical or chemical stability. Increasingly, many drug sources are imported and the manufacturing of these products is regulated by codes or pharmacopeia in other countries. For example, drugs in Europe may be meeting EP (European Pharmacopeia) and since 2006,

TABLE 1-1 Biopharmaceutic Considerations in Drug Product Design

Items	Considerations
Therapeutic objective	Drug may be intended for rapid relief of symptoms, slow extended action given once per day, or longer for chronic use; some drug may be intended for local action or systemic action
Drug (active pharmaceutical ingredient, API)	Physical and chemical properties of API, including solubility, polymorphic form, particle size; impurities
Route of administration	Oral, topical, parenteral, transdermal, inhalation, etc
Drug dosage and dosage regimen	Large or small drug dose, frequency of doses, patient acceptance of drug product, patient compliance
Type of drug product	Orally disintegrating tablets, immediate release tablets, extended release tablets, transdermal, topical, parenteral, implant, etc
Excipients	Although very little pharmacodynamic activity, excipients may affect drug product performance including release of drug from drug product
Method of manufacture	Variables in manufacturing processes, including weighing accuracy, blending uniformity, release tests, and product sterility for parenterals

agreed uniform standards are harmonized in ICH guidelines for Europe, Japan, and the United States. In the US, the USP-NF is the official compendia for drug quality standards.

Finally, the equipment used during manufacturing, processing, and packaging may alter important product attribute. Despite compliance with testing and regulatory guidance involved, the issues involving

pharmaceutical equivalence, bioavailability, bioequivalence, and therapeutic equivalence often evolved by necessity. The implications are important regarding availability of quality drug product, avoidance of shortages, and maintaining an affordable high-quality drug products. The principles and issues with regard to multisource drug products are discussed in subsequent chapters:

Chapter 14	Physiologic Factors Related to Drug Absorption	How stomach emptying, GI residence time, and gastric window affect drug absorption
Chapter 15	Biopharmaceutic Considerations in Drug Product Design	How particle size, crystal form, solubility, dissolution, and ionization affect <i>in vivo</i> dissolution and absorption. Modifications of a product with excipient with regard to immediate or delayed action are discussed. Dissolution test methods and relation to <i>in vivo</i> performance
Chapter 16	Drug Product Performance, <i>In Vivo</i> : Bioavailability and Bioequivalence	Bioavailability and bioequivalence terms and regulations, test methods, and analysis examples. Protocol design and statistical analysis. Reasons for poor bioavailability. Bioavailability reference, generic substitution. PE, PA, BA/BE, API, RLD, TE SUPAC (Scale-up postapproval changes) regarding drug products. What type of changes will result in changes in BA, TE, or performances of drug products from a scientific and regulatory viewpoint
Chapter 17	Biopharmaceutic Aspects of the Active Pharmaceutical Ingredient and Pharmaceutical Equivalence	Physicochemical differences of the drug, API due to manufacturing and synthetic pathway. How to select API from multiple sources while meeting PE (pharmaceutical equivalence) and TE (therapeutic equivalence) requirement as defined in CFR. Examples of some drug failing TE while apparently meeting API requirements. Formulation factors and manufacturing method affecting PE and TE. How particle size and crystal form affect solubility and dissolution. How pharmaceutical equivalence affects therapeutic equivalence. Pharmaceutical alternatives. How physicochemical characteristics of API lead to pharmaceutical inequivalency
Chapter 18	Impact of Drug Product Quality and Biopharmaceutics on Clinical Efficacy	Drug product quality and drug product performance Pharmaceutical development. Excipient effect on drug product performance. Quality control and quality assurance. Risk management Scale-up and postapproval changes (SUPAC) Product quality problems. Postmarketing surveillance

Thus, biopharmaceutics involves factors that influence (1) the design of the drug product, (2) stability of the drug within the drug product, (3) the manufacture of the drug product, (4) the release of the drug from the drug product, (5) the rate of dissolution/release of the drug at the absorption site, and (6) delivery of drug to the site of action, which may involve targeting the drug to a localized area (eg, colon for Crohn disease) for action or for systemic absorption of the drug.

Both the pharmacist and the pharmaceutical scientist must understand these complex relationships to objectively choose the most appropriate drug product for therapeutic success.

The study of biopharmaceutics is based on fundamental scientific principles and experimental methodology. Studies in biopharmaceutics use both *in vitro* and *in vivo* methods. *In vitro* methods are procedures employing test apparatus and equipment without involving laboratory animals or humans. *In vivo* methods are more complex studies involving human subjects or laboratory animals. Some of these methods will be discussed in Chapter 15. These methods must be able to assess the impact of the physical and chemical properties of the drug, drug stability, and large-scale production of the drug and drug product on the biologic performance of the drug.

PHARMACOKINETICS

After a drug is released from its dosage form, the drug is absorbed into the surrounding tissue, the body, or both. The distribution through and elimination of the drug in the body varies for each patient but can be characterized using mathematical models and statistics. *Pharmacokinetics* is the science of the kinetics of drug absorption, distribution, and elimination (ie, metabolism and excretion). The description of drug distribution and elimination is often termed *drug disposition*. Characterization of drug disposition is an important prerequisite for determination or modification of dosing regimens for individuals and groups of patients.

The study of pharmacokinetics involves both experimental and theoretical approaches. The experimental aspect of pharmacokinetics involves the development of biologic sampling techniques,

analytical methods for the measurement of drugs and metabolites, and procedures that facilitate data collection and manipulation. The theoretical aspect of pharmacokinetics involves the development of pharmacokinetic models that predict drug disposition after drug administration. The application of statistics is an integral part of pharmacokinetic studies. Statistical methods are used for pharmacokinetic parameter estimation and data interpretation ultimately for the purpose of designing and predicting optimal dosing regimens for individuals or groups of patients. Statistical methods are applied to pharmacokinetic models to determine data error and structural model deviations. Mathematics and computer techniques form the theoretical basis of many pharmacokinetic methods. Classical pharmacokinetics is a study of theoretical models focusing mostly on model development and parameterization.

PHARMACODYNAMICS

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body; this includes the mechanisms of drug action and the relationship between drug concentration and effect. A typical example of pharmacodynamics is how a drug interacts quantitatively with a drug receptor to produce a response (effect). Receptors are the molecules that interact with specific drugs to produce a pharmacological effect in the body.

The pharmacodynamic effect, sometimes referred to as the pharmacologic effect, can be therapeutic and/or cause toxicity. Often drugs have multiple effects including the desired therapeutic response as well as unwanted side effects. For many drugs, the pharmacodynamic effect is dose/drug concentration related; the higher the dose, the higher drug concentrations in the body and the more intense the pharmacodynamic effect up to a maximum effect. It is desirable that side effects and/or toxicity of drugs occurs at higher drug concentrations than the drug concentrations needed for the therapeutic effect. Unfortunately, unwanted side effects often occur concurrently with the therapeutic doses. The relationship between pharmacodynamics and pharmacokinetics is discussed in Chapter 21.

CLINICAL PHARMACOKINETICS

During the drug development process, large numbers of patients are enrolled in clinical trials to determine efficacy and optimum dosing regimens. Along with safety and efficacy data and other patient information, the FDA approves a label that becomes the package insert discussed in more detail later in this chapter. The approved labeling recommends the proper starting dosage regimens for the general patient population and may have additional recommendations for special populations of patients that need an adjusted dosage regimen (see Chapter 23). These recommended dosage regimens produce the desired pharmacologic response in the majority of the anticipated patient population. However, intra- and interindividual variations will frequently result in either a subtherapeutic (drug concentration below the MEC) or a toxic response (drug concentrations above the *minimum toxic concentration*, MTC), which may then require adjustment to the dosing regimen. *Clinical pharmacokinetics* is the application of pharmacokinetic methods to drug therapy in patient care. Clinical pharmacokinetics involves a multidisciplinary approach to individually optimized dosing strategies based on the patient's disease state and patient-specific considerations.

The study of clinical pharmacokinetics of drugs in disease states requires input from medical and pharmaceutical research. Table 1-2 is a list of 10 age adjusted rates of death from 10 leading causes of death in the United States in 2003. The influence of many diseases on drug disposition is not adequately studied. Age, gender, genetic, and ethnic differences can also result in pharmacokinetic differences that may affect the outcome of drug therapy (see Chapter 23). The study of pharmacokinetic differences of drugs in various population groups is termed *population pharmacokinetics* (Sheiner and Ludden, 1992; see Chapter 22). Application of Pharmacokinetics to Specific Populations, Chapter 23, will discuss many of the important pharmacokinetic considerations for dosing subjects due to age, weight, gender, renal, and hepatic disease differences. Despite advances in modeling and genetics, sometimes it is necessary to monitor the plasma drug concentration precisely in a patient for safety and multidrug dosing consideration. Clinical pharmacokinetics is also applied to

TABLE 1-2 Ratio of Age-Adjusted Death Rates, by Male/Female Ratio from the 10 Leading Causes of Death* in the US, 2003

Disease	Rank	Male:Female
Disease of heart	1	1.5
Malignant neoplasms	2	1.5
Cerebrovascular diseases	3	4.0
Chronic lower respiration diseases	4	1.4
Accidents and others*	5	2.2
Diabetes mellitus	6	1.2
Pneumonia and influenza	7	1.4
Alzheimers	8	0.8
Nephrotis, nephrotic syndrome, and nephrosis	9	1.5
Septicemia	10	1.2

*Death due to adverse effects suffered as defined by CDC.

Source: National Vital Statistics Report Vol. 52, No. 3, 2003.

therapeutic drug monitoring (TDM) for very potent drugs, such as those with a narrow therapeutic range, in order to optimize efficacy and to prevent any adverse toxicity. For these drugs, it is necessary to monitor the patient, either by monitoring plasma drug concentrations (eg, theophylline) or by monitoring a specific pharmacodynamic endpoint such as prothrombin clotting time (eg, warfarin). Pharmacokinetic and drug analysis services necessary for safe drug monitoring are generally provided by the *clinical pharmacokinetic service* (CPKS). Some drugs frequently monitored are the aminoglycosides and anti-convulsants. Other drugs closely monitored are those used in cancer chemotherapy, in order to minimize adverse side effects (Rodman and Evans, 1991).

Labeling For Human Prescription Drug and Biological Products

In 2013, the FDA redesigned the format of the prescribing information necessary for safe and effective use of the drugs and biological products

(FDA Guidance for Industry, 2013). This design was developed to make information in prescription drug labeling easier for health care practitioners to access and read. The practitioner can use the prescribing information to make prescribing decisions. The labeling includes three sections:

- *Highlights of Prescribing Information (Highlights)*—contains selected information from the Full Prescribing Information (FPI) that health care practitioners most commonly reference and consider most important. In addition, highlights may contain any boxed warnings that give a concise summary of all of the risks described in the **Boxed Warning** section in the **FPI**.
- *Table of Contents (Contents)*—lists the sections and subsections of the FPI.
- *Full Prescribing Information (FPI)*—contains the detailed prescribing information necessary for safe and effective use of the drug.

An example of the Highlights of Prescribing Information and Table of Contents for Nexium (esomeprazole magnesium) delayed release capsules appears in Table 1-3B. The prescribing information sometimes referred to as the approved label or the package insert may be found at the FDA website, Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>). Prescribing information is updated periodically as new information becomes available. The prescribing information contained in the label recommends dosage regimens for the average patient from data obtained from clinical trials. The indications and usage section are those indications that the FDA has approved and that have been shown to be effective in clinical trials. On occasion, a practitioner may want to prescribe the drug to a patient drug for a non-approved use or indication. The pharmacist must decide if there is sufficient evidence for dispensing the drug for a non-approved use (off-label indication). The decision to dispense a drug for a non-approved indication may be difficult and often made with consultation of other health professionals.

Clinical Pharmacology

Pharmacology is a science that generally deals with the study of drugs, including its mechanism, effects, and uses of drugs; broadly speaking, it includes

pharmacognosy, pharmacokinetics, pharmacodynamics, pharmacotherapeutics, and toxicology. The application of pharmacology in clinical medicine including clinical trial is referred to as clinical pharmacology. For pharmacists and health professionals, it is important to know that NDA drug labels report many important study information under **Clinical Pharmacology** in Section 12 of the standard prescription label (Tables 1-3A and 1-3B).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

Question

Where is toxicology information found in the prescription label for a new drug? Can I find out if a drug is mutagenic under side-effect sections?

Answer

Nonclinical toxicology information is usefully in Section 13 under **Nonclinical Toxicology** if available. Mutagenic potential of a drug is usually reported under animal studies. It is unlikely that a drug with known humanly mutagenicity will be marketed, if so, it will be labeled with special warning. Black box warnings are usually used to give warnings to prescribers in Section 5 under Warnings and Precautions.

Pharmacogenetics

Pharmacogenetics is the study of drug effect including distribution and disposition due to genetic differences, which can affect individual responses to drugs, both in terms of therapeutic effect and adverse effects. A related field is pharmacogenomics, which emphasizes different aspects of genetic effect on drug response. This important discipline is discussed in Chapter 13. Pharmacogenetics is the main reason why many new drugs still have to be further studied after regulatory approval, that is, postapproval phase 4 studies. The clinical trials prior to drug approval are generally limited such that some side effects and special responses due to genetic differences may not be adequately known and labeled.

TABLE 1-3A Highlights of Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules

HIGHLIGHTS OF PRESCRIBING INFORMATION		
<p>These highlights do not include all the information needed to use NEXIUM safely and effectively. See full prescribing information for NEXIUM.</p> <p>NEXIUM (esomeprazole magnesium) delayed-release capsules, for oral use</p> <p>NEXIUM (esomeprazole magnesium) for delayed-release oral suspension</p> <p>Initial U.S. Approval: 1989 (omeprazole)</p>		
RECENT MAJOR CHANGES		
Warnings and Precautions. Interactions with Diagnostic Investigations for Neuroendocrine Tumors (5.8)		03/2014
INDICATIONS AND USAGE		
<p>NEXIUM is a proton pump inhibitor indicated for the following:</p> <ul style="list-style-type: none"> • Treatment of gastroesophageal reflux disease (GERD) (1.1) • Risk reduction of NSAID-associated gastric ulcer (1.2) • <i>H. pylori</i> eradication to reduce the risk of duodenal ulcer recurrence (1.3) • Pathological hypersecretory conditions, including Zollinger-Ellison syndrome (1.4) 		
DOSAGE AND ADMINISTRATION		
Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Adults	20 mg or 40 mg	Once daily for 4 to 8 weeks
12 to 17 years	20 mg or 40 mg	Once daily for up to 8 weeks
1 to 11 years	10 mg or 20 mg	Once daily for up to 8 weeks
1 month to less than 1 year 2.5 mg, 5 mg or 10 mg (based on weight). Once daily, up to 6 weeks for erosive esophagitis (EE) due to acid-mediated GERD only.		
Risk Reduction of NSAID-Associated Gastric Ulcer		
	20 mg or 40 mg	Once daily for up to 6 months
<i>H. pylori</i> Eradication (Triple Therapy):		
NEXIUM	40 mg	Once daily for 10 days
Amoxicillin	1000 mg	Twice daily for 10 days
Clarithromycin	500 mg	Twice daily for 10 days
Pathological Hypersecretory Conditions		
	40 mg	Twice daily
See full prescribing information for administration options (2)		
Patients with severe liver impairment do not exceed dose of 20 mg (2)		
DOSAGE FORMS AND STRENGTHS		
<ul style="list-style-type: none"> • NEXIUM Delayed-Release Capsules: 20 mg and 40 mg (3) • NEXIUM for Delayed-Release Oral Suspension: 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg (3) 		
CONTRAINDICATIONS		
Patients with known hypersensitivity to proton pump inhibitors (PPIs) (angioedema and anaphylaxis have occurred) (4)		

(Continued)

TABLE 1-3A Highlights of Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules (Continued)

HIGHLIGHTS OF PRESCRIBING INFORMATION	
WARNINGS AND PRECAUTIONS	
<ul style="list-style-type: none"> • Symptomatic response does not preclude the presence of gastric malignancy (5.1) • Atrophic gastritis has been noted with long-term omeprazole therapy (5.2) • PPI therapy may be associated with increased risk of <i>Clostridium difficile</i>-associated diarrhea (5.3) • Avoid concomitant use of NEXIUM with clopidogrel (5.4) • Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine (5.5) • Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.6) • Avoid concomitant use of NEXIUM with St John's Wort or rifampin due to the potential reduction in esomeprazole levels (5.7,7.3) • Interactions with diagnostic investigations for Neuroendocrine Tumors: Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased chromogranin A levels which may interfere with diagnostic investigations for neuroendocrine tumors (5.8,12.2) 	
ADVERSE REACTIONS	
<p>Most common adverse reactions (6.1):</p> <ul style="list-style-type: none"> • Adults (≥ 18 years) (incidence $\geq 1\%$) are headache, diarrhea, nausea, flatulence, abdominal pain, constipation, and dry mouth • Pediatric (1 to 17 years) (incidence $\geq 2\%$) are headache, diarrhea, abdominal pain, nausea, and somnolence • Pediatric (1 month to less than 1 year) (incidence 1%) are abdominal pain, regurgitation, tachypnea, and increased ALT <p>To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.</p>	
DRUG INTERACTIONS	
<ul style="list-style-type: none"> • May affect plasma levels of antiretroviral drugs – use with atazanavir and nelfinavir is not recommended: if saquinavir is used with NEXIUM, monitor for toxicity and consider saquinavir dose reduction (7.1) • May interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, erlotinib, and digoxin) Patients treated with NEXIUM and digoxin may need to be monitored for digoxin toxicity. (7.2) • Combined inhibitor of CYP 2C19 and 3A4 may raise esomeprazole levels (7.3) • Clopidogrel: NEXIUM decreases exposure to the active metabolite of clopidogrel (7.3) • May increase systemic exposure of cimetidine and an active metabolite. Consider dose reduction (7.3) • Tacrolimus: NEXIUM may increase serum levels of tacrolimus (7.5) • Methotrexate: NEXIUM may increase serum levels of methotrexate (7.7) 	
USE IN SPECIFIC POPULATIONS	
<ul style="list-style-type: none"> • Pregnancy: Based on animal data, may cause fetal harm (8.1) <p>See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.</p>	
Revised: 03/2014	

PRACTICAL FOCUS

Relationship of Drug Concentrations to Drug Response

The initiation of drug therapy starts with the manufacturer's recommended dosage regimen that includes the drug dose and frequency of doses (eg, 100 mg every 8 hours). Due to individual differences in the patient's genetic makeup (see Chapter 13 on

pharmacogenetics) or pharmacokinetics, the recommended dosage regimen drug may not provide the desired therapeutic outcome. The measurement of plasma drug concentrations can confirm whether the drug dose was subtherapeutic due to the patient's individual pharmacokinetic profile (observed by low plasma drug concentrations) or was not responsive to drug therapy due to genetic difference in receptor response. In this case, the drug concentrations

TABLE 1-3B Contents for Full Prescribing Information for Nexium (Esomeprazole Magnesium) Delayed Release Capsules

FULL PRESCRIBING INFORMATION: CONTENTS*	
1. INDICATIONS AND USAGE	
1.1 Treatment of Gastroesophageal Reflux Disease (GERD)	
1.2 Risk Reduction of NSAID-Associated Gastric Ulcer	
1.3 <i>H. pylori</i> Eradication to Reduce the Risk of Duodenal Ulcer Recurrence	
1.4 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	
2. DOSAGE AND ADMINISTRATION	
3. DOSAGE FORMS AND STRENGTHS	
4. CONTRAINDICATIONS	
5. WARNINGS AND PRECAUTIONS	
5.1 Concurrent Gastric Malignancy	
5.2 Atrophic Gastritis	
5.3 <i>Clostridium difficile</i> associated diarrhea	
5.4 Interaction with Clopidogrel	
5.5 Bone Fracture	
5.6 Hypomagnesemia	
5.7 Concomitant Use of NEXIUM with St John's Wort or rifampin	
5.8 Interactions with Diagnostic Investigations for Neuroendocrine Tumors	
5.9 Concomitant Use of NEXIUM with Methotrexate	
6. ADVERSE REACTIONS	
6.1 Clinical Trials Experience	
6.2 Postmarketing Experience	
7. DRUG INTERACTIONS	
7.1 Interference with Antiretroviral Therapy	
7.2 Drugs for Which Gastric pH Can Affect Bioavailability	
7.3 Effects on Hepatic Metabolism/Cytochrome P-450 Pathways	
7.4 Interactions with Investigations of Neuroendocrine Tumors	
7.5 Tacrolimus	
7.6 Combination Therapy with Clarithromycin	
7.7 Methotrexate	
8. USE IN SPECIFIC POPULATIONS	
8.1 Pregnancy	
8.3 Nursing Mothers	
8.4 Pediatric Use	
8.5 Geriatric Use	
10. OVERDOSAGE	
11. DESCRIPTION	
12. CLINICAL PHARMACOLOGY	
12.1 Mechanism of Action	
12.2 Pharmacodynamics	
12.3 Pharmacokinetics	
12.4 Microbiology	
13. NONCLINICAL TOXICOLOGY	
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	
13.2 Animal Toxicology and/or Pharmacology	
14. CLINICAL STUDIES	
14.1 Healing of Erosive Esophagitis	
14.2 Symptomatic Gastroesophageal Reflux Disease (GERD)	
14.3 Pediatric Gastroesophageal Reflux Disease (GERD)	
14.4 Risk Reduction of NSAID-Associated Gastric Ulcer	
14.5 <i>Helicobacter pylori</i> (<i>H. Pylon</i>) Eradication in Patients with Duodenal Ulcer Disease	
14.6 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	
16. HOW SUPPLIED/STORAGE AND HANDLING	
17. PATIENT COUNSELING INFORMATION	

*Sections or subsections omitted from the full prescribing information are not listed.

Source: FDA Guidance for Industry (February 2013).

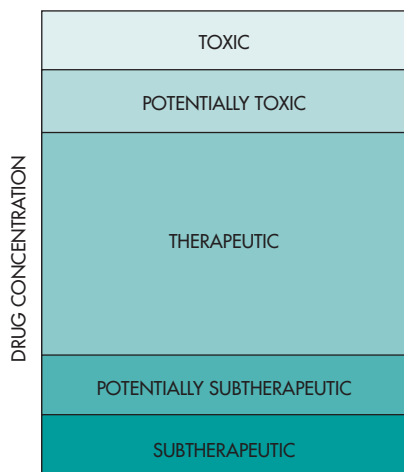


FIGURE 1-2 Relationship of drug concentrations to drug response.

are in the therapeutic range but the patient does not respond to drug treatment. Figure 1-2 shows that the concentration of drug in the body can range from subtherapeutic to toxic. In contrast, some patients respond to drug treatment at lower drug doses that result in lower drug concentrations. Other patients may need higher drug concentrations to obtain a therapeutic effect, which requires higher drug doses. It is desirable that adverse drug responses occur at drug concentrations higher relative to the therapeutic drug concentrations, but for many potent drugs, adverse effects can also occur close to the same drug concentrations as needed for the therapeutic effect.

Frequently Asked Questions

- ▶ Which is more closely related to drug response, the total drug dose administered or the concentration of the drug in the body?
- ▶ Why do individualized dosing regimens need to be determined for some patients?

PHARMACODYNAMICS

Pharmacodynamics refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical

and physiologic effects that influence the interaction of drug with the receptor. The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events resulting in a pharmacologic or toxic response. Pharmacokinetic–pharmacodynamic models are constructed to relate plasma drug level to drug concentration at the site of action and establish the intensity and time course of the drug. Pharmacodynamics and pharmacokinetic–pharmacodynamic models are discussed more fully in Chapter 21.

DRUG EXPOSURE AND DRUG RESPONSE

Drug exposure refers to the dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (eg, C_{max} , C_{min} , C_{ss} , AUC) (FDA Guidance for Industry, 2003). *Drug response* refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from the clinically remote biomarkers (eg, receptor occupancy) to a presumed mechanistic effect (eg, ACE inhibition), to a potential or accepted surrogate (eg, effects on blood pressure, lipids, or cardiac output), and to the full range of short-term or long-term clinical effects related to either efficacy or safety.

Toxicologic and efficacy studies provide information on the safety and effectiveness of the drug during development and in special patient populations such as subjects with renal and hepatic insufficiencies. For many drugs, clinical use is based on weighing the risks of favorable and unfavorable outcomes at a particular dose. For some potent drugs, the doses and dosing rate may need to be titrated in order to obtain the desired effect and be tolerated.

TOXICOKINETICS AND CLINICAL TOXICOLOGY

Toxicokinetics is the application of pharmacokinetic principles to the design, conduct, and interpretation of drug safety evaluation studies (Leal et al, 1993) and in validating dose-related exposure in animals. Toxicokinetic data aid in the interpretation

of toxicologic findings in animals and extrapolation of the resulting data to humans. Toxicokinetic studies are performed in animals during preclinical drug development and may continue after the drug has been tested in clinical trials.

Clinical toxicology is the study of adverse effects of drugs and toxic substances (poisons) in the body. The pharmacokinetics of a drug in an overmedicated (intoxicated) patient may be very different from the pharmacokinetics of the same drug given in lower therapeutic doses. At very high doses, the drug concentration in the body may saturate enzymes involved in the absorption, biotransformation, or active renal secretion mechanisms, thereby changing the pharmacokinetics from linear to *nonlinear pharmacokinetics*. Nonlinear pharmacokinetics is discussed in Chapter 10. Drugs frequently involved in toxicity cases include acetaminophen, salicylates, opiates (eg, morphine), and the tricyclic antidepressants (TCAs). Many of these drugs can be assayed conveniently by fluorescence immunoassay (FIA) kits.

MEASUREMENT OF DRUG CONCENTRATIONS

Because drug concentrations are an important element in determining individual or population pharmacokinetics, drug concentrations are measured in biologic samples, such as milk, saliva, plasma, and urine. Sensitive, accurate, and precise analytical methods are available for the direct measurement of drugs in biologic matrices. Such measurements are generally validated so that accurate information is generated for pharmacokinetic and clinical monitoring. In general, chromatographic and mass spectrometric methods are most frequently employed for drug concentration measurement, because chromatography separates the drug from other related materials that may cause assay interference and mass spectrometry allows detection of molecules or molecule fragments based on their mass-to-charge ratio.

Sampling of Biologic Specimens

Only a few biologic specimens may be obtained safely from the patient to gain information as to the drug concentration in the body. *Invasive methods*

include sampling blood, spinal fluid, synovial fluid, tissue biopsy, or any biologic material that requires parenteral or surgical intervention in the patient. In contrast, *noninvasive methods* include sampling of urine, saliva, feces, expired air, or any biologic material that can be obtained without parenteral or surgical intervention.

The measurement of drug and metabolite concentration in each of these biologic materials yields important information, such as the amount of drug retained in, or transported into, that region of the tissue or fluid, the likely pharmacologic or toxicologic outcome of drug dosing, and drug metabolite formation or transport. Analytical methods should be able to distinguish between protein-bound and unbound parent drug and each metabolite, and the pharmacologically active species should be identified. Such distinctions between metabolites in each tissue and fluid are especially important for initial pharmacokinetic modeling of a drug.

Drug Concentrations in Blood, Plasma, or Serum

Measurement of drug and metabolite concentrations (levels) in the blood, serum, or plasma is the most direct approach to assessing the pharmacokinetics of the drug in the body. Whole blood contains cellular elements including red blood cells, white blood cells, platelets, and various other proteins, such as albumin and globulins (Table 1-4). In general, serum or plasma is most commonly used for drug measurement. To obtain serum, whole blood is allowed to clot and the serum is collected from the supernatant after centrifugation. Plasma is obtained from the supernatant of centrifuged whole blood to which an anticoagulant, such as heparin, has been added. Therefore, the protein content of serum and plasma is not the same. Plasma perfuses all the tissues of the body, including the cellular elements in the blood. Assuming that a drug in the plasma is in dynamic equilibrium with the tissues, then changes in the drug concentration in plasma will reflect changes in tissue drug concentrations. Drugs in the plasma are often bound to plasma proteins, and often plasma proteins are filtered from the plasma before drug concentrations are measured. This is the unbound

TABLE 1-4 Blood Components

Blood Component	How Obtained	Components
Whole blood	Whole blood is generally obtained by venous puncture and contains an anticoagulant such as heparin or EDTA	Whole blood contains all the cellular and protein elements of blood
Serum	Serum is the liquid obtained from whole blood after the blood is allowed to clot and the clot is removed	Serum does not contain the cellular elements, fibrinogen, or the other clotting factors from the blood
Plasma	Plasma is the liquid supernatant obtained after centrifugation of non-clotted whole blood that contains an anticoagulant	Plasma is the noncellular liquid fraction of whole blood and contains all the proteins including albumin

drug concentration. Alternatively, drug concentration may be measured from unfiltered plasma; this is the total plasma drug concentration. When interpreting plasma concentrations, it is important to understand what type of plasma concentration the data reflect.

Frequently Asked Questions

- *Why are drug concentrations more often measured in plasma rather than whole blood or serum?*
- *What are the differences between bound drug, unbound drug, total drug, parent drug, and metabolite drug concentrations in the plasma?*

Plasma Drug Concentration–Time Curve

The plasma drug concentration (level)–time curve is generated by obtaining the drug concentration in plasma samples taken at various time intervals after a drug product is administered. The concentration of drug in each plasma sample is plotted on rectangular-coordinate graph paper against the corresponding time at which the plasma sample was removed. As the drug reaches the general (systemic) circulation, plasma drug concentrations will rise up to a maximum if the drug was given by an extravascular route. Usually, absorption of a drug is more rapid than elimination. As the drug is being absorbed into the systemic circulation, the drug is distributed to all the tissues in the body and is also *simultaneously* being eliminated. Elimination of a drug can proceed by excretion, biotransformation, or a combination of both. Other elimination mechanisms may also be

involved, such as elimination in the feces, sweat, or exhaled air.

The relationship of the drug level–time curve and various pharmacologic parameters for the drug is shown in Fig. 1-3. MEC and MTC represent the *minimum effective concentration* and *minimum toxic concentration* of drug, respectively. For some drugs, such as those acting on the autonomic nervous system, it is useful to know the concentration of drug that will just barely produce a pharmacologic effect (ie, MEC). Assuming the drug concentration in the plasma is in equilibrium with the tissues, the MEC reflects the minimum concentration of drug needed

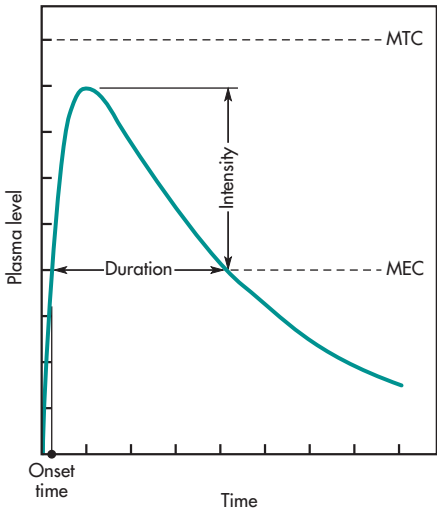


FIGURE 1-3 Generalized plasma level–time curve after oral administration of a drug.

at the receptors to produce the desired pharmacologic effect. Similarly, the MTC represents the drug concentration needed to just barely produce a toxic effect. The *onset time* corresponds to the time required for the drug to reach the MEC. The intensity of the pharmacologic effect is proportional to the number of drug receptors occupied, which is reflected in the observation that higher plasma drug concentrations produce a greater pharmacologic response, up to a maximum. The *duration of drug action* is the difference between the onset time and the time for the drug to decline back to the MEC.

The *therapeutic window* is the concentrations between the MEC and the MTC. Drugs with a wide therapeutic window are generally considered safer than drugs with a narrow therapeutic window. Sometimes the term *therapeutic index* is used. This term refers to the ratio between the toxic and therapeutic doses.

In contrast, the pharmacokineticist can also describe the plasma level–time curve in terms of such pharmacokinetic terms as *peak plasma level* ($C_{\max}$), *time for peak plasma level* ($T_{\max}$), and *area under the curve*, or AUC (Fig. 1-4). The time for peak plasma level is the time of maximum drug concentration in the plasma and is a rough marker of average rate of drug absorption. The peak plasma

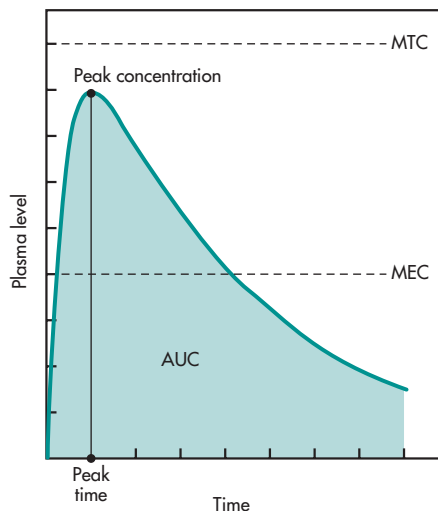


FIGURE 1-4 Plasma level–time curve showing peak time and concentration. The shaded portion represents the AUC (area under the curve).

level or maximum drug concentration is related to the dose, the rate constant for absorption, and the elimination constant of the drug. The AUC is related to the amount of drug absorbed systemically. These and other pharmacokinetic parameters are discussed in succeeding chapters.

Frequently Asked Questions

- At what time intervals should plasma drug concentration be taken in order to best predict drug response and side effects?
- What happens if plasma concentrations fall outside of the therapeutic window?

Drug Concentrations in Tissues

Tissue biopsies are occasionally removed for diagnostic purposes, such as the verification of a malignancy. Usually, only a small sample of tissue is removed, making drug concentration measurement difficult. Drug concentrations in tissue biopsies may not reflect drug concentration in other tissues nor the drug concentration in all parts of the tissue from which the biopsy material was removed. For example, if the tissue biopsy was for the diagnosis of a tumor within the tissue, the blood flow to the tumor cells may not be the same as the blood flow to other cells in this tissue. In fact, for many tissues, blood flow to one part of the tissues need not be the same as the blood flow to another part of the same tissue. The measurement of the drug concentration in tissue biopsy material may be used to ascertain if the drug reached the tissues and reached the proper concentration within the tissue.

Drug Concentrations in Urine and Feces

Measurement of drug in urine is an indirect method to ascertain the bioavailability of a drug. The rate and extent of drug excreted in the urine reflects the rate and extent of systemic drug absorption. The use of urinary drug excretion measurements to establish various pharmacokinetic parameters is discussed in Chapter 4.

Measurement of drug in feces may reflect drug that has not been absorbed after an oral dose or may

reflect drug that has been expelled by biliary secretion after systemic absorption. Fecal drug excretion is often performed in mass balance studies, in which the investigator attempts to account for the entire dose given to the patient. For a mass balance study, both urine and feces are collected and their drug content measured. For certain solid oral dosage forms that do not dissolve in the gastrointestinal tract but slowly leach out drug, fecal collection is performed to recover the dosage form. The undissolved dosage form is then assayed for residual drug.

Drug Concentrations in Saliva

Saliva drug concentrations have been reviewed for many drugs for therapeutic drug monitoring (Pippenger and Massoud, 1984). Because only free drug diffuses into the saliva, saliva drug levels tend to approximate free drug rather than total plasma drug concentration. The saliva/plasma drug concentration ratio is less than 1 for many drugs. The saliva/plasma drug concentration ratio is mostly influenced by the pKa of the drug and the pH of the saliva. Weak acid drugs and weak base drugs with pKa significantly different than pH 7.4 (plasma pH) generally have better correlation to plasma drug levels. The saliva drug concentrations taken after equilibrium with the plasma drug concentration generally provide more stable indication of drug levels in the body. The use of salivary drug concentrations as a therapeutic indicator should be used with caution and preferably as a secondary indicator.

Forensic Drug Measurements

Forensic science is the application of science to personal injury, murder, and other legal proceedings. Drug measurements in tissues obtained at autopsy or in other bodily fluids such as saliva, urine, and blood may be useful if a suspect or victim has taken an overdose of a legal medication, has been poisoned, or has been using drugs of abuse such as opiates (eg, heroin), cocaine, or marijuana. The appearance of social drugs in blood, urine, and saliva drug analysis shows short-term drug abuse. These drugs may be eliminated rapidly, making it more difficult to prove that the subject has been using drugs of abuse. The analysis for drugs of abuse in hair samples by very sensitive assay

methods, such as gas chromatography coupled with mass spectrometry, provides information regarding past drug exposure. A study by Cone et al (1993) showed that the hair samples from subjects who were known drug abusers contained cocaine and 6-acetylmorphine, a metabolite of heroin (diacetylmorphine).

Significance of Measuring Plasma Drug Concentrations

The intensity of the pharmacologic or toxic effect of a drug is often related to the concentration of the drug at the receptor site, usually located in the tissue cells. Because most of the tissue cells are richly perfused with tissue fluids or plasma, measuring the plasma drug level is a responsive method of monitoring the course of therapy.

Clinically, individual variations in the pharmacokinetics of drugs are quite common. Monitoring the concentration of drugs in the blood or plasma ascertains that the calculated dose actually delivers the plasma level required for therapeutic effect. With some drugs, receptor expression and/or sensitivity in individuals varies, so monitoring of plasma levels is needed to distinguish the patient who is receiving too much of a drug from the patient who is supersensitive to the drug. Moreover, the patient's physiologic functions may be affected by disease, nutrition, environment, concurrent drug therapy, and other factors. Pharmacokinetic models allow more accurate interpretation of the relationship between plasma drug levels and pharmacologic response.

In the absence of pharmacokinetic information, plasma drug levels are relatively useless for dosage adjustment. For example, suppose a single blood sample from a patient was assayed and found to contain 10 $\mu\text{g/mL}$. According to the literature, the maximum safe concentration of this drug is 15 $\mu\text{g/mL}$. In order to apply this information properly, it is important to know when the blood sample was drawn, what dose of the drug was given, and the route of administration. If the proper information is available, the use of pharmacokinetic equations and models may describe the blood level–time curve accurately and be used to modify dosing for that specific patient.

Monitoring of plasma drug concentrations allows for the adjustment of the drug dosage in order

to individualize and optimize therapeutic drug regimens. When alterations in physiologic functions occur, monitoring plasma drug concentrations may provide a guide to the progress of the disease state and enable the investigator to modify the drug dosage accordingly. Clinically, sound medical judgment and observation are most important. Therapeutic decisions should not be based solely on plasma drug concentrations.

In many cases, the *pharmacodynamic response* to the drug may be more important to measure than just the plasma drug concentration. For example, the electrophysiology of the heart, including an electrocardiogram (ECG), is important to assess in patients medicated with cardiotonic drugs such as digoxin. For an anticoagulant drug, such as dicumarol, prothrombin clotting time may indicate whether proper dosage was achieved. Most diabetic patients taking insulin will monitor their own blood or urine glucose levels.

For drugs that act irreversibly at the receptor site, plasma drug concentrations may not accurately predict pharmacodynamic response. Drugs used in cancer chemotherapy often interfere with nucleic acid or protein biosynthesis to destroy tumor cells. For these drugs, the plasma drug concentration does not relate directly to the pharmacodynamic response. In this case, other pathophysiologic parameters and side effects are monitored in the patient to prevent adverse toxicity.

BASIC PHARMACOKINETICS AND PHARMACOKINETIC MODELS

Drugs are in a dynamic state within the body as they move between tissues and fluids, bind with plasma or cellular components, or are metabolized. The biologic nature of drug distribution and disposition is complex, and drug events often happen simultaneously. Such factors must be considered when designing drug therapy regimens. The inherent and infinite complexity of these events requires the use of mathematical models and statistics to estimate drug dosing and to predict the time course of drug efficacy for a given dose.

A *model* is a hypothesis using mathematical terms to describe quantitative relationships concisely.

The predictive capability of a model lies in the proper selection and development of mathematical function(s) that parameterizes the essential factors governing the kinetic process. The key parameters in a process are commonly estimated by fitting the model to the experimental data, known as *variables*. A *pharmacokinetic parameter* is a constant for the drug that is estimated from the experimental data. For example, estimated pharmacokinetic parameters such as k depend on the method of tissue sampling, the timing of the sample, drug analysis, and the predictive model selected.

A pharmacokinetic function relates an *independent variable* to a *dependent variable*, often through the use of parameters. For example, a pharmacokinetic model may predict the drug concentration in the liver 1 hour after an oral administration of a 20-mg dose. The independent variable is the time and the dependent variable is the drug concentration in the liver. Based on a set of time-versus-drug concentration data, a model equation is derived to predict the liver drug concentration with respect to time. In this case, the drug concentration depends on the time after the administration of the dose, where the time-concentration relationship is defined by a pharmacokinetic parameter, k , the elimination rate constant.

Such mathematical models can be devised to simulate the rate processes of drug absorption, distribution, and elimination to describe and *predict* drug concentrations in the body as a function of time. Pharmacokinetic models are used to:

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually
3. Estimate the possible accumulation of drugs and/or metabolites
4. Correlate drug concentrations with pharmacologic or toxicologic activity
5. Evaluate differences in the rate or extent of availability between formulations (bioequivalence)
6. Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug
7. Explain drug interactions

Simplifying assumptions are made in pharmacokinetic models to describe a complex biologic system concerning the movement of drugs within the body. For example, most pharmacokinetic models assume that the plasma drug concentration reflects drug concentrations globally within the body.

A model may be empirically, physiologically, or compartmentally based. The model that simply interpolates the data and allows an empirical formula to estimate drug level over time is justified when limited information is available. *Empirical models* are practical but not very useful in explaining the mechanism of the actual process by which the drug is absorbed, distributed, and eliminated in the body. Examples of empirical models used in pharmacokinetics are described in Chapter 25.

Physiologically based models also have limitations. Using the example above, and apart from the necessity to sample tissue and monitor blood flow to the liver *in vivo*, the investigator needs to understand the following questions. What is the clinical implication of the liver drug concentration value? Should the drug concentration in the blood within the tissue be determined and subtracted from the drug in the liver tissue? What type of cell is representative of the liver if a selective biopsy liver tissue sample can be collected without contamination from its surroundings? Indeed, depending on the spatial location of the liver tissue from the hepatic blood vessels, tissue drug concentrations can differ depending on distance to the blood vessel or even on the type of cell in the liver. Moreover, changes in the liver blood perfusion will alter the tissue drug concentration. If heterogeneous liver tissue is homogenized and assayed, the homogenized tissue represents only a hypothetical concentration that is an *average* of all the cells and blood in the liver at the time of collection. Since tissue homogenization is not practical for human subjects, the drug concentration in the liver may be estimated by knowing the liver extraction ratio for the drug based on knowledge of the physiologic and biochemical composition of the body organs.

A great number of models have been developed to estimate regional and global information about drug disposition in the body. Some physiologic pharmacokinetic models are also discussed in Chapter 25. Individual pharmacokinetic processes are discussed

in separate chapters under the topics of drug absorption, drug distribution, drug elimination, and pharmacokinetic drug interactions involving one or all of the above processes. Theoretically, an unlimited number of models may be constructed to describe the kinetic processes of drug absorption, distribution, and elimination in the body, depending on the degree of detailed information considered. Practical considerations have limited the growth of new pharmacokinetic models.

A very simple and useful tool in pharmacokinetics is *compartmentally based models*. For example, assume a drug is given by intravenous injection and that the drug dissolves (distributes) rapidly in the body fluids. One pharmacokinetic model that can describe this situation is a tank containing a volume of fluid that is rapidly equilibrated with the drug. The concentration of the drug in the tank after a given dose is governed by two parameters: (1) the fluid volume of the tank that will dilute the drug, and (2) the elimination rate of drug per unit of time. Though this model is perhaps an overly simplistic view of drug disposition in the human body, a drug's pharmacokinetic properties can frequently be described using a fluid-filled tank model called the *one-compartment open model* (see below). In both the tank and the one-compartment body model, a fraction of the drug would be continually eliminated as a function of time (Fig. 1-5). In pharmacokinetics, these parameters are assumed to be constant for a given drug. If drug concentrations in the tank are determined at various time intervals following administration of a known dose, then the volume of fluid in the tank or compartment (V_D , volume of distribution) and the rate of drug elimination can be estimated.

In practice, pharmacokinetic parameters such as k and V_D are determined experimentally from a set of drug concentrations collected over various times and

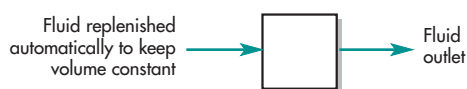


FIGURE 1-5 Tank with a constant volume of fluid equilibrated with drug. The volume of the fluid is 1.0 L. The fluid outlet is 10 mL/min. The fraction of drug removed per unit of time is 10/1000, or 0.01 min⁻¹.

known as *data*. The number of parameters needed to describe the model depends on the complexity of the process and on the route of drug administration. In general, as the number of parameters required to model the data increases, accurate estimation of these parameters becomes increasingly more difficult. With complex pharmacokinetic models, computer programs are used to facilitate parameter estimation. However, for the parameters to be valid, the number of data points should always exceed the number of parameters in the model.

Because a model is based on a hypothesis and simplifying assumptions, a certain degree of caution is necessary when relying totally on the pharmacokinetic model to predict drug action. For some drugs, plasma drug concentrations are not useful in predicting drug activity. For other drugs, an individual's genetic differences, disease state, and the compensatory response of the body may modify the response to the drug. If a simple model does not fit all the experimental observations accurately, a new, more elaborate model may be proposed and subsequently tested. Since limited data are generally available in most clinical situations, pharmacokinetic data should be interpreted along with clinical observations rather than replacing sound judgment by the clinician. Development of pharmacometric statistical models may help to improve prediction of drug levels among patients in the population (Sheiner and Beal, 1982; Mallet et al, 1988). However, it will be some time before these methods become generally accepted.

Compartment Models

If the tissue drug concentrations and binding are known, physiologic pharmacokinetic models, which are based on actual tissues and their respective blood flow, describe the data realistically. Physiologic pharmacokinetic models are frequently used in describing drug distribution in animals, because tissue samples are easily available for assay. On the other hand, tissue samples are often not available for human subjects, so most physiological models assume an average set of blood flow for individual subjects.

In contrast, because of the vast complexity of the body, drug kinetics in the body are frequently simplified to be represented by one or more tanks, or

compartments, that communicate reversibly with each other. A *compartment* is not a real physiologic or anatomic region but is considered a tissue or group of tissues that have similar blood flow and drug affinity. Within each compartment, the drug is considered to be uniformly distributed. Mixing of the drug within a compartment is rapid and homogeneous and is considered to be "well stirred," so that the drug concentration represents an average concentration, and each drug molecule has an equal probability of leaving the compartment. *Rate constants* are used to represent the overall rate processes of drug entry into and exit from the compartment. The model is an *open system* because drug can be eliminated from the system. Compartment models are based on linear assumptions using linear differential equations.

Mammillary Model

A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from the central or plasma compartment. The *mammillary model* is the most common compartment model used in pharmacokinetics. The mammillary model is a strongly connected system, because one can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment. In the one-compartment model, drug is both added to and eliminated from a central compartment. The central compartment is assigned to represent plasma and highly perfused tissues that rapidly equilibrate with drug. When an intravenous dose of drug is given, the drug enters directly into the central compartment. Elimination of drug occurs from the central compartment because the organs involved in drug elimination, primarily kidney and liver, are well-perfused tissues.

In a two-compartment model, drug can move between the central or plasma compartment to and from the tissue compartment. Although the tissue compartment does not represent a specific tissue, the mass balance accounts for the drug present in all the tissues. In this model, the total amount of drug in the body is simply the sum of drug present in the central compartment plus the drug present in the tissue compartment. Knowing the parameters of either the one-compartment or the two-compartment model,

one can estimate the amount of drug left in the body and the amount of drug eliminated from the body at any time. The compartmental models are particularly useful when little information is known about the tissues.

Several types of compartment models are described in Fig. 1-6. The pharmacokinetic rate constants are represented by the letter k . Compartment 1 represents the plasma or central compartment, and compartment 2 represents the tissue compartment. The drawing of models has three functions. The model (1) enables the pharmacokineticist to write differential equations to describe drug concentration changes in each compartment, (2) gives a visual representation of the rate processes, and (3) shows how many pharmacokinetic constants are necessary to describe the process adequately.

Catenary Model

In pharmacokinetics, the mammillary model must be distinguished from another type of compartmental model called the catenary model. The *catenary model* consists of compartments joined to one another like the compartments of a train (Fig. 1-7). In contrast, the mammillary model consists of one or

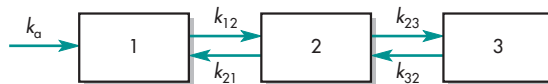


FIGURE 1-7 Example of catenary model.

more compartments around a central compartment like satellites. Because the catenary model does not apply to the way most functional organs in the body are directly connected to the plasma, it is not used as often as the mammillary model.

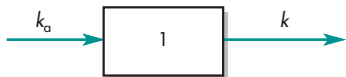
Physiologic Pharmacokinetic Model (Flow Model)

Physiologic pharmacokinetic models, also known as blood flow or perfusion models, are pharmacokinetic models based on known anatomic and physiologic data. The models describe the data kinetically, with the consideration that blood flow is responsible for distributing drug to various parts of the body. Uptake of drug into organs is determined by the

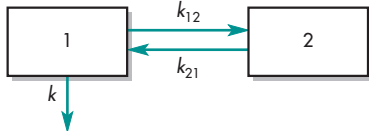
MODEL 1. One-compartment open model, IV injection.



MODEL 2. One-compartment open model with first-order absorption.



MODEL 3. Two-compartment open model, IV injection.



MODEL 4. Two-compartment open model with first-order absorption.

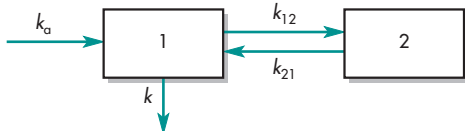


FIGURE 1-6 Various compartment models.

EXAMPLE ▶▶▶

Two parameters are needed to describe model 1 (Fig. 1-6): the volume of the compartment and the elimination rate constant, k . In the case of model 4, the pharmacokinetic parameters consist of the volumes of compartments 1 and 2 and the rate constants— k_a , k , k_{12} , and k_{21} —for a total of six parameters.

In studying these models, it is important to know whether drug concentration data may be sampled directly from each compartment. For models 3 and 4 (Fig. 1-6), data concerning compartment 2 cannot be obtained easily because tissues are not easily sampled and may not contain homogeneous concentrations of drug. If the amount of drug absorbed and eliminated per unit time is obtained by sampling compartment 1, then the amount of drug contained in the tissue compartment 2 can be estimated mathematically. The appropriate mathematical equations for describing these models and evaluating the various pharmacokinetic parameters are given in subsequent chapters.

binding of drug in these tissues. In contrast to an estimated tissue volume of distribution, the actual tissue volume is used. Because there are many tissue organs in the body, each tissue volume must be obtained and its drug concentration described. The model would potentially predict realistic tissue drug concentrations, which the two-compartment model fails to do. Unfortunately, much of the information required for adequately describing a physiologic pharmacokinetic model is experimentally difficult to obtain. In spite of this limitation, the physiologic pharmacokinetic model does provide much better insight into how physiologic factors may change drug distribution from one animal species to another. Other major differences are described below.

First, no data fitting is required in the perfusion model. Drug concentrations in the various tissues are predicted by organ tissue size, blood flow, and experimentally determined drug tissue–blood ratios (ie, partition of drug between tissue and blood).

Second, blood flow, tissue size, and the drug tissue–blood ratios may vary due to certain pathophysiological conditions. Thus, the effect of these variations on drug distribution must be taken into account in physiologic pharmacokinetic models.

Third, and most important of all, physiologically based pharmacokinetic models can be applied to several species, and, for some drugs, human data may be extrapolated. Extrapolation from animal data is not possible with the compartment models, because the volume of distribution in such models is a mathematical concept that does not relate simply to blood volume and blood flow. To date, numerous drugs (including digoxin, lidocaine, methotrexate, and thiopental) have been described with perfusion models. Tissue levels of some of these drugs cannot be predicted successfully with compartment models, although they generally describe blood levels well. An example of a perfusion model is shown in Fig. 1-8.

The number of tissue compartments in a perfusion model varies with the drug. Typically, the tissues or organs that have no drug penetration are excluded from consideration. Thus, such organs as the brain, the bones, and other parts of the central nervous system are often excluded, as most drugs have little penetration into these organs. To describe each organ separately with a differential equation

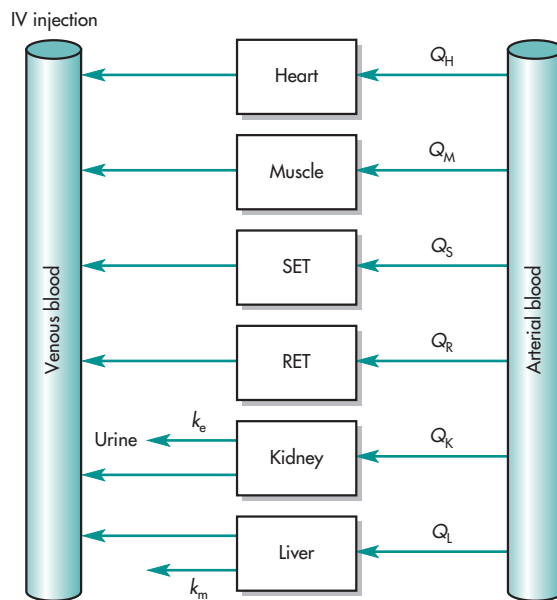


FIGURE 1-8 Pharmacokinetic model of drug perfusion. The k s represent kinetic constants: k_e is the first-order rate constant for urinary drug excretion and k_m is the rate constant for hepatic elimination. Each “box” represents a tissue compartment. Organs of major importance in drug absorption are considered separately, while other tissues are grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue). The size or mass of each tissue compartment is determined physiologically rather than by mathematical estimation. The concentration of drug in the tissue is determined by the ability of the tissue to accumulate drug as well as by the rate of blood perfusion to the tissue, represented by Q .

would make the model very complex and mathematically difficult. A simpler but equally good approach is to group all the tissues with similar blood perfusion properties into a single compartment.

A physiologic based pharmacokinetic model (PBPK) using known blood flow was used to describe the distribution of lidocaine in blood and various organs (Benowitz et al 1974) and applied in anesthesiology in man (Tucker et al 1971). In PBPK models, organs such as lung, liver, brain, and muscle were individually described by differential equations as shown in Fig. 1-8, sometimes tissues were grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue) for simplicity to account for the mass balance of the drug. A general scheme showing blood flow for typical organs is shown in Fig. 1-8.

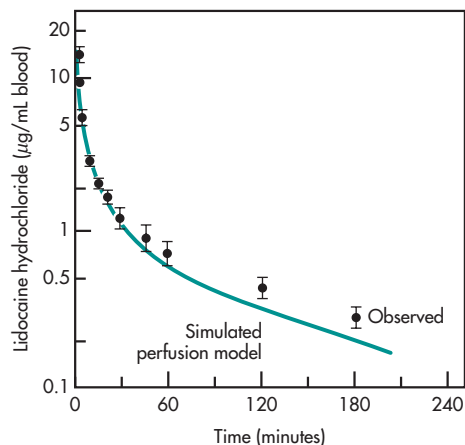


FIGURE 1-9 Observed mean (•) and simulated (—) arterial lidocaine blood concentrations in normal volunteers receiving 1 mg/kg/min constant infusion for 3 minutes. (From Tucker GT, Boas RA: Pharmacokinetic aspects of intravenous regional anesthesia. *Anesthesiology* 34(6):538–549, 1971, with permission.)

The data showing blood concentration of lidocaine after an IV dose declining biexponentially (Fig. 1-9) was well predicted by the model. A later PBPK model was applied to model cyclosporine (Fig. 1-10). Drug level in various organs were well predicted and scaled to human based on this physiologic model (Kawai R et al, 1998). The tissue cyclosporine levels in the lung, muscle, and adipose and other organs are shown in Fig. 1-10. For lidocaine, the tissue such as adipose (fat) tissue accumulates drugs slowly because of low blood supply. In contrast, vascular tissues, like the lung, equilibrate rapidly with the blood and start to decline as soon as drug level in the blood starts to fall resulting in curvature of plasma profile. The physiologic pharmacokinetic model provides a realistic means of modeling tissue drug levels. However, drug levels in tissues are not available. A criticism of physiologic pharmacokinetic models in general has been that there are fewer data points than parameters that one tries to fit. Consequently, the projected data are not well *constrained*.

The real significance of the physiologically based model is the potential application of this model in the prediction of human pharmacokinetics from animal data (Sawada et al, 1985). The mass of various body organs or tissues, extent of protein binding,

drug metabolism capacity, and blood flow in humans and other species are often known or can be determined. Thus, physiologic and anatomic parameters can be used to predict the effects of drugs on humans from the effects on animals in cases where human experimentation is difficult or restricted.

Frequently Asked Questions

- ▶ What are the reasons to use a multicompartment model instead of a physiologic model?
- ▶ What do the boxes in the mammillary model mean?

More sophisticated models are introduced as the understanding of human and animal physiology improves. For example, in Chapter 25, special compartment models that take into account transporter-mediated drug disposition are introduced for specific drugs. This approach is termed Physiologic Pharmacokinetic Model Incorporating Hepatic Transporter-Mediated Clearance. The differences between the physiologic pharmacokinetic model, the classical compartmental model, and the noncompartmental approach are discussed. It is important to note that mass transfer and balances of drug in and out of the body or body organs are fundamentally a kinetic process. Thus, the model may be named as physiologically based when all drug distributed to body organs are identified. For data analysis, parameters are obtained quantitatively with different assumptions. The model analysis may be compartmental or noncompartmental (Chapter 25). One approach is to classify models simply as empirically based models and mechanistic models. Although compartment models are critically referred to as a “black box” approach and not physiological. The versatility of compartment models and their easy application are based on simple mass transfer algorithms or a system of differential equations. This approach has allowed many body processes such as binding, transport, and metabolic clearance to be monitored. The advantage of a noncompartmental analysis is discussed in Chapter 25. In Appendix B, softwares used for various type of model analysis are discussed, for example, noncompartmental analysis is often used for pharmacokinetic and bioavailability data analysis for regulatory purpose.

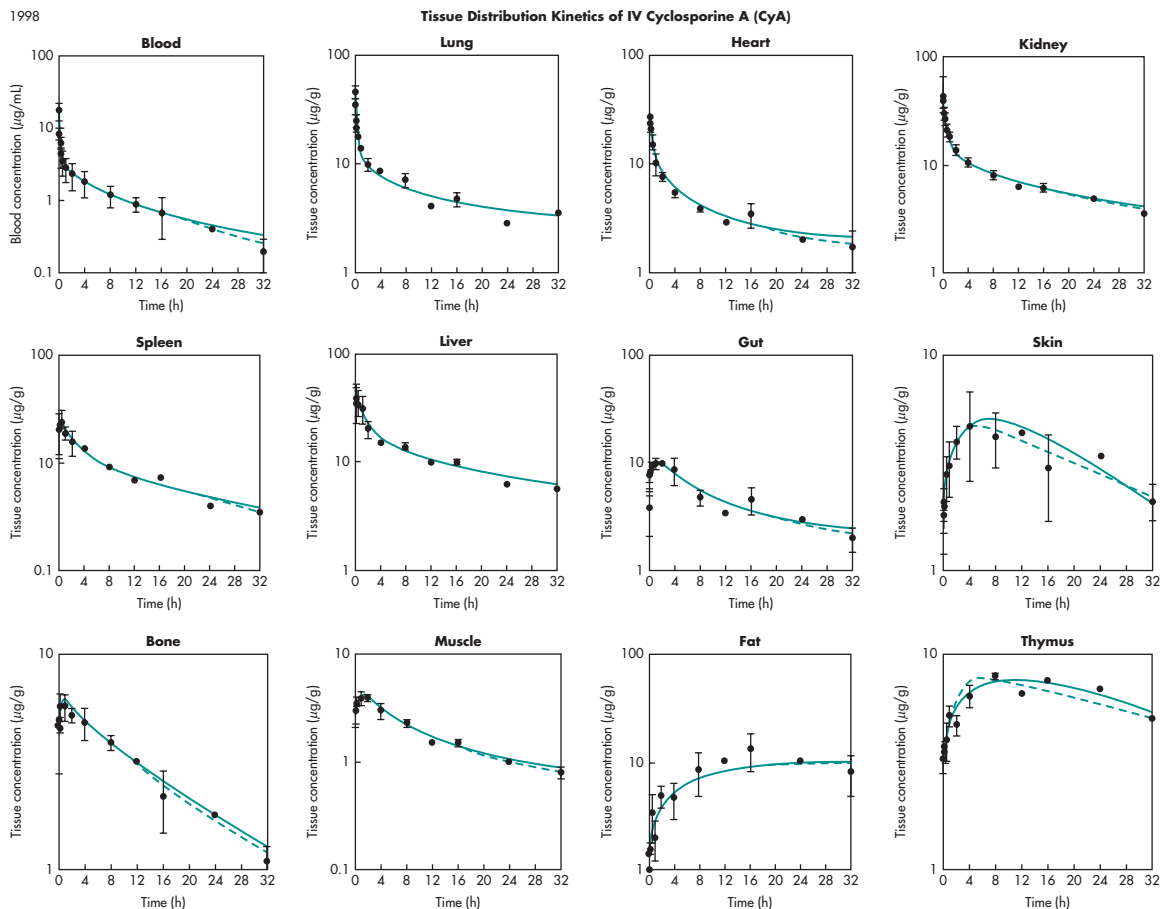


FIGURE 1-10 Measured and best fit predictions of CyA concentration in arterial blood and various organs/tissues in rat. Each plot and vertical bar represent the mean and standard deviation, respectively. Solid and dotted lines are the physiological-based pharmacokinetic (PBPK) best fit predictions based on the parameters associated with the linear or nonlinear model, respectively. (Reproduced with permission from Kawai R, Mathew D, Tanaka C, Rowland M: Physiologically based pharmacokinetics of cyclosporine A: Extension to tissue distribution kinetics in rats and scale-up to human. *JPET* **287**:457–468, 1998.)

CHAPTER SUMMARY

Drug product performance is the release of the drug substance from the drug product leading to bioavailability of the drug substance and eventually leading to one or more pharmacologic effects, both desirable and undesirable. *Biopharmaceutics* provides the scientific basis for drug product design and drug product performance by examining the interrelationship of the physical/chemical properties of the drug, the drug product in which the drug is given, and the

route of administration on the rate and extent of systemic drug absorption. *Pharmacokinetics* is the science of the dynamics (kinetics) of drug absorption, distribution, and elimination (ie, excretion and metabolism), whereas *clinical pharmacokinetics* considers the applications of pharmacokinetics to drug therapy.

The quantitative measurement of drug concentrations in the plasma after dose administration is

important to obtain relevant data of systemic drug exposure. The plasma drug concentration-versus-time profile provides the basic data from which various pharmacokinetic models can be developed that predict the time course of drug action, relates the

drug concentration to the pharmacodynamic effect or adverse response, and enables the development of individualized therapeutic dosage regimens and new and novel drug delivery systems.

LEARNING QUESTIONS

1. What is the significance of the plasma level–time curve? How does the curve relate to the pharmacologic activity of a drug?
2. What is the purpose of pharmacokinetic models?
3. Draw a diagram describing a three-compartment model with first-order absorption and drug elimination from compartment 1.
4. The pharmacokinetic model presented in Fig. 1-11 represents a drug that is eliminated by renal excretion, biliary excretion, and drug metabolism. The metabolite distribution is described by a one-compartment open model. The following questions pertain to Fig. 1-11.
 - a. How many parameters are needed to describe the model if the drug is injected intravenously (ie, the rate of drug absorption may be neglected)?
 - b. Which compartment(s) can be sampled?
 - c. What would be the overall elimination rate constant for elimination of drug from compartment 1?
 - d. Write an expression describing the rate of change of drug concentration in compartment 1 (dC_1/dt).
5. Give two reasons for the measurement of the plasma drug concentration, C_p , assuming (a) the C_p relates directly to the pharmacodynamic activity of the drug and (b) the C_p does not relate to the pharmacodynamic activity of the drug.
6. Consider two biologic compartments separated by a biologic membrane. Drug A is found in compartment 1 and in compartment 2 in a concentration of c_1 and c_2 , respectively.
 - a. What possible conditions or situations would result in concentration $c_1 > c_2$ at equilibrium?
 - b. How would you experimentally demonstrate these conditions given above?
 - c. Under what conditions would $c_1 = c_2$ at equilibrium?
 - d. The total amount of Drug A in each biologic compartment is A_1 and A_2 , respectively. Describe a condition in which $A_1 > A_2$, but $c_1 = c_2$ at equilibrium.

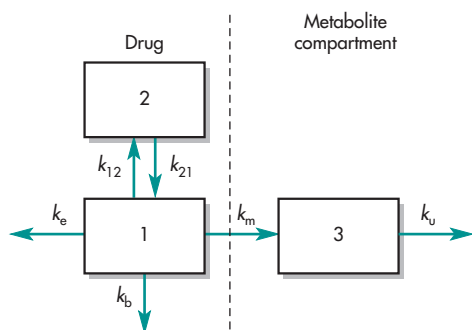


FIGURE 1-11 Pharmacokinetic model for a drug eliminated by renal and biliary excretion and drug metabolism. k_m = rate constant for metabolism of drug; k_u = rate constant for urinary excretion of metabolites; k_b = rate constant for biliary excretion of drug; and k_e = rate constant for urinary drug excretion.

Include in your discussion, how the physicochemical properties of Drug A or the biologic properties of each compartment might influence equilibrium conditions.

7. Why is it important for a pharmacist to keep up with possible label revision in a drug newly approved? Which part of the label you expect to be mostly likely revised with more phase 4 information?
 - a. The chemical structure of the drug
 - b. The Description section
 - c. Adverse side effect in certain individuals

8. A pharmacist wishing to find if an excipient such as aspartame in a product is mostly found under which section in the SPL drug label?
 - a. How supplied
 - b. Patient guide
 - c. Description
9. A pregnant patient is prescribed pantoprazole sodium (Protonix) delayed release tablets for erosive gastroesophageal reflux disease (GERD). Where would you find information concerning the safety of this drug in pregnant women?

ANSWERS

Frequently Asked Questions

Why are drug concentrations more often measured in plasma rather than whole blood or serum?

- Blood is composed of plasma and red blood cells (RBCs). Serum is the fluid obtained from blood after it is allowed to clot. Serum and plasma do not contain identical proteins. RBCs may be considered a cellular component of the body in which the drug concentration in the serum or plasma is in equilibrium, in the same way as with the other tissues in the body. Whole blood samples are generally harder to process and assay than serum or plasma samples. Plasma may be considered a liquid tissue compartment in which the drug in the plasma fluid equilibrates with drug in the tissues and cellular components.

At what time intervals should plasma drug concentration be taken in order to best predict drug response and side effects?

- The exact site of drug action is generally unknown for most drugs. The time needed for the drug to reach the site of action, produce a pharmacodynamic effect, and reach equilibrium are deduced from studies on the relationship of the time course for the drug concentration and the pharmacodynamic effect. Often, the drug concentration is sampled during the elimination phase after the drug has been distributed and reached equilibrium. For multiple-dose studies, both the peak and trough drug concentrations are frequently taken.

What are the reasons to use a multicompartment model instead of a physiologic model?

- Physiologic models are complex and require more information for accurate prediction compared to compartment models. Missing information in the physiologic model will lead to bias or error in the model. Compartment models are more simplistic in that they assume that both arterial and venous drug concentrations are similar. The compartment model accounts for a rapid distribution phase and a slower elimination phase. Physiologic clearance models postulate that arterial blood drug levels are higher than venous blood drug levels. In practice, only venous blood samples are usually sampled. Organ drug clearance is useful in the treatment of cancers and in the diagnosis of certain diseases involving arterial perfusion. Physiologic models are difficult to use for general application.

Learning Questions

1. The plasma drug level–time curve describes the pharmacokinetics of the systemically absorbed drug. Once a suitable pharmacokinetic model is obtained, plasma drug concentrations may be predicted following various dosage regimens such as single oral and IV bolus doses, multiple-dose regimens, IV infusion, etc. If the pharmacokinetics of the drug relates to its pharmacodynamic activity (or any adverse drug response or toxicity), then a drug regimen based on the drug's pharmacokinetics may be designed to provide optimum drug efficacy. In lieu of a direct

pharmacokinetic–pharmacodynamic relationship, the drug’s pharmacokinetics describes the bioavailability of the drug including inter- and intrasubject variability; this information allows for the development of drug products that consistently deliver the drug in a predictable manner.

2. The purpose of pharmacokinetic models is to relate the time course of the drug in the body to its pharmacodynamic and/or toxic effects. The pharmacokinetic model also provides a basis for drug product design, the design of dosage regimens, and a better understanding of the action of the body on the drug.

3. (Figure A-1)

4. a. Nine parameters: $V_1, V_2, V_3, k_{12}, k_{21}, k_e, k_b, k_m, k_u$
b. Compartment 1 and compartment 3 may be sampled.
c. $k = k_b + k_m + k_e$
d. $\frac{dC_1}{dt} = k_{21}C_2 - (k_{12} + k_m + k_e + k_b)C_1$

6.

Compartment 1	Compartment 2
C_1	C_2

a. C_1 and C_2 are the *total* drug concentration in each compartment, respectively. $C_1 > C_2$ may occur if the drug concentrates in compartment 1 due to protein binding (compartment 1 contains a high amount of protein or special protein binding), due to partitioning (compartment 1 has a high lipid content and the drug is poorly water soluble), if the pH is different in each compartment and the drug is a weak electrolyte (the drug may be more ionized in compartment 1), or if there is an active transport mechanism for the drug to be taken up into the

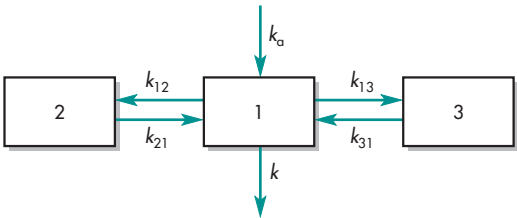


FIGURE A-1

cell (eg, purine drug). Other explanations for $C_1 > C_2$ may be possible.

- b. Several different experimental conditions are needed to prove which of the above hypotheses is the most likely cause for $C_1 > C_2$. These experiments may use *in vivo* or *in vitro* methods, including intracellular electrodes to measure pH *in vivo*, protein-binding studies *in vitro*, and partitioning of drug in chloroform/water *in vitro*, among others.
- c. In the case of protein binding, the total concentration of drug in each compartment may be different (eg, $C_1 > C_2$) and, at the same time, the free (nonprotein-bound) drug concentration may be equal in each compartment—assuming that the free or unbound drug is easily diffusible. Similarly, if $C_1 > C_2$ is due to differences in pH and the nonionized drug is easily diffusible, then the nonionized drug concentration may be the same in each compartment. The total drug concentrations will be $C_1 = C_2$ when there is similar affinity for the drug and similar conditions in each compartment.
- d. The total amount of drug, A , in each compartment depends on the volume, V , of the compartment and the concentration, C , of the drug in the compartment. Since the amount of drug (A) = concentration (C) times volume (V), any condition that causes the product, $C_1V_1 \neq C_2V_2$, will result in $A_1 \neq A_2$. Thus, if $C_1 = C_2$ and $V_1 \neq V_2$, then $A_1 \neq A_2$.
7. A newly approved NDA generally contains sufficient information for use labeled. However, as more information becomes available through postmarketing commitment studies, more information is added to the labeling, including Warnings and Precautions.
8. An excipient such as aspartame in a product is mostly found under the Description section, which describes the drug chemical structure and the ingredients in the drug product.
9. Section 8, Use in Specific Populations, reports information for geriatric, pediatric, renal, and hepatic subjects. This section will report dosing for pediatric subjects as well.

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2

Mathematical Fundamentals in Pharmacokinetics

Antoine Al-Achi

Chapter Objectives¹

- ▶ Algebraically solve mathematical expressions related to pharmacokinetics.
- ▶ Express the calculated and theoretical pharmacokinetic values in proper units.
- ▶ Represent pharmacokinetic data graphically using Cartesian coordinates (rectangular coordinate system) and semilogarithmic graphs.
- ▶ Use the least squares method to find the best fit straight line through empirically obtained data.
- ▶ Define various models representing rates and order of reactions and calculate pharmacokinetic parameters (eg, zero- and first-order) from experimental data based on these models.

CALCULUS

Pharmacokinetic models consider drugs in the body to be in a dynamic state. Calculus is an important mathematic tool for analyzing drug movement quantitatively. Differential equations are used to relate the concentrations of drugs in various body organs over time. Integrated equations are frequently used to model the cumulative therapeutic or toxic responses of drugs in the body.

Differential Calculus

Differential calculus is a branch of calculus that involves finding the rate at which a variable quantity is changing. For example, a specific amount of drug X is placed in a beaker of water to dissolve. The rate at which the drug dissolves is determined by the rate of drug diffusing away from the surface of the solid drug and is expressed by the *Noyes–Whitney equation*:

$$\text{Dissolution rate} = \frac{dX}{dt} = \frac{DA}{l}(C_1 - C_2)$$

where d denotes a very small change; X = drug X ; t = time; D = diffusion coefficient; A = effective surface area of drug; l = length of diffusion layer; C_1 = surface concentration of drug in the diffusion layer; and C_2 = concentration of drug in the bulk solution.

The derivative dX/dt may be interpreted as a change in X (or a derivative of X) with respect to a change in t .

In pharmacokinetics, the amount or concentration of drug in the body is a variable quantity (dependent variable), and time is considered to be an independent variable. Thus, we consider the amount or concentration of drug to vary with respect to time.

¹It is not the objective of this chapter to provide a detailed description of mathematical functions, algebra, or statistics. Readers who are interested in learning more about these topics are encouraged to consult textbooks specifically addressing these subjects.

EXAMPLE ▶▶▶

The concentration C of a drug changes as a function of time t :

$$C = f(t) \quad (2.1)$$

Consider the following data:

Time (hours)	Plasma Concentration of Drug C ($\mu\text{g/mL}$)
0	12
1	10
2	8
3	6
4	4
5	2

The concentration of drug C in the plasma is declining by $2 \mu\text{g/mL}$ for each hour of time. The rate of change in the concentration of the drug with respect to time (ie, the derivative of C) may be expressed as

$$\frac{dC}{dt} = 2 \mu\text{g/mL/h}$$

Here, $f(t)$ is a mathematical equation that describes how C changes, expressed as

$$C = 12 - 2t \quad (2.2)$$

Integral Calculus

Integration is the reverse of differentiation and is considered the summation of $f(x) \cdot dx$; the integral sign $\int$ implies summation. For example, given the function $y = ax$, plotted in Fig. 2-1, the integration is $\int ax \cdot dx$. Compare Fig. 2-1 to a second graph (Fig. 2-2), where the function $y = Ae^{-x}$ is commonly observed after an intravenous bolus drug injection. The integration process is actually a summing up of the small individual pieces under the graph. When x is specified and is given boundaries from a to b , then the expression becomes a definite integral, that is, the summing up of the area from $x = a$ to $x = b$.

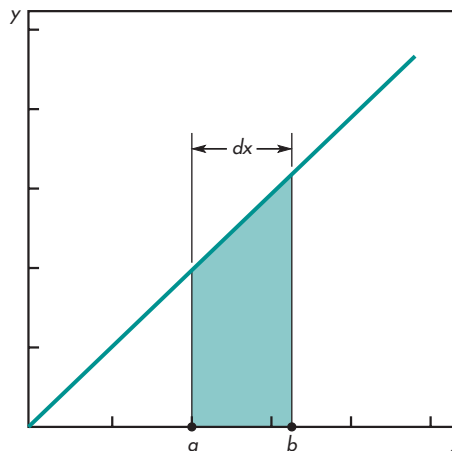


FIGURE 2-1 Integration of $y = ax$ or $\int ax \cdot dx$.

A *definite integral* of a mathematical function is the sum of individual areas under the graph of that function. There are several reasonably accurate numerical methods for approximating an area. These methods can be programmed into a computer for rapid calculation. The *trapezoidal rule* is a numerical method frequently used in pharmacokinetics to calculate the area under the plasma drug concentration-versus-time curve, called the *area under the curve* (AUC). For example, Fig. 2-2 shows a curve depicting the elimination of a drug from the plasma after a single intravenous injection. The drug plasma levels and the corresponding time intervals plotted in Fig. 2-2 are as follows:

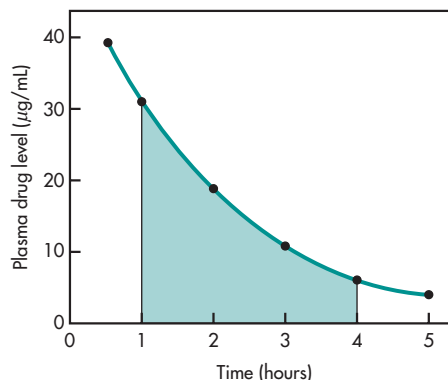


FIGURE 2-2 Graph of the elimination of drug from the plasma after a single IV injection.

Time (hours)	Plasma Drug Level (μg/mL)
0.5	38.9
1.0	30.3
2.0	18.4
3.0	11.1
4.0	6.77
5.0	4.10

The area between time intervals is the area of a trapezoid and can be calculated with the following formula:

$$[AUC]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2} (t_n - t_{n-1}) \quad (2.3)$$

where $[AUC]$ = area under the curve, t_n = time of observation of drug concentration C_n , and t_{n-1} = time of prior observation of drug concentration corresponding to C_{n-1} .

To obtain the AUC from 1 to 4 hours in Fig. 2-2, each portion of this area must be summed. The AUC between 1 and 2 hours is calculated by proper substitution into Equation 2.3:

$$[AUC]_{t_1}^{t_2} = \frac{30.3 + 18.4}{2} (2 - 1) = 24.35 \mu\text{g} \cdot \text{h/mL}$$

Similarly, the AUC between 2 and 3 hours is calculated as $14.75 \mu\text{g} \cdot \text{h/mL}$, and the AUC between 3 and 4 hours is calculated as $8.94 \mu\text{g} \cdot \text{h/mL}$. The total AUC between 1 and 4 hours is obtained by adding the three smaller AUC values together.

$$\begin{aligned} [AUC]_{t_1}^{t_4} &= [AUC]_{t_1}^{t_2} + [AUC]_{t_2}^{t_3} + [AUC]_{t_3}^{t_4} \\ &= 24.3 + 14.3 + 8.94 \\ &= 48.04 \mu\text{g} \cdot \text{h/mL} \end{aligned}$$

The total area under the plasma drug level–time curve from time zero to infinity (Fig. 2-2) is obtained by summation of each individual area between each pair of consecutive data points using the trapezoidal rule. The value on the y axis when time equals 0 is

estimated by back extrapolation of the data points using a log linear plot (ie, $\log y$ vs x). The last plasma level–time curve is extrapolated to $t = \infty$. In this case the residual area $[AUC]_{t_n}^{\infty}$ is calculated as follows:

$$[AUC]_{t_n}^{\infty} = \frac{C_{pn}}{k} \quad (2.4)$$

where C_{pn} = last observed plasma concentration at t_n and k = slope obtained from the terminal portion of the curve.

The trapezoidal rule written in its full form to calculate the AUC from $t = 0$ to $t = \infty$ is as follows:

$$[AUC]_0^{\infty} = \Sigma [AUC]_{t_{n-1}}^{t_n} + \frac{C_{pn}}{k}$$

This numerical method of obtaining the AUC is fairly accurate if sufficient data points are available. As the number of data points increases, the trapezoidal method of approximating the area becomes more accurate.

The trapezoidal rule assumes a linear or straight-line function between data points. If the data points are spaced widely, then the normal curvature of the line will cause a greater error in the area estimate.

Frequently Asked Questions

- What are the units for logarithms?
- What is the difference between a common log and a natural log (ln)?

GRAPHS

The construction of a curve or straight line by plotting observed or experimental data on a graph is an important method of visualizing relationships between variables. By general custom, the values of the independent variable (x) are placed on the horizontal line in a plane, or on the abscissa (x axis), whereas the values of the dependent variable are placed on the vertical line in the plane, or on the ordinate (y axis). The values are usually arranged so that they increase linearly or logarithmically from left to right and from bottom to top.

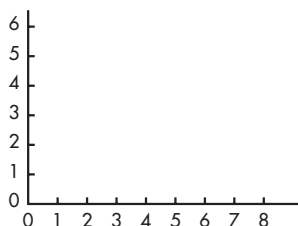


FIGURE 2-3 Rectangular coordinates.

In pharmacokinetics, time is the independent variable and is plotted on the abscissa (x axis), whereas drug concentration is the dependent variable and is plotted on the ordinate (y axis). Two types of graphs or graph papers are usually used in pharmacokinetics. These are Cartesian or rectangular coordinate (Fig. 2-3) and semilogarithmic graph or graph paper (Fig. 2-4). Semilogarithmic allows placement of the data at logarithmic intervals so that the numbers need not be converted to their corresponding log values prior to plotting on the graph.

Curve Fitting

Fitting a curve to the points on a graph implies that there is some sort of relationship between the variables x and y , such as dose of drug versus pharmacologic effect (eg, lowering of blood pressure). Moreover, when using curve fitting, the relationship is not confined to isolated points but is a continuous function of x and y . In many cases, a hypothesis is made concerning the relationship between the variables x and y . Then, an empirical equation is formed that best describes the hypothesis. This empirical equation must satisfactorily fit the experimental or

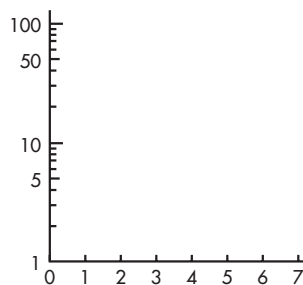


FIGURE 2-4 Semilog coordinates.

observed data. If the relationship between x and y is linearly related, then the relationship between the two can be expressed as a straight line.

Physiologic variables are not always linearly related. However, the data may be arranged or transformed to express the relationship between the variables as a straight line. Straight lines are very useful for accurately *predicting* values for which there are no experimental observations. The general equation of a straight line is

$$y = mx + b \quad (2.5)$$

where m = slope and b = y intercept. Equation 2.5 could yield any one of the graphs shown in Fig. 2-5, depending on the value of m . The absolute magnitude of m gives some idea of the steepness of the curve. For example, as the value of m approaches 0, the line becomes more horizontal. As the absolute value of m becomes larger, the line slopes farther upward or downward, depending on whether m is positive or negative, respectively.

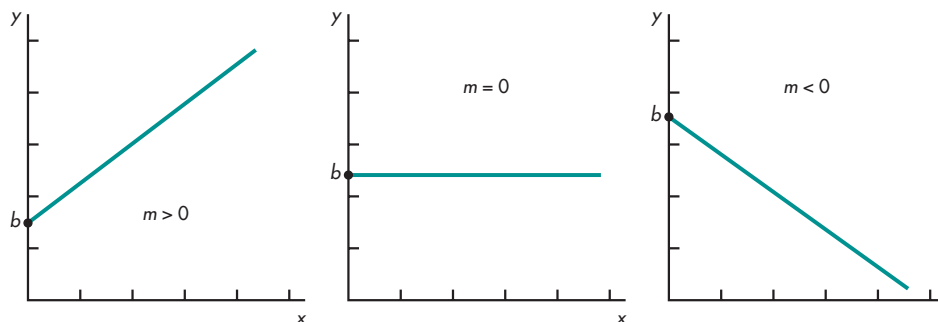


FIGURE 2-5 Graphic demonstration of variations in slope (m).

Linear Regression/Least Squares Method

This method is often encountered and used in clinical pharmacy studies to construct a linear relationship between an independent variable (also known as the input factor or the x factor) and a dependent variable (commonly known as an output variable, an outcome, or the y factor). In pharmacokinetics, the relationship between the plasma drug concentrations versus time can be expressed as a linear function. Because of the availability of computing devices (computer programs, scientific calculators, etc), the development of a linear equation has indeed become a simple task. A general format for a linear relationship is often expressed as:

$$y = mx + b \quad (2.6)$$

where y is the dependent variable, x is the independent variable, m is the slope, and b is the y intercept. The value of the slope and the y intercept may be positive, negative, or zero. A positive linear relationship has a positive slope, and a negative slope belongs to a negative linear relationship (Gaddis and Gaddis, 1990; Munro, 2005).

The strength of the linear relationship is assessed by the correlation coefficient (r). The value of r is positive when the slope is positive and it is negative when the slope is negative. When r takes the value of either +1 or -1, a perfect relationship exists between the variables. A zero value for the slope (or for r) indicates that there is no linear relationship existing between y and x . In addition to r , the coefficient of determination (r^2) is often computed to express how much variability in the outcome is explained by the input factor. For example, if r is 0.90, then r^2 equals to 0.81. This means that the input variable explains 81% of the variability observed in y . It should be noted, however, that a high correlation between the two variables does not necessarily mean causation. For example, the passage of time is not really the cause for the drug concentration in the plasma to decrease. Rather it is the distribution and the elimination functions that cause the level of the drug to decrease over time (Gaddis and Gaddis, 1990; Munro, 2005).

The linear regression/least squares method assumes, for simplicity, that there is a linear relationship

between the variables. If a linear line deviates substantially from the data, it may suggest the need for a nonlinear regression model, although several variables (multiple linear regression) may be involved. Nonlinear regression models are complex mathematical procedures that are best performed with a computer program.

Frequently Asked Questions

- ▶ How is the area under the curve, AUC, calculated? What are the units for AUC?
- ▶ How do you know that the line that you fit to produce a curve on a graph is the line of best fit?
- ▶ What assumptions are made when a line is fitted to the points on a graph?

PRACTICE PROBLEM

Plot the following data and obtain the equation for the line that best fits the data by (a) using a ruler and (b) using the method of least squares. Data can be plotted manually or by using a computer spreadsheet program such as Microsoft Excel.

x (mg)	y (hours)	x (mg)	y (hours)
1	3.1	5	15.3
2	6.0	6	17.9
3	8.7	7	22.0
4	12.9	8	23.0

Solution

Many computer programs have a regression analysis, which fits data to a straight line by least squares. In the least squares method, the slope m and the y intercept b (Equation 2.7) are calculated so that the average sum of the deviations squared is minimized. The deviation, d , is defined by

$$b + mx - y = d \quad (2.7)$$

If there are no deviations from linearity, then $d = 0$ and the exact form of Equation 2.7 is as follows:

$$b + mx - y = 0$$

To find the slope, m , and the intercept, b , the following equations are used:

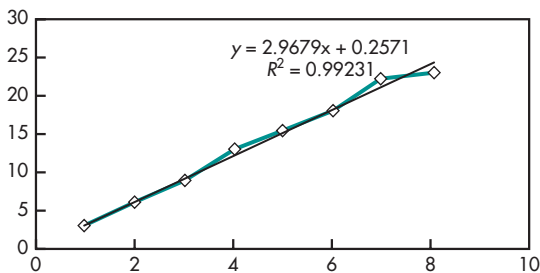
$$m = \frac{\Sigma(x)\Sigma(y) - n\Sigma(xy)}{[\Sigma(x)]^2 - n\Sigma(x^2)} \quad (2.8)$$

where n = number of data points.

$$b = \frac{\Sigma(x)\Sigma(xy) - \Sigma(x^2)\Sigma y}{[\Sigma(x)]^2 - n\Sigma(x^2)} \quad (2.9)$$

where Σ is the sum of n data points.

The following graph was obtained by using a Microsoft Excel spreadsheet and calculating a regression line (sometimes referred to as a trendline in the computer program):



Therefore, the linear equation that best fits the data is

$$y = 2.97x + 0.257$$

Although an equation for a straight line is obtained by the least squares procedure, the reliability of the values should be ascertained. A correlation coefficient, r , is a useful statistical term that indicates the relationship of the x , y data fit to a straight line. For a perfect linear relationship between x and y , $r = +1$. Usually, $r \geq 0.95$ demonstrates good evidence or a strong correlation that there is a linear relationship between x and y .

Problems of Fitting Points to a Graph

When x and y data points are plotted on a graph, a relationship between the x and y variables is sought. Linear relationships are useful for predicting values for the dependent variable y , given values for the independent variable x .

The *linear regression* calculation using the least squares method is used for calculating a straight line through a given set of points. However, it is important to realize that, when using this method, one has already assumed that the data points are related linearly. Indeed, for three points, this linear relationship may not always be true. As shown in Fig. 2-6, Riggs (1963) calculated three different curves that fit the data accurately. Generally, one should consider the *law of parsimony*, which broadly means “keep it simple”; that is, if a choice between two hypotheses is available, choose the more simple relationship.

If a linear relationship exists between the x and y variables, one must be careful as to the estimated value for the dependent variable y , assuming a value for the independent variable x . *Interpolation*, which means filling the gap between the observed data on

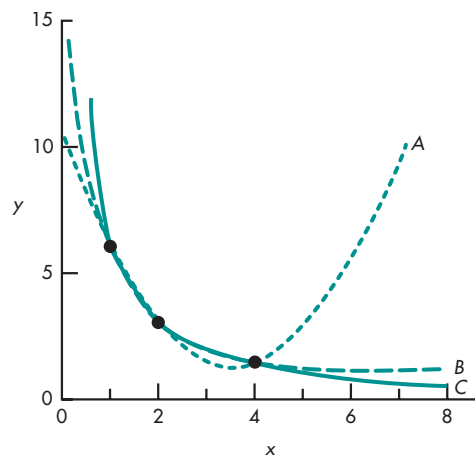


FIGURE 2-6 Three points equally well fitted by different curves. The parabola, $y = 10.5 - 5.25x + 0.75x^2$ (curve A); the exponential, $y = 12.93e^{-1.005x} + 1.27$ (curve B); and the rectangular hyperbola, $y = 6/x$ (curve C) all fit the three points (1,6), (2,3), and (4,1.5) perfectly, as would an infinite number of other curves. (Reprinted with permission from Riggs DS: *The Mathematical Approach to Physiological Problems*. Baltimore, Williams & Wilkins, 1963.)

a graph, is usually safe and assumes that the trend between the observed data points is consistent and predictable. In contrast, the process of *extrapolation* means predicting new data beyond the observed data, and assumes that the same trend obtained between two data points will extend in either direction beyond the last observed data points. The use of extrapolation may be erroneous if the regression line no longer follows the same trend beyond the measured points.

Graphs should always have the axes (abscissa and ordinate) properly labeled with units. For example, the amount of drug on the ordinate (y axis) is given in milligrams and the time on the abscissa (x axis) is given in hours. The equation that best fits the points on this curve is the equation for a straight line, or $y = mx + b$. Because the slope $m = \Delta y / \Delta x$, the units for the slope should be milligrams per hour (mg/h). Similarly, the units for the y intercept b should be the same units as those for y, namely, milligrams (mg).

MATHEMATICAL EXPRESSIONS AND UNITS

Mathematics is a basic science that helps to explain relationships among variables. For an equation to be valid, the units or dimensions must be constant on both sides of the equation. Many different units are used in pharmacokinetics, as listed in Table 2-1. For an accurate equation, both the integers and the units must balance. For example, a common expression for total body clearance is

$$Cl_T = kV_d \quad (2.10)$$

After insertion of the proper units for each term in the above equation from Table 2-1,

$$\frac{\text{mL}}{\text{h}} = \frac{1}{\text{h}} \text{mL}$$

Thus, the above equation is valid, as shown by the equality $\text{mL/h} = \text{mL/h}$.

An important rule in using equations with different units is that the units may be added or subtracted as long as they are alike, but divided or multiplied if they are different. When in doubt, check the equation by inserting the proper units. For example,

$$\begin{aligned} \text{AUC} &= \frac{FD_0}{kV_D} = \text{concentration} \times \text{time} \\ \frac{\mu\text{g}}{\text{mL}} \cdot \text{h} &= \frac{1\text{mg}}{\text{h}^{-1}\text{L}} = \frac{\mu\text{g} \cdot \text{h}}{\text{mL}} \end{aligned} \quad (2.11)$$

Certain terms have no units. These terms include logarithms and ratios. Percent may have no units and is expressed mathematically as a decimal between 0 and 1 or as 0% to 100%, respectively. On occasion, percent may indicate mass/volume, volume/volume, or mass/mass. Table 2-1 lists common pharmacokinetic parameters with their symbols and units.

A constant is often inserted in an equation to quantify the relationship of the dependent variable to the independent variable. For example, *Fick's law of diffusion* relates the rate of drug diffusion, dQ/dt , to the change in drug concentration, C , the surface area of the membrane, A , and the thickness of the membrane, h . In order to make this relationship an equation, a diffusion constant D is inserted:

$$\frac{dQ}{dt} = \frac{DA}{h} \times \Delta C \quad (2.12)$$

To obtain the proper units for D , the units for each of the other terms must be inserted:

$$\begin{aligned} \frac{\text{mg}}{\text{h}} &= \frac{D(\text{cm}^2)}{\text{cm}} \times \frac{\text{mg}}{\text{cm}^3} \\ D &= \text{cm}^2/\text{h} \end{aligned}$$

The diffusion constant D must have the units of area/time or cm^2/h if the rate of diffusion is in mg/h .

TABLE 2-1 Common Units Used in Pharmacokinetics

Parameter	Symbol	Unit	Example
Rate	$\frac{dD}{dt}$	$\frac{\text{Mass}}{\text{Time}}$	mg/h
	$\frac{dC}{dt}$	$\frac{\text{Concentration}}{\text{Time}}$	ug/mL/h
Zero-order rate constant	K_0	$\frac{\text{Concentration}}{\text{Time}}$	μg/mL/h
		$\frac{\text{Mass}}{\text{Time}}$	mg/h
First-order rate constant	k	$\frac{1}{\text{Time}}$	1/h or h ⁻¹
Drug dose	D_0	Mass	mg
Concentration	C	$\frac{\text{Mass}}{\text{Volume}}$	μg/mL
Plasma drug concentration	C_p	$\frac{\text{Drug}}{\text{Volume}}$	μg/mL
Volume	V	Volume	mL or L
Area under the curve	AUC	Constration × time	μg·h/mL
Fraction of drug absorbed	F	No units	0 to 1
Clearance	Cl	$\frac{\text{Volume}}{\text{Time}}$	mL/h
Half-life	$t_{1/2}$	Time	H

UNITS FOR EXPRESSING BLOOD CONCENTRATIONS

Various units have been used in pharmacology, toxicology, and the clinical laboratory to express drug concentrations in blood, plasma, or serum. Drug concentrations or drug levels should be expressed as mass/volume. The expressions mcg/mL, μg/mL, and mg/L are equivalent and are commonly reported in the literature. Drug concentrations may also be reported as mg% or mg/dL, both of which indicate milligrams of drug per 100 mL (1 deciliter). Two older expressions for drug concentration occasionally used in veterinary medicine are the terms ppm and ppb, which indicate the number of parts of drug per million parts of blood (ppm) or per billion parts of blood (ppb), respectively. One ppm is equivalent to 1.0 μg/mL. The accurate interconversion of units is often necessary to prevent confusion and misinterpretation.

MEASUREMENT AND USE OF SIGNIFICANT FIGURES

Every measurement is performed within a certain degree of accuracy, which is limited by the instrument used for the measurement. For example, the weight of freight on a truck may be measured accurately to the nearest 0.5 kg, whereas the mass of drug in a tablet may be measured to 0.001 g (1 mg). Measuring the weight of freight on a truck to the nearest milligram is not necessary and would require a very costly balance or scale to detect a change in a milligram quantity.

Significant figures are the number of accurate digits in a measurement. If a balance measures the mass of a drug to the nearest milligram, measurements containing digits representing less than 1 mg are inaccurate. For example, in reading the weight or mass of a drug of 123.8 mg from this balance, the

0.8 mg is only approximate; the number is therefore rounded to 124 mg and reported as the observed mass.

For practical calculation purposes, all figures may be used until the final number (answer) is obtained. However, the answer should retain only the number of significant figures in the least accurate initial measurement.

PRACTICE PROBLEM

When a patient swallows a tablet containing 325 mg of aspirin (ASA), the tablet comes in contact with the contents of the gastrointestinal tract and the ASA is released from the tablet. Assuming a constant amount of the drug release over time (t), the rate of drug release is expressed as:

$$\begin{aligned}\text{Rate of drug (ASA) release (mg/min)} &= \frac{d(\text{ASA})}{dt} \\ &= k_0\end{aligned}$$

where k_0 is a rate constant.

Integration of the rate expression above gives Equation 2.13:

$$\text{Amount of ASA released (mg)} = at + b \quad (2.13)$$

The symbol “ a ” represents the slope (equivalent to k_0), t is time, and b is the y intercept. Assuming that time was measured in minutes, the following mathematical expression is obtained representing Equation 2.13:

$$\text{Amount of ASA released (mg)} = 0.86t - 0.04 \quad (2.14)$$

To calculate the amount of ASA released at 180 seconds, the following algebraic manipulations are needed:

1. Convert 180 seconds to minutes: 3 minutes.
2. Replace t in Equation 2.14 by the value 3.
3. Solve the equation for the amount of ASA released.

$$\begin{aligned}\text{Amount of ASA released (mg)} &= 0.86(3) - 0.04 \\ &= 2.54 \text{ mg}\end{aligned}$$

A pharmacist is interested in learning the time needed for 90% of ASA to be released from the tablet. To answer her inquiry the following steps are taken:

1. Calculate the amount of ASA in milligrams representing 90% of the drug present in the tablet.

2. Replace the value found in step (1) in Equation 2.14 and solve for time (t):

$$90\% \text{ of } 325 = (0.9)(325 \text{ mg}) = 292.5 \text{ mg}$$

$$292.5 \text{ mg} = 0.86t - 0.04$$

$$292.5 + 0.04 = 0.86t$$

Dividing both sides of the equation by 0.86:

$$(292.5 + 0.04)/0.86 = (0.86t)/0.86$$

$$340.07 \text{ minutes} = t$$

Or it takes 5.7 hours for this amount of ASA (90%) to be released from the tablet.

The above calculations show that this tablet releases the drug very slowly over time and it may not be useful in practice when the need for the drug is more immediate. It should also be emphasized that only the amount of the drug released and soluble in the GI juices is available for absorption. If the drug precipitates out in the GI tract, it will not be absorbed by the GI mucosa. It is also assumed that the unabsorbed portion of the drug in the GI tract is considered to be “outside the body” because its effect cannot be exerted systematically.

To calculate the amount of ASA that was immediately released from the tablet upon contact with gastric juices, the time in Equation 2.14 is set to the value zero:

$$\text{Amount of ASA released (mg)} = 0.86(0) - 0.04$$

$$\text{Amount of ASA released (mg)} = -0.04 \text{ mg}$$

Since an amount released cannot be negative, this indicates that no amount of ASA is released from the tablet instantly upon coming in touch with the juices. Equation 2.14 may be represented graphically using Cartesian or rectangular coordinates (Fig. 2-7).

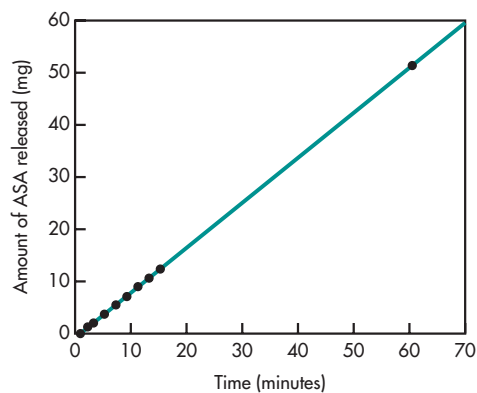


FIGURE 2-7 Amount of ASA released versus time (minutes) plotted on Cartesian coordinates.

PRACTICE PROBLEM

Briefly, $C_{\max}$ is the maximum drug concentration in the plasma and $T_{\max}$ is the time associated with $C_{\max}$. First-order elimination rate constant signifies the fraction of the drug that is eliminated per unit time. The biological half-life of the drug is the time needed for 50% of the drug to be eliminated. The AUC term or the area under the drug plasma concentration-versus-time curve reflects the extent of absorption from the site of administration. The term AUMC is

the area under the moment curve, whereas MRT is the mean residence time, which is estimated from the ratio of $AUMC(0-\infty)/AUC(0-\infty)$. These pharmacokinetic terms are discussed in more details throughout this textbook.

The below table (Ravi Shankar et al., 2012) shows pharmacokinetic data obtained from a study conducted in rabbits following administration of various formulations of rectal suppositories containing aspirin (600 mg each). Various formulations were prepared in a suppository base made of a mixture of gelatin and glycerin. Formulation Fas9 had the same composition as Fs9 with the exception that Fas9 contained ASA in the form of nanoparticles, whereas Fs9 had ASA in its free form (so did formulations Fs2, Fs4, and Fs11, but varied in their gelatin/glycerin composition). The authors concluded that the incorporation of ASA in the form of nanoparticles increased the $T_{\max}$. The other pharmacokinetic parameters taken together indicate that nanoparticles produced a sustained-release profile of ASA when given in this dosage form. In this study, the plasma concentration was expressed in “micrograms per milliliter.” If the $\mu\text{g/mL}$ were not specified, it would have been difficult to compare the results from this study with other similar studies. It is imperative, therefore, that pharmacokinetic parameters such as $C_{\max}$ be properly defined by units.

Pharmacokinetic Parameters	Fs2	Fs4	Fs9	Fs11	Fas9
$C_{\max}$ ($\mu\text{g/mL}$)	34.93 ± 0.60	31.16 ± 1.04	32.66 ± 1.52	35.33 ± 0.57	31.86 ± 0.41
$T_{\max}$ (hours)	1 ± 0.01	1 ± 0.03	1 ± 0.06	1 ± 0.09	6 ± 0.03
Elimination rate constant (h^{-1})	0.14 ± 0.02	0.19 ± 0.06	0.205 ± 0.03	0.17 ± 0.01	0.133 ± 0.004
Half-life (hours)	1.88 ± 0.76	1.9 ± 1.19	1.43 ± 0.56	1.99 ± 0.24	5.11 ± 0.15
$AUC(0-t)$	127.46 ± 8.9	126.62 ± 2.49	132.11 ± 3.88	127.08 ± 1.95	260.62 ± 4.44
$AUC(0-\infty)(\text{ng}\cdot\text{h/mL})$	138.36 ± 13.87	131.61 ± 0.27	136.89 ± 4.40	133.07 ± 2.97	300.48 ± 24.06
$AUMC(0-t)(\text{ng}\cdot\text{h}^2/\text{mL})$	524.51 ± 69.64	516.04 ± 28.25	557.84 ± 16.25	501.29 ± 26.65	2006.07 ± 38.00
$AUMC(0-\infty)(\text{ng}\cdot\text{h}^2/\text{mL})$	382.09 ± 131.45	237.74 ± 64.37	232.93 ± 28.16	257.71 ± 30.04	1494.71 ± 88.21
MRT (hours)	2.45 ± 0.36	2.31 ± 0.80	1.41 ± 0.31	2.95 ± 0.17	8.23 ± 0.06

Ravi Sankar V, Dachinamoorthi D, Chandra Shekar KB: A comparative pharmacokinetic study of aspirin suppositories and aspirin nanoparticles loaded suppositories. *Clinic Pharmacol Biopharm* 1:105, 2012.

Expressing the $C_{\max}$ value by equivalent units is also possible. For example, converting $\mu\text{g/mL}$ to mg/dL follows these steps:

1. Convert micrograms (also written as mcg) to milligrams.
2. Convert milliliters to deciliters:
Since:
 $1 \text{ mg} = 1000 \mu\text{g}$, then $31.86 \mu\text{g/mL} = 0.03186 \text{ mg/mL}$
 $1 \text{ dL} = 100 \text{ mL}$, then $31.86 \mu\text{g/mL} = 3186 \mu\text{g/dL}$
We have to divide the value of $C_{\max}$ by 1000 and multiply it by 100. The net effect is to divide the number by 10, or $(31.86)(100/1000) = 3.19 \text{ mg/dL}$.

Expressing the $C_{\max}$ value $34.93 \mu\text{g/mL}$ in nanograms per microliter ($\text{ng}/\mu\text{L}$) is done as follows:

1. Convert the number of micrograms to nanograms.
2. Convert milliliters to microliters:
 $1 \mu\text{g} = 1000 \text{ ng}$, or $34.93 \mu\text{g/mL} = 34,930 \text{ ng/mL}$
 $1 \text{ mL} = 1000 \mu\text{L}$, or $34.93 \mu\text{g/mL} = 0.03493 \mu\text{g}/\mu\text{L}$
As 34.93 was multiplied and divided by the same number (1000), the final answer is $34.93 \text{ ng}/\mu\text{L}$.

Express the $C_{\max}$ value $35.33 \mu\text{g/mL}$ in %w/v (this is defined as the number of grams of ASA in 100 mL plasma).

$$(35.33 \mu\text{g/mL})(100 \text{ mL}) = 3533 \mu\text{g/dL} = 3.533 \text{ mg/dL} = 0.0035 \text{ g/dL, or } 0.0035\% \text{ w/v}$$

(This means that there is 0.0035 g of ASA in every 100 mL plasma.)

The data ($T_{\max}$, $C_{\max}$) represent a maximum point on the plasma drug level-versus-time curve. This point reflects the *rate of absorption* of the drug from its site of administration. Another pharmacokinetic measure obtained from the same curve is the *area under the curve* (AUC). It reflects the *extent of absorption* for a drug from the site of administration into the circulation. The general format for the AUC

units is $([\text{amount}][\text{time}]/[\text{volume}])$. Together, the rate and extent of absorption refers to the bioavailability of the drug from the site of administration. The term “*absolute bioavailability*” is used when the reference route of administration is the intravenous injection (ie, the IV route). If the reference route is different from the intravenous route, then the term “*relative bioavailability*” is used. The value for the AUC (0 to $+\infty$) following the administration of Fs2, Fs4, and Fas9 was 138.36, 131.61, and 300.48 $\text{ng}\cdot\text{h/mL}$, respectively (Ravi Sankar et al, 2012). The origin of the AUC units is based on the *trapezoidal rule*. The *trapezoidal rule* is a numerical method frequently used in pharmacokinetics to calculate the area under the plasma drug concentration-versus-time curve, called the *area under the curve* (AUC). This rule computes the average concentration value of each consecutive concentration and multiplies them by the difference in their time values. To compute the AUC (0 to time t), the sum of all these products is calculated. For example, $\text{AUC}(0-t) = 127.46 \text{ ng}\cdot\text{h/mL}$ can be written as $127.46 (\text{ng/mL})(\text{h})$.

To convert $260.62 \text{ ng}\cdot\text{h/mL}$ to $\mu\text{g}\cdot\text{h/mL}$, divide the value by 1000 (recall that $1 \mu\text{g}$ is 1000 ng). Therefore, the AUC value becomes $0.26 \mu\text{g}\cdot\text{h/mL}$.

Expressing the AUC (0 to $+\infty$) value $300.48 \text{ ng}\cdot\text{h/mL}$ in $\text{ng}\cdot\text{min/mL}$ can be accomplished by dividing 300.48 by 60 (1 hour is 60 min). Thus, the AUC value becomes $5.0 \text{ ng}\cdot\text{min/mL}$.

Consider the following data:

Plasma Concentration (ng/L)	Time (hours)	AUC (ng·h/L)
0	0	0
0.05	1	0.025
0.10	2	0.075
0.18	3	0.140
0.36	5	0.540
0.13	7	0.490
0.08	9	0.210

To compute the AUC value from initial to 9 hours, sum up the values under the AUC column above ($0.025 + 0.075 + \dots + 0.210 = 1.48 \text{ ng}\cdot\text{h/L}$).

To convert the AUC value 1.48 ng·h/L to mg·min/dL, use the following steps:

1. Divide the value by 10^6 to convert the nanograms to milligrams.
2. Divide the value by 60 to convert the hours to minutes.
3. Divide the value by 10 to convert the liters to deciliters.

$$\begin{aligned} \text{AUC} &= (1.48)/[(10^6)(60)(10)] \\ &= 2.47 \times 10^{-9} \text{ mg} \cdot \text{min}/\text{dL} \end{aligned} \quad (2.15)$$

Figure 2-8 represents the data in a rectangular coordinate-type graph. Time is placed on the x axis (*the abscissa*) and plasma concentration is placed on the y axis (*the ordinate*). The highest point on the graph can simply be determined by spotting it on the graph. Note that the plasma concentration declines *exponentially* from the apex point on the curve over time. Figure 2-9 shows the exponential portion of the graph on its own.

Exponential and Logarithmic Functions

These two mathematical functions are related to each other. For example, the pH of biological fluids (eg, plasma or urine) can influence all pharmacokinetic aspects including drug dissolution/release *in vitro* as well as systemic absorption, distribution, metabolism, and excretion. Since most drugs are either weak

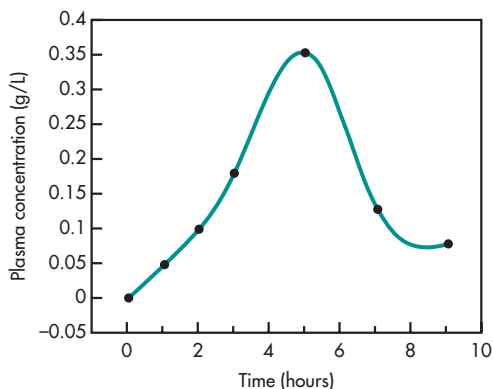


FIGURE 2-8 Plasma concentration (g/L)-versus-time (hours) curve plotted on Cartesian coordinates.

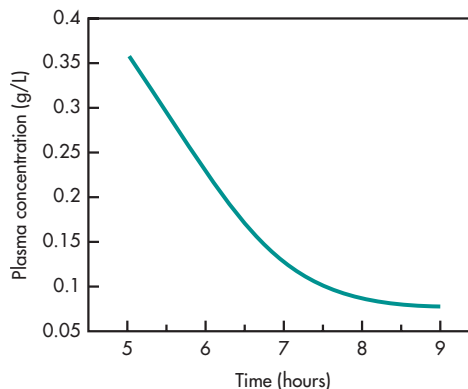


FIGURE 2-9 The exponential decline in plasma concentration over time portion in Fig. 2-8.

bases or weak acids, the pH of the biological fluid determines the degree of ionization of the drug and this in turn influences the pharmacokinetic profile of the drug. The pH scale is a logarithmic scale:

$$\text{pH} = -\log[\text{H}_3\text{O}^+] = \log(1/[\text{H}_3\text{O}^+]) \quad (2.16)$$

where the symbol “log” is the *logarithm to base 10*. The *natural logarithm* has the symbol “ln,” which is the logarithm to base e (the value of e is approximately 2.71828). The two functions are linked by the following expression:

$$\ln x = 2.303 \log x \quad (2.17)$$

The concentration of hydronium ions $[\text{H}_3\text{O}^+]$ can be calculated from Equation 2.16 as follows:

$$[\text{H}_3\text{O}^+] = 10^{-\text{pH}} \quad (2.18)$$

For example, the pH of a patient’s plasma is 7.4 at room temperature. Therefore, the hydronium ion concentration in plasma is:

$$[\text{H}_3\text{O}^+] = 10^{-7.4} = 3.98 \times 10^{-8} \text{ M}$$

The value (3.98×10^{-8}) is the *antilogarithm* of 7.4. With the availability of scientific calculators and computers, these functions can be easily calculated.

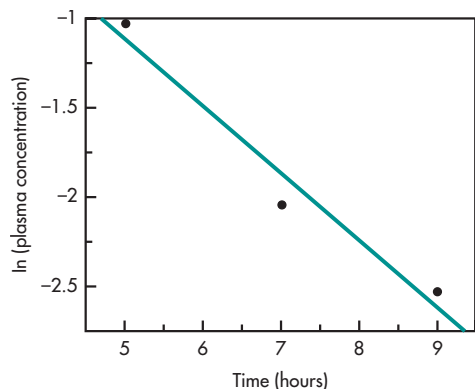


FIGURE 2-10 $\ln$ (Plasma concentration)-versus-time curve plotted on Cartesian coordinates.

Oftentimes, converting plasma concentrations to logarithmic values and plotting the logarithmic values against time would convert an exponential relationship to a linear function between the two variables. Consider, for example, Fig. 2-9. When the concentration values are converted to logarithmic values, the graph now becomes linear (Fig. 2-10). This same linear function may be obtained by plotting the *actual* values of the plasma concentration versus time using a semilogarithmic graph (Fig. 2-11). The following equation represents the straight line:

$$\ln (\text{Plasma concentration}) = 0.77 - 0.38 \text{ Time (hours)} \quad (2.19)$$

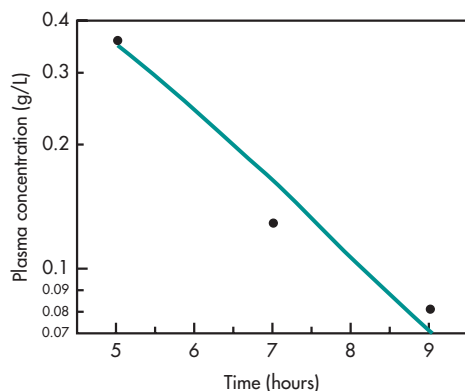


FIGURE 2-11 Plasma concentration-versus-time curve using a semilogarithmic graph.

The slope of the line is (-0.38) . Thus,

$$\text{Slope} = -0.38 = -k_1$$

Multiplying both sides of the equation by (-1) results in:

$$k_1 = 0.38 \text{ h}^{-1}$$

where k_1 is the *first-order elimination rate constant*. The units for this constant are reciprocal time, such as h^{-1} or $1/\text{h}$. The value 0.38 h^{-1} means that 38% of the concentration remaining of the drug in plasma is eliminated every hour.

Using Equation 2.17, Equation 2.19 can be converted to the following expression:

$$2.303 [\log (\text{Plasma concentration})] = 0.77 - 0.38 \text{ Time (hours)}$$

Dividing both sides of the equation by 2.303:

$$2.303 [\log (\text{Plasma concentration})]/2.303 = [0.77 - 0.38 \text{ Time (hours)}]/2.303$$

$$\log (\text{Plasma concentration}) = 0.334 - 0.17 \text{ Time (hours)}$$

$$(2.20)$$

Equation 2.20 is mathematically equivalent to Equation 2.19.

The value 0.77 in Equation 2.19 equals $(\ln C_0)$, where C_0 is the initial concentration of the drug in plasma. Thus,

$$\ln C_0 = 0.77$$

$$C_0 = e^{0.77} = 2.16 \text{ g/L}$$

Once k_1 is known, the AUC from the last data point to t_{∞} can be calculated as follows:

$$\text{AUC} = C_{\text{Last}}/k_1 \quad (2.21)$$

Applying Equation 2.21 on the data used to obtain the AUC value in Equation 2.15 results in the following value:

$$\text{AUC} = 0.08/0.38 = 0.21 \text{ g}\cdot\text{h/L}$$

And the total AUC ($t = 0$ to $t = \text{infinity}$):

$$\text{AUC}_{\text{Total}} = 1.48 + 0.21 = 1.69 \text{ g}\cdot\text{h/L}$$

The following rules may be useful in handling exponential and logarithmic functions. For this, if m and n are positive, then for the real numbers q and s (Howard, 1980):

Exponent rules:

1. $m^0 = 1$
2. $m^1 = m$
3. $m^{-1} = 1/m^1$
4. $m^q/m^s = m^{q-s}$
5. $(m^q)(m^s) = m^{q+s}$
6. $(m^q)^s = m^{qs}$
7. $(m^q/n^q) = (m/n)^q$
8. $(m^q)(n^q) = (mn)^q$

If z is any positive number other than 1 and if $z^y = x$, then following logarithmic rules apply:

Logarithm rules:

1. $y = \log_z x$ (y is the logarithm to the base z of x)
2. For $x > 1$, then $\log_e x = \ln x$ (where e is approximately 2.71828)
3. $\log_z x = (\ln x / \ln z)$
4. $\log_z mn = \log_z m + \log_z n$
5. $\log_q (m/n) = \log_q m - \log_q n$
6. $\log_z (1/m) = -\log_z m$
7. $\ln e = 1$
8. For $z = 10$, then $\log_z 1 = 0$
9. $\log_z m^h = h \log_z m$
10. For $z = 10$, then $(2.303) \log_z x = \ln x$

RATES AND ORDERS OF PROCESSES

Oftentimes a process such as drug absorption or drug elimination may be described by the *rate* by which the process proceeds. The rate of a process, in turn,

may be defined in terms of specifying its *order*. In pharmacokinetics, two orders are of importance, the *zero order* and the *first order*.

Zero-Order Process

The rate of a zero-order process is one that proceeds over time (t) independent from the concentration of the drug (c). The negative sign for the rate indicates that the concentration of the drug decreases over time.

$$-dc/dt = k_0 \quad (2.22)$$

$$dc = -k_0 dt$$

$$c = c_0 - k_0 t \quad (2.23)$$

where c_0 is the initial concentration of the drug at $t = 0$ and k_0 is the zero-order rate constant. The units for k_0 are concentration per unit time (eg, [mg/mL]/h) or amount per unit time (eg, mg/h).

For example, calculate the zero-order rate constant ([ng/mL]/min) if the initial concentration of the drug is 200 ng/mL and that at $t = 30$ minutes is 35 ng/mL.

$$c = c_0 - k_0 t$$

$$35 = 200 - k_0 (30)$$

$$-k_0 = (35 - 200)/30 = -5.5$$

$$k_0 = 5.5 \text{ (ng/mL)/min}$$

When does the concentration of drug equal to 100 ng/mL?

$$100 = 200 - 5.5 t$$

$$(100 - 200)/5.5 = -t$$

$$-18.2 = -t$$

$$t = 18.2 \text{ min}$$

In pharmacokinetics, the time required for one-half of the drug concentration to disappear is known as $t_{1/2}$. Thus, for this drug the $t_{1/2}$ is 18.2 minutes.

In general, $t_{1/2}$ may be calculated as follows for a zero-order process:

$$\begin{aligned}
 c &= c_0 - k_0 t \\
 (0.5 c_0) &= c_0 - k_0 t_{1/2} \\
 (0.5 c_0) - c_0 &= -k_0 t_{1/2} \\
 -0.5 c_0 &= -k_0 t_{1/2} \\
 t_{1/2} &= (0.5 c_0)/k_0 \quad (2.24)
 \end{aligned}$$

Applying Equation 2.24 to the example above should yield the same result:

$$\begin{aligned}
 t_{1/2} &= (0.5 c_0)/k_0 \\
 t_{1/2} &= (0.5)(200)/5.5 = 18.2 \text{ minutes}
 \end{aligned}$$

A plot of x versus time on rectangular coordinates produces a straight line with a slope equal to $(-k_0)$ and a y intercept as c_0 . In a zero-order process the $t_{1/2}$ is not constant and depends upon the initial amount or concentration of drug.

First-Order Process

The rate of a first-order process is dependent upon the concentration of the drug:

$$\begin{aligned}
 -dc/dt &= k_1 c \\
 -dc/c &= k_1 dt \quad (2.25)
 \end{aligned}$$

$$\ln c = \ln c_0 - k_1 t \quad (2.26)$$

While the rate of the process is a function of the drug concentration, the $t_{1/2}$ is not:

$$\begin{aligned}
 \ln c &= \ln c_0 - k_1 t \\
 \ln (0.5 c_0) &= \ln c_0 - k_1 t_{1/2} \\
 \ln (0.5 c_0) - \ln c_0 &= -k_1 t_{1/2} \\
 \ln (0.5 c_0/c_0) &= -k_1 t_{1/2}
 \end{aligned}$$

$$\ln 0.5/-k_1 = t_{1/2}$$

$$t_{1/2} = -0.693/-k_1$$

$$t_{1/2} = 0.693/k_1 \quad (2.27)$$

Unlike a zero-order rate process, the $t_{1/2}$ for a first-order rate process is always a constant, independent of the initial drug concentration or amount (Table 2-2, Fig. 2-12).

A plot between $\ln c$ versus t produces a straight line. A semilogarithmic graph also produces a straight line between c and t . The units of the first-order rate constant (k_1) are in reciprocal time.

TABLE 2-2 Comparison of Zero- and First-Order Reactions

	Zero-Order Reaction	First-Order Reaction
Equation	$-dC/dt = k_0$ $C = -k_0 t + C_0$	$-dC/dt = kC$ $C = C_0 e^{-kt}$
Rate constant—units	(mg/L)/h	1/h
Half-life, $t_{1/2}$ (units = time)	$t_{1/2} = 0.5C/k_0$ (not constant)	$t_{1/2} = 0.693/k$ (constant)
Effect of time on rate	Zero-order rate is constant with respect to time	First-order rate will change with respect to time as concentration changes
Effect of time on rate constant	Rate constant with respect to time changes as the concentration changes	Rate constant remains constant with respect to time
Drug concentrations versus time—plotted on rectangular coordinates	Drug concentrations decline linearly for a zero-order rate process	Drug concentrations decline nonlinearly for a first-order rate process
Drug concentrations versus time—plotted on a semilogarithmic graph	Drug concentrations decline nonlinearly for a zero-order rate process	Drug concentrations decline linearly for a single first-order rate process

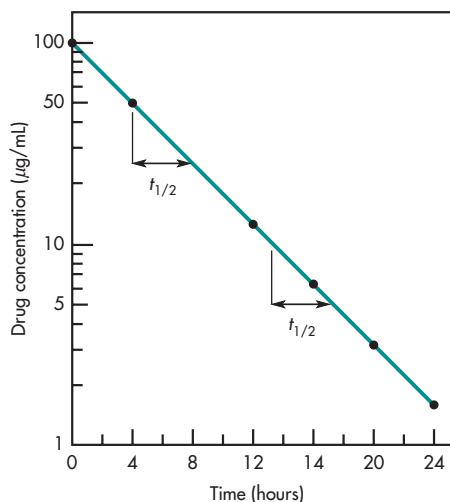


FIGURE 2-12 The $t_{1/2}$ in a first-order rate process is a constant.

For a drug with $k_1 = 0.04 \text{ h}^{-1}$, find $t_{1/2}$.

$$t_{1/2} = 0.693/k_1$$

$$t_{1/2} = 0.693/0.04 = 17.3 \text{ hours}$$

The value 0.04 h^{-1} for the first-order rate constant indicates that 4% of the drug disappears every hour.

Calculate the time needed for 70% of the drug to disappear.

$$\ln c = \ln c_0 - k_1 t$$

$$\ln (0.3 c_0) = \ln c_0 - k_1 t$$

$$\ln (0.3 c_0) - \ln c_0 = -k_1 t$$

$$\ln 0.3 / -k_1 = t$$

$$t = -1.2 / -0.04 = 30 \text{ hours}$$

The value 30 hours may be written as $t_{30} = 30$ hours (it is t_{30} because 70% of the drug is eliminated).

Determination of Order

Graphical representation of experimental data provides a visual relationship between the x values (generally time) and the y axis (generally drug concentrations). Much can be learned by inspecting the line that connects the data points on a graph. The relationship between the x and y data will determine the order of the process, data quality, basic kinetics, and number of outliers, and provide the basis for an underlying pharmacokinetic model. To determine the order of reaction, first plot the data on a rectangular graph. If the data appear to be a curve rather than a straight line, the reaction rate for the data is non-zero order. In this case, plot the data on a semilog graph. If the data now appear to form a straight line with good correlation using linear regression, then the data likely follow first-order kinetics. This simple graph interpretation is true for one-compartment, IV bolus (Chapter 4). Curves that deviate from this format are discussed in other chapters in terms of route of administration and pharmacokinetic model.

Frequently Asked Questions

- How is the rate and order of reaction determined graphically?
- What is the difference between a rate and a rate constant?

CHAPTER SUMMARY

Pharmacokinetic calculations require basic skills in mathematics. Although the availability of computer programs and scientific calculators facilitate pharmacokinetic calculations, the pharmaceutical scientist should be familiar with fundamental rules pertaining to calculus. The construction of a curve or straight

line by plotting observed or experimental data on a graph is an important method of visualizing relationships between variables. The linear regression calculation using the least squares method is used for calculation of a straight line through a given set of points. However, it is important to realize that, when

using this method, one has already assumed that the data points are related linearly. For all equations, both the integers and the units must balance. The rate of a process may be defined in terms of specifying its

order. In pharmacokinetics, two orders are of importance, the *zero order* and the *first order*. Mathematical skills are important in pharmacokinetics in particular and in pharmacy in general.

LEARNING QUESTIONS

- Plot the following data on both semilog graph paper and standard rectangular coordinates.

Time (minutes)	Drug A (mg)
10	96.0
20	89.0
40	73.0
60	57.0
90	34.0
120	10.0
130	2.5

- Does the decrease in the amount of drug A appear to be a zero-order or a first-order process?
 - What is the rate constant k ?
 - What is the half-life $t_{1/2}$?
 - Does the amount of drug A extrapolate to zero on the x axis?
 - What is the equation for the line produced on the graph?
- Plot the following data on both semilog graph paper and standard rectangular coordinates.

Time (minutes)	Drug A (mg)
4	70.0
10	58.0
20	42.0
30	31.0
60	12.0
90	4.5
120	1.7

Answer questions **a**, **b**, **c**, **d**, and **e** as stated in Question 1.

- A pharmacist dissolved a few milligrams of a new antibiotic drug into exactly 100 mL of distilled water and placed the solution in a refrigerator (5°C). At various time intervals, the pharmacist removed a 10-mL aliquot from the solution and measured the amount of drug contained in each aliquot. The following data were obtained:

Time (hours)	Antibiotic ($\mu\text{g/mL}$)
0.5	84.5
1.0	81.2
2.0	74.5
4.0	61.0
6.0	48.0
8.0	35.0
12.0	8.7

- Is the decomposition of this antibiotic a first-order or a zero-order process?
 - What is the rate of decomposition of this antibiotic?
 - How many milligrams of antibiotics were in the original solution prepared by the pharmacist?
 - Give the equation for the line that best fits the experimental data.
- A solution of a drug was freshly prepared at a concentration of 300 mg/mL. After 30 days at 25°C, the drug concentration in the solution was 75 mg/mL.
 - Assuming first-order kinetics, when will the drug decline to one-half of the original concentration?
 - Assuming zero-order kinetics, when will the drug decline to one-half of the original concentration?

5. How many half-lives ($t_{1/2}$) would it take for 99.9% of any initial concentration of a drug to decompose? Assume first-order kinetics.
6. If the half-life for decomposition of a drug is 12 hours, how long will it take for 125 mg of the drug to decompose by 30%? Assume first-order kinetics and constant temperature.
7. Exactly 300 mg of a drug is dissolved into an unknown volume of distilled water. After complete dissolution of the drug, 1.0-mL samples were removed and assayed for the drug. The following results were obtained:

Time (hours)	Concentration (mg/mL)
0.5	0.45
2.0	0.3

Assuming zero-order decomposition of the drug, what was the original volume of water in which the drug was dissolved?

8. For most drugs, the overall rate of drug elimination is proportional to the amount of drug remaining in the body. What does this imply about the kinetic order of drug elimination?
9. A single cell is placed into a culture tube containing nutrient agar. If the number of cells doubles every 2 minutes and the culture tube is completely filled in 8 hours, how long does it take for the culture tube to be only half full of cells?
10. Cunha (2013) reported the following: "...CSF levels following 2 g of ceftriaxone are approximately 257 mcg/mL, which is well above the minimal inhibitory concentration (MIC) of even highly resistant (PRSP) in CSF..." What is the value of 257 mcg/mL in mg/mL?
11. Refer to Question 10 above; express the value 257 mcg/mL in mcg/dL.

12. The following information was provided by Steiner et al (2013):

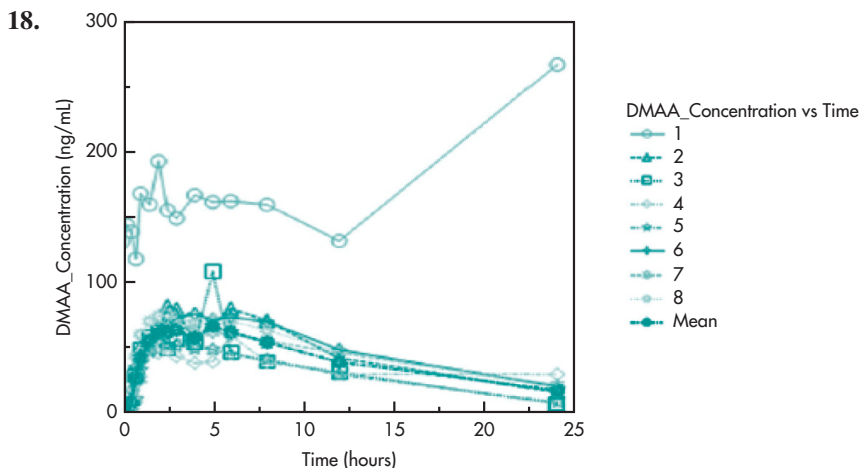
"ACT-335827 hydrobromide (Actelion Pharmaceuticals Ltd., Switzerland) was freshly prepared in 10% polyethylene glycol 400/0.5% methylcellulose in water, which served as vehicle (Veh). It was administered orally at 300 mg/kg based on the weight of the free base, in a volume of 5 mL/kg, and administered daily 2 h before the onset of the dark phase."

How many milligrams of ACT-335827 hydrobromide would be given orally to a 170-g rat?

13. Refer to Question 12; how many milliliters of drug solution would be needed for the 170-g rat?
14. Refer to Question 12; express 0.5% methylcellulose (%w/v) as grams in 1 L solution.
15. The $t_{1/2}$ value for aceclofenac tablet following oral administration in Wistar male rats was reported to be 4.35 hours (Shakeel et al, 2009). Assuming a first-order process, what is the elimination rate constant value in hours⁻¹?
16. Refer to Question 15; express the value of $t_{1/2}$ in minutes.
17. Refer to Question 15; the authors reported that the relative bioavailability of aceclofenac from a transdermally applied gel is 2.6 folds higher compared to that of an oral tablet. The following equation was used by the authors to calculate the relative bioavailability:

$$F\% = \left\{ \frac{[(AUC \text{ sample})(Dose \text{ oral})]}{[(AUC \text{ oral})(Dose \text{ sample})]} \right\} * 100 \quad (2.28)$$

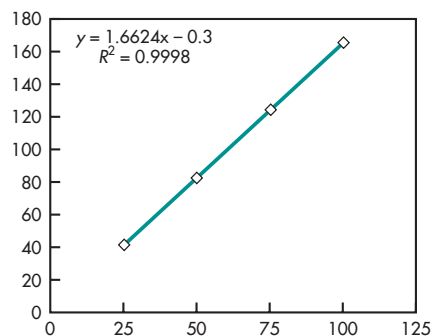
where AUC/Dose sample is for the gel and AUC/Dose oral is for the tablet. $F\%$ is the relative bioavailability expressed in percent. If oral and transdermal doses were the same, calculate AUC sample given AUC oral of 29.1 $\mu\text{g}\cdot\text{h/mL}$. What are the units for AUC sample in (mg-day/mL)?



The above figure (from Basu Sarkar et al, 2013) shows the plasma concentration–time profile of DMAA (1,3-dimethylamylamine) in eight men following a single oral dose of the DMAA (25 mg).

What type of graph paper is the above graph? (Semilogarithmic or rectangular?)

19. Refer to Question 18; what are the $C_{\max}$ and $T_{\max}$ values for subject #1? (subject #1) occurred at $T_{\max}$ of ____ hour.
20. Refer to Question 18; what is the average $C_{\max}$ value for all eight subjects? Please use the correct units for your answer.
21. Refer to Question 18; what are the units for AUC obtained from the graph?
22. Refer to Question 18; for subject #3, the $C_{\max}$ value is approximately 105 ng/mL. Express this concentration in %w/v.
23. Consider the following graph (Figure 2a in the original article) presented in Schilling et al (2013):



The equation in the graph is that for the standard curve generated for progesterone using a high-performance liquid chromatography method. In the equation, y is the area under the curve of progesterone peak and x represents the concentration of the drug in $\mu\text{g/mL}$. Using this equation, predict the AUC for a drug concentration of 35 $\mu\text{g/mL}$.

24. Refer to Question 23; predict the concentration of progesterone (mg/L) for a peak area (AUC) of 145.
25. Consider the following function $dc/dt = 0.98$ with c and t being the concentration of the drug and time, respectively. This equation can also be written as _____.
 - a. $x = x_0 - 0.98 t$
 - b. $x = 0.98 - t$
 - c. $x = x_0 + 0.98 t$
 - d. $x = t/0.98$

ANSWERS

Learning Questions

1. a. Zero-order process (Fig. A-1).

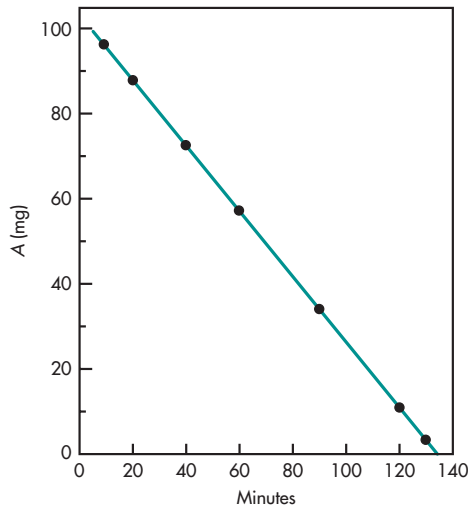


FIGURE A-1

- b. Rate constant, k_0 :

Method 1

Values obtained from the graph (see Fig. A-1):

t (minutes)	A (mg)
40	70
80	41

$$-k_0 = \text{slope} = \frac{\Delta Y}{\Delta X} = \frac{y_2 - y_1}{x_2 - x_1}$$

$$-k_0 = \frac{41 - 71}{80 - 40} \quad k_0 = 0.75 \text{ mg/min}$$

Notice that the negative sign shows that the slope is declining.

Method 2

By extrapolation:

$$A_0 = 103.5 \text{ at } t = 0; A = 71 \text{ at } t = 40 \text{ min}$$

$$A = k_0 t + A_0$$

$$71 = -40k_0 + 103.5$$

$$k_0 = 0.81 \text{ mg/min}$$

Notice that the answer differs in accordance with the method used.

- c. $t_{1/2}$

For zero-order kinetics, the larger the initial amount of drug A_0 , the longer the $t_{1/2}$.

Method 1

$$t_{1/2} = \frac{0.5A_0}{k_0}$$

$$t_{1/2} = \frac{0.5(103.5)}{0.78} = 66 \text{ min}$$

Method 2

The zero-order $t_{1/2}$ may be read directly from the graph (see Fig. A-1):

$$\text{At } t = 0, A_0 = 103.5 \text{ mg}$$

$$\text{At } t_{1/2}, A = 51.8 \text{ mg}$$

Therefore, $t_{1/2} = 66 \text{ min}$.

- d. The amount of drug, A , does extrapolate to zero on the x axis.
e. The equation of the line is

$$A = -k_0 t + A_0$$

$$A = -0.78t + 103.5$$

2. a. First-order process (Fig. A-2).

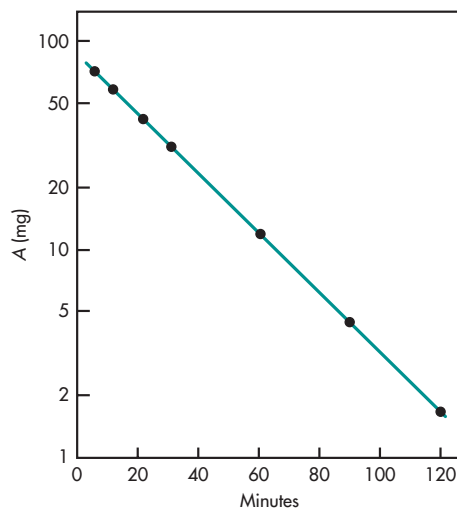


FIGURE A-2

b. Rate constant, k :**Method 1**

Obtain the first-order $t_{1/2}$ from the semilog graph (see Fig. A-2):

t (minutes)	A (mg)
30	30
53	15

$$t_{1/2} = 23 \text{ min}$$

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{23} = 0.03 \text{ min}^{-1}$$

Method 2

$$\text{Slope} = \frac{-k}{2.3} = \frac{\log Y_2 - \log Y_1}{X_2 - X_1}$$

$$k = \frac{-2.3(\log 15 - \log 30)}{53 - 30} = 0.03 \text{ min}^{-1}$$

c. $t_{1/2} = 23 \text{ min}$ (see Method 1 above).

d. The amount of drug, A , does not extrapolate to zero on the x axis.

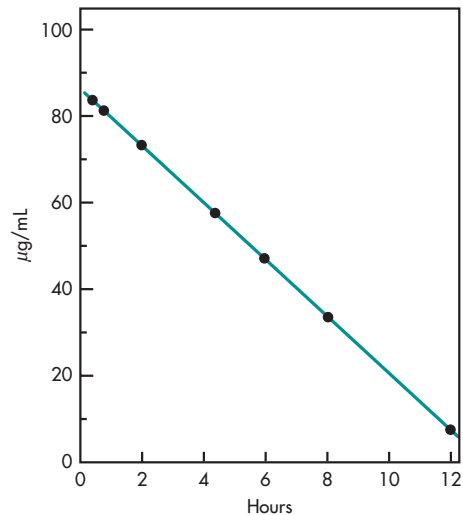
e. The equation of the line is

$$\log A = -\frac{kt}{2.3} + \log A_0$$

$$\log A = -\frac{0.03t}{2.3} + \log 78$$

$$A = 78e^{-0.03t}$$

On a rectangular plot, the same data show a curve (not plotted).

3. a. Zero-order process (Fig. A-3).**FIGURE A-3**

$$\text{b. } k_0 = \text{slope} = \frac{\Delta Y}{\Delta X}$$

Values obtained from the graph (see Fig. A-3):

t (hours)	C ($\mu\text{g/mL}$)
1.2	80
4.2	60

It is always best to plot the data. Obtain a regression line (ie, the line of best fit), and then use points C and t from that line.

$$-k_0 = \frac{60 - 80}{4.2 - 1.2}$$

$$k_0 = 6.67 \mu\text{g/mL/h}$$

c. By extrapolation:

At t_0 , $C_0 = 87.5 \mu\text{g/mL}$.

d. The equation (using a ruler only) is

$$A = -k_0 t + A_0 = -6.67t + 87.5$$

A better fit to the data may be obtained by using a linear regression program. Linear regression programs are available on spreadsheet programs such as Excel.

4. Given:

C (mg/mL)	t (days)
300	0
75	30

$$\text{a. } \log C = -\frac{-kt}{2.3} + \log C_0$$

$$\log 75 = -\frac{-30k}{2.3} + \log 300$$

$$k = 0.046 \text{ days}^{-1}$$

$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.046} = 15 \text{ days}$$

b. Method 1

$$300 \text{ mg/mL} = C_0 \text{ at } t = 0$$

$$75 \text{ mg/mL} = C \text{ at } t = 30 \text{ days}$$

225 mg/mL = difference between initial and final drug concentration

$$k_0 = \frac{225 \text{ mg/mL}}{30 \text{ days}} = 7.5 \text{ mg/mL/d}$$

The time, $t_{1/2}$, for the drug to decompose to one-half C_0 (from 300 to 150 mg/mL) is calculated by (assuming zero order):

$$t_{1/2} = \frac{150 \text{ mg/mL}}{7.5 \text{ mg/mL/day}} = 20 \text{ days}$$

Method 2

$$C = -k_0 t + C_0$$

$$75 = -30k_0 + 300$$

$$k_0 = 7.5 \text{ mg/mL/d}$$

$$\text{At } t_{1/2}, C = 150 \text{ mg/mL}$$

$$150 = -7.5t_{1/2} + 300$$

$$t_{1/2} = 20 \text{ days}$$

Method 3

A $t_{1/2}$ value of 20 days may be obtained directly from the graph by plotting C against t on rectangular coordinates.

5. Assume the original concentration of drug to be 1000 mg/mL.

Method 1

mg/mL	No. of Half-Lives	mg/mL	No. of Half-Lives
1000	0	15.6	6
500	1	7.81	7
250	2	3.91	8
125	3	1.95	9
62.5	4	0.98	10
31.3	5		

$$99.9\% \text{ of } 1000 = 999$$

Concentration of drug remaining = 0.1% of 1000

$$1000 - 999 = 1 \text{ mg/mL}$$

It takes approximately 10 half-lives to eliminate all but 0.1% of the original concentration of drug.

Method 2

Assume any $t_{1/2}$ value:

$$t_{1/2} = \frac{0.693}{k}$$

Then

$$k = \frac{0.693}{t_{1/2}}$$

$$\log C = \frac{-kt}{2.3} + \log C_0$$

$$\log 1.0 = \frac{-kt}{2.3} + \log 1000$$

$$t = 9.96 t_{1/2}$$

Substituting $0.693/t_{1/2}$ for k :

$$\log 1.0 = \frac{-0.693 t}{2.3 \times t_{1/2}} + \log 1000$$

$$t = 9.96 t_{1/2}$$

6. $t_{1/2} = 12$ h

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{12} = 0.058 \text{ h}^{-1}$$

If 30% of the drug decomposes, 70% is left.

Then 70% of $125 \text{ mg} = (0.70)(125) = 87.5 \text{ mg}$

$$A_0 = 125 \text{ mg}$$

$$A = 87.5 \text{ mg}$$

$$k = 0.058 \text{ h}^{-1}$$

$$\log A = -\frac{kt}{2.3} + \log A_0$$

$$\log 87.5 = -\frac{0.058t}{2.3} + \log 125$$

$$t = 6.1 \text{ hours}$$

7. Immediately after the drug dissolves, the drug degrades at a constant, or zero-order rate. Since concentration is equal to mass divided by volume, it is necessary to calculate the initial drug concentration (at $t = 0$) to determine the original volume in which the drug was dissolved. From the data, calculate the zero-order rate constant, k_0 :

$$-k_0 = \text{slope} = \frac{\Delta Y}{\Delta X} = \frac{0.45 - 0.3}{2.0 - 0.5}$$

$$k_0 = 0.1 \text{ mg/mL/h}$$

Then calculate the initial drug concentration, C_0 , using the following equation:

$$C = -k_0 t + C_0$$

At $t = 2$ hours,

$$0.3 = -0.1(2) + C_0$$

$$C_0 = 0.5 \text{ mg/mL}$$

Alternatively, at $t = 0.5$ hour,

$$0.45 = -0.1(0.5) - C_0$$

$$C_0 = 0.5 \text{ mg/mL}$$

Since the initial mass of drug D_0 dissolved is 300 mg and the initial drug concentration C_0 is 0.5 mg/mL , the original volume may be calculated from the following relationship:

$$C_0 = \frac{D_0}{V}$$

$$0.5 \text{ mg/mL} = \frac{300 \text{ mg}}{V}$$

$$V = 600 \text{ mL}$$

8. First order.
9. The volume of the culture tube is not important. In 8 hours (480 minutes), the culture tube is completely full. Because the doubling time for the cells is 2 minutes (ie, one $t_{1/2}$), then in 480 minutes less 2 minutes (478 minutes) the culture tube is half full of cells.
10. b. Since $1 \text{ mg} = 1000 \mu\text{g}$, then $(257 \mu\text{g/mL})/1000 = 0.257 \text{ mg/mL}$.
11. c. Since $1 \text{ dL} = 100 \text{ mL}$, then $(257 \mu\text{g/mL}) \times 100 = 25,700 \mu\text{g/dL}$.
12. a. Since $1 \text{ kg} = 1000 \text{ g}$, then $(170 \text{ g})/1000 = 0.17 \text{ kg}$.
The oral dose was 300 mg/kg ; therefore, for 0.17 kg rat, $(0.17 \text{ kg})(300 \text{ mg})/1 \text{ kg} = 51 \text{ mg}$.
13. c. The volume given was 5 mL/kg . For 0.17 kg rat, $(0.17 \text{ kg})(5 \text{ mL})/1 \text{ kg} = 0.85 \text{ mL}$.
14. d. 0.5% of methylcellulose ($\% \text{ w/v}$) means 0.5 g of methylcellulose in 100 mL solution. Or 5 g of methylcellulose in 1 L solution.
15. b. $k_{el} = 0.693/t_{1/2} = 0.693/4.35 = 0.16 \text{ h}^{-1}$
16. b. $4.35 \text{ hours} \times 60 \text{ min/h} = 261 \text{ minutes}$.
17. c. $F\% = \{[(\text{AUC sample})(\text{Dose oral})]/[(\text{AUC oral})(\text{Dose sample})]\} \times 100$ (2.28)
 $F\% = [(\text{AUC sample})/(\text{AUC oral})] \times 100$
 $2.6 \text{ folds higher} = 260\%$
 $260 = [(\text{AUC sample})/29.1] \times 100$
 $\text{AUC sample} = 75.66 \mu\text{g} \cdot \text{h/mL} = 0.07566 \text{ mg} \cdot \text{h/mL}$
 $1.8 \text{ mg} \cdot \text{day/mL}$

18. **b.** A rectangular coordinate graph.
19. **d.** According to the figure, the highest plasma concentration for subject #1 occurred at 24 hours.
20. **b.** From the graph, the average $C_{\max}$ was between 50 and 100 ng/mL.
21. **c.** It is (concentration units) $\times$ (time) = (ng/mL) $\times$ (hours) = (ng·h/mL).
22. **c.** $105 \text{ ng/mL} = 10,500 \text{ ng/100 mL} = 10.5 \text{ } \mu\text{g/100 mL} = 0.0105 \text{ mg/100 mL} = 0.0000105 \text{ g/100 mL}.$
23. **c.** $y = 1.6624 \times -0.3$
 $y = 1.6624 (35) - 0.3 = 57.9 = \text{AUC}$
24. **a.** $y = 1.6624 \times -0.3$
 $145 = 1.6624 \times -0.3$
 $x = 87.4 \text{ } \mu\text{g/mL} = 87.4 \text{ mg/L}$
25. **c.** $dc/dt = 0.98$
 $dc = 0.98 \text{ } dt$
 $\int dc = 0.98 \int dt$
 $c = c_0 + 0.98t$

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8

Pharmacokinetics of Oral Absorption

John Z. Duan

Chapter Objectives

- ▶ Define oral drug absorption and describe the absorption process.
- ▶ Introduce two general approaches used for studying absorption kinetics and their similarities and differences.
- ▶ Understand the basic principles for physiologically based absorption kinetics.
- ▶ Describe the oral one-compartment model and explain how this model simulates drug absorption from the gastrointestinal tract.
- ▶ Calculate the pharmacokinetic parameters of a drug that follows the oral one-compartment model.
- ▶ Calculate the fraction of drug absorbed in a one-compartment model using the Wagner–Nelson method.
- ▶ Calculate the fraction of drug absorbed in a two-compartment model using the Loo–Riegelman method.
- ▶ Describe the conditions that may lead to flip-flop of k_a and k during pharmacokinetics (PK) data analysis.

INTRODUCTION

Extravascular delivery routes, particularly oral dosing, are important and popular means of drug administration. Unlike intravenous administration, in which the drug is injected directly into the general circulation (see Chapters 4–7), pharmacokinetic models after extravascular drug administration must consider drug absorption from the site of administration, for example, the gut, the lung, etc.

The aim of this chapter is to study the kinetics of absorption. Before delving into the details, it is important to clarify the definition of absorption.

There are three different definitions of absorption in existence. Traditionally, absorption occurs when drug reaches the systemic circulation, or sometimes when it reaches the portal vein blood stream. In recent years, a new definition is presented, in which drug is assumed to be absorbed when it leaves the lumen and crosses the apical membrane of the enterocytes lining the intestine (GastroPlus manual). It is important to distinguish among these definitions when the kinetics study is performed, especially during comparisons of the study results.

Drug absorption from the gastrointestinal (GI) tract or any other extravascular site is dependent on (1) the physicochemical properties of the drug and the environment in the small intestine, (2) the dosage form used, and (3) the anatomy and physiology of the absorption site, such as surface area of the GI tract, stomach-emptying rate, GI mobility, and blood flow to the absorption site. Extravascular drug delivery is further complicated by variables at the absorption site, including possible drug degradation and significant inter- and inpatient differences in the rate and extent of absorption. The variability in drug absorption can be minimized to some extent by proper biopharmaceutical design of the dosage form to provide predictable and reliable drug therapy (Chapters 15–18). Although this chapter will focus primarily on oral dosing, the concepts discussed here may be easily extrapolated to other extravascular routes.

There are generally two methodologies to study the kinetics of absorption. Pharmacokinetic models can be built based mainly on

- Describe the model parameters that form the foundation of drug absorption and bioavailability of oral dosage forms.
- Discuss how k_a and k may influence $C_{\max}$, $t_{\max}$, and AUC and how changes in these parameters may affect drug safety in a clinical situation.

the observed clinical data (“top-down” approach) or based on the broader understanding of the human body and its mechanisms (“bottom-up” approach) (Jamei et al, 2009). A top-down model is often specified with the assistance of “black boxes” (such as the compartment model). In a bottom-up approach the elements of the system are first specified in great detail. These elements are then linked together to form larger subsystems, which in turn are linked, sometimes in many levels, until a complete top-level system is formed. The goals of the two approaches are the same: to make physiologically plausible predictions.

This chapter will introduce the basic concept of the physiologically based absorption kinetics (the bottom-up approach) with some examples followed by the detailed explanation of the traditional top-down approach, and finally, the combination of the two approaches is proposed.

BASIC PRINCIPLES OF PHYSIOLOGICALLY BASED ABSORPTION KINETICS (BOTTOM-UP APPROACH)

The physiologically based absorption models provide a quantitative mechanistic framework by which scaled drug-specific parameters can be used to predict the plasma and, importantly, tissue concentration–time profiles of drugs following oral administration. The main advantage of *physiology-based pharmacokinetic* (PBPK) models is that they can be used to extrapolate outside the studied population and experimental conditions. For example, PBPK can be used to extrapolate the absorption process in healthy volunteers to that in a disease population if the relevant physiological properties of the target population are available. The trade-off for this advantage is a complex system of differential equations with a considerable number of model parameters. When these parameters cannot be informed from *in vitro* or *in silico*¹ experiments, PBPK models are usually optimized with respect to observed clinical data. Parameter estimation in complex models is a challenging task associated with many methodological issues.

Historically, PBPK approach stemmed from a natural thinking for elucidating the kinetics of absorption. The first pharmacokinetic model described in the scientific literature was in fact a PBPK model (Teorell, 1937). However, this model led to great difficulty in computations due to lack of computers. Additionally, the *in vitro* science was not advanced enough to obtain the necessary key information. Therefore, the lack of *in vitro* and *in silico* techniques hindered the development of PBPK approach for many

¹*In silico* refers to computer-based models.

years. Recently, PBPK development has been accelerated mainly due to the explosion of computer science and the increasing availability of *in vitro* systems that act as surrogates for *in vivo* reactions relevant to absorption.

Parameter estimation in PBPK models is challenging because of the large number of parameters involved and the relative small amount of observed data usually available. An absorption model consists of a set of values for the absorption scale factors, transit times, pH assignments, compartment geometries (individual compartment radii and lengths, and volume), and pharmacokinetic parameters that provide the best predictions for a compound in human. For example, an advanced absorption transit model developed in *GastroPlus*^{TM2} contains nine compartments, which represent the five segments of the GI tract—stomach, duodenum, jejunum, ileum, and colon. The fluid content, carrying dissolved and undissolved compound, passes from one compartment to the next, simulating the action of peristaltic motion. Within each compartment, the dynamic interconversion between dissolved and undissolved compound is modeled. Dissolved compound can be absorbed across the GI tract epithelium. The volume of each compartment, which represents the fluid content, is modeled dynamically, simulating the following processes:

- Transit of the fluid with characteristic rate constants through each compartment
- Gastric secretion into the stomach, and biliary and pancreatic secretions into the duodenum
- Absorption of fluid from duodenum, jejunum, ileum, and large intestine

Figure 8-1 shows the graphic representation of this model. As seen, each of the nine compartments is divided into four subcompartments: unreleased, undissolved, dissolved, and enterocyte.

In the figure, the compartments and subcompartments in GI tract are connected to each other by arrows. These arrows are of either one direction or

two directions, indicating the drug transit among these compartments. Each transit process, represented by an arrow in Fig. 8-1, can be expressed by a differential equation. The model equations follow the principles of mass transport, fluid dynamics, and biochemistry in order to simulate the fate of a substance in the body. Most of the equations involve linear kinetics. For example, for non-eliminating tissues, the following principles are followed: the “rate of change of drug in the tissue” is equal to the “rate in” ($Q_T \cdot C_A$) minus the “rate out” ($Q_T \cdot C_{vT}$) as shown in Equation 8.1.

$$V_T \frac{dC_T}{dt} = Q_T C_A - Q_T C_{vT} \quad (8.1)$$

where Q = blood flow (L/h), C = concentration (mg/L), V = volume (L), T = tissues, A = arterial, v = venous, $C_{vT} = C_T / (K_p B:P)$, $B:P$ = blood-to-plasma ratio. On the other hand, Michaelis–Menten nonlinear kinetics is used to describe saturable metabolism and carrier-mediated transport.

The PBPK approach can specifically define the absorption for a specific drug product. Figure 8-2 shows the simulation results using PBPK software *GastroPlus* for several drugs with different physicochemical properties. The first column lists the drug names and the second column is the pK_a of the compound. The solubility factor (Sol Factor) is the ratio of the solubility of the completely ionized form of an ionizable group to the completely unionized form. The figure also lists the solubility and logD pH profiles for each drug (two green vertical lines indicate pH 1.2 and 7.5, respectively). Notice that the color of the cells for dose number (Dose No), absorption number (Abs No), and dissolution number (Dis No) changes depending on the physicochemical and biopharmaceutical properties of the drug selected. The colors approximate the four Biopharmaceutical Classification System (BCS) categories. All green indicates high permeability, high solubility, and rapid dissolution (BCS Class I). Red absorption number and green dose number may indicate low permeability and high solubility (BCS Class III). All red may indicate low permeability and low solubility (BCS Class VI). These color systems are not perfect cutoffs for the BCS, but they represent most drugs.

²GastroPlus is a mechanistically based simulation software package that simulates absorption, pharmacokinetics, and pharmacodynamics in human and animals (<http://www.simulations-plus.com/Products.aspx?GastroPlus&grpID=3&cID=16&pID=11>).

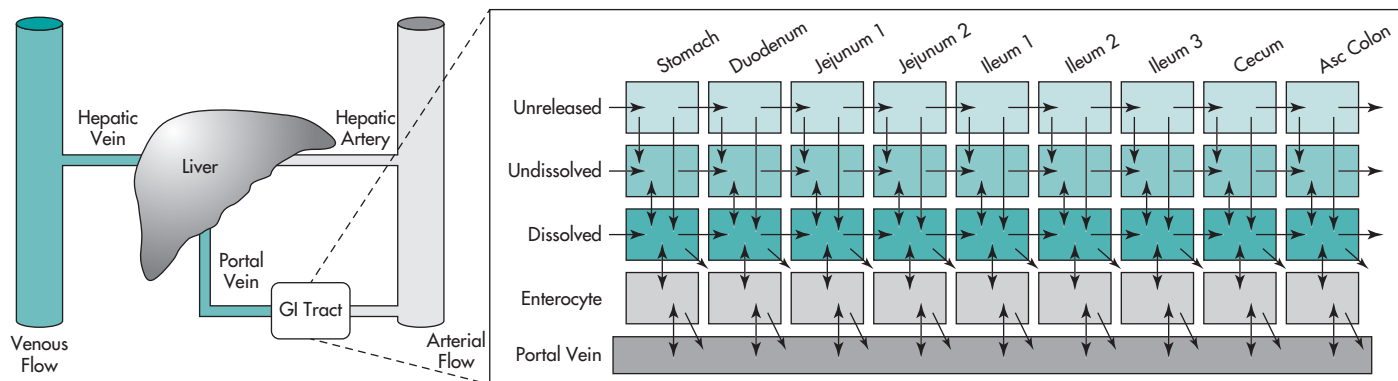


FIGURE 8-1 A graphic representation of drug absorption from the GI tract.

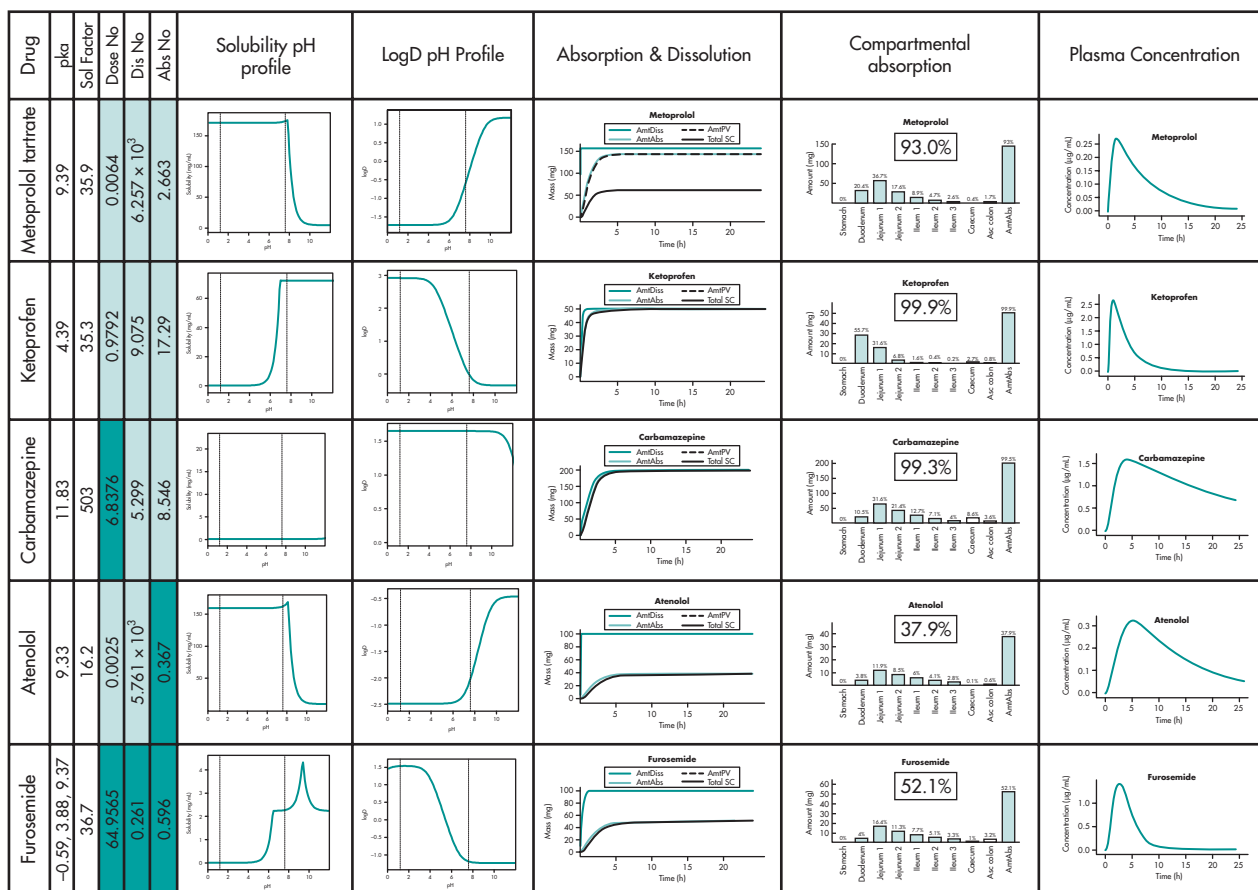


FIGURE 8-2 The modeling results for several drugs using GastroPlus software.

Based on the *in vitro* properties and assuming a set of general physiological conditions, the absorption profiles, the absorption amount in each of the nine compartments, and the plasma concentration profiles are predicted in the last three columns, respectively. In the “Absorption & Dissolution” column, the profiles for the total dissolved (red), the absorbed (cyan, the absorption is defined as the drug leaves the lumen and crosses the apical membrane of the enterocytes lining the intestine), the cumulative amount entering portal vein (blue), and the cumulative amount entering systemic circulation (green) are characterized. These profiles along with the information about the amount absorbed in each compartment give the plasma concentration profiles as shown in the last column. As seen, due to the physicochemical property differences, the rate and the extent of absorption vary among the drugs listed.

Drug absorption from the gastrointestinal tract is a highly complex process dependent upon numerous factors. In addition to the physicochemical properties of the drug as shown in Fig. 8-2 (with limited extents), characteristics of the formulation and interplay with the underlying physiological properties of the GI tract play important roles. In GastroPlus, the formulation types that can be selected include both immediate release (IR) formulations (solution, suspension, tablet, and capsule) and controlled release (CR) formulations (enteric-coated or other form of delayed release [DR]). For CR, release of either dissolved material (drug in solution) or undissolved material (solid particles, which then dissolve according to the selected dissolution model) can be evoked.

In addition to GastroPlus, there are several other physiologically based softwares available for studying absorption kinetics, such as *SimCyp* (<http://www.simcyp.com/>) and *PK-Sim* (<http://www.systems-biology.com/products/pk-sim.html>).

The major advantage of the PBPK approach is that if adequate information of physicochemical properties of a drug is available, a reasonable prediction for the performance of the drug product can be made with certain assumptions according to previous experience. With little or no human PK data generated, the predictions would be very valuable for further drug development.

ABSORPTION KINETICS (THE TOP-DOWN APPROACH)

The top-down approach is a traditional methodology to study the kinetics of drug absorption. With the advances of statistical methods and computer science, many software packages are available to calculate the pharmacokinetic parameters. The following sections provide the basic concepts and rationales.

PHARMACOKINETICS OF DRUG ABSORPTION

In pharmacokinetics, the overall rate of drug absorption may be described as either a first-order or a zero-order input process. Most pharmacokinetic models assume first-order absorption unless an assumption of zero-order absorption improves the model significantly or has been verified experimentally.

The rate of change in the amount of drug in the body, dD_B/dt , is dependent on the relative rates of drug absorption and elimination (Fig. 8-3). The net rate of drug accumulation in the body at any time is equal to the rate of drug absorption less the rate of drug elimination, regardless of whether absorption rate is zero-order or first-order.

$$\frac{dD_B}{dt} = \frac{dD_{GI}}{dt} - \frac{dD_E}{dt} \quad (8.2)$$

where D_{GI} is the amount of drug in the gastrointestinal tract and D_E is the amount of drug eliminated. A plasma level–time curve showing drug absorption and elimination rate processes is given in Fig. 8-4. During the *absorption phase* of a plasma level–time curve (Fig. 8-4), the rate of drug absorption³ is greater than



FIGURE 8-3 Model of drug absorption and elimination.

³The rate of drug absorption is dictated by the product of the drug in the gastrointestinal tract, D_{GI} times the first-order absorption rate constant, k_a .

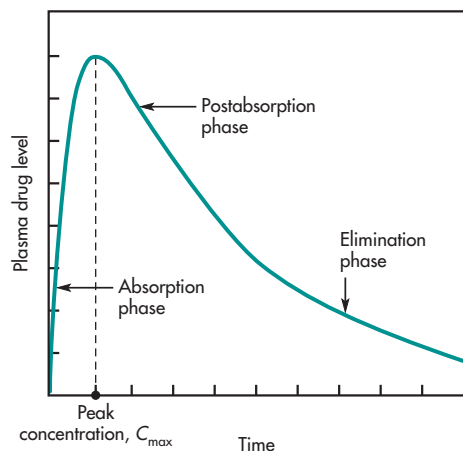


FIGURE 8-4 Plasma level–time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.

the rate of drug elimination.⁴ Note that during the absorption phase, elimination occurs *whenever* drug is present in the plasma, even though absorption predominates.

$$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt} \quad (8.3)$$

At the *peak drug concentration* in the plasma (Fig. 8-4), the rate of drug absorption just equals the rate of drug elimination, and there is no net change in the amount of drug in the body.

$$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt} \quad (8.4)$$

Immediately after the time of peak drug absorption, some drug may still be at the absorption site (ie, in the GI tract or other site of administration). However, the rate of drug elimination at this time is faster than the rate of absorption, as represented by the *postabsorption phase* in Fig. 8-4.

$$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt} \quad (8.5)$$

When the drug at the absorption site becomes depleted, the rate of drug absorption approaches zero,

⁴The rate of drug elimination is dictated by the product of the amount of drug in the body, D_B times the first-order elimination rate constant, k .

or $dD_{GI}/dt = 0$. The plasma level–time curve (now the *elimination phase*) then represents only the elimination of drug from the body, usually a first-order process. Therefore, during the elimination phase the rate of change in the amount of drug in the body is described as a first-order process:

$$\frac{dD_B}{dt} = -kD_B \quad (8.6)$$

where k is the first-order elimination rate constant.

Clinical Application

Manini et al (2005) reported a case of adverse drug reaction in a previously healthy young man who ingested a recommended dose of an over-the-counter (OTC) cold remedy containing pseudoephedrine. Forty-five minutes later, he had an acute myocardial infarction (MI). Elevations of cardiac-specific creatinine kinase and cardiac troponin I confirmed the diagnosis. Cardiac magnetic resonance imaging (MRI) confirmed a regional MI. Cardiac catheterization 8 hours later revealed normal coronary arteries, suggesting a mechanism of vasospasm.

1. Could rapid drug absorption (large k_a) contribute to high-peak drug concentration of pseudoephedrine in this subject?
2. Can an adverse drug reaction (ADR) occur before absorption is complete or, before C_{max} is reached?
3. What is the effect of a small change in k on the time and magnitude of C_{max} (maximum plasma concentration)? (Remember to correctly assign k_a and k values when computing k_a and k from patient data. See Flip-flop in oral absorption model in the next section.) In addition, see Chapter 13 for reasons why some subjects may have a smaller k .
4. Do you believe that *therapeutic drug concentration* and *toxic plasma concentration* are always clearly defined for individual subjects as introduced in Fig. 1-2 (see Chapter 1)?

Discussion

From past experience, generally transient high plasma drug concentrations are not considered unsafe as long as the steady-state plasma concentration is within a

recommended range. This is generally true for OTC drugs. This case highlights a potential danger of some sympathomimetic drugs such as pseudoephedrine and should alert the pharmacist that even drugs with a long history of safe use may still exhibit dangerous ADRs in some susceptible subjects.

Do you believe that pseudoephedrine can be sold safely without advice from a pharmacist? What other types of medication are important to monitor where a large k_a may present transient high drug concentrations in the blood?

A small elimination rate constant, k may be caused by reduced renal drug excretion as discussed in Chapter 7, but a small k may also be due to reduced hepatic clearance caused by relatively inactive metabolic enzymes such as CYPs for some patients (see Chapter 12). What are the kinetic tools that will allow one to make this differentiation?

The pharmacokinetic concepts presented in this chapter will allow you to decide whether an unusual peak plasma drug concentration, $C_{\max}$ is caused by a large k_a , a small k (or Cl), both, or neither.

SIGNIFICANCE OF ABSORPTION RATE CONSTANTS

The overall rate of systemic drug absorption from an orally administered solid dosage form encompasses many individual rate processes, including dissolution of the drug, GI motility, blood flow, and transport of the drug across the capillary membranes and into the systemic circulation. The rate of drug absorption represents the net result of all these processes. The selection of a model with either first-order or zero-order absorption is generally empirical.

The actual drug absorption process may be zero-order, first-order, or a combination of rate processes that is not easily quantitated. For many immediate-release dosage forms, the absorption process is first-order due to the physical nature of drug diffusion. For certain controlled-release drug products, the rate of drug absorption may be more appropriately described by a zero-order rate constant.

The calculation of k_a is useful in designing a multiple-dosage regimen. Knowledge of the k_a and k values allows for the prediction of peak and trough

plasma drug concentrations following multiple dosing. In bioequivalence studies, drug products are given in chemically equivalent (ie, pharmaceutical equivalents) doses, and the respective rates of systemic absorption may not differ markedly. Therefore, for these studies, $t_{\max}$, or time of peak drug concentration, can be very useful in comparing the respective rates of absorption of a drug from chemically equivalent drug products.

ZERO-ORDER ABSORPTION MODEL

Zero-order drug absorption from the dosing site into the plasma usually occurs when either the drug is absorbed by a saturable process or a zero-order controlled-release delivery system is used (see Chapter 19). The pharmacokinetic model assuming zero-order absorption is described in Fig. 8-5. In this model, drug in the gastrointestinal tract, D_{GI} , is absorbed systemically at a constant rate, k_0 . Drug is simultaneously and immediately eliminated from the body by a first-order rate process defined by a first-order rate constant, k . This model is analogous to that of the administration of a drug by intravenous infusion (see Chapter 6).

The rate of first-order elimination at any time is equal to $D_B k$. The rate of input is simply k_0 . Therefore, the net change per unit time in the body can be expressed as

$$\frac{dD_B}{dt} = k_0 - kD_B \quad (8.7)$$

Integration of this equation with substitution of $V_D C_p$ for D_B produces

$$C_p = \frac{k_0}{V_D k} (1 - e^{-kt}) \quad (8.8)$$

The rate of drug absorption is constant until the amount of drug in the gut, D_{GI} , is depleted. The time for complete drug absorption to occur is equal to D_{GI}/k_0 . After this time, the drug is no longer available

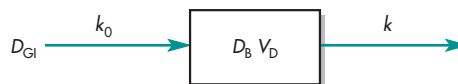


FIGURE 8-5 One-compartment pharmacokinetic model for zero-order drug absorption and first-order drug elimination.

for absorption from the gut, and Equation 8.7 no longer holds. The drug concentration in the plasma subsequently declines in accordance with a first-order elimination rate process.

CLINICAL APPLICATION— TRANSDERMAL DRUG DELIVERY

The stratum corneum (horny layer) of the epidermis of the skin acts as a barrier and rate-limiting step for systemic absorption of many drugs. After application of a transdermal system (patch), the drug dissolves into the outer layer of the skin and is absorbed by a pseudo first-order process due to high concentration and is eliminated by a first-order process. Once the patch is removed, the residual drug concentrations in the skin continues to decline by a first-order process.

Ortho Evra is a combination transdermal contraceptive patch with a contact surface area of 20 cm². Each patch contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE) and is designed to deliver 0.15 mg of NGMN and 0.02 mf EE to the systemic circulation daily. As shown in Fig. 8-6, serum EE (ethinyl estradiol) is absorbed from the patch at a zero-order rate.

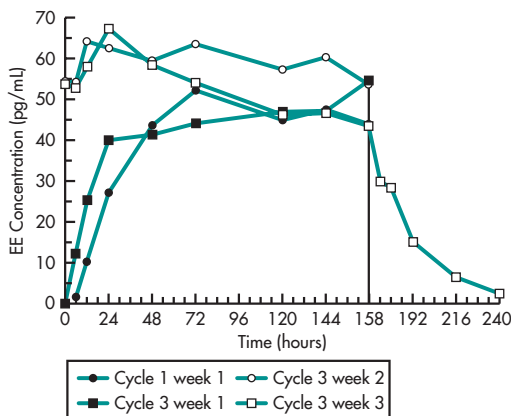


FIGURE 8-6 Mean serum EE concentrations (pg/mL) in healthy female volunteers following application of Ortho Evra on the buttock for three consecutive cycles (vertical arrow indicates time of patch removal). (Adapted from approved label for Ortho Evra, September, 2009.)

FIRST-ORDER ABSORPTION MODEL

Although zero-order drug absorption can occur, systemic drug absorption after oral administration of a drug product (eg, tablet, capsule) is usually assumed to be a first-order process. This model assumes a first-order input across the gut wall and first-order elimination from the body (Fig. 8-7). This model applies mostly to the oral absorption of drugs in solution or rapidly dissolving dosage (immediate release) forms such as tablets, capsules, and suppositories. In addition, drugs given by intramuscular or subcutaneous aqueous injections may also be described using a first-order process.

After oral administration of a drug product, the drug is released from the drug product and dissolves into the fluids of the GI tract. In the case of an immediate-release compressed tablet, the tablet first disintegrates into fine particles from which the drug then dissolves into the fluids of the GI tract. Only drug in solution is absorbed into the body. The rate of disappearance of drug from the gastrointestinal tract is described by

$$\frac{dD_{GI}}{dt} = -k_a D_{GI} F \quad (8.9)$$

where k_a is the first-order absorption rate constant from the GI tract, F is the fraction absorbed, and D_{GI} is the amount of drug in solution in the GI tract at any time t . Integration of the differential Equation (8.8) gives

$$dD_{GI} = D_0 e^{-k_a t} \quad (8.10)$$

where D_0 is the dose of the drug.

The rate of drug elimination is described by a first-order rate process for most drugs and is equal to $-kD_B$. The rate of drug change in the body, dD_B/dt ,



FIGURE 8-7 One-compartment pharmacokinetic model for first-order drug absorption and first-order elimination.

is therefore the rate of drug in, minus the rate of drug out—as given by the differential equation, Equation 8.10:

$$\begin{aligned}\frac{dD_B}{dt} &= \text{rate in} - \text{rate out} \\ \frac{dD_B}{dt} &= Fk_a D_{GI} - kD_B\end{aligned}\quad (8.11)$$

where F is the fraction of drug absorbed systemically. Since the drug in the gastrointestinal tract also follows a first-order decline (ie, the drug is absorbed across the gastrointestinal wall), the amount of drug in the gastrointestinal tract at any time t is equal to $D_0 e^{-k_a t}$.

$$\frac{dD_B}{dt} = Fk_a D_0 e^{-k_a t} - kD_B$$

The value of F may vary from 1 for a fully absorbed drug to 0 for a drug that is completely unabsorbed. This equation can be integrated to give the general oral absorption equation for calculation of the drug concentration (C_p) in the plasma at any time t , as shown below.

$$C_p = \frac{Fk_a D_0}{V_D(k_a - k)}(e^{-kt} - e^{-k_a t}) \quad (8.12)$$

A typical plot of the concentration of drug in the body after a single oral dose is presented in Fig. 8-8.

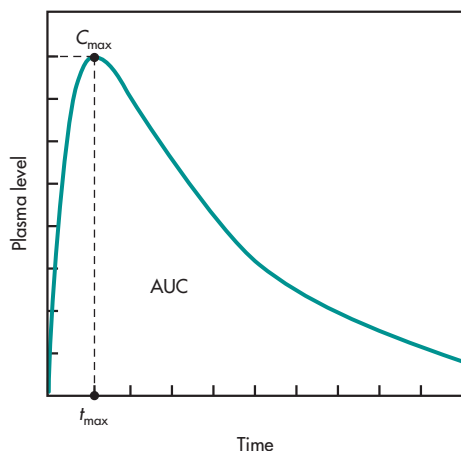


FIGURE 8-8 Typical plasma level–time curve for a drug given in a single oral dose.

The maximum plasma concentration after oral dosing is C_{max} , and the time needed to reach maximum concentration is t_{max} . The t_{max} is independent of dose and is dependent on the rate constants for absorption (k_a) and elimination (k) (Equation 8.13). At C_{max} , sometimes called *peak concentration*, the rate of drug absorbed is equal to the rate of drug eliminated. Therefore, the net rate of concentration change is equal to zero. At C_{max} , the rate of concentration change can be obtained by differentiating Equation 8.11, as follows:

$$\frac{dC_p}{dt} = \frac{Fk_a D_0}{V_D(k_a - k)}(-ke^{-kt} + k_a e^{-k_a t}) = 0 \quad (8.13)$$

This can be simplified as follows:

$$\begin{aligned}-ke^{-kt} + k_a e^{-k_a t} &= 0 \quad \text{or} \quad ke^{-kt} = k_a e^{-k_a t} \\ \ln k - kt &= \ln k_a - k_a t \\ t_{max} &= \frac{\ln k_a - \ln k}{k_a - k} = \frac{\ln(k_a/k)}{k_a - k} \\ t_{max} &= \frac{2.3 \log(k_a/k)}{k_a - k}\end{aligned}\quad (8.14)$$

As shown in Equation 8.13, the time for maximum drug concentration, t_{max} , is dependent only on the rate constants k_a and k . In order to calculate C_{max} , the value for t_{max} is determined via Equation 8.13 and then substituted into Equation 8.11, solving for C_{max} . Equation 8.11 shows that C_{max} is directly proportional to the dose of drug given (D_0) and the fraction of drug absorbed (F). Calculation of t_{max} and C_{max} is usually necessary, since direct measurement of the maximum drug concentration may not be possible due to improper timing of the serum samples.

The first-order elimination rate constant may be determined from the elimination phase of the plasma level–time curve (Fig. 8-4). At later time intervals, when drug absorption has been completed, that is, $e^{-k_a t} \approx 0$, Equation 8.11 reduces to

$$C_p = \frac{Fk_a D_0}{V_D(k_a - k)} e^{-kt} \quad (8.15)$$

Taking the natural logarithm of this expression,

$$\ln C_p = \ln \frac{Fk_a D_0}{V_D(k_a - k)} - kt \quad (8.16)$$

Substitution of common logarithms gives

$$\log C_p = \log \frac{Fk_a D_0}{V_D(k_a - k)} - \frac{kt}{2.3} \quad (8.17)$$

With this equation, a graph constructed by plotting $\log C_p$ versus time will yield a straight line with a slope of $-k/2.3$ (Fig. 8-9A).

With a similar approach, urinary drug excretion data may also be used for calculation of the first-order elimination rate constant. The rate of drug excretion after a single oral dose of drug is given by

$$\frac{dD_u}{dt} = \frac{Fk_a k_e D_0}{k_a - k} (e^{-kt} - e^{-k_a t}) \quad (8.18)$$

where dD_u/dt = rate of urinary drug excretion, k_e = first-order renal excretion constant, and F = fraction of dose absorbed.

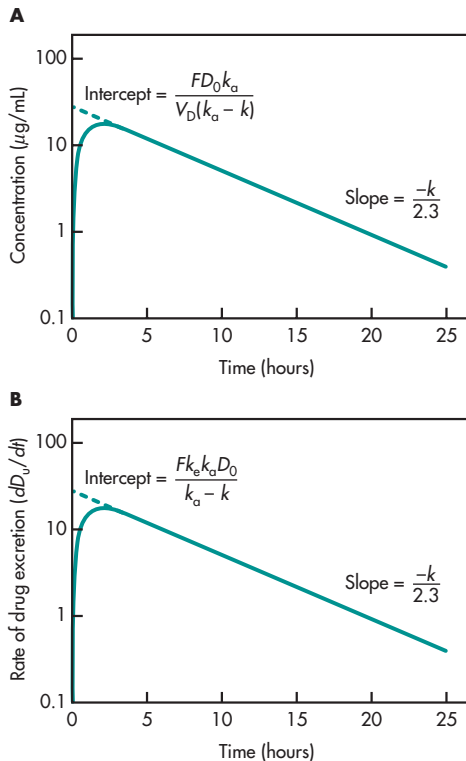


FIGURE 8-9 A. Plasma drug concentration versus time, single oral dose. B. Rate of urinary drug excretion versus time, single oral dose.

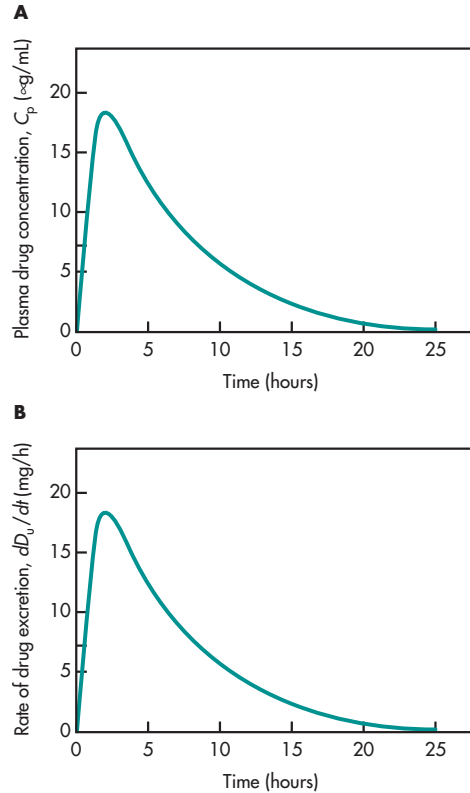


FIGURE 8-10 A. Plasma drug concentration versus time, single oral dose. B. Rate of urinary drug excretion versus time, single oral dose.

A graph constructed by plotting dD_u/dt versus time will yield a curve identical in appearance to the plasma level–time curve for the drug (Fig. 8-10B). After drug absorption is virtually complete, $-e^{-k_a t}$ approaches zero, and Equation 8.18 reduces to

$$\frac{dD_u}{dt} = \frac{Fk_a k_e D_0}{k_a - k} e^{-kt} \quad (8.19)$$

Taking the natural logarithm of both sides of this expression and substituting for common logarithms, Equation 8.19 becomes

$$\log \frac{dD_u}{dt} = \log \frac{Fk_a k_e D_0}{k_a - k} - \frac{kt}{2.3} \quad (8.20)$$

When $\log(dD_u/dt)$ is plotted against time, a graph of a straight line is obtained with a slope of

$-k/2.3$ (Fig. 8-9B). Because the rate of urinary drug excretion, dD_u/dt , cannot be determined directly for any given time point, an average rate of urinary drug excretion is obtained (see also Chapter 4), and this value is plotted against the midpoint of the collection period for each urine sample.

To obtain the cumulative drug excretion in the urine, Equation 8.18 must be integrated, as shown below.

$$D_u = \frac{Fk_a k_e D_0}{k_a - k} \left(\frac{-e^{-k_a t}}{k_a} - \frac{e^{-kt}}{k} \right) + \frac{Fk_e D_0}{k} \quad (8.21)$$

A plot of D_u versus time will give the urinary drug excretion curve described in Fig. 8-11. When all of the drug has been excreted, at $t = \infty$, Equation 8.21 reduces to

$$D_u^\infty = \frac{Fk_e D_0}{k} \quad (8.22)$$

where D_u^∞ is the maximum amount of active or parent drug excreted.

Determination of Absorption Rate Constants from Oral Absorption Data

Method of Residuals

Assuming $k_a \gg k$ in Equation 8.12, the value for the second exponential will become insignificantly small with time (ie, $e^{-k_a t} \approx 0$) and can therefore be omitted. When this is the case, drug absorption is

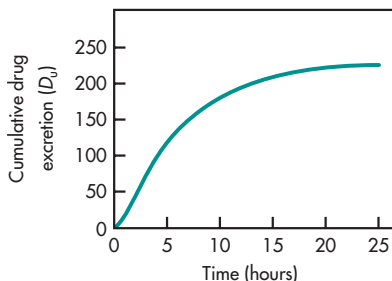


FIGURE 8-11 Cumulative urinary drug excretion versus time, single oral dose. Urine samples are collected at various time periods after the dose. The amount of drug excreted in each sample is added to the amount of drug recovered in the previous urine sample (cumulative addition). The total amount of drug recovered after all the drug is excreted is D_u^∞ .

virtually complete. Equation 8.12 then reduces to Equation 8.23.

$$C_p = \frac{Fk_a D_0}{V_D(k_a - k)} e^{-kt} \quad (8.23)$$

From this, one may also obtain the intercept of the y axis (Fig. 8-12).

$$\frac{Fk_a D_0}{V_D(k_a - k)} = A$$

where A is a constant. Thus, Equation 8.23 becomes

$$C_p = A e^{-kt} \quad (8.24)$$

This equation, which represents first-order drug elimination, will yield a linear plot on semilog paper. The slope is equal to $-k/2.3$. The value for k_a can be obtained by using the method of residuals or a feathering technique, as described in Chapter 5. The value of k_a is obtained by the following procedure:

1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis (Fig. 8-12).
2. Obtain the slope of the terminal phase (line BC , Fig. 8-12) by extrapolation.

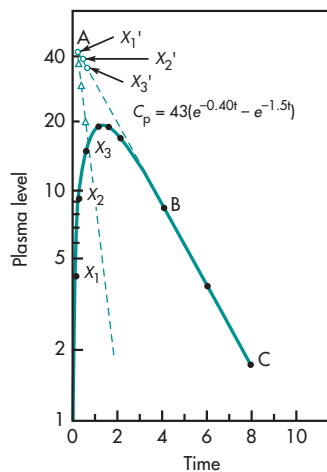


FIGURE 8-12 Plasma level–time curve for a drug demonstrating first-order absorption and elimination kinetics. The equation of the curve is obtained by the method of residuals.

3. Take any points on the upper part of line BC (eg, $x'_1, x'_2, x'_3, \dots$) and drop vertically to obtain corresponding points on the curve (eg, $x_1, x_2, x_3, \dots$).
4. Read the concentration values at x_1 and x'_1, x_2 and x'_2, x_3 and x'_3 , and so on. Plot the values of the differences at the corresponding time points $\Delta_1, \Delta_2, \Delta_3, \dots$. A straight line will be obtained with a slope of $-k_a/2.3$ (Fig. 8-12).

When using the method of residuals, a minimum of three points should be used to define the straight line. Data points occurring shortly after $t_{\max}$ may not be accurate, because drug absorption is still continuing at that time. Because this portion of the curve represents the postabsorption phase, only data points from the elimination phase should be used to define the rate of drug absorption as a first-order process.

If drug absorption begins immediately after oral administration, the residual lines obtained by feathering the plasma level–time curve (as shown in Fig. 8-12) will intersect on the y axis at point A . The value of this y intercept, A , represents a hybrid constant composed of k_a, k, V_D , and FD_0 . The value of A has no direct physiologic meaning (see Equation 8.24).

$$A = \frac{Fk_a D_0}{V_D(k_a - k)}$$

The value for A , as well as the values for k and k_a , may be substituted back into Equation 8.11 to obtain a general theoretical equation that will describe the plasma level–time curve.

Lag Time

In some individuals, absorption of drug after a single oral dose does not start immediately, due to such physiologic factors as stomach-emptying time and intestinal motility. The time delay prior to the commencement of first-order drug absorption is known as *lag time*.

The lag time for a drug may be observed if the two residual lines obtained by feathering the oral absorption plasma level–time curve intersect at a point greater than $t = 0$ on the x axis. The time at the point of intersection on the x axis is the lag time (Fig. 8-13).

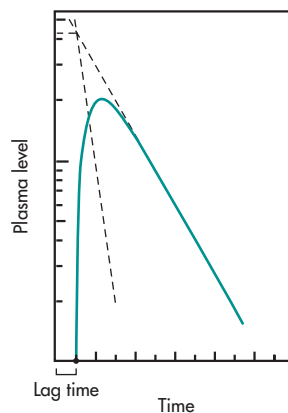


FIGURE 8-13 The lag time can be determined graphically if the two residual lines obtained by feathering the plasma level–time curve intersect at a point where $t > 0$.

The lag time, t_0 , represents the beginning of drug absorption and should not be confused with the pharmacologic term *onset time*, which represents latency, that is, the time required for the drug to reach minimum effective concentration.

Two equations can adequately describe the curve in Fig. 8-13. In one, the lag time t_0 is subtracted from each time point, as shown in Equation 8.25.

$$C_p = \frac{Fk_a D_0}{V_D(k_a - k)} (e^{-k(t-t_0)} - e^{-k_a(t-t_0)}) \quad (8.25)$$

where $Fk_a D_0/V_D(k_a - k)$ is the y value at the point of intersection of the residual lines in Fig. 8-13.

The second expression that describes the curve in Fig. 8-13 omits the lag time, as follows:

$$C_p = B e^{-kt} - A e^{-k_a t} \quad (8.26)$$

where A and B represent the intercepts on the y axis after extrapolation of the residual lines for absorption and elimination, respectively.

Frequently Asked Question

- If drug absorption is simulated using the oral one-compartment model, would a larger absorption rate constant result in a greater amount of drug absorbed?

Flip-Flop of k_a and k

In using the method of residuals to obtain estimates of k_a and k , the terminal phase of an oral absorption curve is usually represented by k , whereas the steeper slope is represented by k_a (Fig. 8-14). In a few cases, the elimination rate constant k obtained from oral absorption data does not agree with that obtained after intravenous bolus injection. For example, the k obtained after an intravenous bolus injection of a bronchodilator was 1.72 h^{-1} , whereas the k calculated after oral administration was 0.7 h^{-1} (Fig. 8-14). When k_a was obtained by the method of residuals, the rather surprising result was that the k_a was 1.72 h^{-1} .

Apparently, the k_a and k obtained by the method of residuals have been interchanged. This phenomenon is called *flip-flop* of the absorption and elimination rate constants. Flip-flop, or the reversal of the rate constants, may occur whenever k_a and k are estimated from oral drug absorption data. Use of computer methods does not ensure against flip-flop of the two constants estimated.

In order to demonstrate unambiguously that the steeper curve represents the elimination rate for a drug given extravascularly, the drug must be given by intravenous injection into the same patient. After intravenous injection, the decline in plasma drug levels over time represents the true elimination rate. The relationship between k_a and k on the shape of the plasma drug concentration–time curve for a constant dose of drug given orally is shown in Fig. 8-14.

Most of the drugs observed to have flip-flop characteristics are drugs with fast elimination (ie, $k > k_a$). Drug absorption of most drug solutions or fast-dissolving products is essentially complete or at least half-complete within an hour (ie, absorption half-life of 0.5 or 1 hour, corresponding to a k_a of

1.38 h^{-1} or 0.69 h^{-1}). Because most of the drugs used orally have longer elimination half-lives compared to absorption half-lives, the assumption that the smaller slope or smaller rate constant (ie, the terminal phase of the curve in Fig. 8-14) should be used as the elimination constant is generally correct.

For drugs that have a large elimination rate constant ($k > 0.69 \text{ h}^{-1}$), the chance for flip-flop of k_a and k is much greater. The drug isoproterenol, for example, has an oral elimination half-life of only a few minutes, and flip-flop of k_a and k has been noted (Portmann, 1970). Similarly, salicylic acid was flip-flopped when oral data were plotted. The k for salicylic acid was much larger than its k_a (Levy et al, 1969). Many experimental drugs show flip-flop of k and k_a , whereas few marketed oral drugs do. Drugs with a large k are usually considered to be unsuitable for an oral drug product due to their large elimination rate constant, corresponding to a very short elimination half-life. An extended-release drug product may slow the absorption of a drug, such that the k_a is smaller than the k and producing a flip-flop situation.

Frequently Asked Question

► How do you explain that k_a is often greater than k with most drugs?

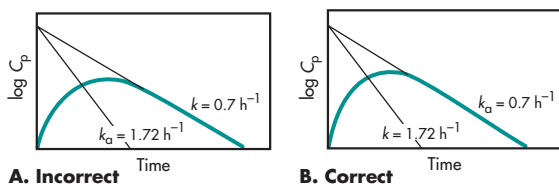


FIGURE 8-14 Flip-flop of k_a and k . Because $k > k_a$, the right-hand figure and slopes represent the correct values for k_a and k .

Determination of k_a by Plotting Percent of Drug Unabsorbed Versus Time (Wagner–Nelson Method)

The Wagner–Nelson method may be used as an alternative means of calculating k_a . This method estimates the loss of drug from the GI over time, whose slope is inversely proportional to k_a . After a single oral dose of a drug, the total dose should be completely accounted for for the amount present in the body, the amount present in the urine, and the amount present in the GI tract. Therefore, dose (D_0) is expressed as follows:

$$D_0 = D_{GI} + D_B + D_u \quad (8.27)$$

Let $Ab = D_B + D_u$ = amount of drug absorbed and let Ab^∞ = amount of drug absorbed at $t = \infty$. At any given time the fraction of drug absorbed is Ab/Ab^∞ ,

and the fraction of drug unabsorbed is $1 - (Ab/Ab^\infty)$. The amount of drug excreted at any time t can be calculated as

$$D_u = kV_D[AUC]_0^t \quad (8.28)$$

The amount of drug in the body (D_B) at any time = $C_p V_D$. At any time t , the amount of drug absorbed (Ab) is

$$Ab = C_p V_D + kV_D[AUC]_0^t \quad (8.29)$$

At $t = \infty$, $C_p^\infty = 0$ (ie, plasma concentration is negligible), and the total amount of drug absorbed is

$$Ab^\infty = 0 + kV_D[AUC]_0^\infty \quad (8.30)$$

The fraction of drug absorbed at any time is

$$\frac{Ab}{Ab^\infty} = \frac{C_p V_D + kV_D[AUC]_0^t}{kV_D[AUC]_0^\infty} \quad (8.31)$$

$$\frac{Ab}{Ab^\infty} = \frac{C_p + k[AUC]_0^t}{k[AUC]_0^\infty} \quad (8.32)$$

The fraction unabsorbed at any time t is

$$1 - \frac{Ab}{Ab^\infty} = 1 - \frac{C_p + k[AUC]_0^t}{k[AUC]_0^\infty} \quad (8.33)$$

The drug remaining in the GI tract at any time t is

$$D_{GI} = D_0 e^{-k_a t} \quad (8.34)$$

Therefore, the fraction of drug remaining is

$$\frac{D_{GI}}{D_0} = e^{-k_a t} \quad \log \frac{D_{GI}}{D_0} = \frac{-k_a t}{2.3} \quad (8.35)$$

Because D_{GI}/D_0 is actually the fraction of drug *unabsorbed*—that is, $1 - (Ab/Ab^\infty)$ —a plot of $1 - (Ab/Ab^\infty)$ versus time gives $-k_a/2.3$ as the slope (Fig. 8-15).

The following steps should be useful in determination of k_a :

1. Plot log concentration of drug versus time.
2. Find k from the terminal part of the slope when the slope = $-k/2.3$.
3. Find $[AUC]_0^t$ by plotting C_p versus t .
4. Find $k[AUC]_0^t$ by multiplying each $[AUC]_0^t$ by k .

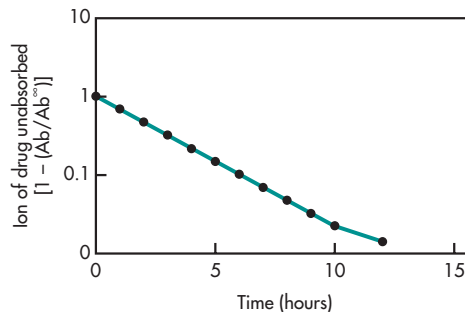


FIGURE 8-15 Semilog graph of data in Table 8-2, depicting the fraction of drug unabsorbed versus time using the Wagner-Nelson method.

5. Find k by adding up all the $[AUC]$ pieces, from $t = 0$ to $t = \infty$.
6. Determine the $1 - (Ab/Ab^\infty)$ value corresponding to each time point t by using Table 8-1.
7. Plot $1 - (Ab/Ab^\infty)$ versus time on semilog paper, with $1 - (Ab/Ab^\infty)$ on the logarithmic axis.

If the fraction of drug unabsorbed, $1 - Ab/Ab^\infty$, gives a linear regression line on a semilog graph, then the rate of drug absorption, dD_{GI}/dt , is a first-order process. Recall that $1 - Ab/Ab^\infty$ is equal to dD_{GI}/dt (Fig. 8-15).

As the drug approaches 100% absorption, C_p becomes very small and difficult to assay accurately. Consequently, the terminal part of the line described by $1 - Ab/Ab^\infty$ versus time tends to become scattered or nonlinear. This terminal part of the curve is excluded, and only the initial linear segment of the curve is used for the estimate of the slope.

PRACTICE PROBLEM

Drug concentrations in the blood at various times are listed in Table 8-1. Assuming the drug follows a one-compartment model, find the k_a value, and compare it with the k_a value obtained by the method of residuals.

Solution

The AUC is approximated by the trapezoidal rule. This method is fairly accurate when there are sufficient data points. The area between each time point

TABLE 8-1 Blood Concentrations and Associated Data for a Hypothetical Drug

Time t_n (h)	Concentration C_p ($\mu\text{g/mL}$)	$[\text{AUC}]_{t_{n-1}}^{t_n}$	$[\text{AUC}]_0^t$	$k[\text{AUC}]_0^t$	$C_p + k[\text{AUC}]_0^t$	$\frac{Ab}{Ab^\infty}$	$\left(1 - \frac{Ab}{Ab^\infty}\right)$
0	0	0	0				1.000
1	3.13	1.57	1.57	0.157	3.287	0.328	0.672
2	4.93	4.03	5.60	0.560	5.490	0.548	0.452
3	5.86	5.40	10.99	1.099	6.959	0.695	0.305
4	6.25	6.06	17.05	1.705	7.955	0.794	0.205
5	6.28	6.26	23.31	2.331	8.610	0.856	0.140
6	6.11	6.20	29.51	2.951	9.061	0.905	0.095
7	5.81	5.96	35.47	3.547	9.357	0.934	0.066
8	5.45	5.63	41.10	4.110	9.560	0.955	0.045
9	5.06	5.26	46.35	4.635	9.695	0.968	0.032
10	4.66	4.86	51.21	5.121			
12	3.90	8.56	59.77	5.977			
14	3.24	7.14	66.91	6.691			
16	2.67	5.92	72.83	7.283			
18	2.19	4.86	77.69	7.769			
24	1.20	10.17	87.85	8.785			
28	0.81	4.02	91.87	9.187			
32	0.54	2.70	94.57	9.457			
36	0.36	1.80	96.37	9.637			
48	0.10	2.76	99.13	9.913			

$k = 0.1 \text{ h}^{-1}$.

is calculated as

$$[\text{AUC}]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2} (t_n - t_{n-1}) \quad (8.36)$$

where C_n and C_{n-1} are concentrations. For example, at $n = 6$, the $[\text{AUC}]$ is

$$\frac{6.28 + 6.11}{2} (6 - 5) = 6.20$$

To obtain $[\text{AUC}]_0^\infty$, add all the area portions under the curve from zero to infinity. In this case, 48 hours is long enough to be considered infinity, because the blood concentration at that point already

has fallen to an insignificant drug concentration, $0.1 \mu\text{g/mL}$. The rest of the needed information is given in Table 8-1. Notice that k is obtained from the plot of $\log C_p$ versus t ; k was found in this example to be 0.1 h^{-1} . The plot of $1 - (Ab/Ab^\infty)$ versus t on semi-log paper is shown in Fig. 8-15.

A more complete method of obtaining k_a is to estimate the residual area from the last observed plasma concentration, C_p at t_n to time equal to infinity. This equation for the residual AUC from C_p to time equal to infinity is

$$[\text{AUC}]_t^\infty = \frac{C_{p_n}}{k} \quad (8.37)$$

The total $[AUC]_0^\infty$ is the sum of the areas obtained by the trapezoidal rule, $[AUC]_0'$, and the residual area $[AUC]_t^\infty$, as described in the following expression:

$$[AUC]_0^\infty = [AUC]_0' + [AUC]_t^\infty \quad (8.38)$$

Estimation of k_a from Urinary Data

The absorption rate constant may also be estimated from urinary excretion data, using a plot of percent of drug unabsorbed versus time. For a one-compartment model:

Ab = total amount of drug absorbed—that is, the amount of drug in the body plus the amount of drug excreted

D_B = amount of drug in the body

D_u = amount of unchanged drug excreted in the urine

C_p = plasma drug concentration

D_E = total amount of drug eliminated (drug and metabolites)

$$Ab = D_B + D_E \quad (8.39)$$

The differential of Equation 8.39 with respect to time gives

$$\frac{dAb}{dt} = \frac{dD_B}{dt} + \frac{dD_E}{dt} \quad (8.40)$$

Assuming first-order elimination kinetics with renal elimination constant k_e ,

$$\frac{dD_u}{dt} = k_e D_B = k_e V_D C_p \quad (8.41)$$

Assuming a one-compartment model,

$$V_D C_p = D_B$$

Substituting $V_D C_p$ into Equation 8.40,

$$\frac{dAb}{dt} = V_D \left(\frac{dC_p}{dt} + \frac{dD_E}{dt} \right) \quad (8.42)$$

And rearranging Equation 8.41,

$$C_p = \frac{1}{k_e V_D} \left(\frac{dD_u}{dt} \right) \quad (8.43)$$

$$\frac{dC_p}{dt} = \frac{d(dD_u/dt)}{dt k_e V_D} \quad (8.44)$$

Substituting for dC_p/dt into Equation 8.42 and kD_u/k_e for D_E ,

$$\frac{dAb}{dt} = \frac{d(dD_u/dt)}{k_e dt} + \frac{k}{k_e} \left(\frac{dD_u}{dt} \right) \quad (8.45)$$

When the above expression is integrated from zero to time t ,

$$Ab_t = \frac{1}{k_e} \left(\frac{dD_u}{dt} \right)_t + \frac{k}{k_e} (D_u)_t \quad (8.46)$$

At $t = \infty$, all the drug that is ultimately absorbed is expressed as Ab^∞ and $dD_u/dt = 0$. The total amount of drug absorbed is

$$Ab^\infty = \frac{k}{k_e} D_u^\infty$$

where D_u^∞ is the total amount of unchanged drug excreted in the urine.

The fraction of drug absorbed at any time t is equal to the amount of drug absorbed at this time, Ab_t , divided by the total amount of drug absorbed, Ab^∞ .

$$\frac{Ab_t}{Ab^\infty} = \frac{(dD_u/dt)_t + k(D_u)_t}{kD_u^\infty} \quad (8.47)$$

A plot of the fraction of drug unabsorbed, $1 - Ab/Ab^\infty$, versus time gives $-k_a/2.3$ as the slope from which the absorption rate constant is obtained (Fig. 8-15; refer to Equation 8.35).

When collecting urinary drug samples for the determination of pharmacokinetic parameters, one should obtain a valid urine collection as discussed in Chapter 4. If the drug is rapidly absorbed, it may be difficult to obtain multiple early urine samples to describe the absorption phase accurately. Moreover, drugs with very slow absorption will have low concentrations, which may present analytical problems.

Effect of k_a and k on C_{max} , t_{max} , and AUC

Changes in k_a and k may affect t_{max} , C_{max} , and AUC as shown in Table 8-2. If the values for k_a and k are reversed, then the same t_{max} is obtained, but the C_{max} and AUC are different. If the elimination rate constant is kept at 0.1 h^{-1} and the k_a changes from 0.2 to 0.6 h^{-1} (absorption rate increases), then the t_{max} becomes shorter (from 6.93 to 3.58 hours), the C_{max} increases

TABLE 8-2 Effects of the Absorption Rate Constant and Elimination Rate^a

Absorption Rate Constant, k_a (h^{-1})	Elimination Rate Constant, k (h^{-1})	t_{max} (h)	C_{max} ($\mu\text{g}/\text{mL}$)	AUC ($\mu\text{g} \cdot \text{h}/\text{mL}$)
0.1	0.2	6.93	2.50	50
0.2	0.1	6.93	5.00	100
0.3	0.1	5.49	5.77	100
0.4	0.1	4.62	6.29	100
0.5	0.1	4.02	6.69	100
0.6	0.1	3.58	6.99	100
0.3	0.1	5.49	5.77	100
0.3	0.2	4.05	4.44	50
0.3	0.3	3.33	3.68	33.3
0.3	0.4	2.88	3.16	25
0.3	0.5	2.55	2.79	20

^a t_{max} = peak plasma concentration, C_{max} = peak drug concentration, AUC = area under the curve. Values are based on a single oral dose (100 mg) that is 100% bioavailable ($F = 1$) and has an apparent V_D of 10 L. The drug follows a one-compartment open model. t_{max} is calculated by Equation 8.14 and C_{max} is calculated by Equation 8.12. The AUC is calculated by the trapezoidal rule from 0 to 24 hours.

(from 5.00 to 6.99 $\mu\text{g}/\text{mL}$), but the AUC remains constant (100 $\mu\text{g} \cdot \text{h}/\text{mL}$). In contrast, when the absorption rate constant is kept at 0.3 h^{-1} and k changes from 0.1 to 0.5 h^{-1} (elimination rate increases), then the t_{max} decreases (from 5.49 to 2.55 hours), the C_{max} decreases

(from 5.77 to 2.79 $\mu\text{g}/\text{mL}$), and the AUC decreases (from 100 to 20 $\mu\text{g} \cdot \text{h}/\text{mL}$). Graphical representations for the relationships of k_a and k on the time for peak absorption and the peak drug concentrations are shown in Figs. 8-16 and 8-17.

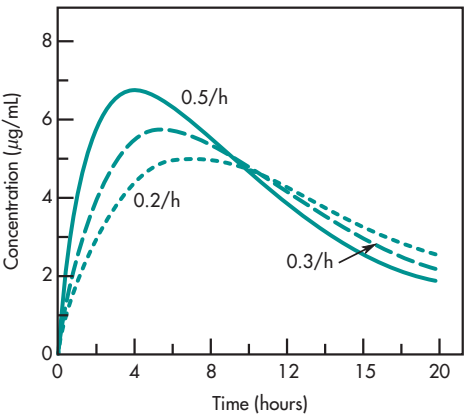


FIGURE 8-16 Effect of a change in the absorption rate constant, k_a , on the plasma drug concentration–time curve. Dose of drug is 100 mg, V_D is 10 L, and k is 0.1 h^{-1} .

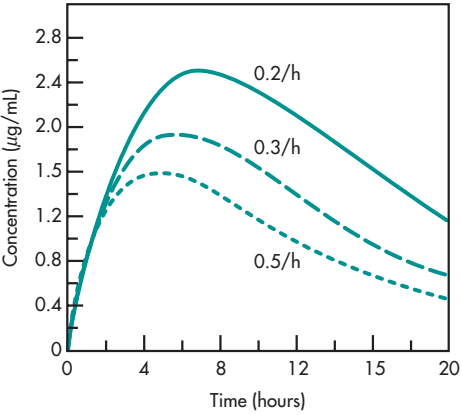


FIGURE 8-17 Effect of a change in the elimination rate constant, k , on the plasma drug concentration–time curve. Dose of drug is 100 mg, V_D is 10 L, and k_a is 0.1 h^{-1} .

Modified Wagner–Nelson Method

Hayashi et al (2001) introduced a modified Wagner–Nelson method to study the subcutaneous absorption of a drug with nonlinear kinetics from the central compartment. Nonlinear kinetics occurs in some drugs where the kinetic parameter such as k change with dose. The method was applicable to a biotechnological drug (recombinant human granulocyte-colony stimulating factors, rhG-CSF) which is eliminated nonlinearly. The drug was absorbed into the blood from the dermal site after subcutaneous injection. Because of nonlinear kinetics the extent of absorption was not easily determined. The amount of drug absorbed, A_b for each time sample, t_n , is given by Equation 8.48. V_1 and V_{ss} are central compartment and steady-state volume of distribution, respectively.

V_{max} and K_m are Michaelis–Menten parameters that describe the saturable elimination (see Chapter 10) of the drug. t_i is the sample time which = 0,1,2,4... 48 hours in this example, and $C(t)$ is the average serum drug concentration between time points, that is, t_i and t_{i+1} .

$$A_{ab}(t_n) = \sum_{i=1}^{n-1} \int_{t_i}^{t_{i+1}} \left[\frac{V_{max}C(t)}{C(t) + K_m} + kV_1C(t) \right] dt + V_{ss}C(t_n) \quad (8.48)$$

From the mass balance of the above equation, the authors did account for the amount of drug present in the tissue compartment. (Note the authors stated that the central compartment V_1 is 4.56 L and that of V_{ss} is 4.90 L.) To simplify the model, the authors used convolution to show that the contribution of the tissue compartment is not significant and therefore may be neglected. Thus, the Loo–Riegelman method which requires a tissue compartment was not used by the authors. Convolution is an analytical method that predicts plasma time drug concentration using input and disposition functions for drugs with linear kinetics. The disposition function may be first obtained by deconvolution of simple IV plasma drug concentration data or from the terminal phase of an oral solution. Alternatively, the method of Lockwood and Gillespie (1996) abbreviated the need for the simple solution.

Models for Estimation of Drug Absorption

There are many models and approaches that have been used to predict drug absorption since the introduction of the classical approaches by John Wagner (1967) and Jack Loo. Deconvolution and convolution approaches are used to predict plasma drug concentration of oral dosage forms. Several commercial software (eg, GastroPlus, iDEA, Intellipharma PK, and PK-Sim) are now available for formulation and drug development or to determine the extent of drug absorption. The new software allows the characteristics of the drug, physiologic factors, and the dosage form to be inputted into the software. An important class of programs involves the Compartmental Absorption and Transit (CAT) models. This model integrates the effect of solubility, permeability, as well as gastric emptying and GI transit time in the estimation of *in vivo* drug absorption. CAT models were successfully used to predict the fraction of drug oral absorption of 10 common drugs based on a small intestine transit time (Yu, 1999). The CAT models compared well overall with other plausible models such as the dispersion model, the single mixing tank model, and some flow models. It is important to note that the models discussed earlier in this chapter are used to compute extent of absorption after the plasma drug concentrations are measured. In contrast, the later models/software allow a comprehensive way to simulate or predict drug (product) performance *in vivo*. The subjects of dissolution, dosage form design, and drug absorption will be discussed in more detail in Chapters 14 and 15.

Determination of k_a from Two-Compartment Oral Absorption Data (Loo–Riegelman Method)

Plotting the percent of drug unabsorbed versus time to determine k_a may also be calculated for a drug exhibiting a two-compartment kinetic model. As in the method used previously to obtain an estimate of the k_a , no limitation is placed on the order of the absorption process. However, this method does require that the drug be given intravenously as well as orally to obtain all the necessary kinetic constants.

After oral administration of a dose of a drug that exhibits two-compartment model kinetics, the amount

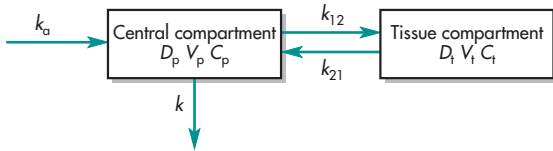


FIGURE 8-18 Two-compartment pharmacokinetic mode. Drug absorption and elimination occur from the central compartment.

of drug absorbed is calculated as the sum of the amounts of drug in the central compartment (D_p), in the tissue compartment (D_t), and the amount of drug eliminated by all routes (D_u) (Fig. 8-18).

$$Ab = D_p + D_t + D_u \quad (8.49)$$

Each of these terms may be expressed in terms of kinetics constants and plasma drug concentrations, as follows:

$$D_p = V_p C_p \quad (8.50)$$

$$D_t = V_t C_t \quad (8.51)$$

$$\frac{dD_u}{dt} = k V_p C_p \quad (8.52)$$

$$D_u = k V_p [AUC]_0^t$$

Substituting the above expression for D_p and D_u into Equation 8.49,

$$Ab = V_p C_p + D_t + k V_p [AUC]_0^t \quad (8.53)$$

By dividing this equation by V_p to express the equation on drug concentrations, we obtain

$$\frac{Ab}{V_p} = C_p + \frac{D_t}{V_p} + k [AUC]_0^t \quad (8.54)$$

At $t = \infty$, this equation becomes

$$\frac{Ab}{V_p} = k [AUC]_0^\infty \quad (8.55)$$

Equation 8.54 divided by Equation 8.55 gives the fraction of drug absorbed at any time as shown in Equation 8.56.

$$\frac{Ab}{Ab^\infty} = \frac{C_p + \left(\frac{D_t}{V_p}\right) + k [AUC]_0^t}{k [AUC]_0^\infty} \quad (8.56)$$

A plot of the fraction of drug unabsorbed, $1 - Ab/Ab^\infty$, versus time gives $-k_a/2.3$ as the slope from which the value for the absorption rate constant is obtained (refer to Equation 8.35).

The values for $k[AUC]_0^t$ are calculated from a plot of C_p versus time. Values for (D_t/V_p) can be approximated by the Loo–Riegelman method, as follows:

$$(C_t)_{t_n} = \frac{k_{12} \Delta C_p \Delta t}{2} + \frac{k_{12}}{k_{21}} (C_p)_{t_{n-1}} (1 - e^{-k_{21} \Delta t}) + (C_t)_{t_{n-1}} e^{-k_{21} \Delta t} \quad (8.57)$$

where C_t is D_t/V_p , or apparent tissue concentration; t = time of sampling for sample n ; t_{n-1} = time of sampling for the sampling point preceding sample n ; and $(C_p)_{t_{n-1}}$ = concentration of drug at central compartment for sample $n - 1$.

Calculation of C_t values is shown in Table 8-3, using a typical set of oral absorption data. After calculation of C_t values, the percent of drug unabsorbed is calculated with Equation 8.56, as shown in Table 8-4. A plot of percent of drug unabsorbed versus time on semilog graph paper gives a k_a of approximately 0.5 h^{-1} .

For calculation of k_a by this method, the drug must be given intravenously to allow evaluation of the distribution and elimination rate constants. For drugs that cannot be given by the IV route, the k_a cannot be calculated by the Loo–Riegelman method. For drugs that are given by the oral route only, the Wagner–Nelson method, which assumes a one-compartment model, may be used to provide an initial estimate of k_a . If the drug is given intravenously, there is no way of knowing whether there is any variation in the values for the elimination rate constant, k and the distributive rate constants, k_{12} and k_{21} . Such variations alter the rate constants. Therefore, a one-compartment model is frequently used to fit the plasma curves after an oral or intramuscular dose. The plasma level predicted from the k_a obtained by this method does deviate from the actual plasma level. However, in many instances, this deviation is not significant.

Cumulative Relative Fraction Absorbed

The fraction of drug absorbed at any time t (Equation 8.32) may be summed or cumulated for each time period for which a plasma drug sample was obtained.

TABLE 8-3 Calculation of C_t Values^a

$(C_p)_t$	$(t)_t$	$\Delta(C_p)$	Δt	$\frac{(k_{12}\Delta C_p \Delta t)}{2}$	$(C_p)_{t_{n-1}}$	$\frac{(k_{12}/k_{21}) \times (C_p)_{t_{n-1}}}{(1 - e^{-k_{21}\Delta t})}$	$\frac{(C_p)_{t_{n-1}}(k_{12}/k_{21}) \times}{(1 - e^{-k_{21}\Delta t})}$	$(C_t)_{t_{n-1}} e^{-k_{21}\Delta t}$	$(C_t)_t$
3.00	0.5	3.0	0.5	0.218	0	0.134	0	0	0.218
5.20	1.0	2.2	0.5	0.160	3.00	0.134	0.402	0.187	0.749
6.50	1.5	1.3	0.5	0.094	5.20	0.134	0.697	0.642	1.433
7.30	2.0	0.8	0.5	0.058	6.50	0.134	0.871	1.228	2.157
7.60	2.5	0.3	0.5	0.022	7.30	0.134	0.978	1.849	2.849
7.75	3.0	0.15	0.5	0.011	7.60	0.134	1.018	2.442	3.471
7.70	3.5	-0.05	0.5	-0.004	7.75	0.134	1.039	2.976	4.019
7.60	4.0	-0.10	0.5	-0.007	7.70	0.134	1.032	3.444	4.469
7.10	5.0	-0.50	1.0	-0.073	7.60	0.250	1.900	3.276	5.103
6.60	6.0	-0.50	1.0	-0.073	7.10	0.250	1.775	3.740	5.442
6.00	7.0	-0.60	1.0	-0.087	6.60	0.250	1.650	3.989	5.552
5.10	9.0	-0.90	2.0	-2.261	6.00	0.432	2.592	2.987	5.318
4.40	11.0	-0.70	2.0	-0.203	5.10	0.432	2.203	2.861	4.861
3.30	15.0	-1.10	4.0	-0.638	4.40	0.720	3.168	1.361	3.891

^aCalculated with the following rate constants: $k_{12} = 0.29 \text{ h}^{-1}$, $k_{21} = 0.31 \text{ h}^{-1}$.

Adapted with permission from Loo and Riegelman (1968).

From Equation 8.32, the term Ab/Ab^∞ becomes the *cumulative relative fraction absorbed* (CRFA).

$$\text{CRFA} = \frac{C_p + k[\text{AUC}]_0'}{k[\text{AUC}]_0^\infty} \quad (8.58)$$

where C_p is the plasma concentration at time t .

In the Wagner–Nelson equation, Ab/Ab^∞ or CRFA will eventually equal unity, or 100%, even though the drug may not be 100% systemically bioavailable. The percent of drug absorbed is based on the total amount of drug absorbed (Ab^∞) rather than the dose D_0 . Because the amount of drug ultimately absorbed, Ab^∞ in fractional term, is analogous to $k[\text{AUC}]_0^\infty$, the numerator will always equal the denominator at time infinity, whether the drug is 10%, 20%, or 100% bioavailable. The percent of drug absorbed based on Ab/Ab^∞ is therefore different from the real percent of drug absorbed unless $F = 1$. However, for the calculation of k_a , the method is acceptable.

To determine the real percent of drug absorbed, a modification of the Wagner–Nelson equation was suggested by Welling (1986). A reference drug product was administered and plasma drug concentrations were determined over time. CRFA was then estimated by dividing $Ab/Ab_{\text{ref}}^\infty$, where Ab is the cumulative amount of drug absorbed from the drug product and Ab_{ref}^∞ is the cumulative final amount of drug absorbed from a reference dosage form. In this case, the denominator of Equation 8.58 is modified as follows:

$$\text{CRFA} = \frac{C_p + k[\text{AUC}]_0^\infty}{k_{\text{ref}}[\text{AUC}]_{\text{ref}}^\infty} \quad (8.59)$$

where k_{ref} and $[\text{AUC}]_{\text{ref}}^\infty$ are the elimination constant and the area under the curve determined from the reference product, respectively. The terms in the numerator of Equation 8.59 refer to the product, as in Equation 8.58.

TABLE 8-4 Calculation of Percentage Unabsorbed^a

Time (h)	(C _p) _{t_n}	[AUC] _{t_{n-1}} ^{t_n}	[AUC] _{t₀} ^{t_n}	k[AUC] _{t₀} ^{t_n}	(C _t) _{t_n}	Ab/V _p	%Ab/V _p	100% – Ab/V _p %
0.5	3.00	0.750	0.750	0.120	0.218	3.338	16.6	83.4
1.0	5.20	2.050	2.800	0.448	0.749	6.397	31.8	68.2
1.5	6.50	2.925	5.725	0.916	1.433	8.849	44.0	56.0
2.0	7.30	3.450	9.175	1.468	2.157	10.925	54.3	45.7
2.5	7.60	3.725	12.900	2.064	2.849	12.513	62.2	37.8
3.0	7.75	3.838	16.738	2.678	3.471	13.889	69.1	30.9
3.5	7.70	3.863	20.601	3.296	4.019	15.015	74.6	25.4
4.0	7.60	3.825	24.426	3.908	4.469	15.977	79.4	20.6
5.0	7.10	7.350	31.726	5.084	5.103	17.287	85.9	14.1
6.0	6.60	6.850	38.626	6.180	5.442	18.222	90.6	9.4
7.0	6.00	6.300	44.926	7.188	5.552	18.740	93.1	6.9
9.0	5.10	11.100	56.026	8.964	5.318	19.382	96.3	3.7
11.0	4.40	9.500	65.526	10.484	4.861	19.745	98.1	1.9
15.0	3.30	15.400	80.926	12.948	3.891	20.139	100.0	0

^a $Ab/V_p = (C_p) + k[AUC]_{t_0}^{t_n} + (C_t)_{t_n}$

$(C_t)_{t_n} = k_{12} \Delta C_p \Delta t / 2 + k_{12} / k_{21} (C_p)_{t_{n-1}} (1 - e^{-k_{21} \Delta t}) + (C_t)_{t_{n-1}} e^{-k_{21} \Delta t}$

$k = 0.16; k_{12} = 0.29; k_{21} = 0.31$

Each fraction of drug absorbed is calculated and plotted against the time interval in which the plasma drug sample was obtained (Fig. 8-19). An example of the relationship of CRFA versus time for the absorption of tolazamide from four different drug products

is shown in Fig. 8-20. The data for Fig. 8-21 were obtained from the serum tolazamide levels–time curves in Fig. 8-20. The CRFA–time graph provides a visual image of the relative rates of drug absorption from various drug products. If the CRFA–time

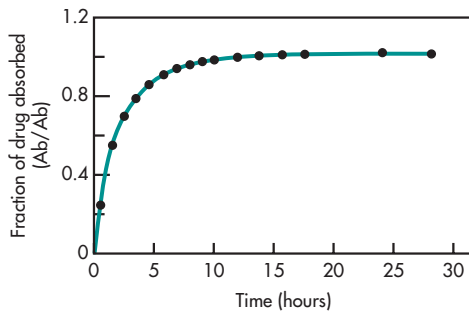


FIGURE 8-19 Fraction of drug absorbed. (Wagner–Nelson method.)

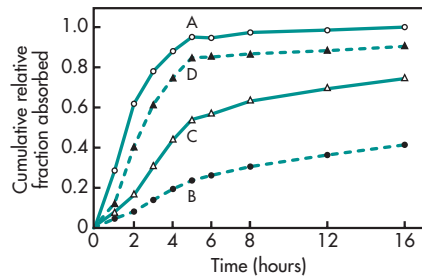


FIGURE 8-20 Mean cumulative relative fractions of tolazamide absorbed as a function of time. (From Welling et al, 1982, with permission.)

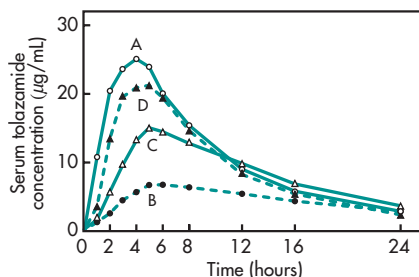


FIGURE 8-21 Mean serum tolazamide levels as a function of time. (From Welling et al, 1982, with permission.)

curve is a straight line, then the drug was absorbed from the drug product at an apparent zero-order absorption rate.

The calculation of k_a is useful in designing a multiple-dosage regimen. Knowledge of the k_a and k allows for the prediction of peak and trough plasma drug concentrations following multiple dosing. In bioequivalence studies, drug products are given in chemically equivalent (ie, pharmaceutical equivalents) doses, and the respective rates of systemic

absorption may not differ markedly. Therefore, for these studies, $t_{\max}$, or time of peak drug concentration, can be very useful in comparing the respective rates of absorption of a drug from chemically equivalent drug products.

Frequently Asked Questions

- Can the Wagner–Nelson method be used to calculate k_a for an orally administered drug that follows the pharmacokinetics of a two-compartment model?
- What is the absorption half-life of a drug and how is it determined?
- In switching a drug from IV to oral dosing, what is the most important consideration?
- Drug clearance is dependent on dose and area under the time–drug concentration curve. Would drug clearance be affected by the rate of absorption?
- Does a larger absorption rate constant affect $C_{\max}$, $t_{\max}$, and AUC if the dose and elimination rate constant, k remains constant?

CHAPTER SUMMARY

Pharmacokinetic absorption models range from being entirely “exploratory” and empirical, to semi-mechanistic and ultimately complex physiologically based pharmacokinetic (PBPK) models. This choice is conditional on the modeling purpose as well as the amount and quality of the available data.

Empirically, the pharmacokinetics of drug absorption may be described by zero-order or first-order kinetics. Drug elimination from the body is generally described by first-order kinetics. Using the compartment model, various important pharmacokinetics parameters about drug absorption such as k_a , k , $C_{\max}$, $t_{\max}$, and other parameters may be computed from data by the method of residuals (feathering) or by computer modeling. The pharmacokinetic parameters are important in evaluating drug absorption and understanding how these parameters affect drug concentrations in the body. The fraction of drug absorbed may be computed in a one-compartment model using the Wagner–Nelson method or in a

two-compartment model using the Loo–Riegelman method. The determination of the fraction of drug absorbed is an important tool in evaluating drug dosage form and design. The Wagner–Nelson method and Loo–Riegelman method are classical methods for determining absorption rate constants and fraction of drug absorbed. Convolution and deconvolution are powerful alternative tools used to predict a plasma drug concentration–time profile from dissolution of data during drug development.

The empirical models presented in this chapter are very basic with simple assumptions. More sophisticated methods based on these basic concepts may be extended to include physiological factors such as GI transit in the physiologically based models that represent the advance drug absorption model development. These models are useful to predict drug absorption over time curves in designing oral dosage forms (see Chapters 14 and 15).

Although the current development of *in vitro* studies and computer science have allowed rapid advances of PBPK models, the combination of physiologically based modeling with parameter estimation techniques seems to be the way forward and its impact on the drug development progressively

increases. Although such an approach has limitations, further methodology research in this field and the advances in computer science can address many of them. It is apparent that “bottom-up” and “top-down” modeling strategies need to approach and borrow skills from each other.

ANSWERS

Frequently Asked Questions

If drug absorption is simulated using the oral one-compartment model, would a larger absorption rate constant result in a greater amount of drug absorbed?

- The fraction of drug absorbed, F , and the absorption rate constant, k_a , are independent parameters. A drug in an oral solution may have a more rapid rate of absorption compared to a solid drug product. If the drug is released from the drug product slowly or is formulated so that the drug is absorbed slowly, the drug may be subjected to first-pass effects, degraded in the gastrointestinal tract, or eliminated in the feces so that less drug (smaller F) may be absorbed systemically compared to the same drug formulated to be absorbed more rapidly from the drug product.

How do you explain that k_a is often greater than k with most drugs?

- A drug with a rate of absorption slower than its rate of elimination will not be able to obtain optimal systemic drug concentrations to achieve efficacy. Such drugs are generally not developed into products. However, the apparent k_a for drugs absorbed from controlled-release products (Chapter 18) may be smaller, but the initial rate of absorption from the GI tract is faster than the rate of drug elimination since, $dD_{GI}/dt = -k_a D_{GI}$.

What is the absorption half-life of a drug and how is it determined?

- For drugs absorbed by a first-order process, the absorption half-life is $0.693/k_a$. Although drug absorption involves many stochastic (system-based random) steps, the overall rate process is often approximated by a first-order process, especially

with oral solutions and immediate-release drug products such as compressed tablets or capsules. The determination of the absorption rate constant, k_a , is most often calculated by the Wagner–Nelson method for drugs, which follows a one-compartment model with first-order absorption and first-order elimination.

In switching a drug from IV to oral dosing, what is the most important consideration?

- The fraction of drug absorbed may be less than 1 (ie, 100% bioavailable) after oral administration. In some cases, there may be a different salt form of the drug used for IV infusion compared to the salt form of the drug used orally. Therefore, a correction is needed for the difference in MW of the two salt forms.

Drug clearance is dependent on dose and area under the time–drug concentration curve. Would drug clearance be affected by the rate of absorption?

- Total body drug clearance and renal drug clearance are generally not affected by drug absorption from most absorption sites. In the gastrointestinal tract, a drug is absorbed via the hepatic portal vein to the liver and may be subject to hepatic clearance.

Learning Questions

1. a. The elimination rate constant is 0.1 h^{-1} ($t_{1/2} = 6.93 \text{ h}$).
b. The absorption rate constant, k_a , is 0.3 h^{-1} (absorption half-life = 2.31 h).

$$\text{The calculated } t_{\max} = \frac{\ln(k_a/k)}{k_a - k} = 5.49 \text{ h}$$

- c. The y intercept was observed to be 60 ng/mL. Therefore, the equation that fits the observed data is

$$C_p = 60(e^{-0.1t} - e^{-0.3t})$$

Note: Answers obtained by “hand” feathering the data on semilog graph paper may vary somewhat depending on graphing skills and skill in reading data from a graph.

2. By direct observation of the data, the $t_{\max}$ is 6 hours and the $C_{\max}$ is 23.01 ng/mL. The apparent volume of distribution, V_D , is obtained from the intercept, I , of the terminal elimination phase, and substituting $F = 0.8$, $D = 10,000,000$ ng, $k_a = 0.3$ h⁻¹, $k = 0.1$ h⁻¹:

$$I = \frac{Fk_a D_0}{V_D(k_a - k)}$$

$$60 = \frac{(0.8)(0.3)(10,000,000)}{V_D(0.3 - 0.1)}$$

$$V_D = 200 \text{ L}$$

3. The percent-of-drug-unabsorbed method is applicable to any model with first-order elimination, regardless of the process of drug input. If the drug is given by IV injection, the elimination rate constant, k , may be determined accurately. If the drug is administered orally, k and k_a may *flip-flop*, resulting in an error unless IV data are available to determine k . For a drug that follows a two-compartment model, an IV bolus injection is used to determine the rate constants for distribution and elimination.
4. After an IV bolus injection, a drug such as theophylline follows a two-compartment model with a rapid distribution phase. During oral absorption, the drug is distributed during the absorption phase, and no distribution phase is observed. Pharmacokinetic analysis of the plasma drug concentration data obtained after oral drug administration will show that the drug follows a one-compartment model.

5. The equations for a drug that follows the kinetics of a one-compartment model with first-order absorption and elimination are

$$C_p = \frac{FD_0 k_a}{VD(k_a - k)}(e^{kt} - e^{-k_a t}) \quad t_{\max} = \frac{\ln(k_a/k)}{k_a - k}$$

As shown by these equations:

- a. $t_{\max}$ is influenced by k_a and k and not by F , D_0 , or V_D .
- b. C_p is influenced by F , D_0 , V_D , k_a , and k .
6. A drug product that might provide a zero-order input is an oral controlled-release tablet or a transdermal drug delivery system (patch). An IV drug infusion will also provide a zero-order drug input.
7. The general equation for a one-compartment open model with oral absorption is

$$C_p = \frac{FD_0 k_a}{V_D(k_a - k)}(e^{-kt} - e^{-k_a t})$$

From $C_p = 45(e^{-0.17t} - e^{-1.5t})$

$$\frac{FD_0 k_a}{V_D(k_a - k)} = 45$$

$$k = 0.17 \text{ h}^{-1}$$

$$k_a = 1.5 \text{ h}^{-1}$$

- a. $t_{\max} = \frac{\ln(k_a/k)}{k_a - k} = \frac{\ln(1.5/0.17)}{1.5 - 0.17} = 1.64 \text{ h}$
- b. $C_{\max} = 45(e^{-(0.17)(1.64)} - e^{-(1.5)(1.64)})$
 $= 30.2 \text{ } \mu\text{g/mL}$
- c. $t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.17} = 4.08 \text{ h}$
8. a. Drug A $t_{\max} = \frac{\ln(1.0/0.2)}{1.0 - 1.2} = 2.01 \text{ h}$
- Drug B $t_{\max} = \frac{\ln(0.2/1.0)}{0.2 - 1.0} = 2.01 \text{ h}$
- b. $C_{\max} = \frac{FD_0 k_a}{V_D(k_a - k)}(e^{-kt_{\max}} - e^{-k_a t_{\max}})$
- Drug A $C_{\max} = \frac{(1)(500)(1)}{(10)(1 - 0.2)}(e^{-(0.2)(2)} - e^{-(1)(2)})$
 $C_{\max} = 33.4 \text{ } \mu\text{g/mL}$

$$\begin{aligned}\text{Drug B } C_{\max} &= \frac{(1)(500)(0.2)}{(20)(0.2 - 1.0)} \\ &= (e^{-1(2)} - e^{-(0.2)(2)}) \\ C_{\max} &= 33.4 \mu\text{g/mL}\end{aligned}$$

9. **a.** The method of residuals using manual graphing methods may give somewhat different answers depending on personal skill and the quality of the graph paper. Values obtained by the computer program ESTRIP gave the following estimates:
- $$k_a = 2.84 \text{ h}^{-1} \quad k = 0.186 \text{ h}^{-1} \quad t_{1/2} = 3.73 \text{ h}$$
- b.** A drug in an aqueous solution is in the most absorbable form compared to other oral dosage forms. The assumption that $k_a > k$ is generally true for drug solutions and immediate-release oral dosage forms such as compressed tablets and capsules. Drug absorption from extended-release dosage forms may have $k_a < k$. To demonstrate unequivocally which slope represents the true k , the drug must be given by IV bolus or IV infusion, and the slope of the elimination curve obtained.

- c.** The Loo–Riegelman method requires IV data. Therefore, only the Wagner–Nelson method may be used on these data.
- d.** Observed $t_{\max}$ and $C_{\max}$ values are taken directly from the experimental data. In this example, $C_{\max}$ is 85.11 ng/mL, which occurred at a $t_{\max}$ of 1 hour. The theoretical $t_{\max}$ and $C_{\max}$ are obtained as follows:

$$\begin{aligned}t_{\max} &= \frac{2.3 \log(k_a/k)}{k_a - k} \\ &= \frac{2.3 \log(2.84/0.186)}{2.84 - 0.186} = 1.03 \text{ h}\end{aligned}$$

$$C_{\max} = \frac{FD_0 k_a}{V_D(k_a - k)}(e^{-k t_{\max}} - e^{-k_a t_{\max}})$$

where $FD_0 k_a / V_D(k_a - k)$ is the y intercept equal to 110 ng/mL and $t_{\max} = 1.03 \text{ h}$.

$$C_{\max} = (110)(e^{-(1.186)(1.0)} - e^{-(2.84)(1.03)})$$

$$C_{\max} = 85 \text{ ng/mL}$$

- e.** A more complete model-fitting program, such as WINNONLIN, is needed to fit the data statistically to a one-compartment model.

APPLICATION QUESTIONS

1. Plasma samples from a patient were collected after an oral bolus dose of 10 mg of a new benzodiazepine solution as follows:

Time (hours)	Concentration (ng/mL)
0.25	2.85
0.50	5.43
0.75	7.75
1.00	9.84
2.00	16.20
4.00	22.15
6.00	23.01
10.00	19.09
14.00	13.90
20.00	7.97

From the given data:

- Determine the elimination constant of the drug.
 - Determine k_a by feathering.
 - Determine the equation that describes the plasma drug concentration of the new benzodiazepine.
2. Assuming that the drug in Question 1 is 80% absorbed, find (a) the absorption constant, k_a ; (b) the elimination half-life, $t_{1/2}$; (c) the $t_{\max}$, or time of peak drug concentration; and (d) the volume of distribution of the patient.
3. Contrast the percent of drug-unabsorbed methods for the determination of rate constant for absorption, k_a , in terms of (a) pharmacokinetic model, (b) route of drug administration, and (c) possible sources of error.

4. What is the error inherent in the measurement of k_a for an orally administered drug that follows a two-compartment model when a one-compartment model is assumed in the calculation?
5. What are the main pharmacokinetic parameters that influence (a) time for peak drug concentration and (b) peak drug concentration?
6. Name a method of drug administration that will provide a zero-order input.
7. A single oral dose (100 mg) of an antibiotic was given to an adult male patient (43 years, 72 kg). From the literature, the pharmacokinetics of this drug fits a one-compartment open model. The equation that best fits the pharmacokinetics of the drug is

$$C_p = 45(e^{-0.17t} - e^{-1.5t})$$

From the equation above, calculate (a) $t_{\max}$, (b) $C_{\max}$, and (c) $t_{1/2}$ for the drug in this patient. Assume C_p is in $\mu\text{g/mL}$ and the first-order rate constants are in h^{-1} .

8. Two drugs, A and B, have the following pharmacokinetic parameters after a single oral dose of 500 mg:

Drug	k_a (h^{-1})	k (h^{-1})	V_D (mL)
A	1.0	0.2	10,000
B	0.2	1.0	20,000

Both drugs follow a one-compartment pharmacokinetic model and are 100% bioavailable.

- a. Calculate the $t_{\max}$ for each drug.
- b. Calculate the $C_{\max}$ for each drug.
9. The bioavailability of phenylpropanolamine hydrochloride was studied in 24 adult male

subjects. The following data represent the mean blood phenylpropanolamine hydrochloride concentrations (ng/mL) after the oral administration of a single 25-mg dose of phenylpropanolamine hydrochloride solution:

Time (hours)	Concentration (ng/mL)	Time (hours)	Concentration (ng/mL)
0	0	3	62.98
0.25	51.33	4	52.32
0.5	74.05	6	36.08
0.75	82.91	8	24.88
1.0	85.11	12	11.83
1.5	81.76	18	3.88
2	75.51	24	1.27

- a. From the above data, obtain the rate constant for absorption, k_a , and the rate constant for elimination, k , by the method of residuals.
- b. Is it reasonable to assume that $k_a > k$ for a drug in a solution? How would you determine unequivocally which rate constant represents the elimination constant k ?
- c. From the data, which method, Wagner–Nelson or Loo–Riegelman, would be more appropriate to determine the order of the rate constant for absorption?
- d. From your values, calculate the theoretical $t_{\max}$. How does your value relate to the observed $t_{\max}$ obtained from the subjects?
- e. Would you consider the pharmacokinetics of phenylpropanolamine HCl to follow a one-compartment model? Why?

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